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ORIGINAL ARTICLES

CASE REPORTS

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E-mail: kmj@kma.org.kw
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Review Article

Medical case presentation and medical reporting; an art of science

Kamel El-Reshaid
Department of Medicine, Faculty of Medicine, Kuwait University

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ABSTRACT

The medical case presentation is a scientific means used by practicing physicians to systematically communicate, define the patient's health status and his need for therapy. It can be supplied as a medico-legal document in the form of "medical report" for future care, marriage, employment and task assignment. It is structured into four parts: (a) history; (b) physical examination; (c) assessment; and (d) management. The first two sections should be done systematically and objectively to ensure factual data analysis by colleagues. On the other hand, assessment defines the (a) active and (b) inactive at a level of diagnosis based on the available data from history and examination. Lastly, management should provide (a) recommendations to improve level of diagnosis in the form of immediate and delayed investigations as permitted by the patient's health status; (b) immediate treatment options to stabilize the current disorder/s; and (c) instructions for future patient care by diet, medications and consultations. In conclusion, medical reporting is an art of science to document the patient's current health status and a means to ease future inter-physician communication and follow up.

KEY WORDS: case presentation, diagnosis, medical history, medical report, physical examination

INTRODUCTION

A medical report form is a document used by medical professionals for defining the patient's past medical history, current health status, treatment need and future recommendations. It should include hereditary and congenital disorders, infectious diseases, substance abuse, psychiatric ailments, allergies, traumatic handicaps, metabolic disorders, autoimmune diseases and acquired illnesses. Such information is essential for the patient's well-being, care by family members, as well as future marriage, employment and task assignments. Moreover, it is the cornerstone of data collection for epidemiological studies and future research. Skills in attaining such data within a limited time frame are essential for practicing physicians and a cornerstone in medical education[1]. It is a medico-legal document and hence a proper legal request and informed patient's consent are essential prior to commencing report preparation and submission[2].

Historical background

Its evolution started 4000 years ago as case histories for didactic use by medieval Islamic and Hellenistic physicians[3]. The change from retrospective to real-time recording of cases first appeared in Paris and Berlin by the 19th century[4]. However, a clinical medical record useful for direct patient care using fixed chart structure was not developed until the 20th century[5]. Finally, electronic medical records offered real advantages in accessing the large volume of patient's data[6].

Sections of the case presentation

To ease the readability and accuracy of case presentation, it should be presented in a structured and objective format (Table 1). The latter is intended to improve the practice of medical reporting, which is oversimplified by the current Subjective Objective Assessment Plan system[7,8] and overwhelming in standard text books of medical examination[9]. As

Address correspondence to:
Dr. Kamel El-Reshaid, Professor, Department of Medicine, Faculty of Medicine, Kuwait University, P O Box 24923, 13110 Safat, Kuwait. Fax: (965) 25318454; E-mail: kamel@hsc.edu.kw

Table 1: Sections of the case presentation/medical report

Section	Details
A. History	
B. Physical examination	
C. Assessment	What do you think the patient has? Based on Problem Oriented Medical Recording (POMR) • Active problems • Inactive problems According to level of diagnosis according to master plan
D. Management	(a) Immediate and delayed investigations. (b) Immediate and delayed treatments and intervention. (c) Patient and family education.

seen in Table 1, the case presentation is divided into four parts: (a) history; (b) physical examination; (c) assessment; and (d) management.

Identification data

They are not part of the true medical practice, yet are essential for identification of the case presented. They include (a) date of reporting; (b) full name of the patient (in 4 to minimize future name confusion); (c) civil ID number; and (d) contact number, address, telephone and e-mail address.

Moreover, it should include the practitioner's full name, practicing address and contact numbers as well as current employment and qualifications (Table 2).

Personal data

Personal data should include the patient's age, gender, nationality and race. To start, those criteria influence future assessment since different infections, tumors, autoimmune diseases and drug dosage and metabolism should be modified with age. Gender diseases are beyond reproductive organs since female sex hormone protects females from atherosclerosis, which is rare before menopause, and on the other hand, increase the incidence of autoimmune diseases, especially systemic lupus erythematosus. Lastly, nationality relates to endemicity of diseases and race to disease predisposition. Addition of marital status and occupation should be avoided in this section and should be reported in details pertinent to the patient's problems in the social section (vida infra).

Table 2: History section

Section	Details
Identification data	Name (4), number of civil ID, hospital record, telephone, e-mail and address
Personal data	Age, sex, nationality and race
Chief complaint / presenting symptom or sign / Cause of: admission / consultation, referral	1 phenomenon X duration (State informant and its reliability)
History of present illness	A- Chronological theme (the condition started and list subsequent events) B- Means of dissection of each event: (1) Questions of pain/S&S: (a) for severity of event (b) Localizing: relieving and aggravating factors + associated manifestations (2) Questions of systems involved anatomically. (3) Questions of etiologies: (trauma, infection, autoimmune, neoplastic) Hx of fever, weight loss, trauma, autoimmune manifestations.
System review	Cardiovascular: SOB (+ paroxysmal nocturnal dyspnea), chest pain, palpitations, oedema Respiratory: SOB, chest pain, cough, wheeze GI / biliary: Changes (upper & lower), abdominal pain (+ jaundice) Nephrourolgical: Changes in quantity or quality of urine, pain Nervous system: Headache, abn. movement or focal weakness or abn. sensations Musculoskeletal: Joint, muscle (pain or swelling) Genital: Menses, conception + pain or discharge Psychiatric: Anxiety, depression, phobia & abn. thought content (delusion, illusion, hallucination)
Social history	House and work environment, three bad habits (esp. that is related to his illness)
Past history	Chronological and without grouping illness
Family history	Diseases in close family members (hereditary diseases)

S&S: symptoms & signs, Hx: history, SOB: shortness of breath, abn: abnormal

History taking

Prior to including any information in this section, the source should be stated viz. patient, relative, friend or attendant. Moreover, a clear statement about reliability of the informant should be stated.

Chief complaint

It is related to presenting symptoms or signs that brought the patient to the hospital. It is neither the first or last patient's health event nor the more serious by the treating doctor. As described, it is "chief" and "single word of complaint" with its duration.

The essence of the chief complaint is that it is similar to the heading of an article which summarizes its contents and reflects its major problem. It is done by the primary physician and can be modified later to (a) cause of admission if the patient needs it; (b) cause of referral or consultation if a tertiary medical assistance is needed.

History of the present illness

It describes chronologically the story of the current patient's illness that includes all the new abnormal symptoms and signs. In this chapter, efforts should be directed to highlight:

A- Dissection of each stated manifestation with the use of:

(a) Questions of pain e.g., site, course, etc. which indicates the severity of the condition, yet two items have additional value viz. associated manifestations and relieving and aggravating factors that can assist with future disease diagnosis. For example, upper abdominal pain that is relieved with vomiting is peptic and that is worse with lying down is pancreatic.
(b) Questions of systems review that are involved by the anatomical site of the problem, e.g., questions on chest and heart in a patient with breathing difficulty.
(c) General questions that assist in disclosing the etiology of his current illness such as history of trauma, weight loss, new medication and fever.

B- Starting this section by stating: "The condition started on.. with…". On the other hand, starting with "the patient is a known case of ischemic heart disease" is a common mistake since history presentation should be objective and not tailored to physician's opinion at this stage.

C- Limiting the presentation to only the positive data and omitting negative ones for sake of summarization is incorrect. Data presentation from the questionnaire should include them both since positive data swings the pendulum towards certain system involvement and diseases while negative ones exclude others.

System review

It entails questions of systems that were involved in the present illness. It assists by disclosing abnormalities that the patient had missed due to the gravidity of the present illness and may be closely related to his illness, e.g., a case of fluid overload due to kidney disease with abnormal urine quantity and quality in a patient with negative system review of heart or chest questions. Most textbooks place this section at the end of the history section[9]. The latter is not correct since it deals with further questions about the current illness and hence should not be done later. Moreover, it complements evaluating the other systems that were not discussed in the history of the present illness.

Past history

It entails chronological descriptions of previous diseases, surgeries, admissions and allergies. It should not be (a) grouped into disease categories; and (b) reported as confirmed unless adequate historic analysis was confirmed. Unconfirmed historic disease-claims should not be ignored, but should be listed for further evaluation and confirmation.

Social history

It entails description of work and house environment as well as the three bad habits if they exist, viz. smoking, alcohol and drug abuse. Details related to the patient's problems should be added to facilitate assessment and future management of his diseases. Hence, it should not be a part of the initial medical personal data and should be evaluated after the history section.

Family history

This entails a search for similar disorders in close family members that fits with transmittable diseases.

Physical examination

A-General one describes four parameters viz. (a) patient's stability with shortness of breath and pain. Those two parameters serve to reflect an initial limitation in history taking and examination. Moreover, they represent a level of initial disease stage that reflects efficacy of future management. (b) Level of consciousness and patient's orientation towards persons, time and place. These two parameters are impaired in organic brain disorders. The first is impaired in bilateral cortical disease viz. systemic infections or cerebritis, drug effect as well as brain stem-disease. The level of consciousness spans from fully conscious to being comatose with intermediate

Table 3: Physical examination

Section	Details
General examination	1. Consciousness level, orientation level (X3), in distress of pain or shortness of breath. 2. Vital signs: blood pressure (lying & standing), pulse, temp, respiration rate, O_2 sat. 3. Pallor, cyanosis, jaundice. 4. Neck: carotids, jugular venous pressure, lymphadenopathy, goiter
Systemic examination	Evaluation by [inspection, palpation, percussion, auscultation] Heart (cardiovascular system): apex, thrill, heart sounds, adventious (gallop, murmur, rub). Chest (respiratory system): trachea, symmetry of expansion, breath sounds, adventious (wheeze, crepitations, rub), vocal & tactile fremitus, percussion note. Abdomen (gastrointestinal & nephro-urological system): inspection for bulge/scars, palpation (liver, spleen, kidneys, urinary bladder, masses, ascites), bowel sounds. Nervous system: consciousness, orientation X3, gait, abnormal movements, higher cortical defects, meningeal irritation signs, cranial nerves, motor, sensory, cerebellum Locomotor: local or diffuse pain/limitation in spines, joints and muscles Skin and extremities: oedema, rashes, peripheral pulses &veins

grades in between. On the other hand, disorientation discloses impaired cognitive function. Assessment of both on follow up reflects disease progress and efficacy of therapy. (c) Vital signs are the front-line signs of physical stability of the patient. Progressive deterioration on follow up reflects erroneous assessment and/or management and vice versa. (d) Lastly, pallor, cyanosis and jaundice reflect multiple organ-derangements and carotid pulsations, jugular venous pressure, lymphadenopathy and goiter reflects local as well as systemic disease.

B-Systematic examination includes chest, heart, abdomen, nervous system, locomotor system, skin and extremities as seen in Table 3. However, system versus organ examination presented a major obstacle in reporting. The logic is to report in the same scenario of examination rather than grouping into closed systems. Two obvious handicaps of the latter: (1) chest rales may reflect fluid overload rather than primary lung disease as well as lower limb oedema, neck veins, peripheral pulsations, apex beat and cyanosis may represent local or multiple system defect rather than being unique to a single system; (2) there is no abdominal system but a region that include gastrointestinal, hepatobiliary, nephron-urological and vascular structures. Hence, it is better to report each region as it was examined systematically and this will assist in design making during assessment part.

Finally, the use of a statement such as no abnormality detected should be avoided during case reporting, since it may reflect inadequate or short-cut examination that was merely subjective throughout.

Assessment

It is the art of clinical problem solving. It includes the 4 procedures:

(1) Generation of a master plan that lists the patient's problems (abnormalities) from history, physical examination and abnormal previous laboratory test or radiological investigation.

(2) Listing of problems in the form of problem oriented medical recording (POMR) as: (a) active problems and (b) inactive ones[10]. The latter is to avoid future mistakes by (a) treating specific illness by drugs that need to be modified by the patient's co-morbid conditions; and (b) implementing investigations that may worsen his inactive diseases. Examples of that include administration of beta-blockers for ischemic heart disease or arrhythmias to a patient with chronic obstructive pulmonary disease, aspirin and anticoagulants to a patient with history of peptic disease, renally excreted drugs viz. digoxin and certain antibiotics to a patient with renal disease. Moreover, problems should be reported at their present and definite level of diagnosis, *i.e.*, chest pain without misleading labels viz. most likely or tentative angina pectoris, since the latter is a definite stage of disease that limits further investigations and therapy. Moreover, unconfirmed diagnosis related to the relatives will shatter the doctor-relatives trust, which is essential in patient's care.

(3) Establishment of differential diagnosis of each problem based on: (a) system involved and (b) its pathophysiological dysfunction (congenital, degenerative, traumatic, infectious, and metabolic immunologic, toxic of functional). Books and search engines can be used at this stage. Categorizing of the dysfunction should not be affected by: (a) most common from personal data; and (b) most serious. Such differential diagnosis should not be related to the relatives, since most will misconceive most serious diagnosis. Moreover, it should not be spelled out in

the report since, if erroneous, it reflects the limited experience of the physician.

(4) Subsumption of some abnormalities, if confirmed, under a single diagnostic heading and highlighting the deviated ones for further work up. Such POMR should be presented after the identification data in the case report and as the first page in the patient's medical record. It should be noted that such POMR is a dynamic record and should be updated with the new data generated from future investigations, follow-up and response to interventions. At present, it is a cornerstone in accreditation of health care systems[11].

Management

It should include (a) future, immediate and delayed investigations, that is required at that level of presentation or permitted by the patient's medical stability; (b) immediate and delayed treatments and intervention; (c) subspecialty consultations and (d) patient and family education, according to the definite level of diagnosis to avoid future medico/legal conflicts.

The overall theme of case presentation

History and physical examination should be objective. This can be achieved by (a) including the patient's own description of his problems rather than diffuse medical terms, e.g., upper abdominal pain rather than dyspepsia; and (b) systematic physical examination that may disclose additional lesions rather than a biased one that has been tailored to his chief complaint.

Finally, it should be noted that the problem list is a dynamic one and can be modified on follow up with (a) evolving manifestations from subsequent examination; (b) new data from the requested investigations and (c) therapeutic response.

CONCLUSION

Medical case reporting is an art of science that documents the medicolegal presentation of the patient and eases future inter-physician communication and follow up.

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Original Article

Could we predict the side branch compromise during provisional bifurcation coronary intervention? A prospective cohort study

Mohamed Salah Abd Elbasit, Mahmoud Hassan Shah, Abdelsalam Elsayed Sherif, Marwa Mohamed Gad, Manar Mostafa Al-zaki, Mohamed Ibrahim Amin
Department of Cardiology, Faculty of Medicine, Zagazig University, Egypt

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ABSTRACT

Objectives: To evaluate the potential angiographic predictors of side branch (SB) compromise after provisional bifurcational coronary intervention in the form of main vessel stenting
Design: Prospective cohort study
Setting: Our study was conducted between June 2018 and February 2020 in the Zagazig University Hospital's catheter unit.
Subjects: We included 200 patients with 200 bifurcation coronary lesions who underwent provisional main vessel stenting.
Interventions: Two separate cardiologists checked coronary angiography and intervention films for potential predictors of SB compromise including the corrected bifurcation angle (BA), which is the sum of proximal and distal bifurcation angles.
Main outcome measures: We checked all patients for SB compromise in the form of decrease in thrombolysis in myocardial infarction grade or increase in the percentage of ostial stenosis.
Results: SB compromise occurred in 56 patients (28% of patients). Compared to the non-SB compromise group, patients in the SB compromise group had significantly narrower distal BA (P=0.022) and narrower corrected BA (P<0.001). Multivariate analysis demonstrated that the corrected BA was the best independent predictor of SB compromise with a best cut off value ≤180°, and an area under the curve of 0.684 (P<0.001). The jailed SB wire, SB stenosis percentage, corrected BA, lesion thrombus, distal main vessel stent oversize, proximal optimization technique (JSC-TOP) factor was calculated from the best predictors of SB compromise with a better area under the curve (0.867; P<0.001).
Conclusion: The corrected bifurcation angle and the JSC-TOP factor are novel predictors of SB compromise during provisional bifurcation coronary intervention.

KEY WORDS: bifurcation coronary artery disease, side branch occlusion, true bifurcation

INTRODUCTION

The procedure of bifurcational percutaneous coronary intervention (PCI) is debatable due to the risk of the side branch (SB) compromise after the deployment of the main vessel (MV) stent. Bifurcational coronary stenosis accounts for up to 20% of all coronary artery lesions[1].

There are unmet clinical needs to determine the predictors of SB compromise and to improve the strategies of bifurcational PCI in order to minimize the risks of occlusion. In addition, efforts to improve the immediate and long-term outcomes of bifurcational PCI are needed[2].

Selecting the appropriate procedure of bifurcational PCI, whether the one stent or the two-stents strategy, plays a role in minimizing the risks of SB compromise. The one stent or the two-stents strategy is an essential determinant of bifurcational PCI outcomes[3]. Many studies discussed one wire and two-wires strategies in bifurcational PCI[4]. To choose between different

Address correspondence to:
Mohamed Salah Abd Elbasit, MD, Msc, Department of Cardiology, Faculty of Medicine, Zagazig University, Zagazig, Sharkia, Egypt. Tel: +201092791494; E-mail: msa_20122002@yahoo.com

decisions about bifurcational PCI, it is wise to predict the risk of SB compromise after provisional stenting of the MV[5].

In order to predict the SB compromise following provisional bifurcational PCI, several studies have examined the predictive role of demographic, clinical and angiographic characteristics, especially the angle of the SB[6]. Some studies concluded that the narrower the SB bifurcation angle (BA), the higher the risk of its occlusion[7]. On the other hand, recent studies recommended that wide SB BA is an independent risk of its occlusion[8]. Adding evidence to that debate is extremely valuable.

Most studies supposed that MV is always a straight vessel. Therefore, they focused only on distal BA, neglecting the proximal BA. However, Reiber *et al*'s study that utilized 3 dimensions, quantitative coronary angiography (QCA), intravascular ultrasound (IVUS) and optical coherence tomography, presented T and Y models of coronary bifurcations[9]. This study aimed to evaluate the potential angiographic predictors of SB compromise after MV provisional PCI including proximal and distal bifurcation angles.

SUBJECTS AND METHODS

The institutional/review board approved this study in Zagazig University Hospitals, Sharkia, Egypt (approval number: 4484/11-4-2018).

Study design, setting and duration

We conducted a prospective cohort study in catheter-unit of Zagazig University Hospital (Zagazig, Egypt) within the period from June 2018 to February 2020.

Study population

We included patients with coronary bifurcation lesions involving SB with a reference diameter equal or more than 1.5 mm. We defined bifurcation lesions according to the recommendations of the European Bifurcation Club[10] as follows:

- European Bifurcation Club defined coronary bifurcation disease as SB involvement in MV lesion with the absence of a normal area between MV minimal luminal diameter and SB.
- Coronary bifurcation lesion was considered true when SB ostium was involved with SB diameter being equal or more than 2 mm.
- Significant SB is the SB that you do not want to lose regardless of its diameter[11].

We excluded patients with chronic total occlusions, patients with in-stent restenosis and patients with bifurcation lesions requiring starting with SB stenting.

Study variables, clinical assessment

Clinical assessment of each patient was performed before coronary angiography with records of age, gender, cardiovascular risk factors, coronary angiography indication, pulse, blood pressure and serum creatinine level.

PCI procedures and peri-procedure medications followed operator decisions and current guidelines. Patients with stable coronary artery disease received 300 mg aspirin and 600 mg clopidogrel 12 hours before PCI. Patients with acute coronary syndromes received either the same regimen or 180 mg ticagrelor instead of clopidogrel if ticagrelor was available and was not contraindicated.

Coronary angiography was analyzed by two separate cardiologists using the RadiAnt DICOM Viewer 5.0.1 (64-bit) program. Each patient was checked for coronary dominance, Syntax I score, site of bifurcation, Medina classification, calcification, angulation, plaque irregularity, presence of thrombus and thrombolysis in myocardial infarction (TIMI) flow grade in both MV and SB. Vessel diameter measurements were corrected for guiding catheter diameter; 2 mm for 6 French catheter and 2.3 mm for 7 French catheter. Lesion length measurements were corrected for coronary wire radio-opaque length. Stenosis percentage was calculated as following:

$$\text{Stenosis percentage} = \frac{\text{(reference diameter-minimal diameter)}}{\text{(reference diameter)}} \times 100$$

We defined distal BA as the angle between distal MV and SB, and defined proximal BA as the angle between proximal MV and SB. In a pilot test on ten patients, sum of proximal and distal bifurcation angles was not always 180°. We proposed corrected BA to be studied among predictors of SB compromise (Fig 1). Corrected BA was calculated as following:

$$\text{Corrected bifurcation angle} = \sum \text{(Proximal bifurcation angle + Distal bifurcation angle)}$$

*(∑ means the sum of)

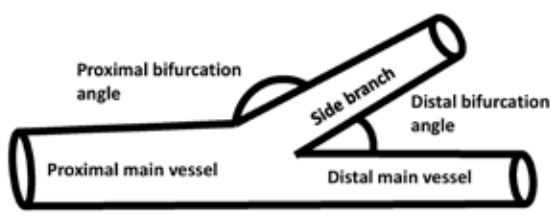

Fig 1: Distal bifurcation angle is the angle between side branch and distal main vessel, proximal bifurcation angle is the angle between side branch and proximal main vessel, corrected bifurcation angle is the sum of proximal and distal bifurcation angles

Bifurcation angles were calculated between the central axis of each branch to avoid the effect of plaque irregularity on measurements accuracy. Furthermore, the calculation of the bifurcation angles was performed at the level of bifurcation core to avoid the impact of vessel tortuosity on measurements accuracy.

Bifurcation angles were calculated using two dimensions QCA in the angiographic view demonstrating the widest angle between the distal MV and the SB. Left main bifurcation angles were calculated in the spider view in case of horizontal left main configuration, and in the left anterior oblique (LAO) view with cranial angulation in case of vertical left main configuration. Left anterior descending/ diagonal bifurcation angles were calculated in the spider view in case of proximal diagonal artery, and in the LAO cranial view in case of mid to distal diagonal branches. Left circumflex/ obtuse marginal bifurcation angles were calculated in either the spider view or the right anterior oblique view with caudal angulation. Also, we calculated the posterior descending artery/ postero-lateral branch bifurcation angles in either the postero-anterior view with cranial angulation or LAO cranial view. Angiographic views angulations were modified in the setting of foreshortened angles to get the widest angle.

PCI procedure was observed for SB wiring, MV pre-dilatation, SB pre-dilatation, vessel dissection in MV or SB, stent diameter/ distal MV diameter ratio, and proximal optimization technique (POT). Successful PCI was defined as less than 20% residual stenosis in stented area with TIMI flow grade 3 in both SB and MV.

Follow up was done during PCI procedure to pick up immediate SB compromise after MV stent deployment in bifurcational provisional PCI. We defined SB compromise after MV stenting as any decrease in SB TIMI flow grade or increase in ostial SB stenosis degree with the absolute value being equal to or more than 70% stenosis.

To avoid selection bias, we studied all patients who met study criteria during the research period. We collected clinical data from all patients case by case to avoid recall bias. Furthermore, analysis of coronary angiography was performed by two separate cardiologists before the start of the PCI procedure. When there was more than a 20% difference between the two recordings, the third cardiologist was called for analysis. This aimed to decrease observer bias. Observation of SB compromise was performed immediately after MV stenting during PCI procedure for all cases to avoid missed cine recordings of SB compromise.

Sample size calculation and statistical analysis

The sample size was calculated using scistat online calculator. As the area under the curve of the distal bifurcation angle was 0.655 for prediction of SB compromise, the minimal required total sample size was calculated to be 106 cases with 80% power and 95% confidence interval[5].

Statistical analysis

Continuous parameters were expressed as mean, standard deviation, median and range. Categorical data were presented as absolute numbers and percentages. We used Shapiro-Wilk test to test the normal distribution of quantitative variables. To compare between the two study groups, we used the non-parametric Mann-Whitney test or the parametric student t-test according to the type of data. The chi-square test was used to compare categorical variables between the two groups.

Multivariate analysis was performed to pick up the best predictors of SB compromise after provisional MV stenting. For the statistically significant independent predictors, the receiver operating characteristic (ROC) curves were constructed to determine the best cutoff valve for the prediction of SB compromise. Multivariate regression analysis utilized the best predictors of SB compromise after MV stenting to construct an equation calculating new factor for better prediction of SB compromise. Also, ROC curve analysis was constructed to the new predictive factor to determine the best cutoff value for the prediction of SB compromise and its sensitivity and specificity.

A two-sided *P*-value below 0.05 was considered for statistical significance. Statistical analysis was performed using the Statistical Package for Social Sciences version 25.0 (SPSS for Windows 25.0, Inc., Chicago, IL, USA).

RESULTS

Characteristics of the study population

This study involved 200 patients who underwent provisional MV stenting in bifurcational coronary lesions. Patients were divided according to SB compromise into two groups; SB compromise group which involved 56 patients and no SB compromise group which involved 144 patients. Fig 2 shows the flow chart of the study.

As regarding demographic data and risk factors, there was no significant difference between groups in most variables. Compared to the non-SB compromise group, ST segment elevation myocardial infarction percentage was higher in the SB compromise group (30.4% vs. 13.2%; *P*=0.017). Basic characteristics are presented in details in Table 1.

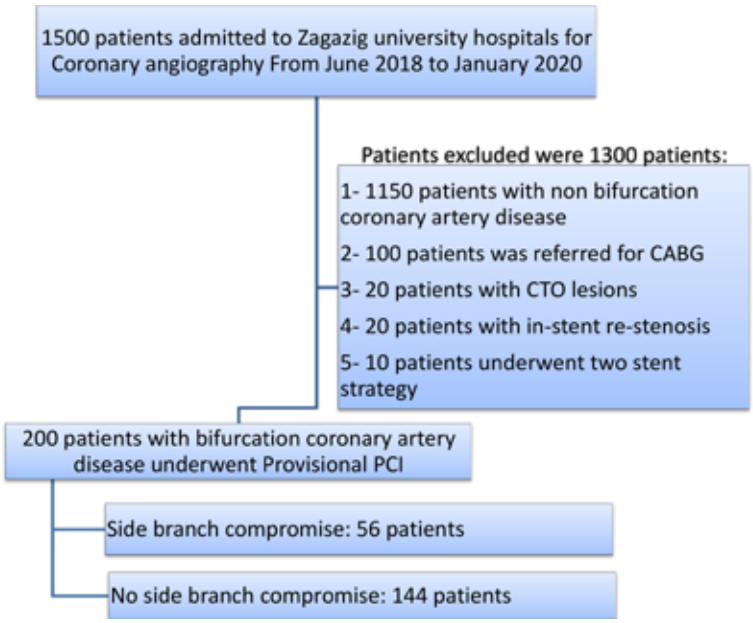

Fig 2: Flow chart of the study. CABG: coronary artery bypass graft, CTO: chronic total occlusion, PCI: percutaneous coronary intervention.

Table 1: Basic characteristics of patients undergoing PCI

Characteristics	SB compromise n=56	No SB compromise n=144	Test value	*P*-value
Age (years)	59.0±7.4	58.8±8.7	4010.000*	0.952
Gender - Male	36(64.3%)	109(75.7%)	2.632**	0.105
BMI (kg/m^2)	26.4±3.3	26.1±3.1	3871.500*	0.662
History of diabetes mellitus	21(37.5%)	46(31.9%)	0.559**	0.455
History of hypertension	23(41.1%)	67(46.5%)	0.485**	0.486
History of smoking	20(35.7%)	58(40.3%)	0.353**	0.552
History of prior STEMI	6(10.7%)	17(11.8%)	0.047**	0.828
History of prior NSTE-ACS	7(12.5%)	20(13.9%)	0.067**	0.796
History of dyslipidemia	18(32.1%)	35(24.3%)	1.272**	0.259
History of stroke	4(7.1%)	3(2.1%)	3.056+	0.098
History of PAD	3(5.4%)	3(2.1%)	1.485+	0.352
Family history of premature CAD	2(3.6%)	2(1.4%)	0.980+	0.313
History of chronic kidney disease	2(3.6%)	8(5.6%)	0.334+	0.729
History of prior PCI	3(5.4%)	12(8.3%)	0.515+	0.565
History of prior CABG	2(3.6%)	3(2.1%)	0.366+	0.621
LVEF (%)	61.5±4.7	62±5.3	3698.500*	0.363
Heart rate before PCI (BPM)	77±8	76±9	3812.500*	0.550
Systolic blood pressure (BPM)	130.6±14	127.3±15.1	3672.500*	0.325
Serum creatinine (mg/dl)	0.9±0.3	0.8±0.3	2822.500*	0.001
Indication of PCI			10.135**	0.017
Stable angina	22(39.3%)	82(56.9%)		
Unstable angina	12(21.4%)	24(16.7%)		
NSTEMI	5(8.9%)	19(13.2%)		
STEMI	17(30.4%)	19(13.2%)		
Anti-platelet used			0.133**	0.715
Clopidogril	50(89.3%)	131(91%)		
Ticagrelor	6(10.7%)	13(9%)		

*Mann Whitney test; **chi-square test; +Fisher exact test
Values are presented as n (%) or mean ± standard deviation
CAD: coronary artery disease; BMI: body mass index; SB: side branch; NSTE-ACS: non-ST elevation acute coronary syndrome; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; mg/dl: milligram per decilitre; BPM: beat per minute; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; LVEF: left ventricular ejection fraction; PAD: peripheral artery disease.

Table 2: Qualitative coronary angiography parameters of study group

Angiography parameters	SB compromise n=56	No SB compromise n=144	Test value	*P*-value
Coronary dominance			4.302**	0.038
Right dominance	45(80.4%)	131(91%)		
Left dominance	11(19.6%)	13(9%)		
Syntax I score	22±4.8	21.9±3.9	3894.000*	0.706
Site of bifurcation lesion			4.763**	0.190
LM bifurcation	3(5.4%)	18(12.5%)		
LAD/D bifurcation	36(64.3%)	91(63.2%)		
LCX/OM bifurcation	14(25%)	22(15.3%)		
PDA/PL bifurcation	3(5.4%)	13(9%)		
True bifurcation lesion	43(76.8%)	63(43.8)	17.665**	<0.001
Medina classification			23.300**	<0.001
0.1.1	10(17.9%)	17(11.8%)		
1.1.1	30(53.6%)	34(23.6%)		
1.1.0	3(5.4%)	22(15.3%)		
1.0.0	4(7.1%)	29(20.1%)		
0.1.0	4(7.1%)	27(18.8%)		
1.0.1	5(8.9%)	15(10.4%)		
Severe main vessel calcification	6(10.7%)	9(6.2%)	1.158+	0.369
Severe main vessel angulations	18(32.1%)	49(34%)	0.064**	0.800
Irregular plaque	13(23.2%)	23(16%)	1.433**	0.231
Thrombus containing lesion	18(32.1%)	22(15.3%)	7.168**	0.007
TIMI flow in main vessel before PCI			10.016**	0.018
TIMI 0	4(7.1%)	3(2.1%)		
TIMI 1	3(5.4%)	5(3.5%)		
TIMI 2	9(16.1%)	8(5.6%)		
TIMI 3	40(71.4%)	128(88.9%)		
TIMI flow in side branch before PCI			14.326**	0.001
TIMI 1	1(1.8%)	3(2.1%)		
TIMI 2	11(19.6%)	5(3.5%)		
TIMI 3	44(78.6%)	136(94.4%)		
Severe side branch calcification	3(5.4%)	5(3.5%)	0.373+	0.689

*Mann Whitney test; **chi-square test; +Fisher exact test
Values are presented as n (%) or mean ± standard deviation.
SB: side branch; TIMI: thrombolysis in myocardial infarction; LAD/D: left anterior descending artery/diagonal bifurcation; LCX/OM: left circumflex/obtuse marginal bifurcation; LM: left main bifurcation; PDA/PL: posterior descending artery/posterolateral artery bifurcation; PCI: percutaneous coronary intervention.

Difference between the study groups

The SB compromise group showed more frequent true bifurcation lesions compared to the non-SB compromise group (76.8 % vs. 43.8%; *P*=0.001). Also, thrombus containing lesions and abnormal TIMI flow grades before PCI were more frequent in the SB compromise group (Table 2).

There was a significant difference between the two groups in terms of the SB lesion parameters and the bifurcation angles. Compared to the non-SB compromise group, patients in the SB compromise group had significantly larger side branches (2.5±0.4 mm vs. 2.4±0.5 mm; *P*=0.015), longer SB lesion length (6.5±4.5 mm vs. 4.9±6.7 mm; *P*=0.002), higher SB stenosis percentages (54.1% vs. 29.9%; *P*<0.001), narrower distal BA (53.5°±17.6° vs. 60.9°±19.9°; *P*=0.022), and narrower corrected BA (179.8°±13.8° vs. 186.1°±12.1°; *P*<0.001). However, the proximal BA was not significantly different between the study groups (*P*=0.820). Quantitative coronary angiography analysis is illustrated in Table 3.

The most relevant factors during PCI procedure were SB wiring, stent diameter/ distal MV diameter ratio and POT. The SB compromise group patients were less likely to have jailed wire in SB (30.4% vs. 45.8%; *P*=0.046). Furthermore, the frequency of oversized stent in the distal MV was substantially higher in the SB compromise group (57.1% vs. 24.3%, *P*<0.001). Also, the SB compromise group patients were less likely to have POT after MV stent deployment (42.9% vs. 65.7%; *P*=0.003). PCI procedure parameters are presented in Table 4.

Predictors of SB compromise

Step wise approach logistic regression analysis revealed that the corrected BA was the independent predictor of SB compromise after MV stent deployment. The best co-predictors were SB stenosis percentage,

Table 3: Quantitative coronary angiography parameters of study groups

Angiography parameters	SB compromise n=56	No SB compromise n=144	Test value	*P*-value
Proximal main vessel				
Reference diameter (mm)	3.6±0.4	3.5±0.6	3386.500*	0.079
Lesion length (mm)	9.9±7.2	8.4±7.3	3388.500*	0.077
Stenosis degree (%)	60.6±37	54±37.8	3609.000*	0.243
Distal main vessel				
Reference diameter (mm)	2.9±0.4	2.9±0.4	3915.500*	0.751
Lesion length (mm)	14.3±9.7	11.6±11	3395.000*	0.080
Stenosis degree (%)	67.8±32.5	54.2±37.5	3084.000*	0.009
Side branch				
Reference diameter (mm)	2.5±0.4	2.4±0.5	3139.500*	0.015
Lesion length (mm)	6.5±4.5	4.9±6.7	2941.000*	0.002
Stenosis degree (%)	54.1±32.4	29.9±33.7	2483.000*	<0.001
Distal bifurcation angle (°)	53.5±17.6	60.9±19.9	3190.500*	0.022
Proximal bifurcation angle (°)	126.4±20.1	125.1±21.1	3948.500*	0.820
Corrected bifurcation angle (°)	179.8±13.8	186.1±12.1	2552.000*	<0.001

*Mann Whitney test. Values are presented as mean ± standard deviation.
SB: side branch; mm: millimetre

stent diameter/ distal MV diameter ratio, jailed wire in SB, lesion thrombus and POT (Table 5).

Accuracy of the corrected BA to predict SB compromise

ROC curve analysis demonstrated that the best cutoff value for the corrected BA to predict SB compromise was ≤180° with sensitivity 71.4% (95% CI: 57.8%-82.7%), specificity 66% (95% CI: 57.6%-73.7%), positive predictive value 44.9% (95% CI: 38.1%-52.0%), negative predictive value 85.6% (95% CI: 79.4%-90.1%), and diagnostic odds ratio 7.032 (95% CI: 2.919-16.940; *P*<0.001) (Fig 3). Furthermore, ROC curve analysis was constructed for SB stenosis percentage and demonstrated that the best cutoff value for prediction of SB compromise was ≥45% with sensitivity 66.1% (95% CI: 52.2%-78.2%), specificity 57.6% (95% CI: 49.1%-65.8%), positive predictive value 37.8% (95% CI: 31.7%-44.2%), negative predictive value 81.4% (95% CI: 74.7%-86.6%) and diagnostic odds ratio 6.154 (95% CI: 2.426-15.613; *P*<0.001).

Regression analysis utilized independent predictor and best co-predictors to construct an equation for calculation of the jailed SB wire, SB stenosis percentage, corrected BA, lesion thrombus, distal main vessel stent oversize, proximal optimization technique (JSC-TOP) factor for better prediction of SB compromise after MV stent deployment in provisional bifurcational PCI. It is calculated as following:

Table 4: PCI procedure and side branch outcome parameters in the study groups

Parameters	SB compromise n=56 (%)	No SB compromise n=144 (%)	Test value	*P*-value
Jailed wire in side branch	17(30.4)	66(45.8)	3.978**	0.046
Main vessel pre-dilatation	35(62.5)	79(54.9)	0.960**	0.327
Side branch pre-dilatation	2(3.6)	8(5.6)	0.334+	0.729
Main vessel dissection	4(7.1)	3(2.1)	3.056+	0.098
Side branch dissection	1(1.8)	1(0.7)	0.485+	0.483
Stent diameter/distal main vessel diameter ratio more than 1	32(57.1)	35(24.3)	19.516**	<0.001
Proximal optimization technique	24(42.9)	94(65.7)	8.726**	0.003
TIMI flow in side branch after PCI			111.986**	<0.001
TIMI 0	10(17.9)	0(0)		
TIMI 1	8(14.3)	0(0)		
TIMI 2	22(39.3)	4(2.8)		
TIMI 3	16(28.6)	140(97.2)		
Percentage of ostial side branch stenosis after PCI (%)	93.5±7.5	40±26.6	132.000*	<0.001

*Mann Whitney test; **chi-square test; +Fisher exact test
Values are presented as n (%) or mean ± standard deviation.
SB: side branch; TIMI: thrombolysis in myocardial infarction; PCI: percutaneous coronary intervention

Table 5: Multivariate analysis using step wise approach logistic regression analysis

Predictors	Odds ratio	95% CI of odds ratio	*P*-value
Corrected bifurcation angle ≤180°*	7.032	(2.919-16.940)	<0.001
Side branch stenosis degree ≥45%	6.154	(2.426-15.613)	<0.001
Stent diameter/distal main vessel reference diameter >1	8.793	(3.588-21.550)	<0.001
Jailed wire in side branch	0.204	(0.079-0.526)	0.001
Lesion thrombus	3.683	(1.357-9.998)	0.011
Proximal optimization technique	0.407	(0.182-0.906)	0.028

*Independent predictor; CI: confidence interval

JSC-TOP factor =∑ [1.234 - (0.251×Jailed SB wire″) + (0.005 × SB Stenosis percentage) - (0.005 × Corrected BA) + (0.173 × Lesion Thrombus″) + (0.271 × Distal MV stent Oversize″) - (0.115 × POT″)]

(″: yes=1 & No=0) (∑ means the sum of)

ROC curve analysis was constructed for JSC-TOP factor to test its power to predict SB compromise. It demonstrated that its area under the curve was 0.867 with 95% CI (0.810-0.924; *P*<0.001). The best cutoff value was 0.4505 above which the risk of SB compromise substantially increased with sensitivity 85.7% (95% CI: 73.8%-93.6%), specificity 70.6% (95% CI: 62.4%-77.9%), positive predictive value 53.3% (95% CI: 46.5%-60.1%), negative predictive value 92.7% (95% CI: 86.8%-96%) and diagnostic accuracy 74.9% (95% CI: 68.3%-80.7%) (Fig 4).

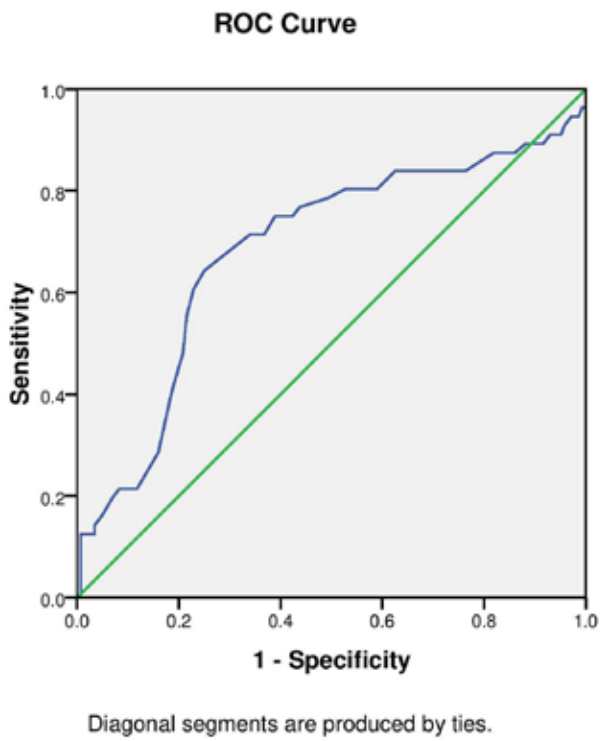

Fig 3: ROC curve analysis of corrected bifurcation angle for prediction of side branch occlusion during provisional bifurcational coronary intervention

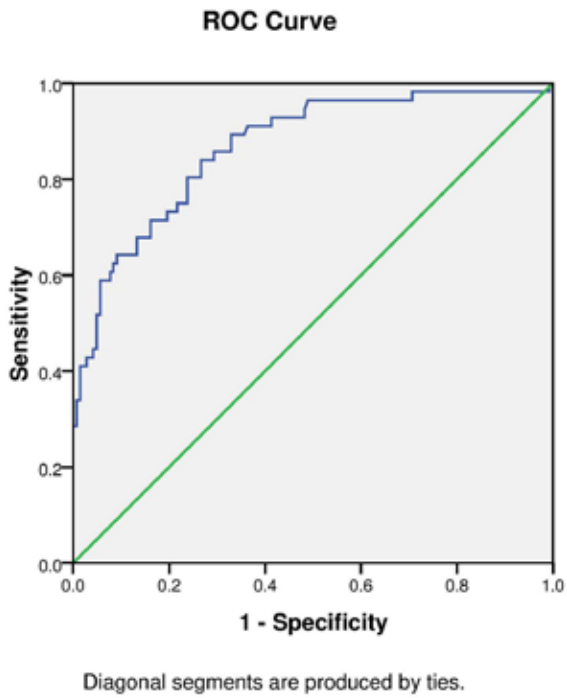

Fig 4: ROC curve analysis of JSC-TOP factor for prediction of side branch occlusion during provisional bifurcational coronary intervention

DISCUSSION

Importance of the study

Coronary bifurcation lesions constitute up to 20% of lesions requiring PCI in clinical practice[1]. The provisional MV stenting is preferred over the two stent strategy in terms of reduction of in-stent re-stenosis, major adverse cardiac events and mortality[11-13]. Therefore, the prediction of SB compromise after MV stent deployment is strongly needed.

Summary of key findings

Our study demonstrated that we could predict SB compromise before provisional MV PCI using simple angiographic predictors. The best independent predictor was the corrected BA. The best co-predictors of SB compromise were high SB stenosis percentage, stent diameter/ distal MV diameter ratio >1, absence of jailed wire in SB, presence of lesion thrombus and

missing POT. Distal BA was significantly narrower in the SB compromise group but was not a strong predictor in multivariate analysis. The JSC-TOP factor is a novel factor that is calculated from the corrected BA and the other co-predictors. It could predict SB compromise with better accuracy. To the best of our knowledge, ours is the first study to evaluate the accuracy of the corrected BA and the JSC-TOP factor to predict the fate of SB in provisional bifurcational PCI.

Previous studies

Previous studies investigated the distal BA as an important predictor of SB compromise. However, its impact on SB compromise was debatable. Our study was concordant with many studies that concluded that a narrow distal BA could increase the risk of SB compromise[7,14-16]. This could be due to the risk of carina shift or plaque shift with a narrow distal BA[17]. However, many equivocal studies, one of them was IVUS guided, reported that the distal BA did not affect the fate of SB[18-20].

On the other hand, Dou *et al* and Zhang *et al* studies revealed that wider distal BA carries a higher risk of SB compromise[5,6,8]. They explained their results with many factors. The first explanation was the pressure drop in SB with a higher BA[21]. The second explanation was the smaller ostium area and ostium length with a higher BA[2,22]. Kang *et al*'s study proposed the SB lumen area as a sensitive predictor of SB compromise[22]. The third explanation was the increase in bifurcation core plaque burden with higher bifurcation angles due to a decrease in wall shear stress[23-26].

This debate could be due to the neglect of proximal BA. Previous research studied only the distal BA between SB and distal MV considering that MV is always a straight vessel[5,6]. However, MV could change its angle at the site of bifurcation. In real life, we have two models of coronary bifurcation; model A that involves a wide corrected BA when the sum of distal and proximal bifurcation angles is more than 180°, and model B that involves a narrow corrected BA when the sum of distal and proximal bifurcation angles is ≤180° (Fig 5). In our study, the SB compromise group had significantly narrower corrected BA (P<0.001). The best cutoff value of the corrected BA was 180°, below which the risk of SB compromise substantially increased. We could explain that new result with the direction of stent struts opening. In our opinion, the direction of stent struts opening could open the SB ostium in the model A and could occlude it in the model B. In model A, the non-deployed MV stent will take the angulation of the distal MV away from the SB. Therefore, the angle between proximal and distal struts opening direction will increase, which could prevent the SB compromise. However, in model B, the stent will be straight in the MV, which will decrease the angle between proximal and distal struts opening direction increasing the risk of carina shift.

In our study, the stent diameter/ distal MV reference diameter ratio was a good predictor of SB compromise. A ratio more than one carried a significant risk of SB compromise after MV stent deployment. Many studies confirmed that stent oversize in the distal MV could increase the risk of carina shift and SB compromise[27]. However, Zhang *et al*'s study reported that stent diameter/ distal MV reference diameter ratio did not affect the fate of SB[5].

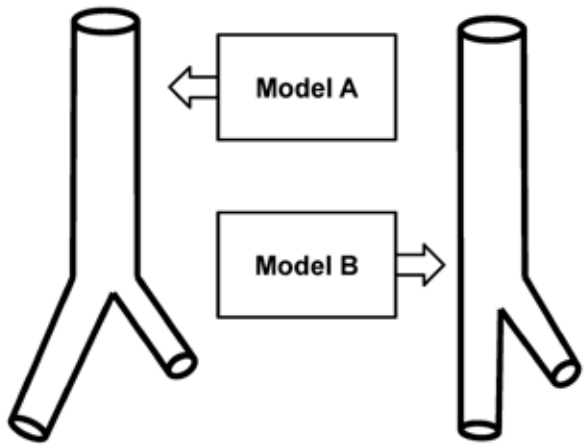

Fig 5: Models of corrected bifurcation angle which is the sum of proximal and distal bifurcation angles. Model A means corrected bifurcation angle larger than 180°. Model B means corrected bifurcation angle ≤180°.

Our study results as regarding jailed wire in SB and POT were discordant with many studies that reported that jailed wire in SB did not impact the fate of SB[5,19]. However, jailed wire and POT are recommended to decrease the risk of carina shift and the risk of SB compromise[10]. POT improves MV flow hemodynamics, decreases the risk of mal-opposition, opens the SB ostium and facilitates re-cross to the SB after MV stenting[28,29]. The site of balloon during POT before or across SB take-off is a debatable point. A recent study reported that performing POT across SB take-off substantially decreased the SB ostial lumen area[30]. Zuin *et al*'s study recommended performing POT one mm distal to the carina cut-plane to minimize the reduction in SB wall shear stress[31]. Furthermore, the jailed wire could help as a marker for re-cross to the SB if occlusion occurred[19]. However, POT and jailed wire are not yet sufficient to prevent SB compromise[32].

In our study, increased pre-procedure ostial SB stenosis percentage carried a substantial risk of SB compromise. The best cutoff value was 45%, above which the risk of SB compromise increased. This is concordant with Dou *et al*'s study that proposed the

SB stenosis degree as an independent predictor of SB compromise[8]. Hahn *et al*'s study demonstrated that a SB stenosis more than 50% is an independent predictor of SB compromise during provisional MV PCI[19]. This could explain why SB compromise was more frequent among patients with true bifurcation lesions as demonstrated by our study. Furthermore, Medina classifications 1.1.1 and 0.1.1 were more frequent in the SB compromise group. This is concordant to many studies[5,6,19].

The SB lesion length was significantly longer in the SB compromise group in our study. This is concordant with the Hahn *et al* study, which confirmed that SB lesions were longer in the SB compromise group[19]. However, other studies did not find a significant impact of SB lesion length on the fate of SB after MV stenting[6,8,33]. In our study, larger side branches were more liable to occlusion than small side branches. This is discordant with many studies that demonstrated that the SB reference diameter was significantly lower in the SB compromise group[8,19]. However, Zhang *et al*'s study did not find a significant difference between groups regarding the SB reference diameter[6]. In most studies, small side branches were less likely to have jailed wire before MV stenting. This could explain why small side branches were more liable for SB compromise in these studies. The occlusion of small SB did not affect the long-term angina grade, according to the Canadian Cardiovascular Society angina grading scale, or major adverse cardiac events[34]. We could explain this contradiction as large side branch will have ostial area larger than stent strut area and are more liable for carina shift.

Our study demonstrated that the SB compromise group involved a higher frequency of ST segment elevation myocardial infarction patients and a higher frequency of lesion thrombi. This is concordant with many studies that recommended acute coronary syndrome as a strong predictor of SB compromise[19]. Furthermore, IVUS guided studies concluded that unstable plaques at bifurcation lesions were more liable for SB compromise[35]. TIMI flow grade in MV and SB before PCI was significantly lower in the SB compromise group. However, multivariate analysis did not pick it among independent predictors of SB compromise. However, Risk prediction of side branch occlusion in coronary bifurcation intervention (RESOLVE) score system involved TIMI flow grade in MV as one of the strong predictors of SB compromise[8].

RESOLVE score and JSC-TOP factor involved the use of the SB stenosis percentage before PCI for prediction of SB compromise after MV stenting. However, RESOLVE score involved other factors as plaque distribution and bifurcation core stenosis require the availability of advanced bifurcation QCA. As regarding bifurcation angles, RESOLVE score utilized the distal BA and gave a bad score for wider angles[8]. Our JSC-TOP factor utilized the corrected BA, which is a newly applied parameter for prediction of SB compromise after provisional PCI, together with PCI procedure related factors as jailed wire and POT. Furthermore, JSC-TOP factor calculation did not require an advanced bifurcation QCA. Finally, JSC-TOP factor had a comparable area under the curve with RESOLVE score system (0.867 vs. 0.77; P=0.103).

Our study has several strong points: (1) the study was a prospective cohort study; (2) clinical data were recorded from each patient before coronary angiography to avoid information bias in medical records; (3) potential angiographic predictors were analyzed by two separate cardiologists to minimize observing bias; (4) the analysis of coronary angiography was performed before the start of PCI procedure not to be biased with PCI result; and (5) follow up was performed for all cases during the PCI procedure to avoid missing recordings. However, we have few limitations: (1) the sample size was small; (2) the study was an observational study; (3) a dedicated bifurcation lesions QCA tool was not available; and (4) long term clinical follow up was not performed to study the impact of SB compromise on major adverse cardiac events.

Future research is needed with a larger sample size and longer follow up duration in order to verify the ability of the corrected BA and the JSC-TOP factor to predict SB compromise in provisional PCI. On the other hand, long term follow up will study the effect of different levels SB compromise on major adverse cardiac events and cardiovascular outcomes.

CONCLUSION

Corrected BA, which is the sum of distal and proximal bifurcation angles, is a new independent predictor of SB compromise after MV provisional PCI. The best cutoff value is 180° below which the risk of SB compromise substantially increases. The best co-predictors are SB stenosis degree, presence of lesion thrombus, absence of jailed wire in SB, missing POT and large stent diameter/ distal MV diameter ratio. The JSC-TOP factor is a novel, easy to calculate and strong predictor of SB compromise after provisional bifurcational PCI. Larger studies are warranted to verify the accuracy of both the corrected BA and the JSC-TOP factor.

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Elbasit, Marwa Mohamed Gad and Mohamed Ibrahim Amin did data collection, coronary angiography film analysis and statistical analysis. MAE did manuscript writing. All authors revised the work critically for important intellectual content, approved the final version of the manuscript for publication, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Original Article

Clinicopathological patterns and outcomes of ovarian borderline tumors: A tertiary center experience

Nisreen Abu Shahin[1], Duaa' Aljarrah[1,2], Tala Ar'ar[1], Lama Amer[3], Maysa Khadra[4]
[1]Department of Pathology, Faculty of Medicine, University of Jordan, Amman, Jordan
[2]Department of Pathology, King Hussein Cancer Center, Amman, Jordan
[3]Faculty of Medicine, University of Jordan, Amman, Jordan
[4]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Jordan, Amman, Jordan

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ABSTRACT

Objectives: To study clinical/ morphological parameters of ovarian borderline tumors (OBT) and outcomes at a major national center
Design: Retrospective study
Setting: Jordan University Hospital, Amman, Jordan
Subjects: We studied 42 OBTs meeting inclusion criteria from 2009 to 2019.
Interventions: Data from medical and histopathology sources were collected. Microscopic review of study cases for morphological parameters.
Main outcome measures: Clinicopathological parameters and outcome were explored using descriptive statistics and correlations.
Results: The mean age was 38.5 years, the 5th decade was the most common age group (38.1%), 21.4% were menopausal and mean follow up was 46 months. Surgery included fertility sparing (27; 64.3%) and non-fertility sparing procedures (15; 35.7%). The most common presentation was pain (17; 40.5%), 81% were unilateral, mean tumor diameter was 10.54 cm. Serum CA125 was elevated in 16 (38.1%). CA19.9 was elevated in 3 (7.1%). Twenty-eight were serous (66.7%) and 14 (33.3%) mucinous. FIGO stage included I (34; 81%); II (1; 2.3%), and III (7; 16.7%). Recurrence occurred in 6 (14.2%). Successful pregnancy was documented in 8 (19%). Death occurred in 4 (9.5%). Recurrences and deaths respectively were significantly correlated to higher stage (Pearson chi^2 0.000; 0.000); positive peritoneal washings (0.002; 0.000); omental metastasis (0.000; 0.000); and residual mass post op (0.002; 0.013). Other studied parameters did not reveal significance including age, histotype, surgery type, diameter, CA125, CA19.9, lymph node status, ovarian surface involvement, lymphovascular invasion, micropapillary architecture, microinvasion and intraepithelial carcinoma.
Conclusion: OBTs have excellent prognosis with low rates of recurrences and death. Conservative surgery for desired fertility preservation balanced by longterm followup is recommended.

KEY WORDS: ovarian borderline tumors, mucinous tumors, serous tumors

INTRODUCTION

Ovarian tumors are a common gynecological problem that can occur at any time during a woman's life[1]. The prevalence of an ovarian tumor on ultrasound examination varies broadly among different studies and it seems to be higher in reproductive-age women than in postmenopausal women[2]. The etiology varies from benign in some individuals to aggressive malignant conditions in others.

Ovarian borderline tumors (OBTs) are an intermediate category of ovarian neoplasms, first described in 1929, and then the World Health Organization (WHO) made further characterization and designations over the past two decades. OBT represent about a fourth of epithelial ovarian tumors, with an annual incidence rate of 1.8 to 4.8 cases per 100000 females[2]. Although they may affect any age, pre-menopausal women are predominantly affected.

Address correspondence to:
Nisreen Abu Shahin, M.D., Associate Professor of Pathology, Department of Pathology, Faculty of Medicine, University of Jordan, Queen Rania Street, Aljubaiha 11942, Amman, Jordan. Tel: +962 798504920; Fax: +962 5353388; E-mail: n.abushahin@ju.edu.jo

OBT are said to have excellent prognosis[2]. The key difference between OBT and malignant tumors is histopathological confirmation of ovarian stromal invasion in the latter.

According to the current 2014 WHO classification[2], these tumors are also called atypical proliferative tumors. Six histologic subtypes are distinguished on the base of the epithelial cell type they derive from: serous OBT (S-OBT) that represent around 50% of all cases, mucinous (M-OBT) around 45% and other rare subtypes (endometrioid, clear cell and Brenner) that account for the remaining 5% of the cases. Most of the knowledge about the prognosis of OBT derive from the serous subtype that represents the most common type[2]. As the histologic types display conspicuous differences in clinical presentation and behavior, determination of the histological type is critical in the assessment of OBTs, and the different types should be assessed distinctly.

Symptoms are non-specific including abdominal mass, abdominopelvic pain, abnormal vaginal bleeding or menstrual abnormalities[3]. Some cases are even completely asymptomatic and the diagnosis is purely incidental, during for instance, routine ultrasound examination[4]. Ultrasound[5] as well as magnetic resonance imaging[6] findings are not highly sensitive to predict accurate diagnosis. In addition, preoperative evaluation of OBTs is still a controversial issue. Currently, specific serum tumor markers for OBTs do not exist. Relevant data are available for the broader spectrum ovarian tumor markers such as CA125 and CA19.9. Since serum CA125 levels increase in both OBTs as well as benign and malignant epithelial ovarian tumors, the use of this parameter in preoperative evaluation would not be suitable[7]. On the other hand, other research groups reveal CA125 levels were noted in 40% of patients in stage I OBT and 83% of those with advanced-stage OBT[7]. Large-scale studies on other serum tumor markers including CA19-9, CA15-3 and CEA in OBTs are still needed**.** Thus, it is difficult to diagnose OBT clinically, radiologically and serologically[8]. The mainstay in diagnosis of OBT is still histopathological examination of resected tumors[3].

The aim of the current study was to examine the clinicopathological features and outcome in OBTs at a major national tertiary care center.

MATERIALS AND METHODS

The Faculty of Medicine and Scientific Research Deanship's Research Ethics Committee, and hospital IRB committee approved the current study. We conducted this retrospective study at the University Hospital and it covered the period from January 2009 to December 2019.

First, a search for all epithelial ovarian tumors diagnosed at that period was performed. 299 primary ovarian epithelial tumors were found, of which 158 (52.8%) were benign (including 120 serous cystadenoma and 38 mucinous cystadenoma), 47 (15.7%) were borderline tumors (including 31 serous borderline tumors and 16 mucinous borderline tumors), and 94 (31.5%) were malignant (including 71 serous carcinoma, 6 mucinous carcinoma, 8 endometrioid carcinoma, 5 clear cell carcinoma and 4 carcinosarcoma).

Inclusion criteria in the study incorporated patients who were diagnosed with OBTs and underwent diagnostic/ therapeutic surgical procedures at our institution (including both fertility-sparing and non-fertility-sparing procedures) and had documented follow up data from gynecology clinic visits and follow up radiological imaging studies. Cases were included regardless of patient age, fertility and co-morbidities. Accordingly, 42 OBTs were included in our study (28 S-OBTs and 14 M-OBTs).

The patients' medical records were used to obtain clinical data, including age at diagnosis, presenting symptoms, fertility, follow up periods, pelvic washings, staging results, residual mass, treatment regimens, pregnancy post therapy, recurrences, final outcome and death due to disease. The hospital database was used to retrieve biochemical test results for tumor markers Cancer Antigen 125 (CA125) and Cancer Antigen 19.9 (CA19.9), from blood samples taken around the time of diagnosis.

Morphometric features of the tumors were obtained from histopathology reports of Pathology Department at our institute for all specimens. These included maximum diameter, bilaterality, histotype, extra-adnexal masses, stage at presentation, ascites, surface involvement, presence of micropapillary pattern, microinvasion, implant type and residual disease. Corresponding formalin-fixed, paraffin-embedded tissue blocks for the surgical specimens were retrieved with representative hematoxylin and eosin-stained microscopic slides for each specimen and reviewed by two pathologists.

Statistical analysis was performed using the Statistical Package for Social Sciences software version 20 (IBM Corp., Armonk, NY, USA). Descriptive frequency statistics and correlations were performed using Pearson Chi square with $P<0.05$ considered significant.

RESULTS

Forty-two OBTs were studied, including 28 S-OBTs (66.7%) and 14 M-OBTs (33.3%). Patient's age ranged from 20 to 71 years, and the mean patient age was 39.2 years for S-OBT and 37.4 years for M-OBT. Thirty-three

patients (78.6%) were in reproductive years and nine (21.4%) were menopausal. Follow-up periods ranged from 6 months to 130 months. The mean follow up periods (FUP) in order for all cases, S-OBT and M-OBT was 46.02, 39.4 and 65 months, respectively.

According to standardized laboratory measures, a well-recognized tumor marker that is widely used in ovarian oncology is Cancer Antigen 125 (CA125). The normal CA125 serum values are ≤35 U/ml. CA125 serum levels in the study cases ranged from 5 to 1000 (mean =69.6 U/ml). Serum CA125 was elevated in 16 cases (38.1%), including 11 S-OBT (39.3%) and 5 M-OBT (35.7%). Similarly, normal CA19.9 serum levels are ≤37 U/ml. CA19.9 serum levels ranged from one to 6407.7 U/ml (mean= 148.91±728.38 SD). CA19.9 was elevated in three cases (7.1%): all were M-OBTs, and none of S-OBT.

Tumors were unilateral in 34 (81%). They were bilateral in seven S-OBT cases (25%) and unilateral in all M-OBT (100%). Cases were initially divided into groups according to the patient's age (refer to Table 1), where group one includes ages 20 to 30; group two (31-40); group three (41-50); group four (51-60); group five (61-70) and group six (≥71). S-OBT were more frequent in all age groups, with the highest frequency in age group 3 (41-50 years) with 11 out of 16 cases (68.8%). M-OBT were most frequent in age group 1, with 6 out of 14 cases (42.9%).

Table 1: OBT distribution among age groups

Age groups	Group by years	Total	%	S-OBT no. (%)	M-OBT no. (%)
1	20-30	14	33.3	8(57.1)	6(42.9)
2	31-40	7	16.7	6(85.7)	1(14.3)
3	41-50	16	38.1	11(68.8)	5(31.3)
4	51-60	3	7.1	2(66.7)	1(33.3)
5	61-70	1	2.4	0 (0)	1(100)
6	≥ 71	1	2.4	1(100)	0(0)
Total		42	100.0	28	14

S-OBT: serous ovarian borderline tumor; M-OBT: mucinous ovarian borderline tumor; no.: number of cases.

Primary surgery included both 27 fertility-sparing procedures (including cystectomy in 13 (31%), oophorectomy in 14 (33.3%)); as well as 15 non-fertility sparing procedures (including total abdominal hysterectomy and bilateral salpingoopherectomy (TAH & BSO) in 10 (23.8%) and debulking in five (11.9%)). The most common presentation was abdominal pain in 17 (40.5%). Tumor diameters ranged from two to 32 cm (mean=10.54 cm). Pelvic lymph node involvement was detected in 2/42 (4.8%). Cases were staged according to the conventional criteria of the International Federation of Gynecology and Obstetrics (FIGO). Thirty-four (81%) cases of FIGO stage I; one (2.3%) in stage 2, and 7 (16.7%) stage 3. Recurrence/metastasis were documented in six cases (14.2%). Residual mass post-surgery was diagnosed in five cases.

Successful pregnancy post-treatment was documented in eight cases (19%). Death due to disease occurred in four cases (9.5%), two patients with S-OBT (7.1%) and two cases with M-OBT (14.3%). Ovarian endometriosis was identified in two cases (4.8%), ovarian endosalpingiosis in five cases (11.9%), microinvasion in four cases (9.5%), lymphovascular invasion (LVI) in one case (2.4%) and ovarian surface involvement in five cases (11.9%). Micropapillary morphology was detected in 8 (28.5%) S-OBT and

Table 2: Clinicopathological characteristics of OBTs

Characteristics	All cases	S-OBT	M-OBT
Mean age (range)	38.5 (20-71)yrs	39.2 (20-71)	37.4 (20-63)
Age no. (%)			
<50 years' old	37(88.1%)	25(89.3)	12(85.7)
>50 years' old	5(11.9%)	3(10.7)	2(14.3)
Menopause			
No	33(78.6)	22(78.6)	11(78.6)
Yes	9(21.4)	6(21.4)	3(21.4)
Serum CA125			
Mean (range) U/ml	69.6(5- 1000)	86.8(6-1000)	35.9(5- 103)
Elevated [no. (%)]	16(38.1)	11(39.3)	5(35.7)
Serum CA19.9			
Mean (range) U/ml	148.9(1-6407.7)	7.9(1-19.81)	431.7(1-4607.7)
Elevated in [no. (%)]	3(7.1)	0(0)	3(21.4)
Fertility-sparing procedure			
No	15(35.7)	17(60.7)	10(71.4)
Yes	27(64.3)	11(39.3)	4(28.6)
FIGO stage			
I	34(81)	24(85.7)	10(71.4)
II	1(2.3)	0(0)	1(7.1)
III	7(16.7)	4(14.3)	3(21.4)
IV	0(0)	0(0)	0(0)
Histotype	42	28(66.7)	14(33.3)
Histopathology			
Mean diameter (cm)	10.54(2-32)	7.5(2-18)	16.4(3-32)
Bilateral tumor	7(16.6%)	7(25%)	0(0%)
+Microinvasion	4(9.5%)	1(3.6)	3(21.4)
+Peritoneal invasion	5(35.7)	3(10.7%)	2(14.3)
+Micropapillary	8(28.6)	8(28.6)	0(0)
+Peritoneal washings	4(9.5)	2(7.1%)	2(14.3)
+Ovarian surface	5(11.9)	4(14.3)	1(7.1)
+IEC	6(42.9)	0(0)	6(42.9)
+LVI	1(2.4)	0(0)	1(7.1)
+Lymph nodes	2(4.8)	2(7.1)	0(0)
Residual mass post-op	5(11.9)	1(3.5)	4(28.6)
Pregnancy post-op	8(19)	6(21.4)	2(14.3)
Recurrences	6(14.2)	3(10.7)	3(21.4)
Outcome			
Alive without disease	36(85.7)	25(89.3)	11(78.5)
Alive with disease	2(4.8%)	1(3.6)	1(7.1)
Dead	4(9.5%)	2(7.1)	2(14.3)

S-OBT: serous ovarian borderline tumor; M-OBT: mucinous ovarian borderline tumor; no.: number of cases; CA125: cancer antigen 125; CA19.9: cancer antigen 19.9; FIGO: International Federation of Gynecology and Obstetrics; IEC: intraepithelial carcinoma; LVI: lympho-vascular invasion; Post-op: after surgery.

intraepithelial carcinoma was detected in 6 (42.9%) M-OBT. Clinicopathological characteristics are summarized in Table 2.

Statistical correlations between each of disease recurrence and death with various clinical and morphological parameters were explored using Pearson chi^2. The statistical results are summarized in Table 3.

Table 3: Statistical correlation of clinico-pathological parameters with recurrences and death.

Study parameter	No.	Recurrences (P-value)	Death (P-value)
FIGO stage >I	8	5 (0.000)*	4 (0.000)*
Residual mass post-op	5	3 (0.002)*	2 (0.013)*
Omental metastasis	6	4 (0.000)*	4 (0.000)*
Positive peritoneal washings	5	3 (0.002)*	4 (0.000)*
Age (≥50 years)	5	1 (0.939)	1 (0.309)
Fertility-sparing procedure	27	3 (0.802)	3 (0.513)
Tumor diameter (≥15 cm)	9	3 (0.101)	2 (0.231)
CA 125 ≥35 U/ml	16	2 (0.302)	1 (0.302)
CA 19.9 ≥37 U/ml	3	1 (0.469)	1 (0.756)
S-OBT	28	3	2
M-OBT	14	3 (0.350)	2 (0.457)
Positive lymph nodes	2	0 (0.554)	0 (0.638)
Positive ovarian surface	5	1 (0.697)	0 (0.440)
Lymphovascular invasion	1	0 (0.679)	0 (0.743)
Micropapillary pattern	8	0 (0.382)	0 (0.554)
Stromal microinvasion	4	1 (0.520)	0 (0.495)
Intraepithelial carcinoma	6	2 (0.352)	1 (0.733)

S-OBT: serous ovarian borderline tumor; M-OBT: mucinous ovarian borderline tumor; no.: number of cases; CA 125: cancer antigen 125; CA19.9: cancer antigen 19.9; FIGO: International Federation of Gynecology and Obstetrics; Post-op: after surgery. *P*-values with * indicate significant Pearson chi^2.

Characteristics of S-OBT

Patient age ranged from 20 to 71, and the mean patient age was 39 years. Twenty-two (78.6%) were in reproductive years and six were menopausal. The most common presentation was abdominal pain (50%). Other presenting symptoms included abdominal mass in four (14.3%), ascites in one (3.6%), abnormal cycles or vaginal bleeding in five (17.9%) and four described other symptoms. Mean tumor diameter was 7.5 cm, and ranged from two to 18 cm. The mass was unilateral in 21 cases (75%) and bilateral in 7 (25%). Serum CA125 was elevated in 11 cases (39.3%). The values ranged from 6 and 1000 IU/ml (mean=86.8 IU/ml). Serum CA19.9 was not elevated in any of S-OBTs (0%), the values ranged from one to 19.81 U/ml (mean=7.9 IU/ml).

Primary surgical procedure was cystectomy in six (21.4%), oophorectomy/ salpingectomy in 11 (39.3%); TAH & BSO in nine (32.1%), debulking (TAH, BSO, omentectomy) in two (7.1%). Appendectomy was performed adjunct to primary surgery in four cases (14.3%). Peritoneal washings were positive in two cases (7.1%) and negative in the remaining 26 cases. Omental metastasis was diagnosed in three cases (10.7%). Residual mass post primary surgery was identified in one case (3.5%). Recurrence was diagnosed in three cases (10.7%). Pregnancy post op was successful in six cases (21.4%). FUP ranged from six to 127 months, with a mean value of 39.4 months. Lymph node involvement by tumor was detected in two cases (7.1%). Secondary surgery was performed

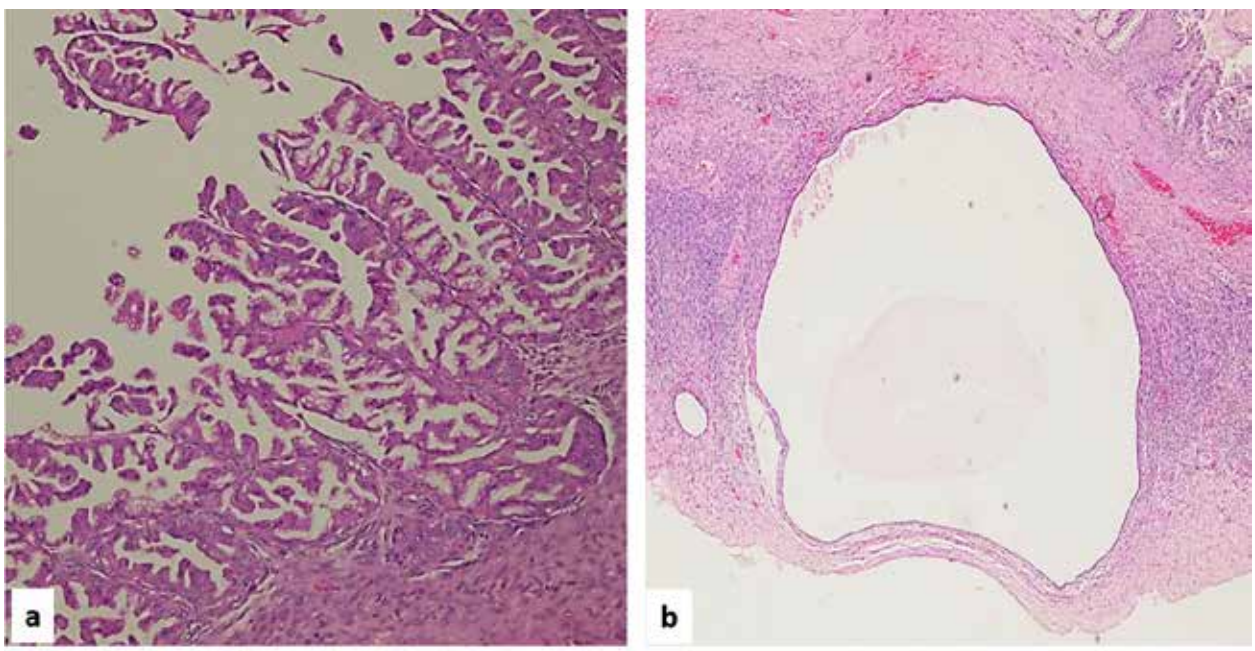

Fig 1. Histopathological findings in a case of S-OBT. **(a)** Micropapillary configuration. **(b)** Endosalpingiosis adjacent to tumor (H&E stain 100×).

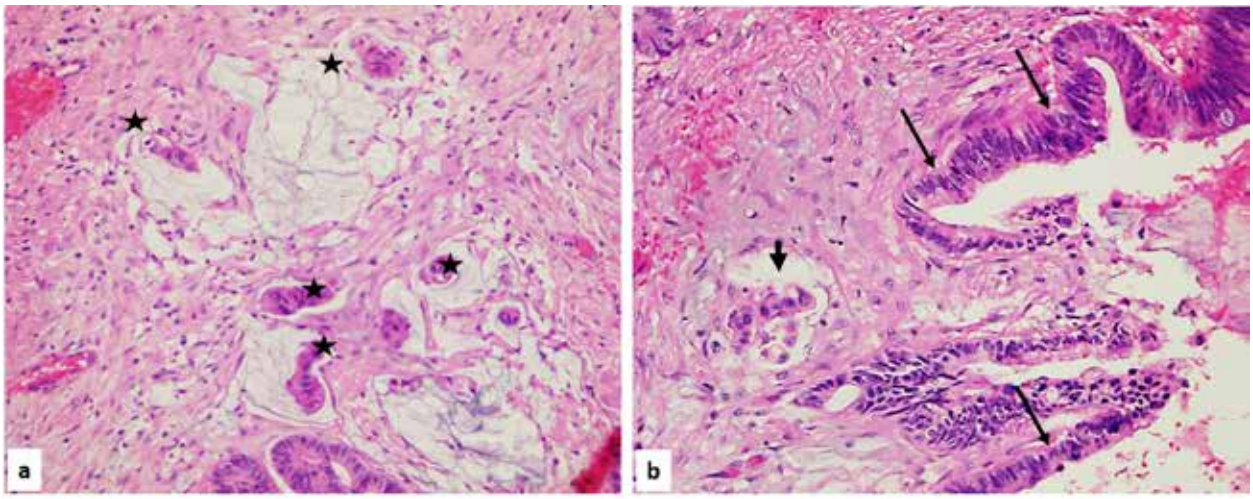

Fig 2. Histopathological findings in a case of M-OBT. **(a; black stars)** Stromal microinvasion. **(b; black arrows)** Intraepithelial carcinoma; **(b; arrowhead)** lymphovascular invasion (Original magnification 100×).

in 19 cases (67.9%). Chemotherapy was given to one patient (3.6%). Death due to disease complications was documented in 2 patients (7.1%).

Histopathological slide review revealed the following: endometriosis was diagnosed in one case (3.6%). Micropapillary architecture was detected in eight cases (28.6%) (Figure 1a). Endosalpingiosis was diagnosed in three cases (10.7%; Figure 1b). Microinvasion was found in one case (3.6%). Ovarian surface involvement was detected in 4 cases (14.3%). LVI was not identified in any of the cases (0%).

Characteristics of M-OBT

Fourteen cases of M-OBT were studied. Patient age ranged from 20 to 63 (mean: 37.4) years. Eleven (78.6%) were in reproductive years and three were menopausal. The most common presentation was abdominal mass (57.1%). Other presenting symptoms included pain in four (28.6%), ascites in one (7.1%) and abnormal cycles or vaginal bleeding in one (7.1%). Mean tumor diameter was 16.4 cm and ranged from 3 to 32 cm. The mass was unilateral in all 14 cases (100%). Serum CA125 was elevated in 5 cases (35.7%), with values ranging from 5-103 IU/ml, with a mean value of 35.9 IU/ml. Serum CA19.9 was elevated in three cases (21.4%); the values ranged from 1-4607.7 U/ml, with a mean value of 431.7 IU/ml.

Primary surgical procedure was cystectomy in seven (50%), oophorectomy/ salpingectomy in 3 (21.4%), TAH & BSO in one (7.1%), and debulking (TAH, BSO, omentectomy) in three (21.4%). Appendectomy as adjunct to surgical procedure was performed in three cases (21.4%). Peritoneal washings were positive in two cases (14.3%) and negative in the remaining 12 cases. Omental mass was diagnosed in two cases (14.3%). Residual mass post primary surgery was identified in four cases (28.6%). Recurrence was diagnosed in three cases (21.4%). Pregnancy post op was successful in two cases (14.3%). FUP ranged from six to 134 months, with a mean value of 65 months. Lymph node metastasis was not detected in any of the cases. Secondary surgery was performed in seven cases (50%). Chemotherapy was given in one case (7.1%). Death due to disease complications occurred in two cases (14.3%; 2/14).

Histopathological slide review revealed the following: endometriosis was diagnosed in one case (3.6%), endosalpingiosis was diagnosed in two cases (14.3%) and microinvasion was identified in three cases (21.4%) (Figure 2a). Ovarian surface involvement was identified in one case (7.1%), LVI was identified in one case (7.1%) (Figure 2b) and intraepithelial carcinoma was seen in 6 cases (42.9%).

DISCUSSION

OBTs

OBT are epithelial neoplasms characterized by proliferation with nuclear atypia but lacking stromal invasion or destructive growth pattern[9], that frequently affect reproductive aged women. The terminology "borderline" derives from the intermediate biological behavior of these tumors that is somewhere in between benign and malignant counterparts, despite the potential occurrence of peritoneal involvement[10].

OBT were first described in 1929 by Taylor and designated as semi-malignant[11]. Further characterization and designation of OBT was serially made by WHO over the past 2 decades[2].

OBTs represent about a fourth of epithelial ovarian tumors in different series, with an annual incidence rate of 1.8 to 4.8 cases per 100000 females[2]. Although they may affect any age, pre-menopausal women are

predominantly affected. OBT are said to have excellent prognosis[2]. The key difference between OBT and malignant tumors is histopathological confirmation of ovarian stromal invasion in the latter.

As previously mentioned, it is difficult to diagnose OBT clinically, radiologically and serologically[8]. The mainstay in diagnosis of OBT is still histopathological examination of resected tumors[3].

Intraoperative frozen section (FS) has a controversial role in OBT. Many papers including large meta-analysis indicate that FS analysis of OBTs has low accuracy, sensitivity and positive predictive value. In addition, it may lead to under-diagnosis and over-diagnosis, or even worse, misdiagnosis[12]. Conversely, other researchers believe that FS analysis plays an important role in selected situations and is associated to a high sensitivity and specificity in cases of ovarian and endometrial tumors[13], and increase the possibility of obtaining an optimal surgical treatment at first surgical approach.

Compared to their frankly malignant counterparts, OBTs have a notable favorable prognosis, with early-stage disease (FIGO stage I and II) exhibiting a five-year and 10-year overall survival rate of almost 98% and 95%; and with more advanced disease (FIGO stage III and IV) demonstrating a rate of 92% and 86%, respectively[14,15]. Many research papers tried to explore clinical and morphological factors that may play a role in outlining the prognosis of OBTs.

Lymph node involvement was reported in up to 25% of patients with advanced stage OBTs (FIGO stages III and IV). Many studies, however, have failed to demonstrate that lymph node involvement in patients with OBT did exert an adverse effect on survival[16].

Decisions for surgical treatment in patients with OBTs include fertility-sparing procedures (like simple cystectomy; unilateral oophorectomy/ salpingo-oophorectomy with contralateral ovarian biopsy to assess the opposite ovary) along with non-fertility-sparing procedures (*i.e.* hysterectomy with bilateral salpingo-oophorectomy; with or without multiple peritoneal biopsies, and fluid samples from peritoneal washing for cytological evaluation). The first option is usually used for young, fertility-desiring patients; and considered generally safe approaches. In some studies, recurrence rates ranged from 12% to 58% in patients with OBT who had conservative surgery (cystectomy), whereas patients treated by non-fertility-sparing surgery recurrence rates ranged between 0 and 20%[14].

Appendectomy and lymphadenectomy are currently non-compulsory surgical managements for OBT, because it has been shown that even in cases with lymph node involvement, survival and recurrence rates have not changed[17]. Studies validating advantageous effects of adjuvant treatments like chemotherapy and radiotherapy in patients with advanced stage OBT are lacking. Despite that, some patients with advanced stage OBT respond well to cisplatin-based adjuvant chemotherapeutic regimens; still, there is no promising effect on long-term survival[14].

S-OBT

S-OBT subtype comprise 43% to 53% of all OBTs[18]. Literature review reveals the peak age at presentation to be 40-50 years[16]. Roughly 30% of S-OBTs are bilateral and extra ovarian invasion in the form of non-invasive peritoneal implants is frequently detected[19]. Peritoneal implants in the current WHO criteria are noninvasive by definition. The incidence of bilaterality and extra ovarian spread is well known to be higher in S-OBT than that in M-OBTs[15].

Macroscopically, S-OBT are usually cystic masses with thin fluid and intra-cystic papillary projections; however, gross examination is not dependable to differentiate benign, borderline and malignant serous tumors. Histologically, a diagnosis of S-OBT is confirmed when at least 10% of the tumor exhibits a hierarchical, branching architecture lined by cuboidal to columnar epithelium, including ciliated cells, with mild cytological atypia.

Micropapillary growth pattern is another important morphological characteristic of S-OBTs. Whether its presence may affect prognosis adversely is still controversial, however, the increased rates of invasive recurrence in patients with micropapillary structure had been proved in some studies[20], in one study for instance (75.9% vs. 94.3%)[17].

Stromal microinvasion in S-OBT has become an arguable issue. It is defined as invasion of less than 3 mm or 10 mm^2 in one or more than one focus[21]. The main source of debate is whether the risk of recurrences increases in cases with microinvasion. Still, literature indicates that microinvasion should be regarded as a prognostic factor for S-OBT[17].

In addition, morphometric parameters were evaluated looking for potential prognostic markers in OBT. Those parameters included bilaterality, surface involvement, capsular rupture[22], presence of micropapillary pattern and microinvasion[23]. Advanced stage at presentation[24], peritoneal implants[14] and residual disease are reportedly associated with more aggressive disease in S-OBT.

M-OBT

M-OBTs comprise 42%-52% of all OBTs[18] and around 10% of all primary ovarian mucinous tumors[2]. Geographical variation in incidence is interestingly seen in M-OBT; while they rank second to serous OBT in frequency[25] in Western and Middle Eastern

populations, they appear to be the most common histotype in Asian communities, with about 70% of all OBT[18].

First described by Fisher in 1955[26], the entity since then has gone through many controversies and nomenclature arguments till 2004 where national cancer institute declared that "M-OBT", "atypical proliferative tumor", and "low malignant potential" are interchangeable terms[15], and hence adopted by WHO 2014 tumor classification[2].

M-OBT are famous for being of enormous size, and masses reaching more than 50 cm in diameter had been reported[16]. Several tumor markers had been said to be elevated, especially CA19.9 and CEA[16]. Even CA125 may be elevated in some cases as well[7]. M-OBT are frequently unilateral adnexal masses, with ≤10% of cases being bilateral[19]. Most of these tumors tend to be confined to the ovary at the time of first diagnosis.

Macroscopically, M-OBT displays a cystic mass with smooth outer-surface and a multiloculated inner aspect, and variable amounts of solid component on cut section. The cysts contain thick viscous mucoid material. Histologically, the epithelium may look like gastric or intestinal-type epithelium admixed with inconstant numbers of goblet cells. A diagnosis of M-OBT is confirmed when at least 10% of the cyst epithelium display areas of stratified, tufted and villiform growth[19]. If the lining epithelial cells display pronounced nuclear pseudo stratification and high-grade cytological atypia associated with high mitotic activity, a diagnosis of M-OBT with intraepithelial carcinoma is made; regardless of the degree of architectural complexity[27].

The prognostic value of intra-epithelial carcinoma in M-OBT is a matter of controversy; however, it is a general guideline that M-OBTs with intraepithelial carcinoma should be sampled comprehensively to exclude any invasive focus[15]. Some studies claimed that intraepithelial carcinoma is associated with higher recurrence rates[28].

Stromal microinvasion as defined for S-OBTs also holds accurate for M-OBTs. However, M-OBTs were not associated with increment in disease recurrences or worse prognosis[21]. Overall survival in patients with M-OBT with intraepithelial carcinoma is about 95% in early stage disease[16]**.** It is not known if the prognosis is different in cases with microinvasion in M-OBT, due to the limited number of available studied cases[28]. Recurrences of M-OBT are described and could be either in the form of OBT or invasive mucinous carcinoma.

To recap, the main dispute concerning treatment choices in OBTs is the critical balance between fertility-sparing desire and risk of disease recurrence. According to some studies, histological subtyping seems to have implications on this choice[17], which proposed that the risk maybe higher in M-OBTs, compared to S-OBTs[17]. Some researchers even suggested that salpingo-oophorectomy is favored over cystectomy during conservative surgery for patients with M-OBT[15].Similarly, in a large-scale meta-analysis, higher recurrence rates were observed for patients who underwent bilateral salpingo-oophorectomy when compared to those with hysterectomy with bilateral salpingo-oophorectomy. As mentioned earlier, noteworthy variance in recurrence rates were suggested by other papers between OBTs treated by conservative surgery (cystectomy alone) and those treated by extensive surgery (bilateral salpingo-oophorectomy)[17]. Conversely, it was not proved that these recurrences deduce an adverse outcome on survival rates[16].

The results of the current study explore the clinicopathological features and outcomes in patients with OBTs at a major tertiary center in our country. Three fourths of the patients were in reproductive years. Peri-menopausal years were the most frequent age at presentation. The majority of OBTs were in FIGO stage I. Two thirds were serous subtype. Serum CA125 was elevated in a third of cases (both S-OBT and M-OBTs). CA19.9 was elevated in a minority of cases and all were M-OBT. Two thirds had fertility-sparing surgical procedures, with eight successful gestations afterwards. Long-term follow up was the protocol used in management. Our results agree with previous literature that OBTs have excellent survival rates, with recurrences occurring in only 14.2% of cases, and deaths in 9.5%. The current results are also comparable with previous studies that both recurrences and deaths of OBTs were directly linked to initial staging and disease extent including stage at diagnosis, peritoneal washings, peritoneal implants and residual mass post-op.

In addition, we also had similar findings to literature regarding demographic and some clinical parameters. This study failed to show any statistical significance of age, menopausal status, laterality, serum CA125, serum CA19.9 and type of surgical procedure. In fact, fertility sparing procedures in our patients had comparable outcome to non-fertility sparing surgery.

As discussed formerly, the impact of certain histo-morphological parameters had been studied before, yet different studies had controversial results. Similar to other studies, we did not find statistically significant association between patient outcomes with each of tumor diameter, histotype or pelvic lymph node involvement. On the other hand, the current results, unlike some previous papers[14,16,23,24], display no significant impact on outcome and survival rates with ovarian surface involvement, LVI, stromal

microinvasion, intraepithelial carcinoma in M-OBT or micropapillary morphology in S-OBT.

CONCLUSIONS

Our results are in agreement with literature from other parts of the world, that OBTs have an excellent prognosis. Conservative surgery is to be considered for patients of reproductive age who desire preservation of fertility. A longterm followup, however, is highly recommended for these tumors.

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Original Article

The role of using multimodal imaging and elastography for diagnosing male breast cancer: new challenges and new diagnostic tools

Turkan Ikizceli[1], Gokce Gulsen[1], Defne Gurbuz[2], Yildiray Savas[1]
[1]Department of Radiology, University of Health Sciences Haseki Training and Research Hospital, Istanbul, Turkey
[2]Department of Radiology, University of Health Sciences, Okmeydani Training and Research Hospital, Istanbul, Turkey

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ABSTRACT

Objectives: This study evaluates the contribution of imaging modalities for male breast cancer and the initial clinical experience of elastography in male breast cancer. Our research is a unique and a pioneer study in this respect.
Design: Prospective study
Setting: Department of Radiology, Haseki Training and Research Hospital, Istanbul, Turkey
Subjects: Fifteen men who had malign breast lesions were included.
Intervention: Mammography, ultrasonography (US) with real-time strain elastography (RTE) and magnetic resonance imaging were performed.
Main outcome measures: The lesions were classified into the final Breast Imaging Reporting and Data System category. All patients underwent core-needle biopsies.
Results: A total of 17 malignant breast lesions with a mean size of 24.29±12.51 mm were diagnosed on 15 men. The mean age was 62.21±11.00 years (age range: 39-75 years). Fourteen of the 16 solid breast lesions were invasive ductal carcinomas (IDC), one was papillary carcinoma (PC) and one was ductal carcinoma in situ. One patient had bilateral breast cancer: the right breast was IDC, and the left breast was PC. The RTE was performed on only ten patients; elasticity score had two false negatives, although the elasticity index (EI) of two patients was malignant. The EI showed two false-negative results. The elastography's performance combined with the conventional US had no false-negative result.
Conclusion: The multimodality approach leads to a more accurate assessment of male breast cancer. Elastography combined with conventional ultrasound can provide specific benefits and information on breast malignancy in men.

KEY WORDS: breast, elastography, male breast cancer, multimodal imaging

INTRODUCTION

Defining male breast lesions begin with knowing the male breast anatomy. Diseases in the male breast can affect the skin, stroma and glandular elements, and neurovascular and lymphatic nodes[1].

The male breast masses involve a large differential diagnosis that includes gynecomastia, lipoma, inclusion cyst, oil cyst, abscess, panniculitis, hematoma, fat necrosis, cysts, ductal ectasia, intraductal papilloma, carcinoma, sarcoma and metastasis. All breast lumps in men aged 50 years or older deserve further investigation[2,3]. Many lesions have mammographic (MG), ultrasonographical (US) and magnetic resonance imaging (MRI) findings that allow differentiation between benign and malignant lesions that do not require biopsy[4]. Breast cancers are quite rare in men and are found in approximately 1% of cases.

Nevertheless, breast cancer is the second most frequent pathology in men after gynecomastia. Due to its rarity, our data on men's breast cancer is very limited and derives mainly from case reports and female patients[5,6]. Gynecomastia, the most common breast lesion in men, is very similar to other nodular

Address correspondence to:
Dr. Turkan Ikizceli, Asistant Prof., University of Health Sciences Haseki Training and Research Hospital, Adnan Adivar Street, Number: 9, 34130, Fatih, Istanbul, Turkey. Tel: +90 5324556302; E-mail: turkan.ikizceli@sbu.edu.tr

diseases. Also, breast malignancies in men mostly occur at the subareolar part of the breast as localized, painful masses[6]. For this reason, the malignancy should be recognized and examined thoroughly in the initial stage. A delay in diagnosis and treatment leads to disease progression and decreases survival rates[7].

Elastography is a non-invasive method of measuring the hardness of a tissue and has been a useful method in radiology practices recently[8]. By measuring the tissue strain induced by hand-free compression, tissue hardness is estimated, analogous to clinical palpation. Elastography has been found to be useful for differentiating malignant from benign masses in female patients[9,10]. Recently, the most used elastographic techniques have been strain elastography and shear wave elastography. Strain elastography analyzes the deformation of tissue induced by manual compression, and the information is encoded in a color scale result from the tissue displacement[11]. However, there is currently no study using the elastography technique for elastographic findings in male breast cancers.

This study evaluates the contribution of imaging modalities for male breast cancer and the initial clinical experience of elastography in male breast cancer. Our research is unique and a pioneer study in this respect.

SUBJECTS AND METHODS

Patient population

This study took place at the University Hospital from 2012 to 2018 and was approved by the Human Subjects Institutional Review Board. Informed written consent was obtained from all the patients before any interventional procedures. In this study, 524 consecutively male patients who had breast lesions were evaluated prospectively, 15 men who had malign breast lesions were included. Benign lesions and suspicious lesions that were verified to be histopathologically benign were excluded. The patients who had breast mass but declined core-needle biopsies were also excluded from the study.

Data acquisition

MG, US with real-time strain elastography (RTE) and MRI were performed. MG (IMS Giotto Digital Radiography and Tomosynthesis, Bologna, Italy) was primarily performed for the appropriate patients. If the patient's breast was too small for the device to compress automatically, the MG shooting could not be achieved.

US and RTE (Hitachi Medco's Digital Ultrasound Examination Device, HI-VISION Avius, Tokyo, Japan) were performed for all patients using the 6-13 Mhz probe after MG whenever possible. Otherwise, performing the US was the first imaging method. The lesions were localized in the B-mode first, and then elastography was performed. For elastography, compression and relaxation movements were performed manually to measure tissue density and stiffness. The elastography index (EI) and the scoring (ES) were obtained. The elastography scoring system based on the Ueno system suggested by Itoh *et al*[9] assigns a score from 1 to 5. According to the Tsukuba elasticity score, 1 shows a tri-stratified pattern and the lesion is entirely green; score 2 shows a mainly elastic lesion with a mosaic pattern; score 3 is a primarily elastic lesion, but with some stiff areas, is peripheral blue; score 4 shows that most of the lesion is nondeformable and entirely blue; score 5 shows a nondeformable lesion surrounded by stiff tissue and surrounded by a blue margin around the lesion (Figure 1). If a lesion is classified from 1 to 3, it is considered benign; 4 or 5 is considered malignant. EI was calculated automatically by the device. The ROI was placed to contain the maximum area of the solid mass. According to the research by Itoh *et al*, the cut-off value is accepted as 4.2. With freehand compression, if the elasticity of lesion values was unstable, no elastography was done for certain cases.

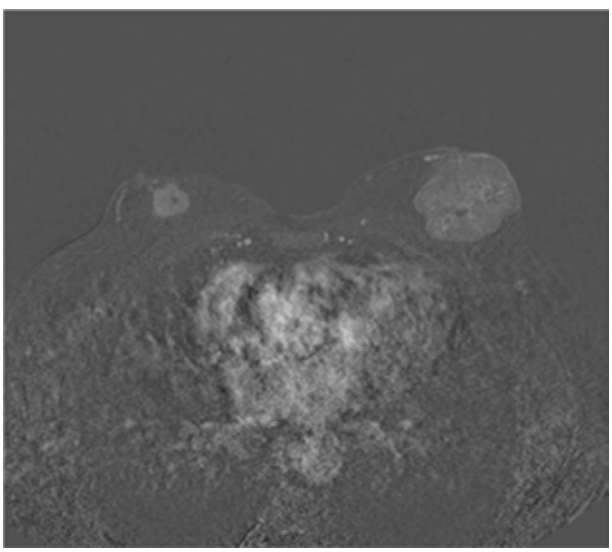

Figure 1: A 73-year-old male patient who had invasive ductal carcinoma in the right breast, papillary carcinoma in the left breast: MRI, axial contrast-enhanced subtraction image shows that he has bilateral breast masses.

Breast MRI was performed at 1.5 Tesla (Achieva, Philips, The Netherlands) while the patients were placed in a prone position by using dedicated eight-channel breast coils. Dynamic contrast-enhanced imaging was performed, and subtraction images were created for each contrast-enhanced series by subtraction of the non-enhanced series from the enhanced series.

Table 1: Imaging methods of all patients

Patient No	Age (years)	Diameter (mm)	Risk factor	Skin Changes	LAP	MG	US	Elastography		MRI	BI-RADS	Pathology
								ES	EI			
1	72	20	Paget's Disease	Paget's skin	-	+	+	-	-	-	BI-RADS-4	IDC
2	73	60	Family	Edema,	+	-	+	-	-	+	BI-RADS-5	IDC
		25	History	Ulceration								PC
3	72	27	-	-	-	+	+	3	5.18	+	BI-RADS-5	IDC
4	57	13	-	Areolar	-	+	+	5	12.5	+	BI-RADS-5	
				Retraction								IDC
5	67	18	-	-	-	-	+	2	4.3	-	BI-RADS-5	IDC
6	62	14	-	-	-	-	+	4	12	-	BI-RADS-5	IDC
7	50	28	-	-	-	-	+	4	1.6	+	BI-RADS-4	DCIS
8	75	12	-	-	-	-	+	-	-	+	BI-RADS-4	IDC
9	71	22	-	-	-	-	+	-	-	+	BI-RADS-4	IDC
10	50	40	-	Edema	+	-	+	4	4.75	+	BI-RADS-5	IDC
11	59	30	-	Edema	+	+	+	5	4.85	+	BI-RADS-5	IDC
12	39	30	Gynecomastia	Retraction	+	+	+	5	4.8	+	BI-RADS-5	IDC
		15										
13	54	18	-	-	-	+	+	5	7.8	+	BI-RADS-5	IDC
14	70	20	-	-	-	-	+	-	17.7	+	BI-RADS-4	IDC
15	60	21	-	-	-	+	+	2	1.08	+	BI-RADS-4	IDC

LAP: lymphadenopathy; MG: mammography; US: ultrasonography; ES: elasticity score; EI: elasticity index; MRI: magnetic resonance imaging; BI-RADS: breast imaging reporting and data system; IDC: invasive ductal carcinoma; PC: papillary carcinoma; DCIS: ductal carcinoma in situ

Diffusion MRI was obtained as fat-suppressed FATSET and non-fat suppressed T1 weighted scan on the axial plane (TR: 550 ms TE: 10 ms THK: 3 mm, FOV: 300 mm NSA: 2 T: 1.55 min), T2 weighted spoiled gradient echo scans with fat-suppression were acquired in the axial plane (TR: 4000 ms TE: 125 ms FOV 300 mm NSA: 2 T: 1.40 min) and apparent diffusion coefficient (ADC) was calculated by the device automatically. Dynamic contrast-enhanced imaging was performed using a high-resolution T1-weighted gradient-echo sequence with an automated intravenous bolus application. Subtraction images were obtained for each contrast-enhanced series by subtraction of the non-enhanced series from the enhanced series. The patients who had claustrophobia, renal dysfunction and were unable to use contrast agents did not undergo MRI.

Data analysis

Based on the US, MG and MRI findings, the lesions were classified into the final Breast Imaging Reporting and Data System (BI-RADS) category according to the American College of Radiology BI-RADS lexicon, without knowledge of the final pathologic diagnosis. US and RTE, MRI reports and biopsy applications were analyzed by a single consultant radiologist (T.I, seven years of experience in breast radiology). All patients underwent core-needle biopsies using 16-gauge automatic needles (GEOTEK, Ankara, Turkey) under sonographic guidance and were verified histopathologically.

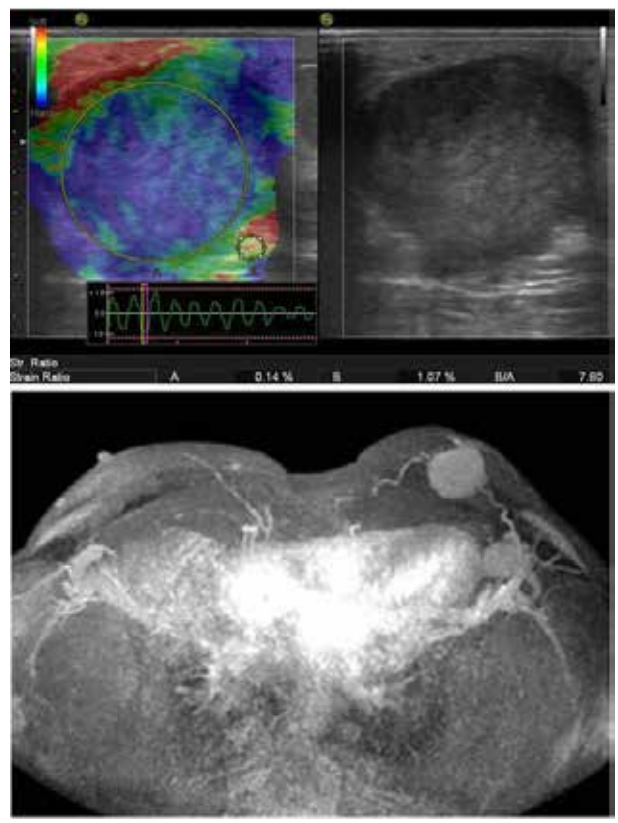

Figure 2: Invasive ductal carcinoma in the left breast of a 39-year-old male patient. a) Maximum intensity projection shows that there are 2 irregular-shaped and margined masses with axillary lymph nodes in the left breast. b) The elastogram demonstrates elastography score 4, elastography index 7.80 according to Ueno classification

Table 2: Core needle biopsy results

Type of breast cancer	n	Percentage
Invasive ductal carcinoma	15	88.24
Papillary carcinoma	1	5.88
Ductal carcinoma in situ	1	5.88
Total	17	100

RESULTS

The demographic and imaging findings of the patients were shown in Table 1. Due to histopathology, a total of 17 malignant breast lesions were diagnosed (mean size: 24.29±12.51 mm) on 15 men. The mean age was 62.21±11.00 years (age range: 39-75 years). Fourteen of the 16 solid breast lesions were invasive ductal carcinomas (IDC), one was papillary carcinoma (PC) and one was ductal carcinoma in situ. One patient had bilateral breast cancer: the right breast was IDC and the left breast was PC (Table 2), and had a primary risk factor. His daughter was undergoing breast cancer chemotherapy at the same time. Another patient had multicentric breast cancer (Figure 2 a,b; patient-12). He had been diagnosed with gynecomastia in both breasts. Another patient had Paget's disease. The remaining 11 patients had no risk factor for breast cancer or no history of taking estrogen, irradiation or any other disease.

Out of 15 patients, six patients (40%) were assessed as BI-RADS 4 and 9 (60%) as BI-RADS 5 by MG, US, RTE and MRI findings.

MG was obtained from seven patients, seven patients had unilateral, nodular breast masses, two patients had microcalcifications and macrocalcifications (Figure 3; patient 4), six patients had skin changes such as edema, nipple retraction, ulceration and skin thickening (Figure 4; patient 11) and five patients already had positive axillary nodes.

The conventional US was obtained from all patients and RTE was performed on only ten patients; ES had two false negatives, although the EI of two patients was malignant. The EI showed two false-negative results. The elastography's performance combined with the conventional US had no false-negative result.

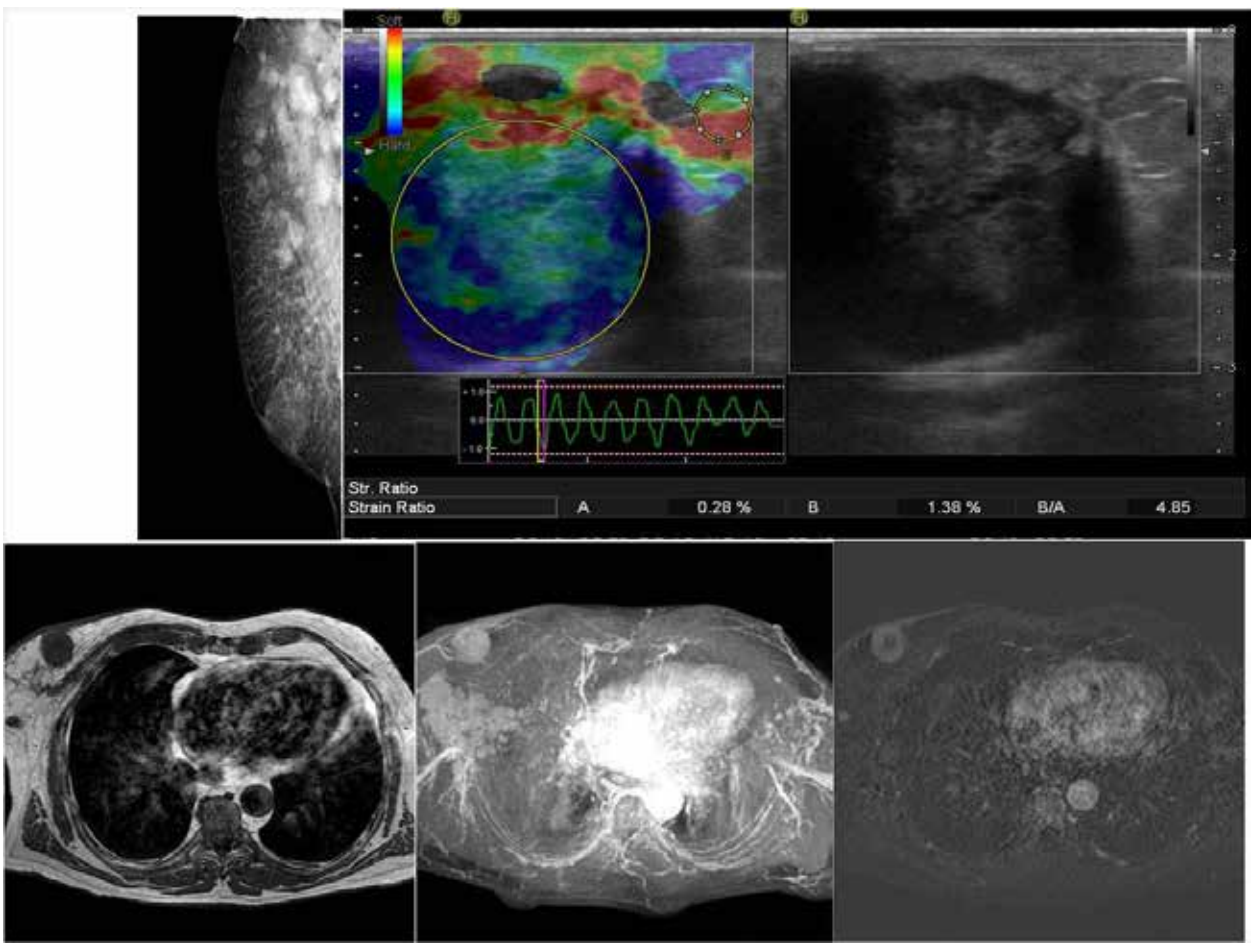

Figure 3: A 59-year-old male patient a) right MLO mammogram shows a mass at the subareolar plane with axillary nodes; b) elastography score, elastography index according to Ueno classification system; c, d, e) T1-weighted image, maximum intensity image and DCE-MRI show the mass and multiply axillary lymph nodes in the right breast.

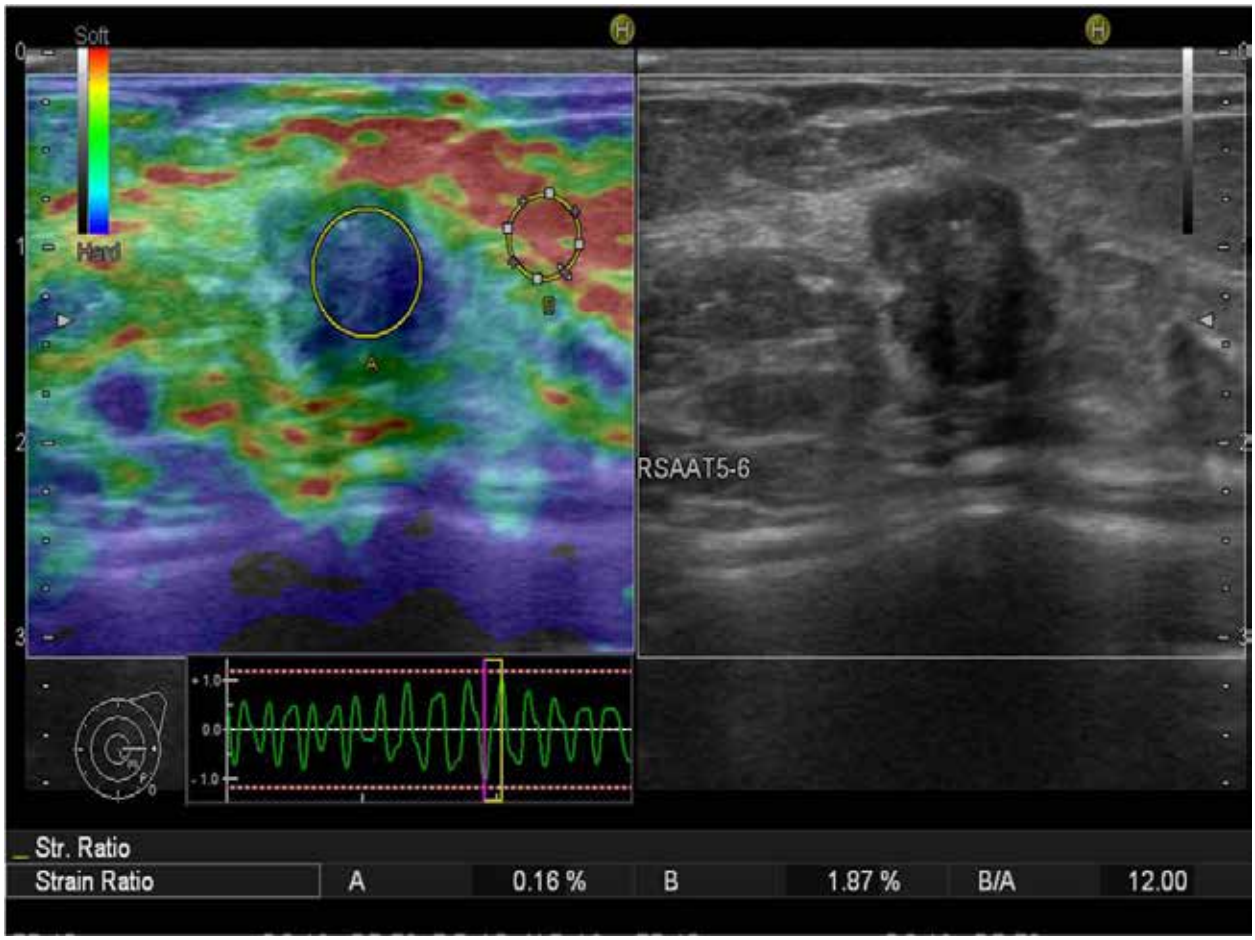

Figure 4: A 62-year-old male patient; the elastogram shows elastography score 4, elastography index 12.00 according to Ueno classification system.

MRI in selected patients (n=12) had no false negative. Diffusion-weighted imaging and ADC combined with MRI had no false-negative.

DISCUSSION

Breast cancer is the most frequent cancer worldwide affecting females[12,13], whereas male breast cancer is quite rare and representing nearly 1.0% of all breast malignancies[5]. The first comprehensive study of male breast tumors was published in 1927[14]. Risk factors for breast cancer in men have a wide spectrum that includes Klinefelter syndrome, presence of BRCA1 or BRCA2 mutation, a family history of breast cancer in a first-degree male or female relative, a hormonal abnormality such as hypoestrogenism or exogenous estrogen treatment for feminization purposes, advanced age or presence of chest irradiation history. Especially the presence of family history is remarkable and increases breast cancer risk two- to fourfold[15]. In our case series, only one patient who had bilateral breast cancer had a risk factor; his daughter was undergoing breast cancer chemotherapy at the same time. One patient had Paget's disease. Breast cancer with Paget's disease in male patients has been reported in very limited cases in the literature, and it is a known fact that breast cancer can coexist with Paget's disease[16]. The real risk factor is not known in the literature because of the lack of male breast cancer studies.

Breast cancer in men is usually diagnosed at an age approximately 5 years older than women, with a mean age at diagnosis of approximately 67 years and unilateral, occurring bilaterally in less than 1% of cases[17]. There are very limited cases in the literature about multicentric and bilateral male breast cancers. In addition, men usually present a more advanced stage of cancer than do women due to delays in diagnosis. It has been reported that approximately 50% of men have positive axillary nodes at initial evaluation[7,17]. Due to the inability of their breast parenchyma, the malignancy rapidly progresses to the next stage[18]. Our result was 62.21±11.00 years, and one patient had synchronous bilateral breast cancer, one had unilateral and multicentral breast masses. The youngest man in our study was 39 years old. Therefore, our average age is lower than in the literature. Five patients had axillary LAP at the first examination[19,20].

Many of the male breast lesions seem clearly benign by mammographic, ultrasonographic and MRI findings and those that do not require biopsy. The most common male breast mass is gynecomastia, followed by lipoma and epidermal inclusion cysts as a painless, palpable, localized mass and are usually found at the sub-areolar plane or in the upper outer quadrant of the breast[21-22]. Other symptoms include nipple ulceration or retraction, discharge from the nipple with blood or without blood, skin thickening and axillary lymph nodes[22]. In our study, five patients had skin changes without nipple discharge. According to literature, 13 of 15 patients had a palpable painless mass on their breast. The mean lesion size was 24.29±12.51. Two patients had a large lesion size.

MG is the first imaging modality for a clinically suspicious mass in men as it is the method of female breast examination. Breast cancer in men has mammographic features that allow it to be recognized. Still, there is a significant overlap in the mammographic appearance of benign nodular breast lesions and breast cancer. Both malignant and benign lesions may show the same appearance. Micro-calcification and coarse calcification are seen in both benign and malignant breast lesions[4]. Radiologists are generally less familiar with breast disease in male patients compared with female patients[18]. Sometimes MG added little information to the initial patient evaluation. However, MG, a useful tool in the assessment of breast tissue, may be reserved for patients whose clinical diagnosis is unclear, for patients who have more than one diagnostic possibility. This determination should be made on a case-by-case basis, with the use of MG on a selected basis rather than as a routine imaging procedure[23]. In our study, we only used MG in seven patients. The remaining eight patients had very small breast tissue, and the MG device couldn't compress to their breasts. Three patients had palpable breast masses and did not require visualisation by MG. A case-based decision was made.

If a palpable mass is occult or incompletely imaged at MG, it then requires US examination. The US is more important in diagnosing male breast lesions, especially true gynecomastia and other nodular breast lesions. However, performing US examinations of the breast requires an experienced radiologist. The US, together with history and physical examination, can generally provide a diagnosis[24,25]. We didn't find any false-negative result in the BI-RADS category in the diagnosis of patients due to experienced radiologists.

RTE has been a step ahead in the diagnostic algorithm of palpable breast lesions in women. It helps in characterizing malignant breast lumps with quite an accuracy[26,27]. RTE local strain by the freehand movement. The strain is shown as a color image. The main limitation of the method is that the applied stress is unknown. Therefore, the absolute value of the elasticity cannot be calculated. The technique relies on an even distribution of stress over the region of interest, but this is sometimes difficult to obtain in practice, and the stress is attenuated as it is transmitted through tissues. Anisotropy of tissues in vivo can cause variable stress distributions and, thus, variable strains. The boundaries of tissue and the movement between organs also result in challenges for this imaging method[10,11]. We performed US and real-time RTE for all patients, but only had ten patient's elastography values. This result was mainly the lack of male breast tissue beyond the limitation of the method. We could not get an equal frequency of elastography techniques from some patients. ES had three and EI had two false negatives. One patient had both benign ES and EI, although the lesion seemed malignant, according to B-mode US. This makes us think that the male breast tumor may be soft. There is no study in the literature on this subject. Our research is an initial study and pioneer study in this respect.

Breast MRI is not an experimental modality anymore in radiology practice; it also has achieved a solid position in the diagnosis of breast lesions[28]. MRI of male breast lesions will enable the radiologist to confidently identify the small part of patients who require a biopsy to confirm or exclude malignancy. MRI especially is the best imaging method to evaluate the pectoral invasion of the tumors[21,29]. In our study, 12 patients underwent MRI to assess the invasion of the masses we reported. With combined diffusion MRI and ADC values, MRI had no false negative. We suggested that MRI is the most sensitive method in male breast cancers.

Suspicious or indeterminate masses require a biopsy, but is not required routinely when gynecomastia is seen. The biopsy can usually be performed with US guidance, and sometimes MG guidance.

Core biopsy of the male breast is a very reliable preoperative diagnostic procedure, which should be used more often because it can help to avoid unnecessary surgery and in planning surgery for cancer[30]. Histopathologically, 90% of male breast cancers are IDC. The remaining 10% are insitu of the ductal type, with 75% of these being of the papillary subtype[31,32]. The biopsy is compulsory in cases classified as BI-RADS categories 3, 4 and 5. Follow-up is not considered in male breast classified as BI-RADS category 3. In our study, 14 of 17 malignant breast lesions were IDC (88.24%), one was PC (5.88%) and the other one was ductal carcinoma in situ (5.88%). In our present study, all patients underwent biopsy and

showed that core needle biopsy of male breast lesions is a reliable method for achieving a preoperative diagnosis.

CONCLUSION

Radiologic imaging played an essential role in diagnosing male breast cancer. Using combinations of imaging methods improves diagnostic performance. Elastography combined with conventional ultrasound can provide specific benefits and information on breast malignancy in men, as well as better characterization when diagnosing breast masses. The multimodality approach leads to a more accurate assessment of male breast cancer.

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Ethics: The institutional review board approved this retrospective study in our academic institution

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Author contributions: Turkan Ikizceli contributed to the study design, data collection and drafted the manuscript; Gokce Gulsen contributed to the study; Defne Gurbuz supervised the study; Yildiray Savas contributed to the analysis in the study. All authors read and approved the final manuscript.

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Original Article

Diameter and collapse index of inferior vena cava as a clinical indicator of resuscitation for critically ill hypotensive patients

Seongpyo Mun
Department of Surgery, School of Medicine, Chosun University, Gwangju, South Korea

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ABSTRACT

Objectives: The role of diameter and collapse index of inferior vena cava (DCIIVC) in reflecting intravascular volume status and fluid responsiveness remains unclear. We aimed to evaluate the effectiveness of DCIIVC as a clinical indicator for fluid resuscitation (FR) in critically ill hypotensive patients.
Design: Retrospective cohort study
Setting: Department of Surgery, School of Medicine, Chosun University, South Korea
Subjects: Hypotensive patients admitted to the surgical intensive care unit (SICU) between May 2018 and April 2019.
Intervention: Fluid therapy was conducted by a physician's decision (non-DCIIVC group, 32 patients) and DCIIVC (DCIIVC group, 30 patients). Clinical outcomes of the two groups were compared.
Main outcomes measure: In hospital mortality, duration of SICU stay, duration of mechanical ventilation, incidence of acute kidney injury, congestive heart failure and pulmonary edema, total amount of fluid resuscitation
Results: Total amount of fluid intake (TAFI) of non-DCIIVC and DCIIVC group in 24 hours was 4130 and 3560, respectively (P<0.05). TAFI in 48 hours was 8420 and 6910, respectively (P<0.01). Lactate levels at admission, 24 and 48 hours after admission were 4.1 vs 3.8, 3.2 vs 3.1 and 1.9 vs 2.1 mmol/L, respectively. Mean duration of mechanical ventilation, ICU stay and hospital stay were 4.1 vs 4.5, 7.2 vs 6.3 and 18.1 vs 17.2, respectively. Overall mortality was 16.7% vs 13.3%. There was no significant difference in any other characteristic except TAFI.
Conclusion: DCIIVC can be used as a tool for indicating FR in critically ill hypotensive patients. This can help physicians infuse fluid restrictively without adverse outcomes.

KEY WORDS: collapse index, diameter, fluid resuscitation, inferior vena cava

INTRODUCTION

Fluid therapy is one of the most important management procedures for critically ill hypotensive patients. Previously, Swan-Ganz catheter has been used to assess the preload and afterload of the patients; however, it is losing popularity due to its invasiveness. The surviving sepsis campaign guidelines 2012 recommend using central venous pressure (CVP), but it is not recommended in Sepsis 3 anymore because of its poor correlation with the volume status of the patients[1]. Pulse pressure variation, stroke volume variation or echocardiogram is also used for this purpose, but these require special equipment and examination technique[2].

Lactate is used as an indicator for fluid therapy in septic patients. The sepsis 3-hour recommends administering 30 ml/kg of crystalloid when mean arterial pressure reaches <65 mmHg or lactate levels are 4 mmol/L. However, obtaining venous lactate levels takes dozens of minutes to several hours. When lactate is used as a clinical guide, it is quite confusing to decide whether patients need more fluid. Blind fluid therapy without a clinical indicator for fluid therapy can result in adverse outcomes when patients' hemodynamics has a very narrow range of compensation.

Measuring the diameter and collapse index of inferior vena cava (DCIIVC) with ultrasound is quite simple, and it can be examined by medical or non-

Address correspondence to:
Seongpyo Mun, M.D., Ph.D., 365 Philmundaero, Donggu, Gwangju, South Korea. Tel: +82 1073275683; E-mail: spmun@chosun.ac.kr; ORCID No: 0000-0002-7067-4751

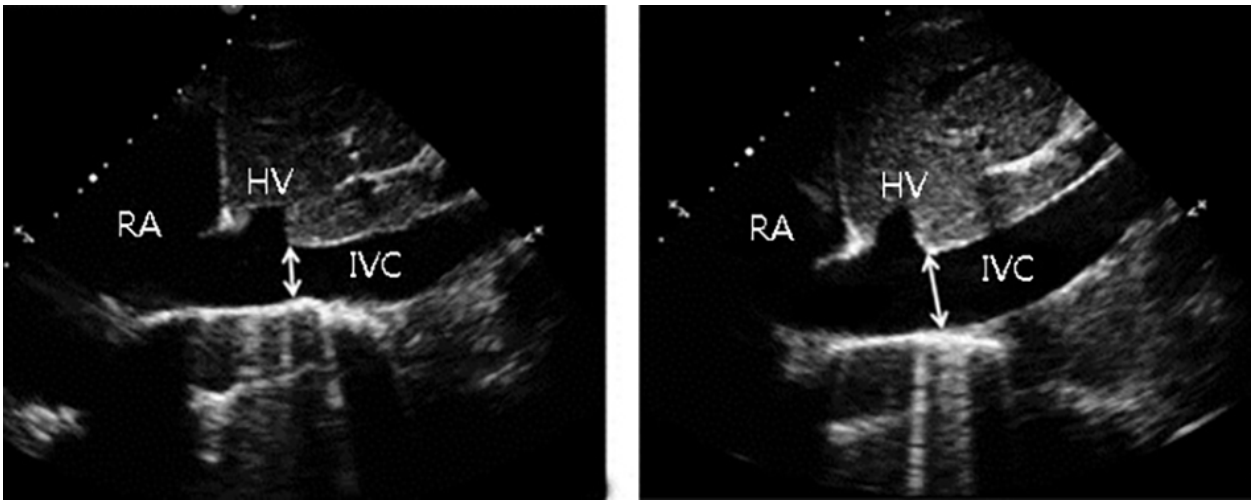

Figure 1: Diameter and collapse index were checked at the point of the lower margin at the inlet of the hepatic vein during expiration (left) and inspiration (right). RA: right atrium, HV: hepatic vein, IVC: inferior vena cava.

medical staff after short-term instructions[3]. Contrary to lactate measurement, ultrasound provides results simultaneously with the procedure. DCIIVC is well known as a tool of point-of-care for restrictive fluid therapy for heart failure or fluid removal for hemodialysis[4,5]. We aimed to evaluate the clinical usefulness of DCIIVC as a tool of point-of-care for fluid resuscitation (FR) in critically ill hypotensive patients.

SUBJECTS AND METHODS

Ethics Committee Approval

Institutional review board of Chosun University Hospital approved this study on June 10th, 2019

(NO: CHOSUN 2019-04-005-002)

DCIIVC measurement and FR

If a patient's systolic blood pressure was <90 mmHg, DCIIVC was checked at the time of admission. Abnormal DCIIVC was defined as diameter <15 mm and collapse index >50%. Collapse index was calculated by [(maximum diameter – minimum diameter) /maximum diameter] during respiratory cycles. During FR, DCIIVC was checked by two physician assistants. The checking point of DCIIVC was inferior vena cava (IVC) at the lower margin of the inlet of the hepatic vein (Figure 1). When a patient had abnormal DCIIVC, FR was conducted until the IVC diameter became >15 mm or the IVC collapse index became <50%. Before using DCIIVC, the amount of FR was decided by physician's decision using CVP, lactate level or patient's weight. FR was carried out at a rate of 2,000 ml/hour until DCIIVC became normal. DCIIVC was checked every 15 minutes. After DCIIVC became normal, fluid infusion was maintained at 120 ml/hour.

Clinical data and statistical analysis

This retrospective study enrolled hypotensive patients admitted to the surgical intensive care unit between May 2018 and April 2019. Fluid therapy was conducted by a physician's decision (non-DCIIVC group, 32 patients) and DCIIVC (DCIIVC group, 30 patients). The total amount of fluid intake (TAFI); lactate levels at admission, 24 and 48 hours after admission; duration of mechanical ventilation; intensive care unit stay; total hospital stay, incidence of acute kidney injury, pulmonary edema and congestive heart failure; and overall mortality were compared between the two periods. Student t-test was used to analyze statistical significance.

RESULTS

The number of patients in non-DCIIVC and DCIIVC group was 32 and 30. The average age of patients was 66 and 64 years. The male to female ratio was 20:12 vs 17:13. The main causes of admission were major trauma, post major surgery, abdominal sepsis, brain death and major burn. Mean arterial pressure was 60.14 vs 61.1 mmHg. The mean diameter of IVC was 17.3 vs 16.9 mm. The mean collapse index of IVC was 64% vs 67% (Table 1). There was no statistical significance between the groups.

TAFI of non-DCIIVC and DCIIVC group in 24 hours was 4130 vs 3560, respectively (P<0.05). TAFI in 48 hours was 8420 vs 6910 (P<0.01). Lactate at admission, 24 and 48 hours after admission were 3.5 vs 3.8, 3.2 vs 3.1 and 1.9 vs 2.1. The mean duration of mechanical ventilation, intensive care unit stay and hospital stay were 4.1 vs 4.5, 7.2 vs 6.3 and 18.1 vs 17.2. The number of patients with acute kidney injury were 4 vs 2 in non-DCIIVC and DCIIVC group. The number of pulmonary edema were two and one. Overall mortality was 16.7%

Table 1: Demographics and metrics of the inferior vena cava

Characteristics	Non-DCIIVC (n=32)	DCIIVC (n=30)	*P*
Age (range); years	66 (17-70)	64 (17-70)	NS
Sex (male: female)	20:12	17:13	NS
Main cause of ICU admission			NS
Post major surgery	7	6	NS
Abdominal sepsis	7	6	NS
Brain death	2	1	NS
Major trauma (ISS score; range)	16 (18.1; 17-27)	17(17.3; 17-34)	
Epidural hematoma	1	0	
Spleen injury	3	4	
Pelvic bone fracture	5	3	
Liver injury	3	4	
Multiple long bone fracture	3	4	
Major burn	1	2	
Mechanical ventilation	16	14	
Mean arterial pressure (mmHg)	60.4 (51.6-68.2)	61.1 (52.2-69.4)	NS
Diameter of IVC (mm)	17.3 (14-23)	16.9 (15-24)	NS
Collapse index of IVC (%)	64 (24-84)	67 (22-81)	NS

DCIIVC: diameter and collapse index of inferior vena cava; ICU: intensive care unit; COPD: chronic obstructive lung disease; ISS: injury severity score; IVC: inferior vena cava; NS: not significant

vs 13.3% (Table 2). There was no significant difference in any characteristic, except TAFI.

DISCUSSION

Although fluid therapy is the fundamental method for the management of critically hypotensive patients, the exact assessment of volume status (VS) is not easy. Stroke volume variation or pulse pressure variation needs arterial catherization. Non-invasive methods such as pulse oximeter plethysmography, impedance plethysmography or impedance phlebography require specific devices and its accuracy is still questionable. Ultrasound is widely used in many medical fields. One of the advantages of using ultrasound is that it provides real-time results, contrary to other radiologic tests. The technique for examination is also simple, that can be performed by a nonphysician. Measuring DCIIVC and evaluating VS of the patients is much easier[6]. DCIIVC shows very high potential as a tool for point-of-care. DCIIVC has been introduced as a useful tool for measuring VS in rapid ultrasound in shock for the evaluation of critically ill patients[7]. DCIIVC is used for the real-time monitoring of fluid removal during continuous renal replacement therapy and fluid therapy for heart failure[8-10]. The qualitative assessment of DCIIVC has also been carried out in a prospective study and demonstrated that DCIIVC offers a rapid, non-invasive way to evaluate VS in critically ill patients[11]. Despite its accuracy and usefulness, DCIIVC is not widely used as a clinical indicator for FR.

Table 2: Clinical outcomes of two study groups

Characteristics	Non-DCIIVC (n=32)	DCIIVC (n=30)	*P*
TAFI in 24 hours (ml)	4,130	3,560	0.042
TAFI in 48 hours (ml)	8,420	6,910	0.009
Lactate at admission (mmol/L)	3.5 (2.1-4.2)	3.8 (2.5-4.4)	NS
Lactate in 24 hours (mmol/L)	3.2 (2.2-3.6)	3.1 (2.1-3.2)	NS
Lactate in 48 hours (mmol/L)	1.9 (0.7-2.8)	2.1 (0.6-2.8)	NS
Duration of mechanical ventilation (days)	4.1 (1-11)	4.5 (1-14)	NS
Duration of ICU stay (days)	7.2 (2-19)	6.3 (2-21)	NS
Duration of hospital stay (days)	18.1 (11-45)	17.2 (7-35)	NS
Complication			
Acute kidney injury	4	3	NS
Pulmonary edema	2	1	NS
Congestive heart failure	0	0	NS
Mortality (%)	5 (16.7)	4 (13.3)	NS

TAFI: Total amount of fluid intake; DCIIVC: diameter and collapse index of inferior vena cava; ICU: intensive care unit; NS: not significant

There are several reasons. One of them is that the usefulness of DCIIVC is debatable. DCIIVC is known to reflect VS well. The IVC diameter can be used as a point-of-care to guide heart failure management. In acute heart failure syndrome, DCIIVC ≥0.5 on admission suggests a volume shift from the central vein into the pulmonary vasculature and is helpful in diuretic use[12]. However, some studies had negative conclusions about the metrics of IVC. The IVC diameter checked on computed tomography was not a good indicator of VS in hemodynamically normal trauma patients[13]. Even meta-analysis has different results. Two meta-analyses showed that DCIIVC is a reliable parameter for hypovolemia and has a great value in predicting fluid responsiveness[14,15]. However, other meta-analyses on DCIIVC concluded that it is not a reliable method to predict fluid responsiveness[16,17]. Hence, the effectiveness of DCIIVC to predict VS or fluid responsiveness has not yet reached a conclusion.

We wanted to clarify the effectiveness of DCIIVC as a clinical indicator for FR by retrospective analysis. The uniqueness of this study is the evaluation of the clinical outcomes of DCIIVC, contrary to a previous study that evaluated the accuracy for fluid responsiveness or correlation with hypovolemia or lactate levels. These parameters do not always agree with the clinical outcomes. Moreover, previous studies have mainly evaluated medical patients with cardiac or renal concerns. This study included surgical patients. Usually, hypotension of surgical patients is caused by bleeding, hypovolemia or septic condition due to acute insult. Since their previous hemodynamic function was normal, meticulous control of FR will result in favorable recovery. The results of this study showed that using DCIIVC as the indicator for FR made physicians use lesser fluid than using CVP, lactate or patient's weight with similar hemodynamic recovery and clinical outcomes. DCIIVC can be a useful guide to point-of-care for fluid therapy in shock patients requiring strict volume control.

DCIIVC-guided FR failed to improve clinical outcomes in this study. We believe this is because of the diverse characters of the patients. The cause of hypotension was variable. Some patients had hypovolemia, but others had sepsis or brain death. DCIIVC needs to be evaluated in the same disease group in a future prospective study.

We used the IVC of the hepatic vein inlet as the location of examination. DCIIVC can be measured at the level of the renal vein or junction of the hepatic inlet. Compared to the IVC at the level of the renal vein, the IVC at the hepatic vein inlet is much easier to find and can be checked during Focused Assessment with Sonography in Trauma. If we check the IVC near the heart, the chance of failure is very low, but this location does not show equivalent results and is not recommended[18].

This study has some limitations. The study is an analysis of two different periods and the strength of evidence is very weak. We checked the anteroposterior diameter of the IVC. A previous study recommended not to measure DCIIVC in the vertical direction because true collapse of the vessel does not occur in the vertical direction[19].

CONCLUSION

DCIIVC can be used as a tool of point-of-care for FR in critically ill hypotensive patients. Using DCIIVC as a guide for resuscitation helps physicians infuse fluid restrictively, without adverse outcomes.

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Conflict of interest: The researcher claims no conflicts of interest.

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Author's contribution: This study was designed and conducted by single author.

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Original Article

Is ECG follow-up necessary in hypertensive patients with COVID-19?

Kubra Aydin Bahat[1], Gulay Aydin[2]
[1]Department of Internal Medicine, Division of Nephrology, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey
[2]Department of Cardiology, Darica Farabi Training and Research Hospital, Kocaeli, Turkey

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ABSTRACT

Objectives: COVID-19 associated pneumonia is a health threat, especially in hypertensive patients. Hydroxychloroquine ± azithromycin used in the treatment increases the risk of corrected QT prolongation and cardiac arrhythmia. In our study, we aimed to determine the electrocardiographic findings and their effects on the clinical course of hypertensive patients who received hydroxychloroquine and azithromycin treatment for COVID-19 disease.
Design: A retrospective, clinical study
Setting: Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Turkey
Subjects: Hypertension patients treated with the diagnosis of COVID-19
Interventions: Corrected QT distance was calculated before and after hydroxychloroquine and azithromycin treatment for hypertension patients diagnosed with COVID-19. Pre- and post-treatment corrected QT distance change was evaluated.
Main outcome measures: All patients demographic features, comorbidities, symptoms, clinical course, laboratory parameters, electrocardiography and treatments were recorded.
Results: Thirty-one hypertensive patients were included in the study. In electrocardiograms taken before and 24-48 hours after hydroxychloroquine and azithromycin treatment, corrected QT <500 ms and QT <480 ms, there was no statistically significant increase between corrected QT distances (P=0.762). However, there was a significant relationship between the corrected QT values after treatment and the need for intensive care (P=0.043).
Conclusions: In our study, the corrected QT value observed 24-48 hours after hydroxychloroquine and azithromycin treatment was associated with the need for intensive care. Therefore, electrocardiographic follow-up may be important in patients with hypertension during hydroxychloroquine and azithromycin therapy.

KEY WORDS: corrected QT, COVID-19, hypertension

INTRODUCTION

In December 2019, SARS-CoV-2 infection was seen in Wuhan, Hubei Province, and then it spread around the world. In February 2020, the World Health Organization named it COVID-19 disease, which means coronavirus disease 2019. There is no specific effective treatment for COVID-19 presently. Evidence suggests that older people with cardiovascular diseases, including hypertension (HPT), are at risk of developing severe cases[1-4].

Common symptoms of COVID-19 are fever and respiratory symptoms like cough and shortness of breath. It may be asymptomatic, or present with signs of infection, from mild respiratory tract infection to severe pneumonia. The global mortality rate is about 2.7%[1].

There is no cure for COVID-19 disease. However, the use of hydroxychloroquine (HY) therapy is thought to be beneficial. In addition, there are studies showing that the use of azithromycin (AZ) together with HY is beneficial in controlling the disease[5-8]. Although HY and AZ are generally well-tolerated drugs used in clinical practice, both can cause corrected QT (QTc) prolongation[9,10]. Data on QTc prolongation potential

Address correspondence to:
Kubra Aydin Bahat, MD, Department of Internal Medicine, Division of Nephrology, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Semsi Denizer Street E-5 Highway Cevizli Location 34890 Kartal, Istanbul, Turkey. Tel: +90 5322707060; E-mail: asbkubra@gmail.com

with the use of HY and AZ in COVID-19 patients are limited.

Therefore, in our study, we aimed to reveal the clinical features of HPT patients diagnosed with COVID-19 and the effect of HY and AZ treatment on the QTc value.

SUBJECTS AND METHODS

This study included HPT patients who were diagnosed with COVID-19 between 11.03.2020 and 30.05.2020 and who underwent electrocardiogram (ECG) monitoring. Real-time reverse transcriptase-polymerase chain reaction test (rRT-PCR) was performed for SARS-CoV-2 with nasopharyngeal and oropharyngeal samples to all HPT patients admitted to our hospital with the findings of COVID-19 disease and chest tomography was performed. The presence of ground-glass opacities, and consolidation areas were defined as the findings consistent with COVID-19 disease. HPT patients with the positive rRT-PCR test for SARS-CoV-2 and/or typical lung tomography findings for COVID-19 disease were included in the study. As a center policy, all HPT patients with findings consistent with COVID-19 on chest tomography were hospitalized for close clinical follow-up.

Demographic characteristics (gender, age) and chronic diseases of the patients were evaluated. In addition, symptoms at the time of admission, need for oxygen support (evaluated presence of oxygen saturation in room air <93%), history of secondary infection, need for intensive care and laboratory data were evaluated.

Electrocardiograms were taken before and 24-48 hours after treatment. QT values were calculated with Bazzet formula and QTc values were obtained. In patients with sinus tachycardia or sinus bradycardia, the QTc value was calculated using the Framingham formula. Leukocytosis, neutrophilia, lymphopenia and increased C-reactive protein (CRP) were defined according to the given normal ranges of the hospital laboratory as follows: white blood cells >10800 u/L, leukocytosis; neutrophil count >7700 u/L, neutrophilia; lymphocyte count ≤1300 u/L, lymphopenia; platelets count <130000 u/L, thrombocytopenia and CRP >3 mg/L, increased CRP, respectively.

The treatments prescribed as oseltamivir (30 mg 1x1), HY (2x200 mg loading and 1x200 mg maintenance dose), vitamin C (2x15 g) and azithromycin (AZ) (1x500 mg loading and 4x250 mg maintenance dose) for a total of five days are suggested. Oseltamivir treatment was not given to the patients who were followed up after 14 April by Ministry of Health's COVID-19 adjusted treatment protocol. We planned to discontinue AZ and/ or HY therapy if QTc >500 ms or QT >480 ms at the beginning or during the follow-up. 2x1600 mg loading and 2x600 mg maintenance favipiravir therapy were added to the patients who continued to have complaints after five days of HY treatment or developed clinical and/or laboratory severe disease during HY treatment.

The data were analyzed using SPSS 21.0 statistical program. *P*-value <0.05 was accepted as the statistical significance limit. Numerical variables were given as mean±standard deviation for normally distributed variables and as median for skew-distributed continuous variables. Categorical variables are shown as frequencies. Chi-square test was used to evaluate categorical data. In the analysis of continuous variables, considering the distribution of the data, independent-sample T test, Mann-Whitney U test or Wilcoxon test was used as appropriate.

This study was approved by the local institutional review board and waived the requirement for informed consent.

RESULTS

We included 31 HPT patients, 20 (65%) women and 11 (35%) men. The mean age was 68.5±10.5 (median: 72) years. Fifteen patients (48%) had a positive rRT-PCR. Computed tomography (CT) findings of all patients were consistent with COVID-19 disease. The most common symptoms were cough (15 patients, 48%) and fever (12 patients, 39%). The most common accompanying diseases were diabetes mellitus (DM; 22 patients, 71%) and chronic kidney disease (10 patients, 32%). The most frequent signs were laboratory dysfunction, high CRP and lymphopenia (84%, 26 patients, 48% patients, respectively).

All patients had a QTc <500 ms and a QT <480 ms in their ECGs 24 - 48 hours after the first and after treatment. The mean QT (QT1) was 379±27.5 ms (median: 380 ms) and the mean QTc (QTc1) was 437±35.6 ms (median: 434 ms) on the ECG taken before treatment. The mean QT (QT2) was 386±32.2 ms (median: 385 ms) and the QTc (QTc2) was 440±27.2 ms (mean: 442 ms) in the ECGs taken 24 - 48 hours after the treatment. There was no significant prolongation between pre-treatment QT and QTc values and post-treatment QT and QTc values (Table 1). Thirty (97%) patients were in normal sinus rhythm. One patient (3%) had atrial fibrillation, four patients (13%) had right bundle branch block, and three patients (10%) had a left anterior hemiblock. One patient (3%) had sinus bradycardia and three (10%) patients had sinus tachycardia.

Oxygen support was required in 42% of the patients (13 patients) during follow-up. The mean age of the patients who needed oxygen was 72.8±7.8 years. The mean age of the patients who did not need oxygen was

Table 1: Electrocardiographic measurements of the study groups

Parameters treatment	*P*-value	Before treatment	24-48 hours after
QT, ms	0.597	379±27.5	386±32.2
QTc, ms	0.762	437±35.6	440±27.2

QTc: correction QT value
Data are given as (mean ± standard deviation)

65.3±11.9 years (*P*=0.043). Eight of the 13 patients who needed oxygen were men. Three of the 18 patients who did not need oxygen were male (*P*=0.021). Of the patients in need of oxygen, 12 had DM and six had cardiovascular disease (CVD). Of the patients who did not need oxygen, 10 had DM and two had CVD (*P*=0.045, *P*=0.043).

The average length of hospital stay was 6.3±4.1 days. The average hospital stay of patients who needed oxygen was 8±4.6 days. The average length of stay in the hospital for patients who do not need oxygen was 4.9±3.2 days (*P*=0.049). The mean hospitalization duration of the patients who died was 12.4±8.4 days, and the mean hospital stay of the discharged patients was 5.8±3.6 days (*P*=0.040).

During the follow-up, 13% of the patients (4 patients) required intensive care and 3% (1 patient) developed secondary infection. The presence of consolidation in lung tomography of patients requiring intensive care was significantly higher than those who did not need intensive care (75% vs 19%, respectively; *P*=0.043). The mean QTc2 was 465±16.6 ms (median: 471.5) in patients in need of intensive care. The QTc2 was 436.7±27.3 ms (median: 440) of the patients not requiring intensive care (*P*=0.013). Half of the patients in need of intensive care died. No patients died from patients who did not need intensive care (*P*=0.040). Favipiravir treatment was required in seven patients (23%).

Considering the outcomes, 29 patients (94%) were discharged with cure, and two patients (6%) died to the development of acute respiratory distress syndrome and shock.

There was no significant relationship between age, gender, comorbid diseases, white blood cell, neutrophil, lymphocyte, platelet and CRP values with regard to the need for intensive care or mortality. Demographic characteristics and basic clinical features of the study population related to oxygen support is detailed in Table 2.

DISCUSSION

Since COVID-19 is a very new disease, data on the course of the HPT population and the cardiac effects of HY and AZ therapy are needed to assist and guide clinicians.

In this study, we presented the data on the clinical characteristics and course of 31 HPT patients infected with SARS-CoV2 who were diagnosed consecutively within the first 60 days period of the pandemic in our country. To date, there are few studies in the literature on the cardiac effects of HY and AZ therapy used by HPT patients with COVID-19 disease[11-15]. Therefore, while the number of patients in this study is limited, it is one of the studies with a relatively high number of patients and may contribute to limited evidence in this area.

The mean age in our study was 68.5±10.5 years. Average age can be compared to other studies of HPT (between 64-68)[16-19]. More than half (65%) of the patients in our study were women. Gender distribution varies according to research[16,17,20,21]. As in many studies involving patients with HPT and non-HPT, age and male gender were found to be associated with the need for intensive care and oxygen need[3,17,22-24].

Table 2: The features of the patients stratified by the need for oxygen supply in the follow-up

Parameters	Need for oxygen supply (+) (n=13)	Need for oxygen supply (-) (n=18)	Total (n=31)	*P*-value
Demographic features				
Age	72.8±7.8 (74)	65.3±11.9 (60)	68.5±10.9 (72)	0.045
Sex				0.021
Female, n (%)	5 (38)	15 (83)	20 (65)	
Male, n (%)	8 (62)	3 (17)	11 (35)	
CKD, n (%)	6 (46)	4 (22)	10 (32)	0.247
DM, n (%)	12 (92)	10 (56)	22 (71)	0.045
CVD, n (%)	5 (38)	2 (11)	8 (26)	0.043
Clinical characteristics				
Cough, n (%)	6 (46)	9 (50)	15 (48)	1
Fever, n (%)	8 (61)	4 (22)	12 (39)	0.060
Intensive care need, n (%)	3 (23)	1 (6)	4 (13)	0.284
Mortality, n (%)	2 (15)	0	2 (6)	0.196
Discharge time	8±4.6	4.9±3.2	6.29±4.1(5)	0.035

CKD: chronic kidney disease; CVD: coronary vascular diseases; DM: diabetes mellitus
Data are given as (mean ± standard deviation) (median)

In the first weeks of the epidemic, PCR tests resulted in 48-72 hours due to the limited diagnostic capacity of laboratory tests. For this reason, a CT scan was performed on all patients with suspected COVID-19 symptoms in our center to diagnose faster. In some studies, on patients diagnosed with PCR test and CT, PCR tests on follow-up have been shown to be positive[25,26]. In addition, there are studies suggesting it as the primary tool in the diagnosis of COVID-19 of chest tomography[27]. All of our patients had findings compatible with COVID-19 on their radiographic images. Consistent with the literature, the findings were bilateral, and the presence of consolidation was associated with the need for intensive care[25,28-30].

The most common symptoms of COVID-19 were dyspnea, fever and cough in our study. This is similar to other HPT and non-HPT studies[16,17,31], suggesting that symptomatology is not different in HPT patients. The most common accompanying comorbid disease in the patient group in our study was DM, and in accordance with the literature, the oxygen demand was significantly higher in patients with DM and CVD[24,32,33].

We analyzed the factors associated with oxygen support, intensive care need and mortality. Lymphopenia and CRP elevation were the most common abnormal laboratory parameters in our patients.

In general population studies and studies involving HT patients, intensive care need and increased mortality have been associated with leukocytosis, lymphopenia, neutrophil elevation, thrombocytopenia and increased CRP in COVID-19 patients[3,17,20,32,33]. Lymphopenia was more frequent in the intensive care / mortality group in our patients.

In some studies, the average hospital stay does not vary between 10 and 20 days[3,31,34,35]. In our study, the duration of hospital stay was higher in patients with severe symptoms. However, when all patients were evaluated, the average hospital stay was shorter than other studies. This may be due to the central policy of hospitalization of hypertensive patients and early detection of the need for favipiravir therapy. In addition, providing oxygen and intensive care support to all patients may have caused this difference.

There is evidence to support its effective treatment for coronavirus, but in vitro studies show that HY can be administered alone or in conjunction with AZ[6, 36]. HY and AZ each have been shown to increase the risk of QT interval prolongation, drug-induced torsade de pointes and sudden cardiac death[37-40]. Various studies have shown an increase in QTc interval in patients with COVID-19 who receive HY and AZ treatment[12,14,36,41]. In our study, there was no significant change between pre-treatment and post-treatment QTc distances. However, the mean post-treatment QTc distance was higher than the pre-treatment QTc distance mean. The lack of statistically significant increase in QTc value after treatment may be due to the small number of patients.

Cardiovascular effects of COVID-19 include myocardial damage, thromboembolic events and fatal arrhythmias[42,43]. The relationship between QTc measured after treatment and the need for intensive care determined in our study may be caused by myocardial damage due to COVID-19.

The mortality rate in our patient group in terms of clinical course and outcome was 7%. In the general population, the overall mortality rate of COVID-19 has been reported to be around 2.3%[1]. In many studies, mortality rates in HPT patients (19-28%) are higher than in the general population[17,18]. Our results can be compared with these studies. Although the data are limited, studies in HPT patients show higher mortality rates in HPT patients.

Our study has some limitations. The low number of patients studied should be stated as a limitation. However, due to the high patient load during the pandemic process, regular ECG monitoring could not be performed in all patients. However, despite the small number of patients, clinicians interested in managing this patient group should be informed.

CONCLUSION

In conclusion, this study suggested that in HPT population, the symptoms of COVID-19 were similar to that of non-HPT patients and all HPT patients with symptoms of COVD-19 had developed pneumonia as revealed by CT imaging. Laboratory findings were also similar to other patients with COVID-19. The most common accompanying laboratory finding was CRP elevation and lymphopenia.

ECGs taken before and 24/48 hours after HY and AZ treatment did not have a significant QTc prolongation, but the correlation between post-treatment QTc values and the need for intensive care suggests that regular ECG monitoring may be necessary for the follow-up of COVID-19 patients.

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Original Article

Effect of COVID-19 pandemic on management and the in-hospital outcome of ST segment elevation myocardial infarction

Bektas Murat[1], Selda Murat[2], Eylem Kivanc[1], Rafet Dizman[1]
[1]Department of Cardiology, Eskisehir City TR Hospital, Eskisehir, Turkey
[2]Department of Cardiology, Eskisehir Osmangazi University, Medicine Faculty, Eskisehir, Turkey

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ABSTRACT

Objective: The COVID-19 pandemic caused serious problems in the health system of the world resulting in delays in the management of ST segment elevation myocardial infarction (STEMI).
Design: Retrospective study
Setting: Department of Cardiology, Eskisehir City Hospital and Eskisehir Osmangazi University Faculty of Medicine
Subjects: Two hundred and fourteen STEMI patients (Group 1: 125 patients between 11/03/2019-31/05/2019; Group 2: 89 patients between 11/03/2020-31/05/2020)
Interventions: Coronary angiography
Main outcome measures: To evaluate the effect of COVID-19 pandemic on the incidence, the clinical presentation and the in-hospital outcomes of acute STEMI.
Results: There was a significant decrease in STEMI patients' admission during the COVID-19 period compared to that of the previous year. It was found that patients in Group 2 presented significantly later than Group 1. The longest delay was in the time from symptom-onset to the presentation to the hospital. The ejection fraction was significantly lower in Group 2 ($P<0.05$), and despite being statistically insignificant, cardiogenic shock was higher in Group 2.
Conclusion: With the onset of the COVID-19 pandemic, there was a decrease in the number of hospital admissions for acute STEMI patients and most of the acute STEMI patients were shown to be complicated due to late admission to hospital. It is important that cardiologists have more knowledge about the indirect effects of such diseases on the cardiovascular system and organize their management protocol.

KEY WORDS: acute ST segment elevated MI, corona virus-19, outcomes

INTRODUCTION

Acute ST-elevation myocardial infarction (STEMI) is a complication of coronary artery disease that has the highest mortality and morbidity rate around the world, and percutaneous coronary intervention (PCI) is the proposed specific treatment[1,2]. The treatment strategies for STEMI have been developed to reduce the time from the symptom onset to the entrance to the catheterization laboratory to minimize myocardial damage. The time from the onset of chest pain to wire crossing is directly related to reduced mortality and morbidity in patients sustaining acute STEMI[3]. There is insufficient data regarding the effect of public emergencies related to disease outbreaks on the treatment practices of acute STEMI. The coronavirus disease (COVID-19), which originated from Wuhan, China in December 2019 and spread throughout the world afterwards, hit Turkey on March 11, 2020. The patient care services of the hospitals have changed in many countries after the start of the pandemic. During this period, elective coronary angiography procedures and PCIs for stable coronary artery disease were all suspended in Turkey, as in most countries, to spare healthcare resources such as personal protective equipment and hospital beds for use in the care of patients with COVID-19. Although the American Heart

Address correspondence to:
Bektas Murat, MD, Department of Cardiology, Eskisehir City Hospital, Eskisehir, Turkey. Tel: +90 2226114000; Mob: +90 5074802729; E-mail: dr. bektash@hotmail.com

Association and the Society for Cardiac Angiography and Interventions recommended continuing primary PCI in the treatment of acute STEMI during the COVID-19 pandemic, a significant decline has been reported in the rate of PCIs in the US as well as in the world[4,5]. During this period, there have been changes in the number of patients presenting with acute STEMI, and the type and timing of presentation[6]. The present study aims to evaluate the effect of COVID-19 pandemic on the incidence, the clinical presentation and the in-hospital outcomes of acute STEMI patients.

SUBJECTS AND METHODS

The patients who presented to two pandemic hospitals (Eskisehir City Hospital and Eskisehir Osmangazi University Faculty of Medicine Hospital) serving as PCI centers with high patient loads (>100 PCIs/year) with the diagnosis of STEMI between March 11, 2020, and May 31, 2020, were included in this retrospective, observational study. These patients were compared with those who presented to the same centers during the same season in 2019. The patients with an unknown time of symptom onset, the patients who sustained STEMI in the hospital or cardiac arrest before admission to the hospital, and those without ST-segment elevation on the electrocardiogram were excluded from the study. The patients' demographic data, laboratory results, data on STEMI management procedures, angiographic findings and in-hospital outcomes were retrieved from the hospital records. STEMI was defined according to the Fourth Universal Definition of Myocardial Infarction[7]. The time from the symptom onset to the arrival at the emergency room was defined as the symptom onset-to-door time; the time from the arrival at the emergency room to the successful passage of the wire through the culprit coronary artery was defined as the door-to-wire time; the time from the arrival at the catheterization laboratory to wire crossing through the culprit coronary artery was defined as the Cath Lab to-wire time. A thrombus burden with the largest dimension measuring two times greater than the diameter of the vessel was defined as a large thrombus burden, and a thrombus burden with the largest dimension measuring less than two times the vessel diameter was defined as a small thrombus burden[8,9]. The in-hospital outcomes included major bleeding, non-major bleeding, re-infarction, shock and death. Re-infarction was defined as recurrent ST elevation ≥0.1 mV in at least two contagious leads on electrocardiogram together with ischemic symptoms lasting 20 minutes or longer or the occurrence of new pathognomonic Q waves and 20% or more increase in cardiac troponin levels[10]. Intracranial bleeding, cardiac tamponade, a haemoglobin level less than 5 gr/dL despite the lack of an identifiable bleeding focus, and the death due to bleeding were defined as major bleeding events. Any bleeding was defined according to the Thrombolysis in Myocardial Infarction criteria[11]. The study protocol was approved by the Institutional Review Boards or Ethics Committees of the Eskisehir Osmangazi University (Approval number 20.05.2020/05).

Statistical analysis

Continuous variables were expressed as mean±standard deviation and medians (Q1-Q3); categorical variables were defined as percentages. Kolmogorov-Smirnov test was used to investigate the suitability of the data for normal distribution. To compare continuous variables, we used Student's t test or Mann-Whitney U test, where appropriate. Categorical variables were compared via the chi-square and Fisher's Exact test. For all the tests, a value of $P<0.05$ was considered to be statistically significant. The SPSS statistical software package (SPSS, version 15.0 for Windows; SPSS Inc., Chicago, IL) was used to perform all the statistical calculations.

RESULTS

In this retrospective study, the study sample was divided into two groups by taking into account the time variable in an attempt to evaluate the effect of coronavirus pandemic on the patients with STEMI. Group 1 (n=125, 58.4%) was composed of the patients who were admitted between March 11, 2019 and May 31, 2019, whereas Group 2 (n=89, 41.6%) was composed of the patients who were admitted between March 11, 2020 and May 31, 2020. When the number of patients with STEMI who were admitted to the hospital in March, April and May is evaluated between 2019 (Group 1) and 2020 (Group 2), there was a significant decrease in the number of admitted

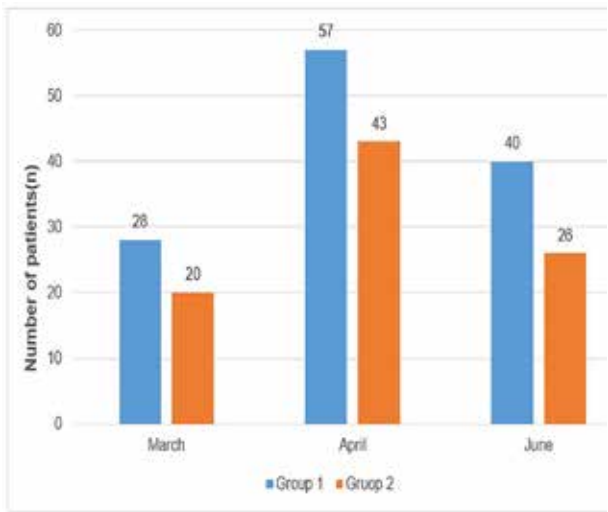

Figure 1: Decline of STEMI patients' admission during COVID-19 pandemic by months

Table 1: Demographic information and angiographic findings of patients

Parameters	Group 1	Group 2	*P*-value
Patients	125	89	
Age ± SD	61.30±11.46	59.48±11.26	0.252
Gender			0.656
Male (%)	98 (78.4%)	72 (80.9%)	
Female (%)	27 (21.6%)	17 (19.1%)	
Smoker (%)	69 (55.2%)	47 (52.8%)	0.729
Diabetes mellitus (%)	56 (44.8%)	24 (27.0%)	0.008
Hypertension (%)	52 (41.6%)	27 (30.3%)	0.092
Previous CAD (%)	30 (24.0%)	23 (25.8%)	0.758
Typical angina (%)	110 (88.0%)	69 (77.5%)	0.041
Dyspnea (%)	18 (14.4%)	24 (27.0%)	0.023
Pre-hospital death (%)	4 (3.2%)	3(3.4%)	>0.999
Type of STEMI			0.712
Anterior MI (%)	50 (40.0%)	45 (50.6%)	
Anterolateral MI (%)	1 (0.8%)	1 (1.1%)	
Inferior MI (%)	62 (49.6%)	37 (41.6%)	
Posterior MI (%)	5 (4.0%)	4 (4.5%)	
Lateral MI (%)	3 (2.4%)	1 (1.1%)	
Inferolateral MI (%)	3 (2.4%)	1 (1.1%)	
Vessel involvement			0.484
1 Vessel (%)	97 (77.6%)	66 (74.2%)	
2 Vessel (%)	20 (16.0%)	14 (15.7%)	
3 Vessel (%)	8 (6.4%)	9 (10.1%)	
Thrombus burden (%)			0.002
No thrombus	116 (92.8%)	69 (77.5%)	
Low thrombus burden < 2 diam	2 (1.6%)	11 (12.4%)	
High thrombus burden > 2 diam	7 (5.6%)	9 (10.1%)	
Culprit coronary			
LMCA (%)	2 (1.6%)	1 (1.1%)	>0.999
LAD (%)	40 (32.0%)	34 (38.2%)	0.347
CX (%)	18 (14.4%)	9 (10.1%)	0.352
RCA (%)	37 (29.6%)	20 (22.5%)	0.245
The others (%)	26 (20.8%)	24 (27.0%)	0.293
Laboratory results 1	**Median (Q1-Q3)/ Mean±SD**	**Median (Q1-Q3)/ Mean±SD**	
Platelet (10^3/μL)	232.0 (190.5-293.0)	266.0 (215.5-298.0)	0.034
Potassium (mmol/L)	4.10 (3.80-4.48)	4.57 (4.10-4.94)	<0.001
ALT (u/L)	29.0 (18.0-89.0)	73.0 (31.0-137.5)	<0.001
AST (u/L)	36.0 (20.0-151.5	160.0 (70.5-274.0)	<0.001
Hs Trp (pg/ml)	324.7 (53.2-2561.0)	1653.0 (115.1-15766.0)	0.001
CKMB (ng/mL)	6.09 (2.10-34.80)	21.00 (2.64-79.50)	0.027
Laboratory results 2			
Hemoglobin (g/dL)	14.60(12.95-16.30)	15.30(13.70-16.25)	0.183
WBC (10^3/μL)	11.30(9.29-13.50)	12.20(10.24-14.10)	0.024
Hematocrit (%)*	42.92±5.60	43.43±5.56	0.510
Neutrophil (10^3/μL)	7.08(5.20-10.11)	7.97(5.91-10.52)	0.099
Lymphocyte (10^3/μL)	2.34(1.54-3.55)	2.16(1.43-3.82)	0.873
Sodium (mmol/L)	137(135-139)	137(134-139)	0.694
Glucose (mg/dL)	138(114-210)	140(110.5-206)	0.971
Bun (mg/dL)	16.20(12.90-20.50)	14.90(12.4-18.95)	0.194
Creatinin (mg/dL)	0.92(0.80-1.12)	0.92(0.79-1.07)	0.811
Given treatment at first 24 hours			
ASA (%)	125 (100%)	89 (100%)	
Statin (%)	124 (99.2%)	87 (97.8%)	0.573
Beta-blockers (%)	83 (66.4%)	64 (71.9%)	0.490
ACEIs/ARBs (%)	78 (62.4%)	50 (56.2%)	0.360
P2Y12 inhibitors (%)	125 (100%)	89 (100%)	
LMWH (%)	125 (100%)	89 (100%)	
Glycoprotein IIb/IIIa inhibitors (%)	8 (6.4%)	10 (11.2%)	0.209

CAD: coronary artery disease; MI: myocardial infarction; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; ALT: alanine transaminase; ASA: acetylsalicylic acid; AST: aspartate aminotransferase; CK-MB: creatine kinase MB; CX: circumflex artery; Hs Trp: high sensitive troponin; LAD: left anterior desceding artery; LMCA, left main coronary artery; LMWH; low molecular weight heparin; RCA: right coronary artery; STEMI: ST segment elevation myocardial infarction; WBC: white blood cells.

Table 2: Duration in STEMI management (by minutes)

Duraiton of patients' management	Group 1 Median (Q1-Q3)	Group 2 Median (Q1-Q3)	*P*-value
Symptom-onset to door	88.0(60.0-119.0)	177.0(120.0-355.0)	<0.001
Door to cath lab	32.0(22.50-44.50)	40.0(29.5-62.5)	<0.001
Cath lab to wire	17.00(13.0-20.50)	20(18.5-30.0)	<0.001
Door to wire	50.0(40.0-63.0)	69.0(50.0-87.00)	<0.001
Total ischemic time	140.0(110.50-170.0)	240.0(175.0-453.0)	<0.001

patients in Group 2 in these three months (Figure 1). When the intergroup distribution of the study patients was evaluated, age, gender, smoking status and history of hypertension and coronary artery disease did not significantly differ between the groups. The number of patients with diabetes mellitus was significantly higher in Group 1 than that in Group 2 (*P*=0.008). Among the symptoms of myocardial infarction (MI), chest pain was more common in Group 1 (*P*=0.041), whereas the dyspnea was more common in Group 2 (*P*=0.023). The rate of cardiac arrest before hospital admission was similar in the two groups (Table 1). Regarding the angiographic findings, the number of patients with high thrombus burden was significantly higher in Group 2 than that in Group 1 (*P*=0.002), while the other angiographic findings did not significantly differ. When the laboratory results of the patients were evaluated, potassium, alanine aminotransferase, aspartate aminotransferase, white blood count, high-sensitivity troponin and creatine kinase-MB were significantly higher in Group 2 than that in Group 1 (*P*<0.05). Table 2 shows numerically longer median times in all components of management time when compared with the previous year. The longest time difference was in the time from symptom-onset to door. In terms of the in-hospital outcomes, the ejection fraction was significantly lower in Group 2 (*P*<0.001), and despite being statistically insignificant, the rate of cardiogenic shock was higher in Group 2 (Table 3).

DISCUSSION

The very first cases of COVID-19 in Turkey were spotted on March 11, 2020. There has been a change in the usual workflow of all the hospitals starting from the onset of coronavirus pandemic and a significant decline in the number of primary PCIs performed in our center for the patients with acute STEMI compared to the previous year, although no change was made in our center in the treatment protocol. When the study months were taken into consideration, there was a significant decrease in the number of interventions during the COVID-19 pandemic when compared to the same seasonal period in the previous year (March, April, May 2020 vs. March, April, May 2019; 28.5%, 24.5% and 35% decrease, respectively) (Figure 1). Consistent with the present findings, a similar decrease in the number of hospital admissions due to acute STEMI was noted in Hong Kong and the US[6,12]. However, previous studies have shown that environmental and psychosocial factors and viral outbreaks such as influenza infection increase hospital admissions due to acute STEMI[13]. Early diagnosis and treatment in myocardial infarction are known to be directly related to mortality and morbidity. The reasons for a decrease in hospital admissions due to STEMI during COVID-19 pandemic could be due to the avoidance or reluctance of patients to seek medical support as part of the social distancing measures or the fear of patients to contract coronavirus infection during such admissions. The most common presenting symptom in the present study during the period one year before the COVID-19 pandemic was typical angina pectoris (*P*<0.05), while the most common observed symptom during the COVID-19 pandemic was the dyspnea (*P*<0.05). Previous studies have reported a prolonged time between the symptom onset and the successful reperfusion in the patients with STEMI[6]. In our study, the most remarkable delay was observed in the time from the symptom onset to the arrival at the emergency room during the COVID-19 pandemic (Group 2) compared to the period before the pandemic (Group 1) (*P*<0.05). This delay may have multiple

Table 3: Patients in-hospital outcomes

Outcome parameters	Group 1 Median (Q1-Q3)	Group 2 Median (Q1-Q3)	*P*-value
EF before discharge	56(45.50-60.0)	50(42.50-56.0)	<0.001
Reinfarction	2(1.6%)	2(2.2%)	>0.999
Major bleeding	3 (2.4%)	1 (1.1%)	0.643
Minor bleeding	2 (1.6%)	2 (2.2%)	>0.999
Cardiojenic shock	6 (4.8%)	10 (11.2%)	0.078
Death	6 (4.8%)	5 (5.6%)	>0.999

EF: ejection fraction

causes. One of the causes may be the avoidance of patients to seek medical support with the fear of contracting coronavirus until the symptoms become intolerable or general medical condition deteriorates. The present study also found a significant delay in the door-to-wire and Cath Lab arrival-to-wire times in the patients with STEMI (P<0.05). These delays were attributed to the time spent for body temperature measurement, recording travel and contact history, and the examination to identify the potential carriers of the infection and running radiological tests to rule out COVID-19. Also, catheterization and laboratory personnel wearing personal protective equipment such as goggles, protective clothing and face masks after the patient was diagnosed with MI may cause an increase in time intervals. The delays in the diagnosis and treatment can cause complications such as in-hospital cardiogenic shock and heart failure. In a study by Tam *et al*, no statistically significant difference was observed in terms of in-hospital outcomes[6]. While the ejection fraction before discharge was significantly lower in Group 2 (P<0.05), despite not being statistically significant, the rate of cardiogenic shock was higher in Group 2 (P=0.07). The results of the present study suggest a decrease in the number of patients with STEMI during the COVID-19 pandemic; however, these results are not sufficient to suggest if the decrease in the number of the patients with STEMI is caused by the avoidance of patients to attend hospital or the death of the majority of the patients at home or decreased likelihood of sustaining MI during the quarantine period as the patients remain immobile and stress-free at their homes. The most important limitation of the study is that, due to the retrospective study design, no face-to-face interview has been made to enquire the reasons for not attending the hospital in detail. There is a need for large-scale multicenter studies to search for a clear answer to these questions.

CONCLUSION

With the onset of the COVID-19 pandemic, there was a decrease in the number of hospital admissions for acute STEMI patients and most of the acute STEMI patients were shown to be complicated due to late admission to hospital. It is important that cardiologists have more knowledge about the indirect effects of such diseases on the cardiovascular system and organize their management protocol. And at the same time, hospitals and the health care systems need to be well prepared for STEMI care and treatment.

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Original Article

Improvement of obstructive sleep apnea syndrome after laparoscopic sleeve gastrectomy: A retrospective study

Laila Al Khaldi[1], Nadia Al Saffar[1], Maryam Alipour[1], Eliana Al Haddad[2], Salman Al-Sabah[2]
[1]Department of Surgery, Faculty of Medicine, Kuwait University, Kuwait
[2]Department of Surgery, Al-Amiri Hospital, Kuwait

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ABSTRACT

Objectives: This study aims to evaluate the change in symptoms of obstructive sleep apnea (OSA) and the use of continuous positive airway pressure (CPAP) after laparoscopic sleeve gastrectomy as a bariatric surgery, given that the data about this subject is lacking in the Gulf region.
Design: A retrospective analysis was conducted in the period between November 2011 and November 2015. Out of 30 eligible patients, 10 participants who couldn't be reached were excluded from the analysis.
Setting: Public Hospital, Kuwait
Subjects: Thirty patients
Intervention(s): Patients who underwent laparoscopic sleeve gastrectomy (LSG) and a sleep study
Main outcome measure(s): The patients were asked about pre- and post-operative weight and OSA symptoms using STOP-Bang and Epworth Sleepiness Scale (ESS) questionnaires.
Result(s): The mean age of the patients was 35.5 years with 45% being females. There was statistically significant improvement in ESS & STOP BANG questionnaire (P<0.001) showing a drop from 8.65 to 0.75, and 4.1 to 1.5, respectively. The mean body mass index showed a decreasing trend from 71 kg/m^2 (47.6-90.2) pre-operatively to 40.1 kg/m^2 (29-81.6) post-op (P<0.001). Fifty-five percent of our patients were on CPAP before LSG; however, all the patients were off CPAP after the surgery. The percent excess body weight loss was 60.31% with a follow-up range after surgery of 9-56 months.
Conclusion(s): In conclusion, LSG plays a major role in the improvement and resolution of OSA symptoms, with a significant reduction in the use of CPAP in morbidly obese patients.

KEY WORDS: bariatric surgery, obesity, sleep apnea, sleeve gastrectomy

INTRODUCTION

Obesity is a worldwide growing health concern, with more than 1.9 billion adults being categorized as overweight by the year 2014, and 600 million of those being obese[1]. When it comes to Kuwait, 42% of the adults in the country were considered as being obese according to the World Health Organization study conducted in 2008, with percentages of 37.5% and 49.8% for males & females, respectively[2].

Obesity is defined by the National Institute of Health as a body mass index (BMI) of 30 and above. The BMI, a key index for relating body weight to height, is used as a screening method to determine body adiposity[3,4].

Being obese has been known to increase the risk of many chronic health conditions as it has been linked to type 2 diabetes, hypertension, dyslipidemia, cerebrovascular accidents, cardiovascular diseases, obstructive sleep apnea (OSA) and osteoarthritis. Furthermore, mental illnesses such as clinical depression and anxiety are higher among this population[3].

Bariatric surgery (BS) is currently the only known modality that provides a significant, sustained weight loss for morbidly obese patients, with resultant improvement in obesity-related comorbidities, including OSA and the usage of continuous positive airway pressure (CPAP) for the management of OSA[5]. According to the 1991 consensus guidelines from the National Institute of Health, patients with a BMI greater than 40 kg/m^2 or a BMI greater than 35 kg/m^2 with a significant obesity-related disease are considered as

Address correspondence to:
Salman Al-Sabah, MD, MBA, FRCSC FACS, Al-Amiri Hospital, Kuwait. Tel: +965 66666911; E-mail: salman.k.alsabah@gmail.com

possible candidates for BS[6]. The objective of this study was to evaluate the change in symptoms of OSA and the use of CPAP after laparoscopic sleeve gastrectomy (LSG) as a type of bariatric surgery, given that the data about this subject is lacking in the Gulf region.

SUBJECTS AND METHODS

Ethical approval statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

On July 2016, a retrospective analysis of 30 patients, who underwent LSG and a sleep study in the period between November 2011 and November 2015, was conducted. Ethical approval was obtained from the medical research ethics committee in Al-Amiri hospital and informed consent was obtained from all participants. The data was collected from Al-Amiri hospital registry; the eligible patients were contacted by telephone. Patients who declined to participate or couldn't be reached by phone were excluded. The patients were asked about pre- and post-operative weight and OSA symptoms using STOP-Bang and Epworth Sleepiness Scale (ESS) questionnaires. The following variables were also obtained: age, gender, nationality, BMI, hypertension, use of CPAP and the type of the sleep study which was conducted.

Sleeve gastrectomy technique

The LSG procedure was performed using five laparoscopic ports in a standard split-leg French position. Devascularization of the greater curvature of the stomach was done starting from 4 to 6 cm from the pylorus and up to the angle of His before a 36-Fr calibrating bougie was passed through the stomach to the duodenum. The sleeve was then performed with a linear laparoscopic stapler. Finally, the bougie was pulled proximally and an assessment of leak was done by injection of 100 ml of methylene blue. No intra-abdominal drains were placed.

Polysomnography

The diagnosis of OSA is best made by a knowledgeable sleep medicine specialist who has an understanding of the individual's health issues. The diagnosis is usually based upon the person's medical history, physical examination and testing, including:

1. A complaint of snoring and ineffective sleep
2. High blood pressure, especially if it is resistant to treatment
3. If a bed partner has observed the patient during episodes of apnea, choking or gasping during sleep, there is a strong possibility of sleep apnea

Testing is usually performed in a sleep laboratory using a polysomnogram (PSG). The PSG measures the breathing effort and airflow, blood oxygen level, heart rate and rhythm, duration of the various stages of sleep, body position and movement of the arms/legs.

Home monitoring devices are available that can perform a sleep study. This is a reasonable alternative to conventional testing in a sleep laboratory if the clinician strongly suspects moderate or severe sleep apnea and the patient does not have other illnesses or sleep disorders that may interfere with the results[7].

ESS

ESS is a self-administered questionnaire with 8 questions that is used to assess 'daytime sleepiness' of patients. Respondents are asked to rate on a 4-point scale (0-3) their usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life, or their 'daytime sleepiness'. The questionnaire takes no more than 2 or 3 minutes to answer, and is available in many different languages[8].

STOP-Bang

The STOP-Bang questionnaire includes the four questions used in the STOP questionnaire plus four additional demographic queries, for a total of eight dichotomous (yes/no) questions related to the clinical features of sleep apnea (snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck circumference and male gender). For each question, answering "yes" scores 1, a "no" response scores 0, and the total score ranges from 0 to 8.

The questionnaire can be completed quickly and easily (usually within 1-2 min), and overall response rates are typically high (90%-100%). If patients score 0 to 2 on the STOP-Bang questionnaire, they are considered to be at low risk of OSA, and the possibility of those patients having moderate to severe sleep apnea can be confidently ruled out.

Due to its ease of use, efficiency and high sensitivity, the STOP-Bang questionnaire has been widely adopted and validated in various populations and among patients with assorted medical conditions[9].

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software for Windows version 20. Out of 30 eligible patients, 10 participants who couldn't be reached were excluded from the analysis. The following results are based on a sample

size of 20 eligible participants. Descriptive statistics were presented as percentages, mean, range and standard deviation; paired sample t-test was used to compare the results pre- and post-surgery. Statistical significance was defined as a *P*-value <0.05.

RESULTS

Weight results

A total of 20 patients in this study had undergone LSG with a diagnosis of morbid obesity. The mean pre-operative weight of the patients was 168.4 kg, corresponding to a mean BMI of 71 kg/m^2. The mean age of the patients at the time of surgery was 35.5 years and the majority were males (55%). Table 1 illustrates the demographic data of the study group, while Table 2 illustrates the pre- and post-operative weight and OSA assessment results.

Table 1: Demographic data and patients baseline characteristics (N=20)

Characteristics	Value
Mean age (SD)	35.5 (10.7)
Gender (Male %)	55
Nationality (Kuwaiti %)	65
Pre-op PSG (Positive %)	65
Pre-op CPAP use %	55

PSG: polysomnography; CPAP: continuous positive airway pressure

Patients demonstrated the following weights post-LSG: 114.9 kg, 134.4 kg, 127.4 kg, 91 kg and 117.5 kg at two weeks, 3 months, 6 months, 1 year and 18 months, respectively. The mean post-operative weight of the patients was shown to be 111 kgs, corresponding to a weight loss of 57.4 kgs at latest follow-up. The percent excess body weight loss at latest follow-up was 60.31%. The excess body weight loss for our patients after 9, 12, 24, 42 and 56 months of follow up is shown in Table 3.

OSA related results

Eleven out of the 20 patients (55%) underwent an overnight PSG pre-operatively, while nine patients (45%) underwent a home sleep study. Thirteen patients were confirmed to have OSA, of which three were mild, two were moderate and eight were severe, while 11 participants started using CPAP before their LSG surgery.

Table 3: The EBWL for the patients after follow up (N=20)

Characteristics	EBWL%, mean (SD)
9 months (n=5)	61.22% (5.83)
12 months (n=4)	53.69% (34.54)
24 months (n=5)	68.02% (8.90)
42 months (n=4)	64.48% (15.31)
56 months (n=2)	24.86% (28.71)

EBWL: excess body weight loss

After the LSG operation, a significant statistical improvement in ESS and STOP-Bang questionnaires data was noticed, as well as in BMI, both with a *P*-value 0.001<. All the patients were off CPAP after the surgery with a better quality of sleep and a documented decrease in OSA symptoms.

DISCUSSION

OSA is a chronic condition characterized by recurrent episodes of partial or complete upper airway collapse during sleep[10]. As a consequence, air flow limitation and decreased oxygen saturation results. If this condition is left untreated, it leads to adverse effects on health such as cognition impairment and excessive daytime sleepiness.

OSA can be clinically defined by the occurrence of daytime sleepiness, loud snoring, witnessed breathing interruptions or awakenings due to gasping or chocking, in the presence of at least five obstructive respiratory events (apneas, hypopneas or respiratory effort related arousals) per hour of sleep. The presence of 15 or more obstructive respiratory events per hour of sleep in the absence of sleep related symptoms is also sufficient for the diagnosis of OSA due to the greater association of the severity of this obstruction with important negative consequences[11,12]. Overnight PSG is the gold standard diagnostic tool for suspected OSA. Adverse effects of this condition range from decreased quality of life to cardiovascular morbidities and mortality. It has also been implicated in the etiology of metabolic syndrome and type 2 diabetes[11].

There is a complex relationship between OSA and obesity. Obesity can worsen OSA as fat deposition in

Table 2: Pre- and post-operative results of the ESS and STOPBANG questionnaires and anthropometric measures

Characteristics	Pre-operative	Post-operative	*P*-value
Weight (kg), mean (range)	168.4 (118-270)	111 (67-217)	>0.001
BMI (kg/m^2), mean (range)	71 (47.6-90.2)	40.1 (29-81.6)	>0.001
EBWL (%, mean (SD)		60.31% (16.82)	
STOPBANG, mean (SD)	4.1 (1.74)	1.5 (0.76)	>0.001
ESS, mean (SD)	8.65 (7.095)	0.75 (0.96)	>0.001

BMI: body mass index; EBWL: excess body weight loss; ESS: Epworth Sleepiness Scale

the tissues surrounding the upper airway can result in a smaller lumen and leads to increased collapsibility of the upper airway, predisposing to apnea[12]. Also, fat deposits around the thorax reduce chest compliance and functional residual capacity and may increase oxygen demand. Accordingly, weight loss and CPAP therapy are the main modalities of managing OSA.

Risk factors of OSA have been shown to include age, male gender, obesity, smoking and a family history positive for OSA[10]. Since obesity is a major reversible risk factor linked to OSA, encouraging patients to lose weight is an efficient method to deal with this process. However, for those who fail to lose weight or reach an advanced stage, CPAP is recommended as a lifelong treatment to improve the symptoms[13].

Since there is a strong correlation between obesity and OSA as many studies have shown, bariatric surgeries were considered an effective method for treating obesity and its comorbidities like OSA[14]. Bariatric surgeries such as Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, LSG and duodenal switch with biliopancreatic diversion aim to decrease weight through BRAVE effects: bile flow alteration, restriction of gastric size, anatomical gut rearrangement and altered flow of nutrients, vagal manipulation and enteric gut hormone modulation[4]. Different mechanisms leading to resolution of OSA symptoms after weight loss were studied. The reduction in nasopharyngeal collapsibility and resistance after weight loss suggests there is an increase in the caliber of the upper airway. Another explanation is that reduction in central adiposity and the resulting reduction in production of adipokines that act on the central nervous system may lead to enhanced neuromuscular control of pharyngeal caliber. Weight loss is also linked with significant improvement of the pulmonary functions and volumes which result in increased tracheal traction on the pharynx[4].

LSG is one of the bariatric surgeries that is commonly performed nowadays as it has low post-operative complications and has proven to aid in achieving sustained weight loss[15].

This study was performed on 20 patients with a follow-up range after surgery of 9-56 months. Different research had different follow up durations ranging from 0.5 to 5 years after BS[16-23]. However, our follow-up range proved to be sufficient for the investigation of the effect of LSG on OSA symptoms, with all patients not requiring CPAP anymore.

In this study, ESS and STOP BANG, two validated questionnaires, were used pre and post LSG to assess the existence of OSA and its symptoms. There was statistically significant improvement in both questionnaires after sleeve gastrectomy (P<0.001), showing a drop from 8.65 to 0.75, and 4.1 to 1.5 in their numbers, respectively. Many other studies had similar results[16,18,24] when it came to assessing the effects of BS on the resolution of OSA symptoms.

Another significant improvement was found in the BMI of our patients. The mean BMI of our patients showed a decreasing trend from 71 (47.6-90.2) pre-operatively to 40.1 (29-81.6) post-op (P<0.001). The study conducted by Suliman *et al*[18] was also able to show a significant reduction in BMI after LSG with a P value <0.001. Many other studies were able to show results consistent with ours as well[16,22-23]. As explained earlier, obesity worsens apnea due to fat deposition in the tissues surrounding the upper airway[25], and therefore, with the weight loss that is resultant from undergoing an LSG, the loss of the fat deposits around the airway improve the diameter of the lumen, and therefore decreases the collapsibility of the airway.

Fifty-five percent of our patients were on CPAP before LSG. It was shown that during follow up after the operation, that number had decreased to 0%. Haines *et al* prescribed preoperative CPAP to all patients diagnosed with moderate to severe OSA and to the majority of patients diagnosed with mild OSA. During follow-up, the number of patients who were using CPAP was shown to have decreased from 83 patients to 31 patients postoperatively[20]. In Suliman *et al*'s study[16], they were also able to show a significant reduction in CPAP use in most of their patients (15 versus 5).

A possible limitation of this study includes the fact that only the effects of LSG were investigated on OSA. Another limiting point would be the fact that a small sample size was used in this study. Therefore, possible future directions would be to conduct studies that include a larger sample size over a longer period of time, which compare different bariatric surgeries on the management of OSA.

CONCLUSION

In conclusion, LSG as a type of BS plays a major role in the improvement and resolution of OSA symptoms, with a signification reduction in the use of CPAP in morbidly obese patients.

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Case Report

The first missense mutation in CSTA causes Acral Peeling Skin Syndrome in a Turkish family: Case report and review of the literature

Ahmet Cevdet Ceylan[1], Selma Emre[2], Gulay Gulec Ceylan[1]
[1]Department of Medical Genetics, Ankara Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Turkey
[2]Department of Dermatology, Ankara Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Turkey

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ABSTRACT

Acral Peeling Skin Syndrome (APSS) is a rare, autosomal recessive genodermatosis. It is commonly caused by mutations in transglutaminase 5 (TGM5, *603805), rarely in Cystatin A (CSTA, *184600). Two siblings were presented for chronic, superficial skin lesions. After dermatological examinations, clinical exome sequencing was performed for molecular diagnosis of one patient. Sanger sequencing was performed for the other patient to find if there is the same mutation. A novel homozygote missense mutation was found in CSTA gene of both siblings.

APSS is heterogeneous clinically and genetically. Different CSTA mutations can also cause APSS unlike previously reported cases, and contribute to better illumination of phenotype regarding literature review.

KEY WORDS: acral peeling skin syndrome, CSTA gene, novel missense mutation

INTRODUCTION

Acral Peeling Skin Syndrome (APSS) is a rare, autosomal recessive genodermatosis with variable age of onset from early childhood to adulthood. The disease is characterized by superficial peeling of cornified epidermal layer, but the mucosa is not affected[1]. Skin fragility often affects hands and feet. There is superficial, painless, continuous exfoliation from birth, which increases with temperature, humidity, water and physical trauma[2].

It is commonly caused by mutations in TGM5 (*603805), CSTA (*184600), SERPINB8 (*601697) and CHST8 (*610190) genes. So far, nonsense, splice site and frameshift mutations have been reported in only five patients[3-5]. Here, we report the sixth family with a novel homozygote missense CSTA mutation and clinical findings.

CASE REPORT

A 31-year-old woman presented because of chronic and superficial itchy skin lesions since one year of age. Parents were consanguine. Her brother was 28-years-old and presented with more severe skin findings. In dermatological examination, there was sharply limited, yellow-colored, mild diffuse hyperkeratosis in palmar and plantar regions of both siblings (Figure 1). There was widespread xerosis in brother's extremities. Furthermore on the dorsum of the brother's hands and feet, extending to wrists and ankles, extensive exfoliative lesions were observed on erythematous surface (Figure 2). The pedigree is shown in Figure 3. Genomic DNA was screened for clinical exome study of patient by Sophia Genetics (Saint Sulpice, Switzerland). Variant filtering process, we considered only nonsense and missense variants, indels and variants at canonical splice sites, excluding variants with minor allele frequency greater than 0.01 in different public and local resources.

A novel missense mutation (c.68T>A(p.Val23Asp)) was detected in CSTA gene. This variation isn't reported in the Genome Aggregation Database, Exome Aggregation Consortium and inhouse databases, it is

Address correspondence to:
Dr. Gulay Gulec Ceylan, Department of Medical Genetics, Ankara Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Turkey. Tel: +90 5323778718; E-mail: gulayceylan23@gmail.com

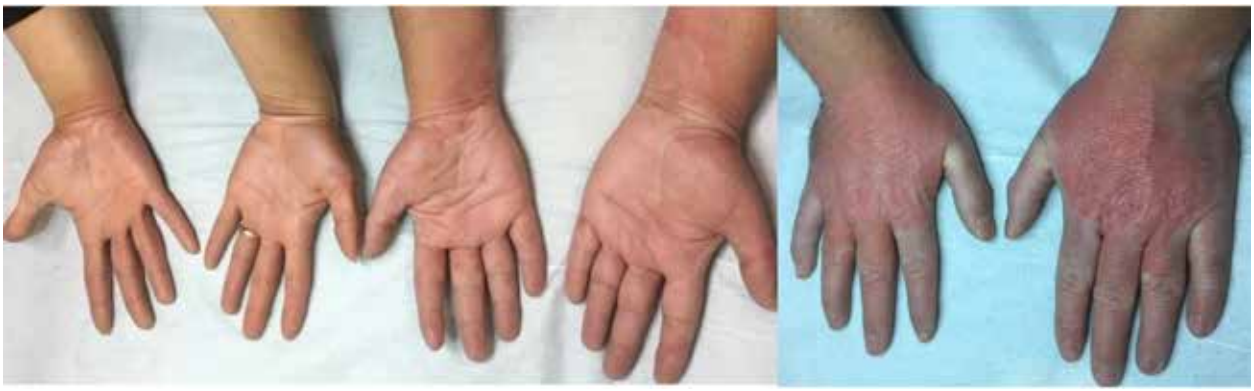

Figure 1: Palmar and plantar regions of the hands in both siblings with hyperkeratosis.

listed as 'disease causing' mutation at several insilico databases and bioinformatics tools (Mutation Tester, PolyPhen2, DANN). This variant fulfills pathogenic moderate (PM1, PM2), pathogenic predictive (PP3 and PP4), and should therefore be regarded as a likely pathogenetic according to the joint consensus recommendation of the American College of Medical Genetics and Association for Molecular Pathology[6]. The allele frequency of the variants is zero at Genome Aggregation Database. However, the Combined Annotation-Dependent Depletion score is 25. Direct Sanger sequencing was performed using ABI 3500 Genetic Analyzer (Life Technologies, USA) for the sibling, same mutation was also found in the second sibling. There was no other family member with the same mutation, so we think that it is a spontaneous new mutation. Written informed consent was obtained from the patients.

DISCUSSION

APSS is a heterogeneous genetic disorder and has two major clinical types; localized (acral) and generalized APSS have been described. Generalized APSS is classified as non-inflammatory and inflammatory subtypes. Atopic diathesis, itching, allergic reactions and growth retardation are accompanied in inflammatory subtype[4]. APSS has been reported to be associated with mutations at TGM5, SERPINB8, and CHST8 genes. The CSTA gene is also associated with APSS[4]. CSTA encodes cystatin A, a cysteine protease inhibitor expressed throughout epidermis. It is important in epidermal cell development. The nonsense (c.64A>T;c.72C>T;c.256C>T), splice site (c.67-2A>T) and exon 1 deletion mutations have been published[1,3-5]. We report first missense mutation (c.68T>A) at CSTA gene which affects the first aminoacid of exon 2 [p. (Val23Asp)]. This is the first missense mutation causing APSS.

The clinical course of patients with the same CSTA mutation in APSS is an important finding in the differential diagnosis and follow-up of patients[1,3-5] (Table 1). A complete genotype-phenotype correlation could not be established. Our case and other published cases indicated only at legs. Besides, we showed accompanying palmoplantar hyperkeratosis and was similar only in cases of Martinz *et al*[1].

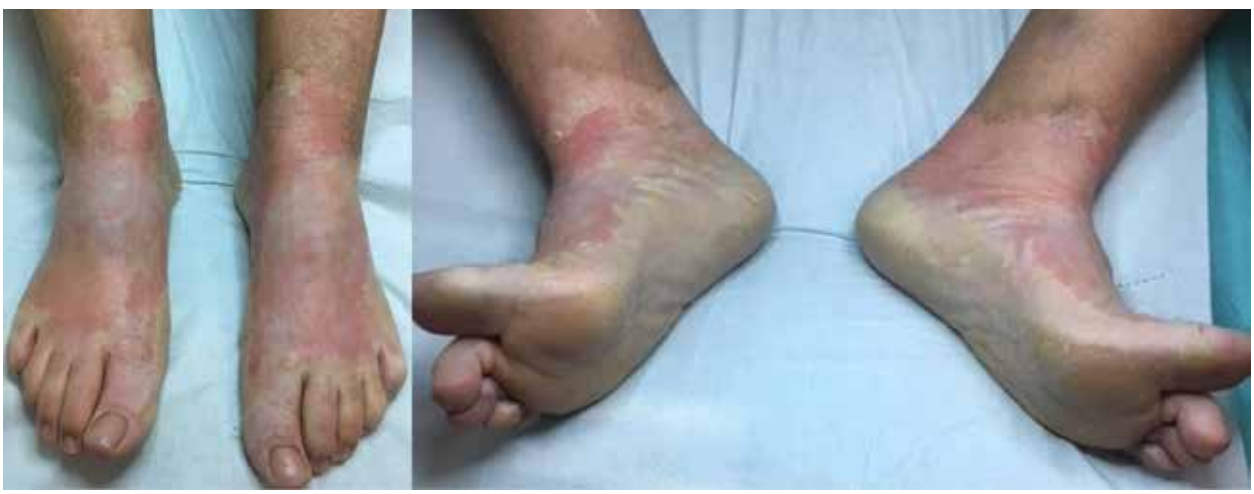

Figure 2: The feet of the brother with exfoliative lesions on the erythematous surface.

Table 1: Clinical features with other previously published cases with CSTA mutation (NM_005213.4)

Reference	Blaydon *et al*, 2011 (two cases)	Krunic *et al*, 2013	Martinz *et al*, 2014	Muttardi *et al*, 2016	Our cases
CSTA mutation	Nonsense mutation: c.256C>T splice-site mutation: c.67–2A>T	Nonsense mutation: c.64A>T	Loss-of-function mutation: c.172C>T	Deletion of exon 1	Missense mutation c.68T>A
Allelic condition	Compound heterozygote	Homozygote	Homozygote	Homozygote	Homozygote
Clinical features of acral peeling	Coarse peeling	Circumscribed peeling	Diffuse hyperkeratosis and circumscribed peeling	Macerated appearance with superficial peeling	Palmoplantar diffuse hyperkeratosis, moderate peeling on the macerated surface
Aggravating factors for peeling	Water and minor trauma	Water, sweating and friction	Water and sweating	Water, sweating and friction	Water and sweating
Associated features	Similar phenotype of dry, scaly skin over most of the body, presenting shortly after birth, and lichenification at ankles.	Dryness and scaling elsewhere	Congenital erythroderma, lichenification of elbows/ankles, palmoplantar hyperhydrosis	Atopic eczema, house dust mite allergy, icthyosis vulgaris, severe hypermetropia	Dryness and scaling

Cystatin A has been associated with house dust mite allergy and atopic eczema. In another study, the patient had atopic dermatitis[4]. However, in our case and other cases, atopic dermatitis was absent. Our patients were clinically consistent with localized APSS. Unlike her brother, skin peeling of our patient was largely prevented by regular skin care and use of moisturizing creams, and avoiding triggering factors.

CONCLUSION

APSS appears to be heterogeneous clinically and genetically. Our case highlights the importance of next-generation sequencing in evaluating rare genodermatoses. We showed that different types of CSTA mutations can also cause APSS. Unlike previously reported cases, this will contribute to better illumination of the phenotype.

ACKNOWLEDGMENT

Author contribution: Selma Emre examined the patient and helped with the diagnosis of the patient; Gulay Gulec Ceylan decided the genetics diagnosis, gave genetic counseling to the patient and the family; Ahmet Cevdet Ceylan analysed the results of next generation sequencing for gene mutations.

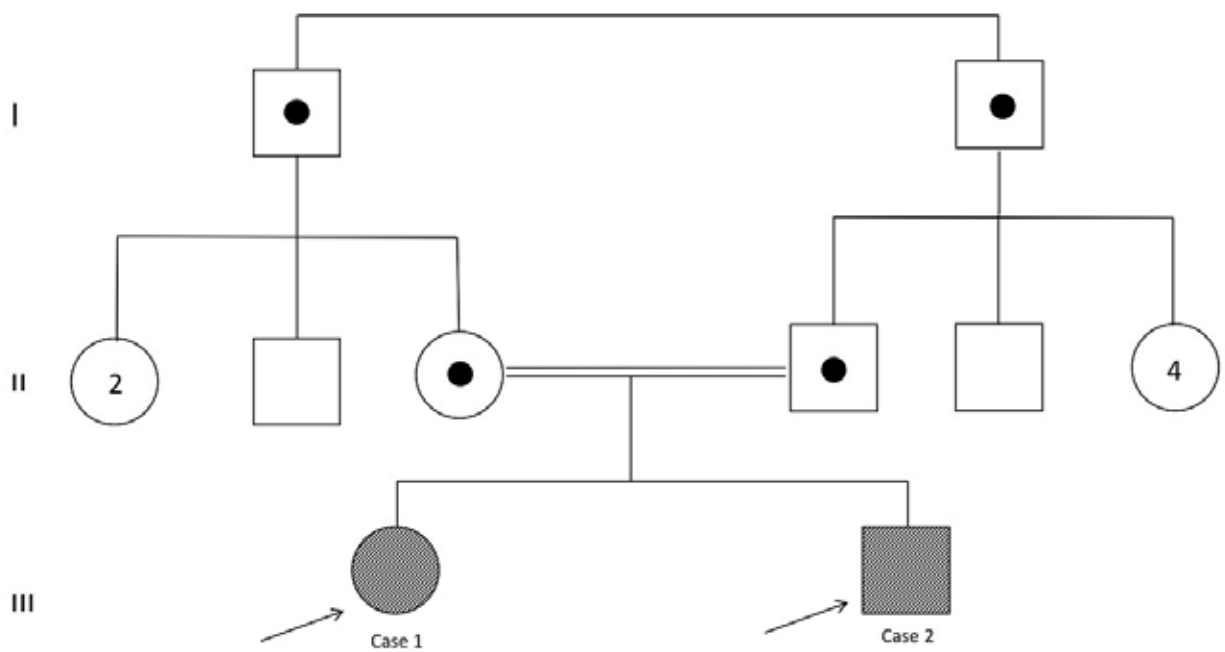

Figure 3: The pedigree of the family.

Conflict of interest: None

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Case Report

An 'aggressive' nasal septal hemangioma

Ng Chong Sian[1], Farah Dayana Zahedi[1,2], Salina Husain[1,2]
[1]Department of Otorhinolaryngology - Head and Neck Surgery, Faculty of Medicine, National University of Malaysia, Kuala Lumpur, Malaysia
[2]Department of Otorhinolaryngology - Head and Neck Surgery, Hospital Canselor Tuanku Muhriz, Kuala Lumpur, Malaysia

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ABSTRACT

Nasal septal hemangiomas are benign vascular tumours which arise from the nasal septum. It is rare and patients usually present with epistaxis and unilateral nasal blockage. Radiological imaging would usually exhibit features of a benign endonasal tumour with local expansion in the absence of bony erosions. Our case is unique as our patient presented with a left nasal mass with local bony destructions, which was initially thought to be an esthesioblastoma.

KEY WORDS: esthesioblastoma, hemangiomas, nasal hemangioma, septal artery

INTRODUCTION

Hemangiomas are benign tumours that account for less than 20% of all benign nasal cavity tumors[1]. It occurs commonly in the skin and mucous membranes and commonly affects the tongue, lips, oral mucosa and gingiva[2,3]. The majority of the cases of haemangioma in the nasal cavity reported in literature showed benign features in radiological imaging with no evidence of bony erosions. Here, we present a unique case of a middle-aged female with left nasal septal hemangioma presented with recurrent epistaxis, nasal blockage and hyposmia, which was initially thought to be an esthesioblastoma due to its radiological imaging findings.

CASE REPORT

A 55-year-old female presented with a history of recurrent epistaxis, progressive unilateral nasal blockage and hyposmia for five years. The episodes of epistaxis were mild and infrequent in the start and progressively worsened over the past four months causing symptomatic anemia requiring blood transfusion. Anterior rhinoscopy of the left nasal cavity revealed a smooth vascular mass located medial to the inferior turbinate (Figure 1). Examination of the right nasal cavity was normal, and there was no evidence of erosion of the mass through the right nasal septum and it did not extend posteriorly into the choanae.

A computed tomography (CT) scan of the paranasal sinuses showed a heterogeneously enhancing mass (Figure 2a and 2b) in the left nasal cavity measuring 3.6x2.7x3.3 cm (APxWxCC) with evidence of destruction of left inferior, middle and superior concha and erosion of the nasal septum medially. There was evidence of destruction of the medial wall of left maxillary sinus. The mass extended superiorly into the olfactory cleft. Radiological impression was an aggressive left sinonasal mass with a differential diagnosis of malignant sinonasal tumour such as esthesioblastoma.

The patient underwent endoscopic sinus surgery, and intraoperatively there was a well-encapsulated, smooth vascular tumor originated from the left posterior septum. It was a pedunculated tumor with a blood supply likely from the posterior septal branch of sphenopalatine artery. The tumor extended anteriorly to the anterior part of middle turbinate, medially nasal septum, laterally to medial maxillary wall and posteriorly to posterior choana. The maxillary ostium was also widened and deviation of the nasal septum was seen due to tumor expansion. The tumor was then excised in total. Histopathological examination

Address correspondence to:
Professor Dr. Salina Husain, M.S. ORL-HNS, MD, Department of Otorhinolaryngology, National University of Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000, Kuala Lumpur, Malaysia. Tel: +60 167775732; E-mail: drsalina_h@yahoo.com

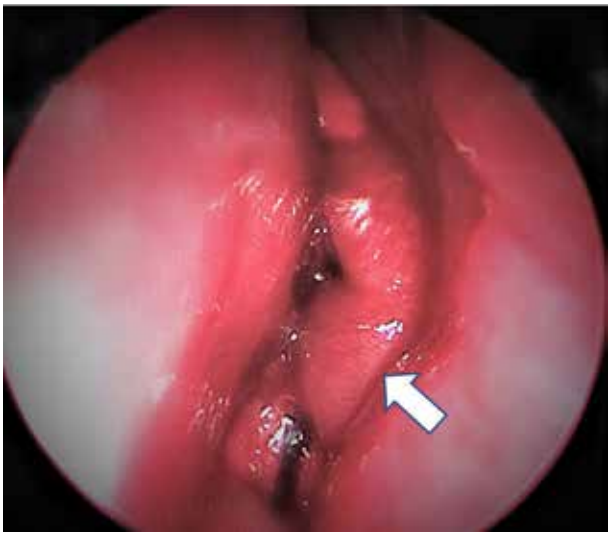

Figure 1: Endoscopic image of the left nasal cavity showed a smooth surfaced mass located medial to the inferior turbinate.

showed fragments of benign fibrovascular tissue with proliferation of multiple thin-walled blood-filled vessels suggestive of a hemangioma.

DISCUSSION

Hemangiomas are benign endothelial tumours arising from the skin and mucous membranes. It is first described by Poncet and Dor in 1897 as human botryomycosis and occurs in all ages, but more often in the middle age and females. In the paediatric population however, it is more common in the males[3]. The gingiva, lips, tongue and buccal mucosa are the most common sites of hemangioma of the head and neck, but it can also occur in the nasal cavity in rare circumstances. Hemangiomas in adults also tend to progressively enlarge and do not usually spontaneously resolve by itself[4]. Therefore, treatment is often needed in adults presenting with hemangioma in the nasal cavity. Due to the rarity of nasal hemangioma, there is only a handful of cases reported worldwide to date.

Patients with hemangioma often present with epistaxis (95%) and nasal obstruction (35%). In rare occasions, rhinorrhoea, facial pain, headache and hyposmia were also present[5]. Endoscopically, the mass is usually unilateral, red or purple associated with or without macroscopic superficial ulceration.

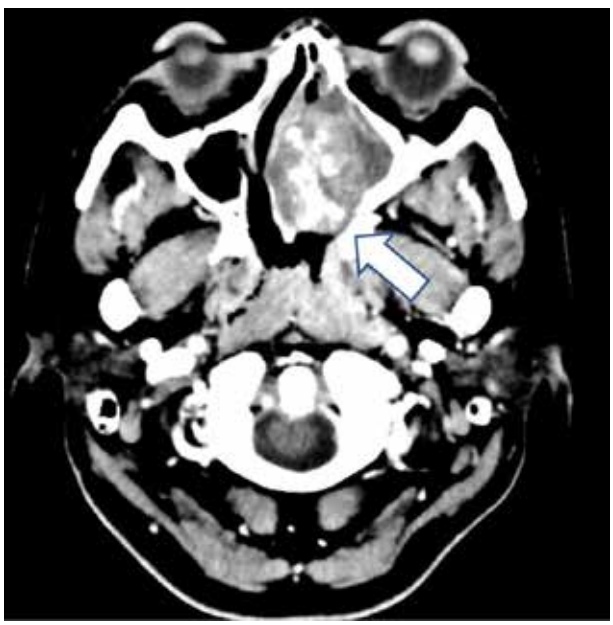

Figure 2a. Axial view of CT image of paranasal sinuses showed a heterogeneously enhancing mass in the left nasal cavity with evidence of destruction of all the turbinates on the left with erosion of the nasal septum medially. There is also evidence of destruction of the medial wall of left maxillary sinus laterally.

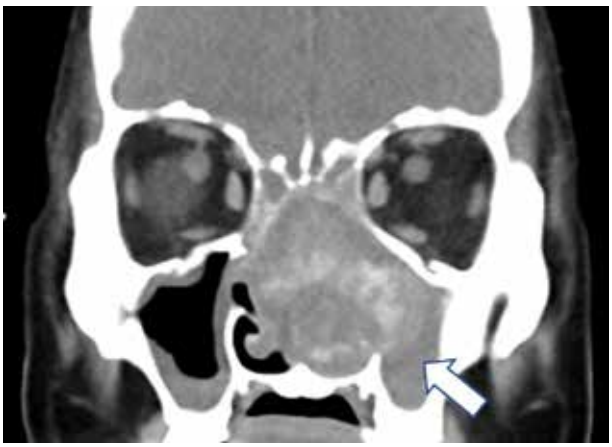

Figure 2b. Coronal view of the paranasal sinuses CT image showed the mass extending superiorly into the olfactory cleft with erosions of all the turbinates and the lateral wall of maxilla, thus giving us the impression of an esthesioblastoma.

Radiological imaging such as CT scan of paranasal sinuses can be performed routinely in patients presenting with a unilateral endonasal mass to look for any evidence of bony erosions which can be a feature of malignancy. Being a benign tumour, nasal hemangiomas rarely cause surrounding bony destructions. There were however a few reported cases of bony erosions caused by nasal hemangioma noted in CT scans, which is rare[6]. Our case is one of the few to report such findings on a CT scan.

Surgical excision is deemed to be the best treatment for nasal hemangioma in adults[5]. Excision of the lesion endoscopically is recommended as it provides good visualization of the mass and its surrounding anatomy, thus reducing the risk of recurrences[6].

CONCLUSION

Nasal hemangiomas should always be at the back of the mind of the treating physician to be one of the differential diagnosis in a patient presenting

with unilateral nasal tumour exhibiting an aggressive behaviour, such as local bony destructions. However, only detailed histopathological examinations can confirm the diagnosis.

ACKNOWLEDGMENT

There is no conflict of interest in this case report. The corresponding author is the operating surgeon for this case and has provided all the relevant data for the write up. She also completed a critical review and participated in the supervision for this case report. The co-author contributed in the literature review and writing of this case report.

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Case Report

Naturally occurring anti-M antibody in a 11-month-old infant with acute pyelonephritis: a case report

Jasmina Grujic[1,2], Nevenka Bujandric[1,2], Zorana Budakov Obradovic[1,2]
[1]Department of Laboratory Diagnostics, Blood Transfusion Institute of Vojvodina, Novi Sad, Serbia
[2]Department of Internal Medicine, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

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ABSTRACT

Anti-M antibody is a relatively common, naturally occurring antibody, a cold reactive and is usually clinically insignificant. Rarely, anti-M antibody can be reactive at 37°C at the antihuman globulin phase (AHG) which can suggest clinical significance.

We present the case of a 11-month-old male first-born child with anti-M antibody who did not have any prior history of a transfusion. The child was admitted to the hospital because of a case of streptococcal acute pyelonephritis and had signs of anemia. The findings were naturally occurring anti-M antibody, which was reactive at 4°C and at 22°C (IgM class) as well as at 37°C at AHG phase (IgG class). The infant's red blood cells were noted as NN.

The antibodies characteristics in this reported case suggested a potential clinical significance of this particular antibody and indicates necessity of careful evaluation of each case of anti-M present so that safe blood can be provided for all patients needing transfusion.

KEY WORDS: anemia, antibodies, Coombs test, pyelonephritis

INTRODUCTION

The MNS antigens are shown mainly on the red blood cell (RBCs) and partly on the renal endothelium and epithelium. The antigens of the MNS blood group are carried on Glycophorins A and B, which are RBC transmembrane single-pass glycoproteins that contain carbohydrate. Glycophorins A and B may also serve as receptors for cytokines and pathogens (bacteria, viruses). The MN determinants are fully developed on fetal RBCs and can be detected as early as during the 9th week of gestation. The MNS blood group system includes 46 antigens[1].

Production and binding of the antibody to the antigen that induces its synthesis are possible a few months upon birth. Naturally occurring antibodies are present in the serum of the healthy individual who has no known exposure to the specific antigen, and was probably induced by exposure to cross-reacting antigens[1].

In general, clinically significant antibodies are those active at 37°C and/or by the indirect antiglobulin test (IAT) in vitro, usually immunoglobulin G (IgG). Clinically significant antibodies are capable of causing adverse occurrence following transfusion, as well as hemolytic disease of the fetus and the newborn (HDFN). Antibodies to the MN blood groups are associated with variable clinical significance. Most anti-M antibodies are naturally occurring immunoglobulin M (IgM), optimally reactive at 4°C and clinically insignificant. Anti-M can rarely be found reactive at 37°C or at anti-human globulin (AHG) phase, IgG class or a combination of both IgG and IgM, having the potential to cause HDFN[2,3]. The prevalence of anti-M in pregnant women ranges from 10 to 14%[4].

CASE REPORT

An 11-month-old male child was hospitalized with the following: a recurrent and high-grade non-specific fever, non-specific dermatitis, left pelvic kidney malrotation and urinary tract infection. Febrile urinary tract infection was defined to be acute pyelonephritis and treated accordingly. Infant had no high blood pressure or reduced kidney function. Peripheral blood smear showed mild hypochromia, anisocytosis

Address correspondence to:
Jasmina Grujic, MD, Department of Laboratory Diagnostics, Blood Transfusion Institute of Vojvodina, Hajduk Veljkova 9A, Novi Sad 21000, Serbia. Tel: +381 641532068; Fax: +381 214877978; E-mail: jasmina.grujic@mf.uns.ac.rs

and poikilocytosis with no signs of RBC's deformity which would indicate membrane defect. Streptococcal (*Streptococcus agalactiae*) acute pyelonephritis was associated with secondary autoimmune hemolytic anemia. Blood test results revealed the signs of anemia: low RBC count of 3,65x10^6 (normal: >3,80 x10^6), hemoglobin of 9 g/dL, hematocrit of 27%, MCV of 81 fL, MCHC of 32 g/dL, reticulocyte count of 3%, indirect bilirubin value of 3.5 mg/dL (normal: <2 mg/dL), LDH of 800 IU/L (normal: <600 IU/L) and decreased haptoglobin levels of 39 mg/dL (normal: >43 mg/dL). Other biochemical analyses were within the normal range. Urine analysis revealed hemoglobinuria and urobilinogen. The young patient did not have any history of a transfusion.

Tests done

Upon finding that the patient has anemia, the antibody screening test was performed to detect the presence of unexpected antibodies. Antepartum record of cord blood testing to ABO blood group and RhD antigen showed that the child has blood group A, RhD-positive. The direct antiglobulin test with polyspecific AHG (IgG and C3d complement components) was negative. Mother's test results were confirmed as A, RhD-positive. Antibody screening of the mother's serum was negative. The passive transfer of antibodies from the mother to the child during pregnancy was excluded.

Forward and reverse complete grouping of the child's freshly collected EDTA-treated venous blood sample was performed using a gel card technique (DiaClon ABO/D+Reverse Grouping, Bio-Rad, DiaMed GmbH, Switzerland). Blood group result is A, RhD-positive, Rh phenotype CcDee, Kell phenotype kk. Iso agglutinin titer, anti-Bwas 2. No discrepancy in the grouping was observed.

Direct antiglobulin test, performed using the gel card technique, was found to be negative with polyspecific AHG (IgG and C3d complement components) and monospecific AHG (anti-IgG1, anti-IgA, anti-IgM, anti-C3c, anti-C3d).

Also, RBC antibody screening was carried out by the gel card technique- IAT using two cell screening panels (BioRad, ID-DiaCell I-II, DiaMed GmbH, Switzerland) on the fully automated immunohematology analyzer (IH-500). IAT was positive (I-, II3+), suggesting IgG class antibody. Antibody screening performed by standard tube technique using 3 cell panels (Reagens Kft, ReaCell I, II, II, Budapest, Hungary) at room temperature (22±2°C) on the immediate spin was positive (I-, II+, III+), suggesting IgM class of antibodies. Antibody screening at low temperatures (4°C) was positive with the same cell panel. Screening performed by standard tube technique using enzyme-treated (papainized) panel cells was negative (I-, II-, III-).

The antibody specificity was determined by the gel card technique using commercial 11 cell RBCs panel (BioRadSet ID-DiaPanel, DiaMed GmbH, Switzerland) at 37°C with AHG. An anti-M antibody was identified. The strength of the reaction was 3+ with homozygous (M+N-) cells and 2+ with heterozygous (M+N+) cells, caused by the antigen dosage effect. Auto control was found to be negative. No other cell panel was needed to exclude other antibodies. Anti-M titer with homozygous (M+N-) cells was 1:4. The child's RBCs were typed as NN and RBC phenotype was therefore confirmed to be M-antigen negative. Six months after the patient's recovery, anti-M antibody titer remained unchanged.

In order to determine the immunoglobulin class of the antibody, the serum was treated with the IgM-reducing agent dithiothreitol prior to performing IAT. The reaction persisted after dithiothreitol treatment, suggesting the presence of an IgG component. Subclass analysis was not performed.

DISCUSSION

We described the case of anti-M RBC antibody in a 11-month-old infant with acute pyelonephritis. As there was no history of transfusion, anti-M detected was labeled as 'naturally occurring'. Anti-M was reactive at both phases of the testing, room temperature and IAT, which is rarely seen. Described antibody characteristics suggested a potential clinical significance of this antibody and the importance of providing antigen-negative blood for this patient. Regarding the fact that Glycophorins A, carriers of M antigen, may also serve as receptors for bacteria and viruses, a child's naturally occurring anti-M was probably induced by the immune defense during acute pyelonephritis.

Others also reported this, as the case of an 18-month-old child with a history of recurring urinary tract infection, where anti-M was detected by an ABO blood grouping discrepancy. Anti-M found in this child was of natural origin, most probably caused by cross-reactivity between RBCs borne structure and microbial infection[2,3].

Our case report confirms the fact that anti-M is a common naturally occurring IgM found in sera of patients who had no exposure to RBCs. Passive transfer of anti-M through transfused blood components or from the mother to the fetus during pregnancy, as well as through lactation, was excluded. Case reports of anti-M at people younger than 10 years of age can be found, but there is no available report about naturally occurring anti-M in an 11-month-old child.

Datta *et al*[4] reported a case of naturally occurring anti-M antibody with IgM and IgG components in a 3-year-old child, who was a hematopoietic stem cell donor for her 6-year-old sister who was M-antigen

positive. As it was a clinically significant antibody, donor received one dose of 'M-antigen' negative, group-specific, leucocyte-reduced, irradiated RBC, while the stem cell recipient received harvested product from a marrow, with the plasma depleted as much as possible, as to reduce the chance of hemolytic transfusion reaction.

Anti-M in the alloimmunized patient population ranges from 2.9% to 13.98%[4]. Anti-M usually occurs as IgM, and it is not considered to be clinically significant, but anti-M can appear as potent IgG that is active at 37°C leading to serious transfusion complications. Therefore, the use of phenotypically matched RBCs in these patients will increase transfusion safety[5]. Even more, anti-M can cause HDFN of varying severity leading to intrauterine death or the necessity for an exchange transfusion[6-10]. Clinically insignificant anti-M in high titer can react at room temperature and also at 37°C or the AHG phase. Anti-M antibodies with higher thermal range considered to be clinically insignificant can also cause hemolysis in patients with induced hypothermia, which is common in certain types of surgery[11].

While assessing the clinical significance of anti-M antibodies, it is important to determine the immunoglobulin class of anti-M and the interpretation should be done with great caution. Due to potential clinical significance of the antibody described in this case, where the antibody was reactive at 22°C and 37°C, it was recommended that the antigen-negative units of RBCs be selected for a transfusion.

CONCLUSION

The antibodies characteristics in this reported case suggested a potential clinical significance of this particular antibody and indicate necessity of carefully evaluation of each case of anti-M present so that safe blood can be provided for all patients needing transfusion.

ACKNOWLEDGMENT

Contributors: Jasmina Grujic and Nevenka Bujandric contributed to diagnosis and management of the case and drafted initial manuscript; Jasmina Grujic and Zorana Budakov Obradovic contributed to manuscript writing and critical inputs into case management; Nevenka Bujandric reviewed and revised the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

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Competing interest: None

Ethics committee approval: The Ethics Committee of the Blood Transfusion Institute of Vojvodina approved study on 29th April 2020, number of the clearance from the committee is: 15/2020.

Consent: Written informed consent was taken from the family for publication of clinical details of the patients.

Availability of data and materials: The datasets used and analyses during the current study are available from the corresponding author on reasonable request.

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Case Report

Spontaneous splenic rupture in a positive COVID-19 patient: case report

Abdulla Qasem, Alia Al-Dhubaib, Emad Aziz Eldien Habib
Department of Surgery, Al-Sabah Hospital, Kuwait

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ABSTRACT

Splenic rupture is often associated with chest or abdominal trauma. Spontaneous splenic rupture is very rare and is usually reported as being secondary to underlying pathological conditions, such as haematological, neoplastic, infectious and inflammatory diseases.

A 43-year-old male presented to the surgical department of Al-Sabah hospital with sever epigastric pain of one day duration. Patient gave history of COVID-19 infection two months back and was admitted as a case of acute surgical abdomen. He underwent diagnostic laparoscopy and then open laparotomy with total splenectomy for spontaneous splenic rupture. The admission PCR result for COVID-19 infection was positive.

The relationship between COVID-19 infection and spontaneous rupture of spleen is strongly suggested in this case. Hence, spontaneous splenic rupture should be considered in the differential diagnosis of patients presenting with acute abdominal pain and having present or past history of COVID-19 infection. We report the first case of spontaneous splenic rupture in Kuwait due to COVID-19 infection.

KEY WORDS: case report, COVID-19, spleen, surgery

INTRODUCTION

Splenic rupture is a potentially life-threatening condition, and the majority of cases are secondary to trauma. Underlying splenic pathologies have also been associated with splenic rupture, including haematological, neoplastic, inflammatory and infectious conditions. Atraumatic splenic rupture rarely occurs[1]. The first reported cases of atraumatic splenic rupture were by Rokitansky and Atkinson. Weidemann first defined 'spontaneous splenic rupture' as 'rupture resulting from an incident without external force.' Knoblish distinguished 'non-traumatic rupture of a pathological spleen' from the extremely rare 'non-traumatic splenic rupture of unknown etiology', *i.e.*, true 'spontaneous splenic rupture'[2].

CASE REPORT

A 43-year-old male presented to the surgical causality of Al-Sabah hospital on January 25, 2021 with a one-day history of sudden-onset of severe agonizing abdominal pain, which is mainly epigastric and radiating to all abdomen and left shoulder. The pain was associated with nausea and fatigue. Patient did not complain of cough or dyspnea.

The patient was not known to have any chronic medical illness or any history of surgical operations. There was no history of any major or minor trauma. Patient gave history of positive COVID-19 infection two months back, for which he was quarantined at home for one week. There was no history of anticoagulants, antiplatelets or NSAIDs intake.

On examination, the patient was in severe pain and laying semi sitting position in bed. The vital signs of the patient were as follow; afebrile with a temperature 37.2 °C, tachycardia at rate of 110 bpm, 110/80 mmHg blood pressure and 97% saturation on room air. On abdominal palpation, he was found to have marked tenderness and guarding all over the abdomen, mainly epigastric area, with rebound tenderness and board like rigidity, bowel sounds very sluggish. Chest X-ray showed no air under diaphragm.

Address correspondence to:
Dr. Emad Aziz Eldien Habib, Hawally, block 10, Street 217, Kuwait. Tel. +965 99300349; E-mail: emadaziz197386@gmail.com

Fig. 1: Subpherinic and perisplenic hemoperitoneum

Initial blood investigations were white blood cell count of 18 x 10^9 /L, haemoglobin of 11.5 g/dL, platelet count of 260 x 10^9 /L, creatinine of 95 umol/ L and INR of 1.04.

Patient underwent diagnostic laparoscopy. The operative findings indicated a diffuse hemoperitoneum (estimated volume 1300-1500 ml) (Fig 1) with deep cavitational lesion in the upper/mid pole of the spleen oozing fresh blood (Fig 2 a,b). As the patient became unstable, the procedure was converted to open laparotomy, and total splenectomy was performed in the standard manner.

The admission PCR result for COVID-19 infection was positive. Investigations to rule out infectious mononucleosis, typhoid, malaria, systemic lupus erythematosus and tuberculosis were negative. Histopathology examination showed normal sized spleen with fibro-congestive spleen with large areas of haemorrhage and fibrin deposition consistent with spontaneous splenic rupture.

Patient was discharged after two weeks with appropriate post-splenectomy antibiotic prophylaxis and immunizations.

DISCUSSION

COVID-19 infection is a novel disease caused by the severe acute respiratory coronavirus (SARS-CoV-2), which has been declared a pandemic by the World Health Organization on March 11, 2020.

COVID-19 affects not only the respiratory system but also other vital organs in the body, such as the kidneys and the liver[3]. A metallopeptidase named angiotensin-converting enzyme 2 (ACE2) has been identified as the functional receptor for SARS-CoV. ACE2 is present in arterial and venous endothelial cells and arterial smooth muscle cells in all organs. The spike glycoprotein (S protein) of SARS-CoV-2 can damage vascular endothelial cells by downregulating ACE2 and consequently leading to endotheliitis[4].

There are several causes for atraumatic splenic rupture including infectious causes, blood and metabolic diseases and pathophysiological disorders[5]. Most splenic rupture occurs in the acute phase of infectious causes[5]. In people undergoing haemodialysis and receiving heparin, non-traumatic rupture of the spleen has been reported because the oedema of the spleen causes a hematoma under the splenic capsule. In people who are under treatment

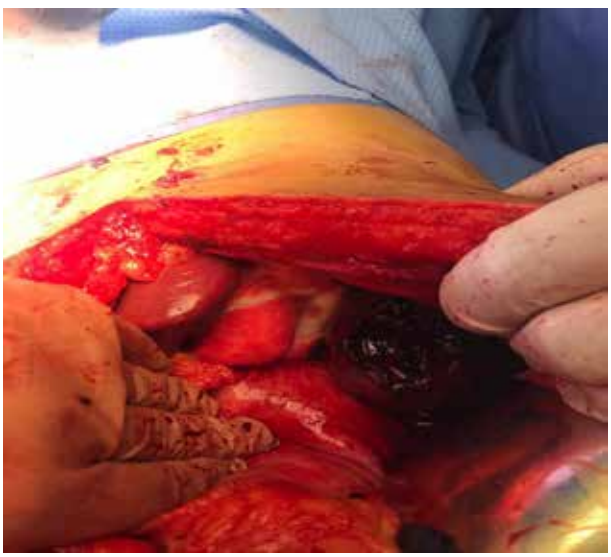

Fig. 2 a-b: Deep cavitational lesion seen at upper/mid pole oozing fresh blood from within the cavity.

with thrombolytic drugs or taking anticoagulant drugs, a disturbance in the mechanism of homeostasis causes splenic rupture due to minor trauma[6].

There is emerging evidence suggesting that COVID-19 virus has a direct impact on the spleen and lymph nodes inducing severe tissue damage with lymphoid follicle depletion, splenic nodule atrophy, histiocytic hyperplasia and lymphocyte reduction. In addition, COVID-19 is reported to induce micro vascular thrombosis and necrosis of the spleen that leads to severe tissue damage[7].

CONCLUSION

Although we are unable to provide direct histological evidence, the trajectory of illness and lack of any other underlying pathology are highly suggestive of a potential role of COVID-19 in the pathogenesis of splenic rupture in the present case. This issue necessitates further investigations and waiting for similar reports.

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Short Communication

Nocardia, hydrocarbons and dust storms: A public health perspective

Ziauddin Khan, Abu Salim Mustafa
Department of Microbiology, Faculty of Medicine, Kuwait University, Safat, Kuwait

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ABSTRACT

The organisms of genus *Nocardia* are aerobic filamentous bacteria that are widely prevalent in soil and can cause opportunistic infections. These are facultative intracellular pathogens and infect primarily the lungs and brains of immunocompromised patients leading to fatal consequences. The incidence of infections caused by *Nocardia* is rising throughout the world. Hence, there is a need to better understand this pathogen and its interaction with humans leading to disease and death.

KEW WORDS: *Nocardia*, occurrence in soil, pathogenesis

INTRODUCTION

The genus *Nocardia* comprises Gram-positive, weakly acid-fast, aerobic filamentous bacteria widely prevalent in soil and other substrates. It has the ability to utilize hydrocarbons as an energy source. Nocardiae can cause cutaneous, subcutaneous and systemic infections both in immunocompetent and immunodeficient individuals[1-2]. The clinical presentations of *Nocardia* infections are quite variable depending upon the immunological status of the host and predilection of certain species to cause a particular type of infection[2,3]. Pulmonary and systemic nocardiosis are acquired through respiratory route, thus soil contaminated with pathogenic nocardiae is a primary source of infection. Pulmonary and cerebral infections are characterized by abscess formation (Fig 1: Left), and diagnosis is made by demonstrating Gram-positive branching filaments (Fig 1: Right). Repeated environmental exposure to *Nocardia* can lead to development of cell-mediated immunity, thus facilitating its removal from respiratory tract through activated macrophages and by lymphocyte-mediated killing[4].

Nocardia in soil

Most studies determining occurrence of *Nocardia* species in soil were carried out in the context of local epidemiology of mycetoma[5], and their distribution has been reported to be quite variable in different geographic regions[6]. Generally, *N. asteroides* is reported to be more common in temperate regions of the world, whereas *N. brasiliensis* is more frequent in tropical and subtropical regions[7]. Most of the early studies used paraffin bait or other modifications of this technique to isolate nocardiae from soil because of their selective ability to utilize hydrocarbons as energy requirements[8], and the technique was also used for isolating nocardiae from clinical specimens[9].

A few studies carried out in Middle East revealed that occurrence of *Nocardia* in soil is not uncommon. In Qazvin province of Iran, 96 (32%) of 300 soil samples were positive for aerobic actinomycetes spp. and the relative prevalence of *Nocardia* species was *N. asteroids* complex isolates (15.6%), followed by *N. otiisdiscaviarum* (9.4%%), *N. brasiliensis* 7.3% and *N. transvalensis* (3.1%)[10]. In a subsequent study carried out in Isfahan province, 153 (19.15%) of 800 soil samples were positive for *Nocardia* spp., predominant among them were *N. asteroides* complex isolates (45.5%), followed by *N. brasiliensis* (24.7%), *N. otiisdiscaviarum* (2.2%), and *N. transvalensis* (1.1%)[11]. All these *Nocardia* species are known human pathogens.

Address correspondence to:
Prof. Abu Salim Mustafa, Department of Microbiology, Faculty of Medicine, Kuwait University, Safat, P. O. Box 24923, Kuwait. E-mail: abusalim@hsc.edu.kw

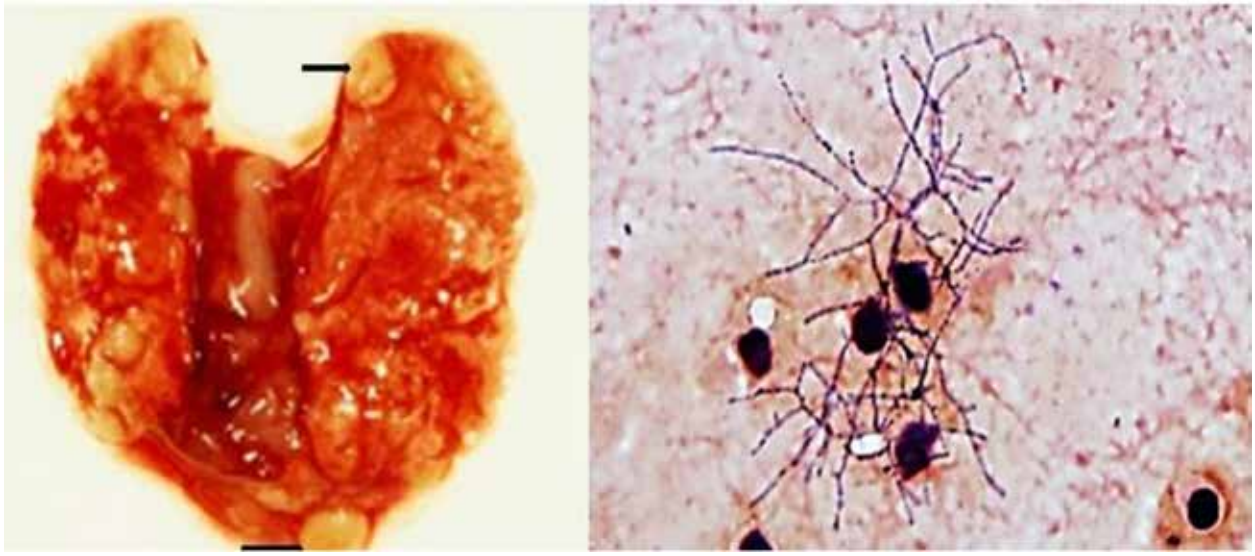

Figure 1: Left: Multiple abscesses in the lung of a normal BALB/c mouse following intravenously inoculation of a soil isolate of *N. asteroids*. **Right:** Gram-stained smear from the lung abscess showing thin branched filaments with beaded appearance.

In Kuwait, prompted by the crude oil contamination of soil during Gulf war, we carried out a study to determine the prevalence of *Nocardia* in soil[12]. Using paraffin bait technique, 42 of 102 (41%) soil/sand samples were positive for *N. asteroides* species (Fig. 2)[12]. Two of the previously identified as *N. asteroides* isolates were later characterized by molecular analysis as *N. ignorata*[13] and *N. coubleae*[14]. There remains a strong possibility that presence of hydrocarbon traces in soil can be a factor in promoting population density of *Nocardia*. Recently, a strain of *N. cyriacigeorgica* (a new name of *N. asteroides* complex antimicrobial susceptibility pattern type VI) isolated from oil-polluted sand samples from Saudi Arabia demonstrated ability to degrade oil or petroleum products[15]. This finding has a significant public health implication because of the emerging role of this species in human nocardiosis in many countries[16], including Kuwait, where 4 of the 5 clinical isolates were identified as *N. cyriacigeorgica* (unpublished). Predominance of *N. cyriacigeorgica* was also supported by molecular analysis of samples collected from 30 hospitals in Isfahan, Iran, posing a potential public health hazard[17].

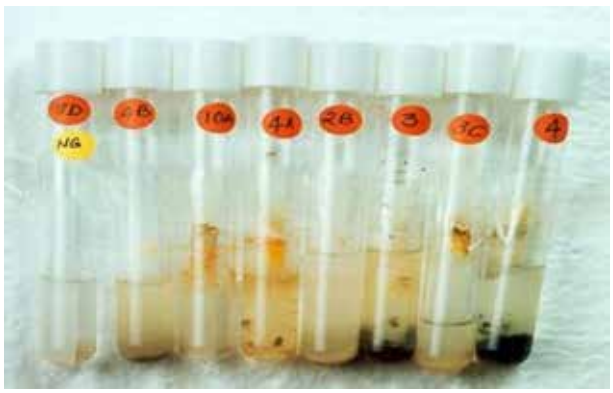

Figure 2: Isolation of *Nocardia asteroides* from soil samples by paraffin bait technique. Glass rods coated with paraffin wax showing yellowish growth of *N. asteroides* (blackish sediment is due to crude oil contamination).

Since *Nocardia* is a soil-borne pathogen and the Kuwait-Iraq area is prone to frequent dust storms, the public health impact of this association remains unknown. It is estimated that 0.5 to 5 billion tons of desert topsoil is displaced annually due to high-wind storms globally[18] and the arid areas of Kuwait and Iraq are the largest sources of airborne dust on the earth[19]. It is unclear up to what extent inhalation of fine dust particles and/or pathogens living in topsoil are responsible for various respiratory disorders described as "desert lung syndrome", "desert storm pneumonitis" or "severe acute pneumonitis" before and after Operation Desert Storm in 1991[20]. So far, the precise cause of this illness characterized by diverse neurological and non-neurological manifestations remained elusive[21].

Nocardia pathogenesis

The mechanisms of *Nocardia* pathogenesis are multiple and complex and have not yet been fully elucidated. Based on animal studies, virulence appears to be associated with stage of nocardial culture, ability to inhibit phagosome-lysosome fusion, neutralization of phagosomal acidification, ability to resist oxidative killing mechanisms of phagocytes and ability to invade and grow within the brain cells[4]. While immunosuppressed patients are the principal target of *Nocardia* infection, one-third of the affected individuals may not have any apparent immunodeficiency[22]. Following primary lung infection, the central nervous

system is the most common extrapulmonary site for nocardiosis[4]. Not all *Nocardia* species/strains have similar propensity to invade brain[3]. Whether some strains have a greater potential to induce neurodegenerative changes leading to movement disorders is a matter of further research[23]. Experimental studies have demonstrated that L-forms of nocardiae can be induced and persist in the host for long periods and possibly play a role in pathogenesis and recurrence even after successful therapy[4]. Not only did these L-forms play a role in persistence and pathogenesis, but mice that survived the initial acute phase of infection developed progressive neurologic signs accompanied with vertical bobbing of the head[4]. There is also evidence to show that *N. asteroides* grows preferentially in some specific areas of the brain, such as substantia nigra, which is more conducive in inducing L-dopa responsive movements following intravenous inoculation in mice[4]. Neuroinvasive strains of *Nocardia* have been described that can cause apoptosis of dopaminergic neurons of the substantia nigra causing L-DOPA-responsive movements in mice resembling Parkinsonism[24]. Apoptosis of dopaminergic neurons is also one of the findings seen in patients with Parkinson's disease. However, Loeffler *et al* suggested that release of protease-resistant, low molecular weight substance during growth of *N. asteroides* strain GUH-2 in culture has shown dopamine depleting activity in rat pheochromocytoma PC2 cells and thus it may be another mechanism for these symptoms[25]. Further studies have revealed presence of filterable forms, characterized by granules-containing spherical structures of *Nocardia* in paraffin-containing broth cultures[26]. Interestingly, acid-fast, lipochrome bodies, like filterable nocardiae have also been seen in glial cells of the midbrain nigral lesions found in Parkinson's disease[26].

In a recent study in mouse model using *N. farcinica*, infections with *Nocardia* led to neurological symptoms, and 15/22 *N. farcinica* clinical strains could cause Parkinson diseases-like symptoms[27]. Furthermore, *Nocardia* infection activated microglia caused M1 microglial polarization, promoted production of iNOS and CXCL-10, and caused neuroinflammation in the substantia nigra, all of which may be involved in causing Parkinson disease-like symptoms[27]. In addition, the study identified the gene *nbtS* as pathologic because deletion of this gene in *N. farcinica* completely attenuated the neurological symptoms[27].

CONCLUSION

Nocardiae are soil-borne, hydrocarbon-utilizing pathogens, widely inhaled by population at large and eventually settling in the lungs. They can survive intracellularly by inhibiting phagosomes-lysosomes fusion and can be carried by the macrophages across the blood-brain barrier causing central nervous system infection. The transformation into non-cultivable L-forms or other filterable propagules and latency are characteristic features, however, their precise role in nocardial pathogenesis remains elusive. Epidemiological proof that patients with nocardiosis or those exposed to higher environmental concentrations of nocardiae have greater prevalence of Parkinson's disease or movement disorders is also lacking. Nonetheless, there is a view that Parkinson's disease may have an infectious etiology[23,28]. With the availability of modern molecular technologies, it should be possible to clarify enigmatic issues that may be linked to the pathogenesis of nocardiosis with possible public health implications.

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Letter to the Editor

The leave cycle among healthcare inspectors working in Preventive Medicine Department: A letter to editor

Eiman Khesroh, Yasmine Alaa El Dien
Preventive Medicine Department, Faiha Clinic, Al-Asima Governance, Kuwait

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Dear Editor,

The department of preventive medicine is composed of multidisciplinary teams who collectively work together to accomplish a set of tasks. The team-based dynamic, which includes physicians, nurses and inspectors' centers around a holistic approach to ensure proper communication and coordination among team members that facilitate seamless delivery of preventive medicine services.

Following a two-year law of denied leaves for healthcare providers, the resume of pre-COVID-19 pandemic workstyle has contributed in allowing healthcare providers to freely use their leaves. According to leave regulations enforced by the ministry of health of Kuwait, a healthcare provider is eligible to apply for annual leave that does not exceed 90 days/year, have four of one-day incident leave/year, 15 days sick leave/year, and 12 hours permission/month which are commonly divided into four permissions per month not exceeding 3 hours each[1]. Further, the law has been structured in a way that allows a healthcare provider to loophole any number of days taken extra to the 15 sick leave days provided by the ministry and switch them to annual leave[1]. The switch of leave types from sick leave to annual leave requires no more than a visit to the leave department within 60 days of issuing sick leave for an instant switch. This law is, to a considerable extent, encouraging a number of healthcare providers to exploit the system.

Absenteeism is noted to be a ubiquitous problem, especially in polyclinics, despite the measures and strategies that have been placed to regulate absence rate by the department of preventive medicine. Part of the factors contributing to absenteeism were reported to be due to family responsibilities, stressors in job environment, commuting issues and lack of incentives. However, when absenteeism becomes an employee habitual behavior, it inflicts contagious attitude among workers leading to engenderment of inferior quality and inefficiency of the services being delivered[2,3].

To investigate further on the issue, we marked our final record to be in January 2023 following a track of leave types utilized by inspectors in year 2022 in one of the primary care centers located in al Asimah area in Kuwait. The materials used to record types of leaves taken and excuses were counted using a departmental chat group on WhatsApp and matched it with official documents signed by the attending physician. Using Microsoft words table, we were able to lay out the switch from sick leave to annual leave during 2022 for the ten inspectors without listing the actual diagnosis for which the sick leave was granted. The reason behind the unavailability of sick leave cause is lack of awareness from physicians' behalf on the intention of switching leave types as this tactic was never introduced to physicians' attention before. In Table 1, six out of nine working inspectors switched exceeding days from sick leave to annual leave. The number of days switched ranged from 2-39 days. One inspector was excluded as she was granted a leave from a medical board and further extended the leave to maternity leave and was therefore excluded from this study. Another inspector was also on leave from a medical board, however the leave was initiated in August 2022. Only three inspectors didn't exceed the 15 days sick leave limit and hence didn't require to switch. Table 1 also shows that six healthcare inspectors exhausted the 4 one-day incident leave and two consumed three days of that leave type.

During January 2023, healthcare inspectors were documented to misuse their sick and incident leaves along with permissions disregarding work demands.

Address correspondence to:
Eiman Khesroh, MBBS DrPH, Department of Preventive Medicine, Ministry of Health of Kuwait. Tel: 22545535; E-mail: malacitetree@yahoo.com

Table 1: The number of days of different leave types taken by each inspector and the number of days switched from sick leave to annual leave.

Inspector	Annual before switch	Annual after switch	Sick before switch	Sick after switch	Before-after	Incident
Insp1	24	47	31	8	23	4
Insp2	62	62	0	0	0	0
Insp3	47	86	48	9	39	3
Insp4	27	33	21	15	6	4
Insp5	70	72	17	15	2	4
Insp6	27	27	3	3	0	4
Insp7	60	66	18	12	6	4
Insp8	27	27	11	14	-	4
Insp9	97	97	2	4	-	4
Insp10	39	162	20	15	5	3

Table 2 shows that on more than 10 days of the month, the percentage of absence surpassed 20% of total attendees. Only two days of the month of January were attended by all inspectors not being on annual leave. The different types of leaves were interchangeably used during the month by healthcare inspectors. Similar trends have been documented in previous months of the year 2022 and perceived as a common issue.

Healthcare inspectors play an integral role in healthcare organizations and the community covered by each organization. In most instances, each inspector is assigned a certain task to be completed within a month. Different tasks are rotated among inspectors to expose them to the diverse services provided by the department. A table including the names of the inspectors and tasks in each month is usually created earlier in the year to emphasize organized work among inspectors. Those who are newly joined or lack exposure were sent on a mission with a more experienced inspector for teaching and supervision.

On days when the attendance rate was nearly 50%, an extra load was placed on the ones already present at work to carry out the duty of the absent colleague. Moreover, an extra load is placed on the ones asked to substitute their colleague for taking a sick leave during the on call. Also, there were reportedly delays in turning statistics to the public health office. The high frequency of absences among inspectors has ignited a sense of tension and emotional exhaustion. This tension injured teamwork spirit and disconnected proper communication among inspectors. Our findings come in parallel with the findings of the studies conducted by Tweheyo *et al* and Kisakye *et al*[4,5].

The leave and permission regulations executed by the ministry of health have secured the right of the employee to use sick leave without the need of head of department approval, except for annual leave, incident leave and permissions. With the switch of leave types from sick leave to annual leave, it permitted the employee to take indirect annual leave without the need for head of department approval. This tactic

Table 2: Different types of leaves used by healthcare inspector during January 2023. Each color represents an inspector use of leaves.

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

● Permission ■ Incident ♥ Sick Leave — Annual Leave

made it hard for the head of department to control the number of employees on leave. It additionally incorporated an element of eligibility injustice towards excellence job rewards when it equates both healthcare inspectors who switched leave types and maintained sick leave days within the 15 days limit, and those who were meticulous regarding their duties and attendance. The latter instigated a sense of lack of appreciation and recognition, which in turn led to frequent disputes and loss of motivation.

We conclude that absenteeism in healthcare organizations has greater impact compelled by the nature of services delivered to the patients and community. In order to achieve maximum efficiency and productivity, the law pertaining to permitting healthcare workers to switch leaves needs reevaluation. Otherwise, a further investigation would be worthwhile as to why healthcare inspectors seek that many days of sick leave to ensure the well-being of healthcare inspectors.

ACKNOWLEDGMENT

Ethics Approval: This study has been reviewed and approved by the Ministry of Health of Kuwait Institutional Review Board: 2023/2313.

Source of Support: Preventive Medicine Office.

Disclaimers: None.

Conflict of Interests: The authors declare that they have no conflict of interests.

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Letter to the Editor

Should we recommend balloon desobstruction treatment?

Serdar Kalemci[1], Huriye Gulistan Bozdag[2], Arife Zeybek[2]
[1]Department of Anesthesia, Kocaeli University of Health and Technology, European Vocational School, Kocaeli, Turkey
[2]Mugla Sitki Kocman University Medical School, Department of Chest Surgery, Mugla, Turkey

Kuwait Medical Journal 2023; 55 (3): 255

Dear Editor,

There are new developments in the diagnosis and treatment of chronic obstructive pulmonary disease (COPD)[1,2]. Coils and endobronchial valves are promising interventional treatments in emphysematous type COPD[3]. Balloon desobstruction treatment (Rezektor Balon, Istanbul, Turkey) is widely used in chronic bronchitis type COPD in Turkey. The device consists of a latex balloon covered with a mesh structure of 0.2-mm polyurethane/lycra fibres, mounted onto the distal end of long single-lumen polyethylene tube. The maximum inflated diameter of the balloon is 10–24 mm and can reach 8-3 mm bronchi. The balloon is inserted into the narrowed bronchial lumen and repeatedly inflated and deflated, resulting in a force applied to the bronchial mucosa of 2.0-2.5 bar, mechanically disrupting the hyperplasic goblet cells. The treatment is performed in a single session, and in total 100-300 segmental bronchi could be treated during a 60-min bronchoscopy[4].

SpO_2 levels, lung function tests and symptoms improved in 188 stage III-IV COPD patients who received maximal therapy over 5 years[4]. There were no intraoperative, perioperative and post-operative complications. Clinical outcomes were evaluated one month after treatment. First pilot study was performed including 10 patients[5]. There are no studies in the literature about this topic. We could not find ongoing or planned trials on the trial registration websites. Further clinical studies are required. It is also an expensive treatment method. As a result, we do not know the effect of balloon desobstruction treatment clearly.

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Address correspondence to:
Prof. Dr. Serdar Kalemci, Yenioy Merkez, Ilıca Cd. No:29, Başiskele/Kocaeli, Postal code: 41275, Turkey. Tel: +90 5079845193; +90 5019845193; E-mail: skalemci79@gmail.com

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2023; 55 (3): 256 - 258

Uncommon fundus presentation of Koolen-De Vries Syndrome in a young boy

Hamad Alomairah [1], Abdullah Ali [1], Rabeah Altemaimi [2], Talal Alabduljalil [3]
[1]Al Bahar Eye Center, Ibn Sina Hospital, Kuwait.
[2]Human Genetics Unit, Department of Pathology, Faculty of Medicine, Kuwait University, Kuwait.
[3]Department of Surgery, Faculty of Medicine, Kuwait University, Kuwait.

Ophthalmic Genet. 2023 Aug 2;1-3. doi: 10.1080/13816810.2023.2237573. Online ahead of print.

INTRODUCTION
Koleen-De Vries syndrome (KDVS) is a rare genetic condition characterized by typical facial features, intellectual disability, cardiac and renal diseases, and ophthalmic manifestations. The syndrome is known to be caused by a microdeletion in the 17q21.31 region, involving multiple genes, including the KANSL1 gene.

CASE PRESENTATION
We present the case of a 9-year-old boy with no family history of ophthalmic syndromes. The patient exhibited bilateral hypopigmented iris and unilateral choroidal and retinal pigment epithelium (RPE) hypopigmentation.

DISCUSSION
The presence of ophthalmic manifestations, such as bilateral hypopigmented iris and unilateral choroidal and RPE hypopigmentation, in a patient with KDVS adds to the clinical spectrum of this syndrome. Although the exact mechanism underlying these ocular findings is not yet fully understood, the microdeletion in the 17q21.31 region, which includes the KANSL1 gene, is likely to play a role.

CONCLUSION
This case highlights the importance of considering ophthalmic manifestations in individuals diagnosed with Koleen-De Vries syndrome. Further research is needed to better understand the pathogenesis and clinical implications of these ocular findings.

Does the severity of untreated dental caries of preschool children influence the oral health-related quality of life?

A Alanzi [1], F Husain [2], H Husain [3], A Hanif [2], J K Baskaradoss [2]
[1]College of Dentistry, Kuwait University, Jabriya, Kuwait. abrar.alanzi@ku.edu.kw.
[2]College of Dentistry, Kuwait University, Jabriya, Kuwait.
[3]Ministry of Health, Kuwait City, Kuwait.

BMC Oral Health. 2023 Aug 10;23(1):552. doi: 10.1186/s12903-023-03274-7.

AIM
To assess the impact of untreated dental caries and its severity on the oral health-related quality of life (OHRQoL) of Kuwaiti preschool children and their caregivers.

METHODS
Participants were 4- and 5-year-old kindergarten children attending preselected public schools from one of the Governorates in Kuwait. Early childhood caries (ECC) was evaluated by clinical examinations and presented using decayed, missed, filled teeth/surface (dmft/dmfs). The clinical consequences of untreated dental caries were assessed using the pufa (pulp, ulcers, fistula, abscess) index for primary teeth. A structured questionnaire obtained demographic information of children and their caregivers. OHRQoL was assessed using the Arabic version of Early Childhood Oral Health Impact Scale (A-ECOHIS).

RESULTS
Among the 334 participants, 171 were kindergarten level-1 (KG1), and 163 were level-2 (KG2). The overall prevalence of dental caries was 78.9% for KG1 children and 67.4% for KG2 children. Decayed teeth were the main component for both dmft (84%) and dmfs (68%). The total mean (SD) pufa score was 0.54 (1.5), and about 19.2% of participants had at least one tooth with pufa > 0. A total of 207 A-ECOHIS were completed. Both family and child impact scores were significantly higher for children with a dmft score of 1 or more ($p < 0.001$) or with one or more pufa ($p < 0.001$). Child impact section scores were significantly higher with the increasing degrees of untreated caries (dt) ($p = 0.004$).

CONCLUSION
The severity of untreated dental caries and caries experience had a negative impact on the OHRQoL of Kuwaiti preschool children and their families. Using the pufa index had provided additional information about the effect of the caries severity on the OHRQoL than assessing the caries experience alone.

The impact of applying various de novo assembly and correction tools on the identification of genome characterization, drug resistance, and virulence factors of clinical isolates using ONT sequencing

Hussain A Safar [1], Fatemah Alatar [2], Kother Nasser [2], Rehab Al-Ajmi [3], Wadha Alfouzan [3 4], Abu Salim Mustafa [5]
[1]OMICS Research Unit, Health Science Centre, Kuwait University, Hawalli Governorate, Kuwait.
[2]Serology and Molecular Microbiology Reference Laboratory, Mubarak Al-Kabeer Hospital, Ministry of Health, Hawalli Governorate, Kuwait.
[3]Department of Microbiology, Faculty of Medicine, Kuwait University, Hawalli Governorate, Kuwait.
[4]Microbiology Unit, Farwaniya Hospital, Ministry of Health, Al Farwaniyah Governorate, Kuwait.
[5]Department of Microbiology, Faculty of Medicine, Kuwait University, Hawalli Governorate, Kuwait. abu.mustafa@ku.edu.kw.

BMC Biotechnol. 2023 Jul 31;23(1):26. doi: 10.1186/s12896-023-00797-3.

Oxford Nanopore sequencing technology (ONT) is currently widely used due to its affordability, simplicity, and reliability. Despite the advantage ONT has over next-generation sequencing in detecting resistance genes in mobile genetic elements, its relatively high error rate (10-15%) is still a deterrent. Several bioinformatic tools are freely available for raw data processing and obtaining complete and more accurate genome assemblies. In this study, we evaluated the impact of using mix-and-matched read assembly (Flye, Canu, Wtdbg2, and NECAT) and read correction (Medaka, NextPolish, and Racon) tools in generating complete and accurate genome assemblies, and downstream genomic analysis of nine clinical Escherichia coli isolates. Flye and Canu assemblers were the most robust in genome assembly, and Medaka and Racon correction tools significantly improved assembly parameters. Flye functioned well in pan-genome analysis, while Medaka increased the number of core genes detected. Flye, Canu, and NECAT assembler functioned well in detecting antimicrobial resistance genes (AMR), while Wtdbg2 required correction tools for better detection. Flye was the best assembler for detecting and locating both virulence and AMR genes (i.e., chromosomal vs. plasmid). This study provides insight into the performance of several read assembly and read correction tools for analyzing ONT sequencing reads for clinical isolates.

Circular external fixation for revision of failed tibia internal fixation

Yousef Marwan [1], Jeffrey Turner [2], Rahul Senan [2], Ross Muir [2], Elizabeth Barron [2], Yvonne Hadland [2], Elizabeth Moulder [2], Hemant Sharma [2]

[1]Department of Surgery, College of Medicine, Health Sciences Centre, Kuwait University, Kuwait City, Kuwait. yousefmarwan@hotmail.com.

[2]Limb Reconstruction Unit, Department of Trauma and Orthopaedic Surgery, Hull University Teaching Hospitals, Hull, UK.

Eur J Orthop Surg Traumatol. 2023 Aug 2. doi: 10.1007/s00590-023-03660-5. Online ahead of print.

BACKGROUND

The management of failed tibial fracture fixation remains a challenge for orthopaedic surgeons. This study investigate the utility and outcomes of circular external fixation in the management of failed internal fixation of tibial fractures.

METHODS

Retrospective review of a prospectively collected database of a complex limb reconstruction unit at a major trauma centre was done during December 2022. Patients with failed internal fixation of tibial fracture who underwent revision surgery with circular external fixation frame were included.

RESULTS

20 patients with a mean age of 47.8 ± 16.5 years (range: 15-69) were included. Fourteen (70.0%) patients had failed plate and screws fixations, and the remaining six (30.0%) failed intramedullary nail fixation. The most common indication for revision surgery was development of early postoperative surgical site infection (5 patients; 25.0%). The mean duration of frame treatment was 199.5 ± 80.1 days (range = 49-364), while the mean follow-up duration following frame removal was 3.2 ± 1.8 years (range = 2-8). The overall union rate in this series was 100%; and all infected cases had complete resolution from infection. The total number of complications was 11, however, only two complications required surgical intervention. The most common complications reported were pin site infection (6; 30.0%) and limb length discrepancy of 2 cm (2; 10.0%).

CONCLUSIONS

Circular external fixation is a reliable surgical option in the treatment of failed internal fixation of tibia fractures. This technique can provide limb salvage in complex infected and noninfected cases with a high union rate and minimal major complications.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2023; 55 (3): 259 - 268

International Conference on **Medical Health Science, Pharmacology & Biotechnology**
Sep 01, 2023
United States, New York
Email: papers.issrd@gmail.com
Event website: http: //issrd.org/Conference/18399/ICMPB/

World **Disability & Rehabilitation** Conference
Sep 02, 2023
China, Beijing
Email: papers.asar@gmail.com
Event website: http: //asar.org.in/Conference/37532/WDRC/

International Conference on **Healthcare and Clinical Gerontology**
Sep 02, 2023
Japan, Saitama
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/24376/ICHCG/

1596th International Conference on **Medical, Biological and Pharmaceutical Sciences**
Sep 02, 2023
United Arab Emirates, Abu Dhabi
Email: info@iastem.org
Event website: http: //iastem.org/Conference2023/UAE/6/ICMBPS/

International Conference on **Medical and Health Sciences**
Sep 03, 2023
United Kingdom, Liverpool
Email: papers.scienceplus@gmail.com
Event website: http: //scienceplus.us/Conference/24242/ICMHS/

International Conference on Latest Research on **Corona Virus** and its Vaccine
Sep 03, 2023
India, New Delhi
Email: info.researchconferences@gmail.com
Event website: http: //researchconferences.in/Conference/3968/ICRCVV/

International Conference on **Nursing Ethics and Medical Ethics**
Sep 05, 2023
Turkey, Ankara
Email: info.wrfase@gmail.com
Event website: http: //wrfase.org/Conference/8754/ICNEME/

International Conference on **Medical, Biological and Pharmaceutical Sciences**
Sep 05, 2023
France, Paris
Email: contact.easrd@gmail.com
Event website: http: //easrd.org/Conference/157/ICMBPS/

World **Disability & Rehabilitation** Conference
Sep 06, 2023
Vietnam, Hanoi
Email: papers.asar@gmail.com
Event website: http: //asar.org.in/Conference/37487/WDRC/

International Conference on **Medical and Biological Engineering**
Sep 08, 2023
Singapore, Singapore
Email: papers.techno@gmail.com
Event website: http: //technoconferences.com/Conference/9774/ICMBE/

1488th International Conference on **Food Microbiology** and Food Safety
Sep 08, 2023
Greece, Crete
Email: info@theires.org
Event website: http: //theires.org/Conference2023/Greece/2/ICFMFS/

International Conference on **Healthcare and Clinical Gerontology**
Sep 09, 2023
Australia, Adelaide
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/24324/ICHCG/

International Conference on **Cardiology and Diabetes**
Sep 10, 2023
France, Paris
Email: info.iared.org@gmail.com
Event website: http: //iared.org/Conference/589/ICCD/

International Conference on **Oncolytic Virus Therapeutics**
Sep 11, 2023
Malaysia, Putrajaya
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1385/ICOVT/

1450th International Conference on **Pharma and Food**
Sep 12, 2023
Morocco, Rabat
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/Morocco/2/ICPAF/

International Virtual Conference on **COVID-19** and its Effect
Sep 13, 2023
Malaysia, Kuala Lumpur
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1374/IVCCE/

International Conference on Recent Advances in **Medical Science**
Sep 14, 2023
United States, San Francisco
Email: info@theiier.org
Event website: http: //theiier.org/Conference2023/US/81/ICRAMS/

1413th International Conference on **Medical & Health Science**
Sep 14, 2023
United Arab Emirates, Dubai
Email: info@researchfora.com
Event website: http: //researchfora.com/Conference2023/UAE/6/ICMHS/

World **Neurology** Conference
Sep 15, 2023
United States, Miami
Email: neurology@precisionglobalconferences.com
Event website: https: //neurologyworldconference.com/

1592nd International Conference on **Medical and Biosciences**
Sep 15, 2023
Saudi Arabia, Mecca
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/SaudiArabia/6/ICMBS/

World **Disability & Rehabilitation** Conference
Sep 16, 2023
Japan, Tokyo
Email: papers.asar@gmail.com
Event website: http: //asar.org.in/Conference/37382/WDRC/

International Conference on **Medical and Health Sciences**
Sep 17, 2023
United States, Boston
Email: papers.academicsconference@gmail.com
Event website: http: //academicsconference.com/Conference/28403/ICMHS/

1454th International Conference on **Pharma and Food**
Sep 17, 2023
United States, Denver
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/USA/13/ICPAF/

1607th International Conference on **Medical and Health Sciences**
Sep 18, 2023
United Kingdom, Manchester
Email: info@iserd.co
Event website: http: //iserd.co/Conference2023/UK/6/ICMHS/

International Conference on **Cell and Tissue Science**
Sep 19, 2023
Saudi Arabia, Taif
Email: info@conferencefora.org
Event website: http: //conferencefora.org/Conference/41501/ICCTS/

1455th International Conference on **Sports Nutrition and Supplements**
Sep 19, 2023
United Kingdom, Oxford
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/UK/6/ICSNS/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences**
Sep 20, 2023
Turkey, Istanbul
Email: info.irfconference@gmail.com
Event website: http: //irfconference.org/Conference/18416/ICRAMNH/

International Conference on **Nutrition & Health**
Sep 20, 2023
United Arab Emirates, Abu Dhabi
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1352/ICNH/

International Virtual Conference on **COVID-19** and its Effect
Sep 20, 2023
United Arab Emirates, Abu Dhabi
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1350/IVCCE/

International Conference on **Obesity and Chronic Diseases**
Sep 24, 2023
Germany, Berlin
Email: info.iared.org@gmail.com
Event website: http: //iared.org/Conference/572/ICOCD/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Sep 25, 2023
France, Paris
Email: info.gsrd@gmail.com
Event website: http: //gsrd.co/Conference/14810/ICMPH/

1623rd International Conferences on **Medical and Health Science**
Sep 27, 2023
Kuwait, Kuwait City
Email: info@theires.org
Event website: http: //theires.org/Conference2023/Kuwait/1/ICMHS/

World Conference on **Pharma Industry and Medical Devices**
Sep 29, 2023
Saudi Arabia, Jeddah
Email: info.ifearpworld@gmail.com
Event website: http: //ifearp.org/Conference/8420/WCPIMD/

International Conference on **Medical and Health Sciences**
Sep 30, 2023
Canada, Montreal
Email: papers.academicsconference@gmail.com
Event website: http: //academicsconference.com/Conference/28264/ICMHS/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Oct 01, 2023
Singapore, Singapore
Email: contact.wrfer@gmail.com
Event website: http: //wrfer.org/Conference/25094/ICRAMMHS/

International Conference on **Cell and Tissue Science**
Oct 01, 2023
Italy, Genoa
Email: info@conferencefora.org
Event website: http: //conferencefora.org/Conference/41321/ICCTS/

1602nd International Conference on **Medical and Biosciences**
Oct 02, 2023
Germany, Berlin
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/Germany/7/ICMBS/

International Conference on **Nursing Ethics and Medical Ethics**
Oct 03, 2023
China, Beijing
Email: info.wrfase@gmail.com
Event website: http: //wrfase.org/Conference/8601/ICNEME/

International Conference on **Healthcare and Clinical Gerontology**
Oct 04, 2023
Switzerland, Bern
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/24545/ICHCG/

1st Regional Conference of the **International Society of Pediatric Dermatology**
Oct 4-6, 2023
Kuwait, Grand Hyatt Hotel
Event website: www.ispdkw.com

International Conference on **Medical, Medicine and Health Sciences**
Oct 05, 2023
Egypt, Cairo
Email: contact.iierd@gmail.com
Event website: http: //iierd.com/Conference/2910/ICMMH/

1467th International Conference on **Sports Nutrition and Supplements**
Oct 07, 2023
New Zealand, Wellington
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/NewZealand/4/ICSNS/

World **Disability & Rehabilitation** Conference
Oct 08, 2023
Thailand, Bangkok
Email: papers.asar@gmail.com
Event website: http: //asar.org.in/Conference/37202/WDRC/

International Conference on **Healthcare and Clinical Gerontology**
Oct 08, 2023
Germany, Berlin
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/24506/ICHCG/

International Conference on **Medical, Medicine and Health Sciences**
Oct 11, 2023
United Kingdom, George Town
Email: contact.iierd@gmail.com
Event website: http: //iierd.com/Conference/2898/ICMMH/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Oct 12, 2023
Qatar, Doha
Email: contact.wrfer@gmail.com
Event website: http: //wrfer.org/Conference/25014/ICRAMMHS/

International Conference on Advances in **Health and Medical Science**
Oct 13, 2023
United Arab Emirates, Dubai
Email: info.saard.org@gmail.com
Event website: http: //saard.org/Conference/2074/ICAHMS/

1622nd International Conference on **Medical and Health Sciences**
Oct 13, 2023
Saudi Arabia, Riyadh
Email: info@iserd.co
Event website: http: //iserd.co/Conference2023/SaudiArabia/7/ICMHS/

International Conference on Latest Research on **Corona Virus** and its Vaccine
Oct 14, 2023
United Arab Emirates, Dubai
Email: info.researchconferences@gmail.com
Event website: http: //researchconferences.in/Conference/4043/ICRCVV/

World Conference on **Pharma Industry and Medical Devices**
Oct 15, 2023
United Arab Emirates, Sharjah
Email: info.ifearpworld@gmail.com
Event website: http: //ifearp.org/Conference/8384/WCPIMD/

International Conference on **Nutrition & Health**
Oct 15, 2023
India, Bangalore
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1472/ICNH/

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Oct 16, 2023
Australia, Melbourne
Email: info.irfconference@gmail.com
Event website: http: //irfconference.org/Conference/17605/ICRAMNH/

1615th International Conference on Recent Advances in **Medical and Health Sciences**
Oct 16, 2023
United States, Boston
Email: info@academicsworld.org
Event website: https: //academicsworld.org/Conference2023/USA/14/ICRAMHS/

International Conference on **Healthcare and Clinical Gerontology**
Oct 17, 2023
United States, Kansas
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/20121/ICHCG/

1474th International Conference on **Sports Nutrition and Supplements**
Oct 17, 2023
United States, Orlando
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/USA/15/ICSNS/

International Conference on **Diabetes, Endocrinology and Obesity**
Oct 18, 2023
Turkey, Istanbul
Email: info.diabetesworld@gmail.com
Event website: http: //diabetesworld.net/Conference/65/ICDEO/

1612th International Conference on **Medical and Biosciences**
Oct 18, 2023
United States, New Orleans
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/USA/18/ICMBS/

International Conference on **Medical and Biological Engineering**
Oct 20, 2023
United States, Edinburg
Email: papers.techno@gmail.com
Event website: http: //technoconferences.com/Conference/9686/ICMBE/

International Conference on Recent Advances in **Medical Science**
Oct 20, 2023
United States, Phoenix
Email: info@theiier.org
Event website: http: //theiier.org/Conference2023/US/96/ICRAMS/

International Conference on **Medical, Medicine and Health Sciences**
Oct 20, 2023
Australia, Sydney
Email: contact.iierd@gmail.com
Event website: http: //iierd.com/Conference/2886/ICMMH/

International Conference on **Obesity and Chronic Diseases**
Oct 21, 2023
United States, Washington D.C
Email: info.iared.org@gmail.com
Event website: http: //iared.org/Conference/612/ICOCD/

International Conference on **Virology**
Oct 22, 2023
United Arab Emirates, Dubai
Email: papers.itrgroup@gmail.com
Event Website: http: //itrgroup.net/Conference/685/ICV/

International Conference on **Cardiology and Diabetes**
Oct 22, 2023
Germany, Berlin
Email: info.iared.org@gmail.com
Event website: http: //iared.org/Conference/605/ICCD/

International Conference on **Medical, Medicine and Health Sciences**
Oct 23, 2023
United States, Boston
Email: contact.iierd@gmail.com
Event website: http: //iierd.com/Conference/2874/ICMMH/

International Conference on **Science, Health and Medicine**
Oct 24, 2023
Canada, Winnipeg
Email: info@iser.co
Event website: http: //iser.co/Conference2023/Canada/51/ICSHM/

International Research Conference on **COVID-19** and its Impact on Mental Health
Oct 25, 2023
India, Kolkata, West Bengal
Email: info.researchconferences@gmail.com
Event website: http: //researchconferences.in/Conference/4004/IRCCIMH/

International Conference on **Medical and Health Sciences**
Oct 25, 2023
Qatar, Doha
Email: info.inderscience.org@gmail.com
Event website: http: //inderscience.org/Conference/743/ICMHS/

International Conference on **Cell and Tissue Science**
Oct 26, 2023
United Arab Emirates, Al Ain
Email: info@conferencefora.org
Event website: http: //conferencefora.org/Conference/40824/ICCTS/

1st **Kuwait Pediatric Association Conference** and Workshop
Oct 26-28, 2023
Kuwait, Radisson Blu Hotel
Event website: https://kpacw2023.com/#slide-a

1618th International Conference on **Medical and Biosciences**
Oct 27, 2023
Philippines, Manila
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/Philippines/3/ICMBS/

1655th International Conference on Recent Advances in **Medical Science**
Oct 28, 2023
Kuwait, Kuwait City
Email: info@theiier.org
Event website: http: //theiier.org/Conference2023/Kuwait/2/ICRAMS/

International Conference on Latest Research on **Corona Virus** and its Vaccine
Oct 30, 2023
United States, New York
Email: info.researchconferences@gmail.com
Event website: http: //researchconferences.in/Conference/3988/ICRCVV/

International Conference on **Medical, Biological and Pharmaceutical Sciences**
Oct 31, 2023
United States, Boston
Email: info.ipharmaconferences@gmail.com
Event website: http: //ipharmaconferences.com/Conference/8/ICMBPS/

International Conference on **Endocrinology, Diabetes and Metabolism**
Nov 01, 2023
Canada, Toronto
Email: info.diabetesworld@gmail.com
Event website: http: //diabetesworld.net/Conference/118/ICEDM/

International Conference on **Healthcare and Clinical Gerontology**
Nov 02, 2023
United Arab Emirates, Dubai
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/19965/ICHCG/

11th Global Conference on **Pharma Industry and Medical Devices**
Nov 03, 2023
United Kingdom, London
Email: igrnetconference@gmail.com
Event website: http: //www.gcpimd.igrnet.org/331/united-kingdom/

International Conference on Latest Research on **Corona Virus** and its Vaccine
Nov 03, 2023
India, Thrissur, Kerala
Email: info.researchconferences@gmail.com
Event website: http: //researchconferences.in/Conference/4188/ICRCVV/

International Conference on Advances in **Health and Medical Science**
Nov 04, 2023
Scotland, Glasgow
Email: info.saard.org@gmail.com
Event website: http: //saard.org/Conference/2050/ICAHMS/

1622nd International Conference on **Medical and Biosciences**
Nov 05, 2023
New Zealand, Auckland
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/NewZealand/6/ICMBS/

1486th International Conference on **Sports Nutrition and Supplements**
Nov 07, 2023
Japan, Tokyo
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/Japan/12/ICSNS/

1624th International Conference on **Medical and Biosciences**
Nov 08, 2023
Greece, Crete
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/Greece/4/ICMBS/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Nov 09, 2023
Qatar, Doha
Email: info.gsrd@gmail.com
Event website: http: //gsrd.co/Conference/9958/ICMPH/

International Conference on **Virology**
Nov 10, 2023
United Arab Emirates, Abu Dhabi
Email: papers.itrgroup@gmail.com
Event website: http: //itrgroup.net/Conference/638/ICV/

1488th International Conference on **Sports Nutrition and Supplements**
Nov 10, 2023
Spain, Madrid
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/Spain/6/ICSNS/

International Research Conference on **COVID-19** and its Impact on Mental Health
Nov 11, 2023
United Arab Emirates, Dubai
Email: info.researchconferences@gmail.com
Event website: http: //researchconferences.in/Conference/4159/IRCCIMH/

1530th International Conference on **Food Microbiology and Food Safety**
Nov 11, 2023
Bulgaria, Plovdiv
Email: info@theires.org
Event website: http: //theires.org/Conference2023/Bulgaria/2/ICFMFS/

Global Conference on **Pharma Industry and Medical Devices**
Nov 12, 2023
France, Paris
Email: igrnetconference@gmail.com
Event website: http: //igrnet.org/Conference/657/GCPIMD/

1641st International Conference on **Medical, Biological and Pharmaceutical Sciences**
Nov 12, 2023
France, Paris
Email: info@iastem.org
Event website: http: //iastem.org/Conference2023/France/6/ICMBPS/

1632nd International Conference on Recent Advances in **Medical and Health Sciences**
Nov 13, 2023
Saudi Arabia, Dammam
Email: info@academicsworld.org
Event website: https: //academicsworld.org/Conference2023/SaudiArabia/18/ICRAMHS/

1628th International Conference on **Medical and Biosciences**
Nov 14, 2023
Brazil, Sao Paulo
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/Brazil/3/ICMBS/

International Conference on **Medical, Biological and Pharmaceutical Sciences**
Nov 15, 2023
Japan, Tokyo
Email: contact.easrd@gmail.com
Event website: http: //easrd.org/Conference/61/ICMBPS/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences**
Nov 17, 2023
Australia, Sydney
Email: info.irfconference@gmail.com
Event website: http: //irfconference.org/Conference/17494/ICRAMNH/

International Conference on **Cell and Tissue Science**
Nov 17, 2023
Spain, Málaga
Email: info@conferencefora.org
Event website: http: //conferencefora.org/Conference/40416/ICCTS/

World **Disability & Rehabilitation** Conference
Nov 17, 2023
India, Mumbai, Maharashtra
Email: papers.asar@gmail.com
Event website: http: //asar.org.in/Conference/44107/WDRC/

International Conference on **Oncolytic Virus Therapeutics**
Nov 18, 2023
United Kingdom, London
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1598/ICOVT/

International Conference on **Oncolytic Virus Therapeutics**
Nov 19, 2023
Taiwan, Taipei
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1574/ICOVT/

International Conference on **Diabetes and Endocrinology**
Nov 21, 2023
Switzerland, Geneva
Email: info.diabetesworld@gmail.com
Event website: http: //diabetesworld.net/Conference/116/ICDE/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Nov 22, 2023
Turkey, Ankara
Email: info.gsrd@gmail.com
Event website: http: //gsrd.co/Conference/9850/ICMPH/

International Conference on **Endocrinology, Diabetes and Metabolism**
Nov 23, 2023
United States, New York
Email: info.diabetesworld@gmail.com
Event website: http: //diabetesworld.net/Conference/115/ICEDM/

International Conference on **Medical Ethics and Professionalism**
Nov 24, 2023
China, Hong Kong
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/19703/ICMEP/

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Nov 26, 2023
United Arab Emirates, Dubai
Email: info.irfconference@gmail.com
Event website: http: //irfconference.org/Conference/17459/ICRAMNH/

International Conference on **Epidemiology & Public Health**
Nov 26, 2023
Hong Kong, Hong Kong
Email: info@meetingfora.com
Event website: http: //meetingfora.com/Conference/42/ICEPH/

1499th International Conference on **Pharma and Food**
Nov 27, 2023
United Arab Emirates, Abu Dhabi
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/UAE/8/ICPAF/

Global Conference on **Pharma Industry and Medical Devices**
Nov 28, 2023
Canada, Toronto
Email: igrnetconference@gmail.com
Event website: http: //igrnet.org/Conference/643/GCPIMD/

International Conference on **Medical and Biological Engineering**
Nov 30, 2023
Indonesia, Bali
Email: papers.techno@gmail.com
Event website: http: //technoconferences.com/Conference/9632/ICMBE/

International Conference on **Medical and Health Sciences**
Dec 02, 2023
Scotland, Glasgow
Email: papers.scienceplus@gmail.com
Event website: http: //scienceplus.us/Conference/25694/ICMHS/

International Conference on **Medical and Biological Engineering**
Dec 03, 2023
Scotland, Edinburgh
Event website: http: //technoconferences.com/Conference/9626/ICMBE/

1461st International Conference on **Medical & Health Science**
Dec 03, 2023
Norway, Oslo
Email: info@researchfora.com
Event website: http: //researchfora.com/Conference2023/Norway/2/ICMHS/

International Conference on **Nutrition & Health**
Dec 04, 2023
Malaysia, Putrajaya
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1711/ICNH/

1643rd International Conference on **Medical and Biosciences**
Dec 06, 2023
Lebanon, Beirut
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/Lebanon/2/ICMBS/

1681st International Conference on Recent Advances in **Medical Science**
Dec 07, 2023
Turkey, Antalya
Email: info@theiier.org
Event website: http: //theiier.org/Conference2023/Turkey/7/ICRAMS/

1682nd International Conference on Recent Advances in **Medical Science**
Dec 08, 2023
Australia, Brisbane
Email: info@theiier.org
Event website: http: //theiier.org/Conference2023/Australia/10/ICRAMS/

International Conference on **Medical Ethics and Professionalism**
Dec 09, 2023
Croatia (*Hrvatska*), Dubrovnik
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/24830/ICMEP/

1645th International Conference on **Medical and Biosciences**
Dec 09, 2023
Netherlands, Amsterdam
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/Netherlands/2/ICMBS/

International Virtual Conference on **COVID-19** and its Effect
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India, Bangalore, Karnataka
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1664/IVCCE/

1648th International Conference on Recent Advances in **Medical and Health Sciences**
Dec 10, 2023
Qatar, Doha
Email: info@academicsworld.org
Event website: https: //academicsworld.org/Conference2023/Qatar/5/ICRAMHS/

International Conference on **Medical, Pharmaceutical and Health Sciences**
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United Arab Emirates, Dubai
Email: info.gsrd@gmail.com
Event website: http: //gsrd.co/Conference/9670/ICMPH/

International Conference on **Oncolytic Virus Therapeutics**
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United Arab Emirates, Abu Dhabi
Email: info.conferenceonline@gmail.com
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International Conference on **Medical Ethics and Professionalism**
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Event website: http: //sciencefora.org/Conference/19457/ICMEP/

International Conference on **Medical Ethics and Professionalism**
Dec 17, 2023
United States, Kansas
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/19444/ICMEP/

International Conference on **Cardiology and Diabetes**
Dec 17, 2023
Germany, Berlin
Email: info.iared.org@gmail.com
Event website: http: //iared.org/Conference/669/ICCD/

1513th International Conference on **Pharma and Food**
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United Kingdom, Manchester
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Event website: http: //academicsera.com/Conference2023/UK/7/ICPAF/

International Conference on **Diabetes, Endocrinology and Obesity**
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Geneva, Switzerland
Email: info.diabetesworld@gmail.com
Event website: http: //diabetesworld.net/Conference/121/ICDEO/

International Conference on **Cell and Tissue Science**
Dec 20, 2023
Turkey, Izmir
Email: info@conferencefora.org
Event website: http: //conferencefora.org/Conference/39804/ICCTS/

International Conference on **Healthcare and Clinical Gerontology**
Dec 21, 2023
Singapore, Singapore
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/19393/ICHCG/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Dec 21, 2023
Japan, Kawasaki
Email: info.gsrd@gmail.com
Event website: http: //gsrd.co/Conference/13127/ICMPH/

World Conference on **Pharma Industry and Medical Devices**
Dec 22, 2023
Thailand, Phuket
Email: info.ifearpworld@gmail.com
Event website: http: //ifearp.org/Conference/8065/WCPIMD/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 22, 2023
United Arab Emirates, Abu Dhabi
Email: contact.wrfer@gmail.com
Event website: http: //wrfer.org/Conference/28672/ICRAMMHS/

1518th International Conference on **Pharma and Food**
Dec 26, 2023
Italy, Milan
Email: info@academicsera.com
Event website: http: //academicsera.com/Conference2023/Italy/9/ICPAF/

1669th International Conference on **Medical, Biological and Pharmaceutical Sciences**
Dec 27, 2023
Japan, Osaka
Email: info@iastem.org
Event website: http: //iastem.org/Conference2023/Japan/14/ICMBPS/

International Conference on **Nursing Ethics and Medical Ethics**
Dec 28, 2023
Japan, Saitama
Email: info.sciencefora@gmail.com
Event website: http: //sciencefora.org/Conference/19325/ICNEME/

1477th International Conference on **Medical & Health Science**
Dec 28, 2023
Kuwait, Kuwait City
Email: info@researchfora.com
Event website: http: //researchfora.com/Conference2023/Kuwait/2/ICMHS/

World **Disability & Rehabilitation** Conference
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Canada, Montreal
Email: papers.asar@gmail.com
Event website: http: //asar.org.in/Conference/36316/WDRC/

1659th International Conference on **Medical and Biosciences**
Dec 29, 2023
Canada, Montreal
Email: info@researchworld.org
Event website: http: //researchworld.org/Conference2023/Canada/6/ICMBS/

International Conference on **Medical, Medicine and Health Sciences**
Dec 30, 2023
New Zealand, Wellington
Email: contact.iierd@gmail.com
Event website: http: //iierd.com/Conference/3210/ICMMH/

International Virtual Conference on **Medical Biological and Pharmaceutical Science**
Dec 30, 2023
United Arab Emirates, Dubai
Email: info.conferenceonline@gmail.com
Event website: http: //conferenceonline.net/Conference/1513/IVCMBPS/

WHO-Facts Sheet

1. Autism
2. Botulism
3. Falls
4. Lead poisoning
5. Primary health care

Compiled and edited by
Vineetha E Mammen

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1. Autism

KEY FACTS

- Autism – also referred to as autism spectrum disorder ◎ constitutes a diverse group of conditions related to development of the brain.
- About 1 in 100 children has autism.
- Characteristics may be detected in early childhood, but autism is often not diagnosed until much later.
- The abilities and needs of autistic people vary and can evolve over time. While some people with autism can live independently, others have severe disabilities and require life-long care and support.
- Evidence-based psychosocial interventions can improve communication and social skills, with a positive impact on the well-being and quality of life of both autistic people and their caregivers.
- Care for people with autism needs to be accompanied by actions at community and societal levels for greater accessibility, inclusivity and support.

Overview

Autism spectrum disorders (ASD) are a diverse group of conditions. They are characterized by some degree of difficulty with social interaction and communication. Other characteristics are atypical patterns of activities and behaviours, such as difficulty with transition from one activity to another, a focus on details and unusual reactions to sensations.

The abilities and needs of autistic people vary and can evolve over time. While some people with autism can live independently, others have severe disabilities and require life-long care and support. Autism often has an impact on education and employment opportunities. In addition, the demands on families providing care and support can be significant. Societal attitudes and the level of support provided by local and national authorities are important factors determining the quality of life of people with autism.

Characteristics of autism may be detected in early childhood, but autism is often not diagnosed until much later.

People with autism often have co-occurring conditions, including epilepsy, depression, anxiety and attention deficit hyperactivity disorder as well as challenging behaviours such as difficulty sleeping and self-injury. The level of intellectual functioning among autistic people varies widely, extending from profound impairment to superior levels.

Epidemiology

It is estimated that worldwide about 1 in 100 children has autism[1]. This estimate represents an average figure, and reported prevalence varies substantially across studies. Some well-controlled studies have, however, reported figures that are substantially higher. The prevalence of autism in many low- and middle-income countries is unknown.

Causes

Available scientific evidence suggests that there are probably many factors that make a child more likely to have autism, including environmental and genetic factors.

Available epidemiological data conclude that there is no evidence of a causal association between measles, mumps and rubella vaccine, and autism. Previous studies suggesting a causal link were found to be filled with methodological flaws[2,3].

There is also no evidence to suggest that any other childhood vaccine may increase the risk of autism. Evidence reviews of the potential association between the preservative thiomersal and aluminium adjuvants

Address correspondence to:
Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: http://www.who.int/

contained in inactivated vaccines and the risk of autism strongly concluded that vaccines do not increase the risk of autism.

Assessment and care

A broad range of interventions, from early childhood and across the life span, can optimize the development, health, well-being and quality of life of autistic people. Timely access to early evidence-based psychosocial interventions can improve the ability of autistic children to communicate effectively and interact socially. The monitoring of child development as part of routine maternal and child health care is recommended.

It is important that, once autism has been diagnosed, children, adolescents and adults with autism and their carers are offered relevant information, services, referrals, and practical support, in accordance with their individual and evolving needs and preferences.

The health-care needs of people with autism are complex and require a range of integrated services, that include health promotion, care and rehabilitation. Collaboration between the health sector and other sectors, particularly education, employment and social care, is important.

Interventions for people with autism and other developmental disabilities need to be designed and delivered with the participation of people living with these conditions. Care needs to be accompanied by actions at community and societal levels for greater accessibility, inclusivity and support.

Human rights

All people, including people with autism, have the right to the enjoyment of the highest attainable standard of physical and mental health.

And yet, autistic people are often subject to stigma and discrimination, including unjust deprivation of health care, education and opportunities to engage and participate in their communities.

People with autism have the same health problems as the general population. However, they may, in addition, have specific health-care needs related to autism or other co-occurring conditions. They may be more vulnerable to developing chronic noncommunicable conditions because of behavioural risk factors such as physical inactivity and poor dietary preferences, and are at greater risk of violence, injury and abuse.

People with autism require accessible health services for general health-care needs like the rest of the population, including promotive and preventive services and treatment of acute and chronic illness. Nevertheless, autistic people have higher rates of unmet health-care needs compared with the general population. They are also more vulnerable during humanitarian emergencies. A common barrier is created by health-care providers' inadequate knowledge and understanding of autism.

WHO resolution on autism spectrum disorders

In May 2014, the Sixty-seventh World Health Assembly adopted a resolution entitled Comprehensive and coordinated efforts for the management of autism spectrum disorders, which was supported by more than 60 countries.

The resolution urges WHO to collaborate with Member States and partner agencies to strengthen national capacities to address ASD and other developmental disabilities.

WHO response

WHO and partners recognize the need to strengthen countries' abilities to promote the optimal health and well-being of all people with autism.

WHO's efforts focus on:

- increasing the commitment of governments to taking action to improve the quality of life of people with autism;
- providing guidance on policies and action plans that address autism within the broader framework of health, mental and brain health and disabilities;
- contributing to strengthening the ability of the health workforce to provide appropriate and effective care and promote optimal standards of health and well-being for people with autism; and
- promoting inclusive and enabling environments for people with autism and other developmental disabilities and providing support to their caregivers.

WHO Comprehensive mental health action plan 2013–2030 and World Health Assembly Resolution WHA73.10 for "global actions on epilepsy and other neurological disorders" calls on countries to address the current significant gaps in early detection, care, treatment and rehabilitation for mental and neurodevelopmental conditions, which include autism. It also calls for counties to address the social, economic, educational and inclusion needs of people living with mental and neurological disorders, and their families, and to improve surveillance and relevant research.

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2. Botulism

KEY FACTS

- *Clostridium botulinum* is a bacterium that produces dangerous toxins (botulinum toxins) under low-oxygen conditions.
- Botulinum toxins are one of the most lethal substances known.
- Botulinum toxins block nerve functions and can lead to respiratory and muscular paralysis.
- Human botulism may refer to foodborne botulism, infant botulism, wound botulism, and inhalation botulism or other types of intoxication.
- Foodborne botulism, caused by consumption of improperly processed food, is a rare but potentially fatal disease if not diagnosed rapidly and treated with antitoxin.
- Homemade canned, preserved or fermented foodstuffs are a common source of foodborne botulism and their preparation requires extra caution.

Foodborne botulism is a serious, potentially fatal disease. However, it is relatively rare. It is an intoxication usually caused by ingestion of potent neurotoxins, the botulinum toxins, formed in contaminated foods. Person to person transmission of botulism does not occur.

Spores produced by the bacteria *Clostridium botulinum* are heat-resistant and exist widely in the environment, and in the absence of oxygen they germinate, grow and then excrete toxins. There are 7 distinct forms of botulinum toxin, types A–G. Four of these (types A, B, E and rarely F) cause human botulism. Types C, D and E cause illness in other mammals, birds and fish.

Botulinum toxins are ingested through improperly processed food in which the bacteria or the spores survive, then grow and produce the toxins. Though mainly a foodborne intoxication, human botulism can also be caused by intestinal infection with *C. botulinum* in infants, wound infections, and by inhalation.

Symptoms of foodborne botulism

Botulinum toxins are neurotoxic and therefore affect the nervous system. Foodborne botulism is characterized by descending, flaccid paralysis that can cause respiratory failure. Early symptoms include marked fatigue, weakness and vertigo, usually followed by blurred vision, dry mouth and difficulty in swallowing and speaking. Vomiting, diarrhoea, constipation and abdominal swelling may also occur. The disease can progress to weakness in the neck and arms, after which the respiratory muscles and muscles of the lower body are affected. There is no fever and no loss of consciousness.

The symptoms are not caused by the bacterium itself, but by the toxin produced by the bacterium. Symptoms usually appear within 12 to 36 hours (within a minimum and maximum range of 4 hours to 8 days) after exposure. Incidence of botulism is low, but the mortality rate is high if prompt diagnosis and appropriate, immediate treatment (early administration of antitoxin and intensive respiratory care) are not given. The disease can be fatal in 5 to 10% of cases.

Exposure and transmission
Foodborne botulism

C. botulinum is an anaerobic bacterium, meaning it can only grow in the absence of oxygen. Foodborne botulism occurs when *C. botulinum* grows and produces toxins in food prior to consumption. *C. botulinum* produces spores and they exist widely in the environment including soil, river and sea water.

The growth of the bacteria and the formation of toxin occur in products with low oxygen content and certain combinations of storage temperature and preservative parameters. This happens most often in lightly preserved foods and in inadequately processed, home-canned or home-bottled foods.

C. botulinum will not grow in acidic conditions (pH less than 4.6), and therefore the toxin will not be formed in acidic foods (however, a low pH will not degrade any pre-formed toxin). Combinations of low storage temperature and salt contents and/or pH are also used to prevent the growth of the bacteria or the formation of the toxin.

The botulinum toxin has been found in a variety of foods, including low-acid preserved vegetables, such as green beans, spinach, mushrooms, and beets; fish, including canned tuna, fermented, salted and smoked fish; and meat products, such as ham and sausage. The food implicated differs between countries and reflects local eating habits and food preservation procedures. Occasionally, commercially prepared foods are involved.

Though spores of *C. botulinum* are heat-resistant, the toxin produced by bacteria growing out of the spores under anaerobic conditions is destroyed by boiling (for example, at internal temperature greater

than 85 °C for 5 minutes or longer). Therefore, ready-to-eat foods in low oxygen-packaging are more frequently involved in cases of foodborne botulism.

Food samples associated with suspect cases must be obtained immediately, stored in properly sealed containers, and sent to laboratories in order to identify the cause and to prevent further cases.

Infant botulism

Infant botulism occurs mostly in infants under 6 months of age. Different from foodborne botulism caused by ingestion of pre-formed toxins in food, it occurs when infants ingest *C. botulinum* spores, which germinate into bacteria that colonize in the gut and release toxins. In most adults and children older than about 6 months, this would not happen because natural defences in intestines that develop over time prevent germination and growth of the bacterium.

C. botulinum in infants include constipation, loss of appetite, weakness, an altered cry and a striking loss of head control. Although there are several possible sources of infection for infant botulism, spore-contaminated honey has been associated with a number of cases. Parents and caregivers are therefore warned not to feed honey to the infants before the age of 1 year.

Wound botulism

Wound botulism is rare and occurs when the spores get into an open wound and are able to reproduce in an anaerobic environment. The symptoms are similar to the foodborne botulism, but may take up to 2 weeks to appear. This form of the disease has been associated with substance abuse, particularly when injecting black tar heroin.

Inhalation botulism

Inhalation botulism is rare and does not occur naturally, for example it is associated with accidental or intentional events (such as bioterrorism) which result in release of the toxins in aerosols. Inhalation botulism exhibits a similar clinical footprint to foodborne botulism. The median lethal dose for humans has been estimated at 2 nanograms of botulinum toxin per kilogram of bodyweight, which is approximately 3 times greater than in foodborne cases.

Following inhalation of the toxin, symptoms become visible between 1–3 days, with longer onset times for lower levels of intoxication. Symptoms proceed in a similar manner to ingestion of botulinum toxin and culminate in muscular paralysis and respiratory failure.

If exposure to the toxin via aerosol inhalation is suspected, additional exposure to the patient and others must be prevented. The patient's clothing must be removed and stored in plastic bags until it can be washed thoroughly with soap and water. The patient should shower and be decontaminated immediately.

Other types of intoxication

Waterborne botulism could theoretically result from the ingestion of the pre-formed toxin. However, as common water treatment processes (such as boiling, disinfection with 0.1% hypochlorite bleach solution) destroy the toxin, the risk is considered low.

Botulism of undetermined origin usually involves adult cases where no food or wound source can be identified. These cases are comparable to infant botulism and may occur when the normal gut flora has been altered as a result of surgical procedures or antibiotic therapy.

Adverse effects of the pure toxin have been reported as a result of its medical and/or cosmetic use in patients, see more on 'Botox' below.

'Botox'

The bacterium *C. botulinum* is the same bacterium that is used to produce Botox, a pharmaceutical product predominantly injected for clinical and cosmetic use. Botox treatments employ the purified and heavily diluted botulinum neurotoxin type A. Treatment is administered in the medical setting, tailored according to the needs of the patient and is usually well tolerated although occasional side effects are observed.

Diagnosis and treatment

Diagnosis is usually based on clinical history and clinical examination followed by laboratory confirmation including demonstrating the presence of botulinum toxin in serum, stool or food, or a culture of *C. botulinum* from stool, wound or food. Misdiagnosis of botulism sometimes occurs as it is often confused with stroke, Guillain-Barré syndrome, or myasthenia gravis.

Antitoxin should be administered as soon as possible after a clinical diagnosis. Early administration is effective in reducing mortality rates. Severe botulism cases require supportive treatment, especially mechanical ventilation, which may be required for weeks or even months. Antibiotics are not required (except in the case of wound botulism). A vaccine against botulism exists but it is rarely used as its effectiveness has not been fully evaluated and it has demonstrated negative side effects.

Prevention

Prevention of foodborne botulism is based on good practice in food preparation particularly during heating/sterilization and hygiene. Foodborne botulism may be prevented by the inactivation

of the bacterium and its spores in heat-sterilized (for example, retorted) or canned products or by inhibiting bacterial growth and toxin production in other products. The vegetative forms of bacteria can be destroyed by boiling but the spores can remain viable after boiling even for several hours. However, the spores can be killed by very high temperature treatments such as commercial canning.

Commercial heat pasteurization (including vacuum packed pasteurized products and hot smoked products) may not be sufficient to kill all spores and therefore the safety of these products must be based on preventing bacterial growth and toxin production. Refrigeration temperatures combined with salt content and/or acidic conditions will prevent the growth of the bacteria and formation of toxin.

The WHO Five Keys to Safer Food serve as the basis for educational programmes to train food handlers and educate the consumers. They are especially important in preventing food poisoning.

The Five Keys are:
- keep clean
- separate raw and cooked
- cook thoroughly
- keep food at safe temperatures
- use safe water and raw materials.

WHO's response

Botulism outbreaks are rare but are public health emergencies that require rapid recognition to identify the disease source, distinguish outbreak types (between natural, accidental or potentially deliberate), prevent additional cases and effectively administer treatment to affected patients.

Successful treatment depends significantly on early diagnosis and the rapid administration of the botulinum antitoxin.

WHO's role in responding to outbreaks of botulism that may be of international concern is as follows.

Surveillance and detection: WHO supports the strengthening of national surveillance and international alert systems to ensure rapid local outbreak detection and an efficient international response. WHO's main tool for these activities of surveillance, coordination and response is the use of the International Network of Food Safety Authorities (INFOSAN) which links national authorities in Member States in charge of managing food safety events. This network is managed jointly by FAO and WHO.

Risk assessment: WHO response is based on a risk assessment methodology that includes consideration of whether the outbreak is natural, accidental, or, possibly, intentional. WHO also provides scientific assessments as basis for international food safety standards, guidelines and recommendations developed by the Codex Alimentarius Commission.

Containment at the disease source: WHO coordinates with national and local authorities in order to contain outbreaks at their source.

Delivery of assistance: WHO coordinates between international agencies, experts, national laboratories, airlines and commercial organizations to mobilize response equipment, materials and supplies, including the provision and administration of botulinum antitoxin.

3. Falls

KEY FACTS
- Falls are the second leading cause of unintentional injury deaths worldwide.
- Each year an estimated 684 000 individuals die from falls globally of which over 80% are in low- and middle-income countries.
- Adults older than 60 years of age suffer the greatest number of fatal falls.
- 37.3 million falls that are severe enough to require medical attention occur each year.
- Prevention strategies should emphasize education, training, creating safer environments, prioritizing fall-related research and establishing effective policies to reduce risk.

A fall is defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level. Fall-related injuries may be fatal or non-fatal(1) though most are non-fatal. For example, of children in the People›s Republic of China, for every death due to a fall, there are 4 cases of permanent disability, 13 cases requiring hospitalization for more than 10 days, 24 cases requiring hospitalization for 1–9 days and 690 cases seeking medical care or missing work/school.

The problem

Globally, falls are a major public health problem. An estimated 684 000 fatal falls occur each year, making it the second leading cause of unintentional injury death, after road traffic injuries. Over 80% of fall-related fatalities occur in low- and middle-income countries, with regions of the Western Pacific and South East Asia accounting for 60% of these deaths. In all regions of the world, death rates are highest among adults over the age of 60 years.

Though not fatal, approximately 37.3 million falls severe enough to require medical attention occur each year. Globally, falls are responsible for over 38 million DALYs (disability-adjusted life years) lost each

year**(2),** and result in more years lived with disability than transport injury, drowning, burns and poisoning combined.

While nearly 40% of the total DALYs lost due to falls worldwide occurs in children, this measurement may not accurately reflect the impact of fall-related disabilities for older individuals who have fewer life years to lose. In addition, those individuals who fall and suffer a disability, particularly older people, are at a major risk for subsequent long-term care and institutionalization.

The financial costs from fall-related injuries are substantial. For people aged 65 years or older, the average health system cost per fall injury in the Republic of Finland and Australia are US$ 3611 and US$ 1049 respectively. Evidence from Canada suggests the implementation of effective prevention strategies with a subsequent 20% reduction in the incidence of falls among children under 10 years of age could create a net savings of over US$ 120 million each year.

Who is at risk?

While all people who fall are at risk of injury, the age, gender and health of the individual can affect the type and severity of injury.

Age

Age is one of the key risk factors for falls. Older people have the highest risk of death or serious injury arising from a fall and the risk increases with age. For example, in the United States of America, 20–30% of older people who fall suffer moderate to severe injuries such as bruises, hip fractures, or head trauma. This risk level may be in part due to physical, sensory, and cognitive changes associated with ageing, in combination with environments that are not adapted for an ageing population.

Another high risk group is children. Childhood falls occur largely as a result of their evolving developmental stages, innate curiosity in their surroundings, and increasing levels of independence that coincide with more challenging behaviours commonly referred to as 'risk taking'. While inadequate adult supervision is a commonly cited risk factor, the circumstances are often complex, interacting with poverty, sole parenthood, and particularly hazardous environments.

Gender

Across all age groups and regions, both genders are at risk of falls. In some countries, it has been noted that males are more likely to die from a fall, while females suffer more non-fatal falls. Older women and younger children are especially prone to falls and increased injury severity. Worldwide, males consistently sustain higher death rates and DALYs lost. Possible explanations of the greater burden seen among males may include higher levels of risk-taking behaviours and hazards within occupations.

Other risk factors include:

- occupations at elevated heights or other hazardous working conditions;
- alcohol or substance use;
- socioeconomic factors including poverty, overcrowded housing, sole parenthood, young maternal age;
- underlying medical conditions, such as neurological, cardiac or other disabling conditions;
- side effects of medication, physical inactivity and loss of balance, particularly among older people;
- poor mobility, cognition, and vision, particularly among those living in an institution, such as a nursing home or chronic care facility;
- unsafe environments, particularly for those with poor balance and limited vision.

Prevention

A range of interventions exist to prevent falls across the life-course. These include, but are not limited to, the following:

<u>For children and adolescents</u>

- Parenting programmes for low-income and marginalized families
- Providing parents with information about child fall risks and supporting them to reduce these risks around the home

<u>For workers</u>

- Enforcement of more stringent workplace safety regulations in high risk occupations such as the construction industry
- Multicomponent workplace safety programmes

<u>For older people</u>

- Gait, balance and functional training
- Tai Chi
- Home assessment and modifications
- Reduction or withdrawal of psychotropic drugs
- Multifactorial interventions (individual fall-risk assessments followed by tailored interventions and referrals to address identified risks)
- Vitamin D supplements for those who are Vitamin D deficient

In addition to the interventions mentioned above there are others that are considered prudent to implement despite the fact that they may never have a body of research to support them. This is because the nature of the intervention is such that they are unlikely to be the subject of high-quality research studies

either due to difficulties in performing the required research, or because the interventions seem so basic or fundamental that research is not deemed necessary. Examples of such interventions include:

- Fence off, or otherwise restrict access to dangerous areas
- Promote policies and playground standards requiring soft play surfaces and restricted fall heights
- Functioning occupational health and safety systems
- Harnesses, restraint systems, fall arrest systems and safe scaffolding for those working at heights
- Requiring landlords to make necessary modifications to homes and the enforcement of building standards
- Improved accessibility of neighbourhoods and public spaces e.g. pavements
- Ensure adequate staff-to-resident ratios in residential care facilities

1. Within the WHO Global Health Estimates, fall-related deaths and non-fatal injuries exclude falls due to assault and self-harm; falls from animals, burning buildings, transport vehicles; and falls into fire, water and machinery.
2. The disability-adjusted life year (DALY) extends the concept of potential years of life lost due to premature death to include equivalent years of "healthy" life lost by virtue of being in states of poor health or disability.

4. Lead poisoning

KEY FACTS

- Exposure to lead can affect multiple body systems and is particularly harmful to young children and women of child-bearing age.
- Lead in the body is distributed to the brain, liver, kidney and bones. It is stored in the teeth and bones, where it can accumulate over time. Human exposure is usually assessed through the measurement of lead in blood.
- Lead in bone is released into blood during pregnancy and becomes a source of exposure to the developing fetus.
- There is no level of exposure to lead that is known to be without harmful effects.
- Lead exposure is preventable.

Overview

Lead is a naturally occurring toxic metal found in the Earth's crust. Its widespread use has resulted in extensive environmental contamination, human exposure and significant public health problems in many parts of the world.

Important sources of environmental contamination come from mining, smelting, manufacturing and recycling activities and use in a wide range of products. Most global lead consumption is for the manufacture of lead-acid batteries for motor vehicles. Lead is, however, also used in many other products, for example pigments, paints, solder, stained glass, lead crystal glassware, ammunition, ceramic glazes, jewellery, toys, some traditional cosmetics such as kohl and sindoor, and some traditional medicines used in countries such as India, Mexico and Viet Nam. Drinking water delivered through lead pipes or pipes joined with lead solder may contain lead. Much of the lead in global commerce is now obtained from recycling.

Young children are particularly vulnerable to the toxic effects of lead and can suffer profound and permanent adverse health impacts, particularly on the development of the brain and nervous system. Lead also causes long-term harm in adults, including increased risk of high blood pressure, cardiovascular problems and kidney damage. Exposure of pregnant women to high levels of lead can cause miscarriage, stillbirth, premature birth and low birth weight.

Sources and routes of exposure

People can become exposed to lead through occupational and environmental sources. This mainly results from:

- inhalation of lead particles generated by burning materials containing lead, for example during smelting, recycling, stripping leaded paint and plastic cables containing lead and using leaded aviation fuel; and
- ingestion of lead-contaminated dust, water (from leaded pipes) and food (from lead-glazed or lead-soldered containers) and from hand-to-mouth behaviour.

Young children are particularly vulnerable to lead poisoning because they absorb 4–5 times as much ingested lead as adults from a given source. Moreover, children's innate curiosity and their age-appropriate hand-to-mouth behaviour result in their mouthing and swallowing lead-containing or lead-coated objects, such as contaminated soil or dust and flakes from decaying lead-containing paint. This route of exposure is magnified in children with a psychological disorder called pica (persistent and compulsive cravings to eat non-food items), who may pick away at and eat leaded paint from walls, door frames and furniture. Exposure to lead-contaminated soil and dust resulting from battery recycling and mining has caused mass lead poisoning and multiple deaths in young children in Nigeria, Senegal and other countries.

Once lead enters the body, it is distributed to organs such as the brain, kidneys, liver and bones. The body stores lead in the teeth and bones, where it accumulates

over time. Lead stored in bone may be released into the blood during pregnancy, thus exposing the growing fetus Undernourished children are more susceptible to lead because their bodies absorb more lead if other nutrients, such as calcium or iron, are lacking. The very young are at the highest risk, as is the developing nervous system is a particularly vulnerable period.

Health effects in children

Lead exposure can have serious consequences for the health of children. At high levels of exposure to lead the brain and central nervous system can be severely damaged causing coma, convulsions and even death. Children who survive severe lead poisoning may be left with permanent intellectual disability and behavioural disorders. At lower levels of exposure that cause no obvious symptoms, lead is now known to produce a spectrum of injury across multiple body systems. In particular, lead can affect children's brain development, resulting in reduced intelligence quotient (IQ), behavioural changes such as reduced attention span and increased antisocial behaviour, and reduced educational attainment. Lead exposure also causes anaemia, hypertension, renal impairment, immunotoxicity and toxicity to the reproductive organs. The neurological and behavioural effects of lead are believed to be irreversible.

There is no known safe blood lead concentration; even blood lead concentrations as low as 3.5 μg/dL may be associated with decreased intelligence in children, behavioural difficulties and learning problems **(1)**.

Burden of disease

The World Health Organization's 2021 update of the **Public health impact of chemicals: knowns and unknowns** estimates that nearly half of the 2 million lives lost to known chemicals exposure in 2019 were due to exposure to lead. Lead exposure is estimated to account for 21.7 million years lost to disability and death (disability-adjusted life years, or DALYs) worldwide due to long-term effects on health, including 30% of the global burden of idiopathic intellectual disability, 4.6% of the global burden of cardiovascular disease and 3% of the global burden of chronic kidney diseases.

WHO response

WHO has identified lead as one of 10 chemicals of major public health concern needing action by Member States to protect the health of workers, children and women of reproductive age. WHO has made available through its website a range of information on lead, including information for policy-makers, technical guidance, training materials and advocacy materials. WHO has developed guidelines on clinical management of lead exposure and recommends that for an individual with a blood lead concentration ≥ 5 μg/dL, the source(s) of lead exposure should be identified, and appropriate action taken to reduce and terminate exposure.

The successful phasing out of leaded gasoline in most countries, together with other lead control measures, has confirmed significant public health benefits with a significant decline in population-level blood lead concentrations in many countries **(2)**. As of July 2021, leaded fuel for cars and lorries is no longer sold anywhere in the world **(3)**. However, more needs to be done to phase out lead paint; as of March 2023, only 48% of countries have introduced legally binding controls on lead paint.

Since leaded paint is a continuing source of exposure in many countries, WHO has joined with the United Nations Environment Programme to form the Global Alliance to Eliminate Lead Paint which has the aim of encouraging all countries to have legally binding laws to control the use of lead in paint. This goal has received further support in the WHO Chemicals Road map to enhance health sector engagement in the Strategic Approach to International Chemicals Management towards the 2020 goal and beyond (decision WHA70(23)), which includes national action to phase out the use of lead paint.

WHO is currently preparing guidelines on prevention of lead exposure, which will provide policy-makers, public health authorities and health professionals with evidence-based guidance on the measures that they can take to protect the health of children and adults from lead exposure.

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5. Primary health care

KEY FACTS

- About 930 million people worldwide are at risk of falling into poverty due to out-of-pocket health spending of 10% or more of their household budget.
- Scaling up primary health care (PHC) interventions

across low and middle-income countries could save 60 million lives and increase average life expectancy by 3.7 years by 2030.
- Achieving the targets for PHC requires an additional investment of around US$ 200 to US$ 370 billion a year for a more comprehensive package of health services.
- At the UN high level UHC meeting in 2019, countries committed to strengthening primary health care. WHO recommends that every country allocate or reallocate an additional 1% of GDP to PHC from government and external funding sources.

What is primary health care?

The concept of PHC has been repeatedly reinterpreted and redefined in the years since 1978, leading to confusion about the term and its practice. A clear and simple definition has been developed to facilitate the coordination of future PHC efforts at the global, national, and local levels and to guide their implementation:

"PHC is a whole-of-society approach to health that aims at ensuring the highest possible level of health and well-being and their equitable distribution by focusing on people's needs and as early as possible along the continuum from health promotion and disease prevention to treatment, rehabilitation and palliative care, and as close as feasible to people's everyday environment." WHO and UNICEF. A vision for primary health care in the 21st century: Towards UHC and the SDGs.

PHC entails three inter-related and synergistic components, including: comprehensive integrated health services that embrace primary care as well as public health goods and functions as central pieces; multi-sectoral policies and actions to address the upstream and wider determinants of health; and engaging and empowering individuals, families, and communities for increased social participation and enhanced self-care and self-reliance in health.

PHC is rooted in a commitment to social justice, equity, solidarity and participation. It is based on the recognition that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction.

For universal health coverage (UHC) to be truly universal, a shift is needed from health systems designed around diseases and institutions towards health systems designed for people, with people. PHC requires governments at all levels to underscore the importance of action beyond the health sector in order to pursue a whole-of government approach to health, including health-in-all-policies, a strong focus on equity and interventions that encompass the entire life-course.

PHC addresses the broader determinants of health and focuses on the comprehensive and interrelated aspects of physical, mental and social health and wellbeing. It provides whole-person care for health needs throughout the lifespan, not just for a set of specific diseases. Primary health care ensures people receive quality comprehensive care - ranging from promotion and prevention to treatment, rehabilitation and palliative care - as close as feasible to people's everyday environment.

Why is primary health care important?

Member States have committed to primary health care renewal and implementation as the cornerstone of a sustainable health system for UHC, health related Sustainable Development Goals (SDGs) and health security. PHC provides the 'programmatic engine' for UHC, the health-related SDGs and health security. This commitment has been codified and reiterated in the Declaration of Astana, the accompanying World Health Assembly Resolution 72/2, the 2019 Global Monitoring Report on UHC, and the United Nations General Assembly high-level meeting on UHC. UHC, the health-related SDGs and health security goals are ambitious but achievable. Progress must be urgently accelerated, and PHC provides the means to do so.

PHC is the most inclusive, equitable, cost-effective and efficient approach to enhance people's physical and mental health, as well as social well-being. Evidence of wide-ranging impact of investment in PHC continues to grow around the world, particularly in times of crisis such as the COVID-19 pandemic.

Across the world, investments in PHC improve equity and access, health care performance, accountability of health systems, and health outcomes. While some of these factors are directly related to the health system and access to health services, the evidence is clear that a broad range of factors beyond health services play a critical role in shaping health and well-being. These include social protection, food systems, education, and environmental factors, among others.

PHC is also critical to make health systems more resilient to situations of crisis, more proactive in detecting early signs of epidemics and more prepared to act early in response to surges in demand for services. Although the evidence is still evolving there is widespread recognition that PHC is the "front door" of the health system and provides the foundation for the strengthening of the essential public health functions to confront public health crises such as COVID-19.

WHO response

WHO is helping countries to reorient their health systems towards PHC as a key means towards achieving UHC, SDG3 and health security. Health systems should be fit for people, fit for context and fit for purpose. Health system strengthening involves strengthening of health governance and financing; the health workforce; gender, equity and rights; information systems; quality and patient safety; maternal, newborn, child and adolescent health through to healthy ageing; sexual and reproductive health; medicines and medical supplies; emergency preparedness, response and recovery; work on communicable and non-communicable diseases, among others.

WHO has identified three strategic areas of work to strengthen PHC worldwide:

1. *Providing a 'one-stop' mechanism for PHC implementation support to Member States, tailored to country context and priorities*. This includes putting into action the Operational Framework for PHC and capitalizing on investment opportunities from the COVID-19 response, building back better PHC-based health systems during recovery efforts. This core function is driven by and builds on existing work and experiences from countries and regions from across the world.

2. *Producing PHC-oriented evidence and innovation, with a sharper focus on people left behind*. This work is based on existing implementation evidence, best practice guidance and implementation solutions, expertise from successful countries, and literature published to drive innovative solutions. Key deliverables include monitoring and measurement guidance to assess PHC progress in countries and, subsequently, a Global report on PHC progress, as well as an innovative capacity building effort as part of the WHO Academy.

3. *Promoting PHC renewal through policy leadership, advocacy and strategic partnerships* with governments, non-governmental organizations, civil society organizations, development partners, UN sister agencies, donors, and other stakeholders at global, regional and country levels. Among other initiatives, this workstream will establish an external Strategic Advisory Group on PHC to advise the WHO on PHC renewal worldwide, it will create a PHC award for recognizing PHC excellence globally, and it will promote new PHC partnerships and collaborative networks incorporating new stakeholders such as young health leaders, parliamentarians and civil society at large.