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Review article

Diaspora of haematological disorder in head and neck region – a systematic review

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ABSTRACT

Manifestation of haematological diseases and disorders can be observed in oral and maxillofacial region. Both domains of population such as paediatric and adult are involved. Equal distribution of oral and maxillofacial manifestations of haematological disorders can be witnessed in both genders. Early diagnosis by dental practitioners can lead to appropriate management, excellent prognosis and outcome. Research and development can be aimed at reduction of haematological diseases and disorders. Multi, inter and intradisciplinary approach is mandatory. Our main aim is to remove oral and maxillofacial manifestations of haemotological diseases and disorders from the global burden of diseases. In this scientific article, oral and maxillofacial manifestations of heamatological diseases and disorders have been discussed in detail.

KEY WORDS: haematology, medical, oral, pathology

INTRODUCTION

A genetic bleeding illness called haemophilia is most frequently brought on by defects in the coagulation factors VIII and IX[1]. Over the decades, it has been difficult to acknowledge that women and girls with haemophilia may bleed as substantially as affected males due to the assumption that haemophilia only affects males and is transmitted through unaffected females. It's possible that the group of women who have been labelled "haemophilic females" have complicated genetic underpinnings for their phenotype. Additionally, women and girls who are heterozygous for either haemophilia A (HA), a fault or deficiency of factor VIII (FVIII), or haemophilia B (HB), a defect or deficiency of factor IX (FIX), may experience severe bleeding that need therapy. Both the FVIII gene and the FIX gene are found towards the end of the long X chromosome arm. The pattern of X-linked inheritance, which has been known for the haemophilias from antiquity, results from the function of the X chromosome in determining sex[2].

There are two prevalent subtypes of haemophilia: HA (blood coagulation factor FVIII deficiency), and HB (blood coagulation factor FIX deficiency). Surveys of the prevalence of these illnesses occasionally include haemophilia C (blood coagulation factor XI deficit) and Von Willibrand disease (Von Willibrand factor deficiency)[3]. Women are more frequently heterozygote carriers with no or minimal symptoms of bleeding. Rarely, women can develop haemophilia due to X-chromosome inactivation (lyonization phenomenon), Turner's disease, partial or whole X chromosome deletion, or if both parents have the defective gene[1].

With 80-85% of all haemophilia cases being HA, it is more prevalent than HB. The oral cavity is a common

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and problematic source of bleeding in the haemophiliac patient. Haemophilia tests the dental professionals' abilities by causing bleeding during procedures, which in some circumstances can be fatal. These people have a high incidence of dental issues, which makes it challenging for them to maintain their dental health on an emotional and psychological level. However, treatment for these people is achievable with the right care and precautions[4]. According to the severity of the haemophilia and the form of the damage, the use of numerous units of plasma cryoprecipitates, or other concentrates are assessed, the treatment of severe bleeding episodes has typically needed hospitalization and continuous replacement therapy for 7 to 10 days[5].

METHODS

Extensive literature survey was conducted to identify the published case study, reviews, original research and bibliography on haemophilia. Search was conducted using internet-based databases such as PubMed and Cochrane library. Key words such as hemophilia A, bleeding and clotting disorders and oral manifestations of haemophilia were used in the broad screening. Inclusion criteria included open access, original papers, reviews that describe the oral manifestations and dental management of haemophilia. Articles in languages other than English were excluded. Articles were filtered by title screening, followed by abstract screening to exclude the irrelevant articles. A total of 30 articles were considered for this systematic review.

REVIEW OF LITERATURE

Two pathways—the intrinsic or contact pathway and the extrinsic or tissue factor (TF) pathway—are both activated during the formation of blood clots. Both processes involve a series of cascade enzyme activation events that result in the crosslinking of fibrin monomers and the activation of platelets, which result in the development and stabilisation of a blood clot. Disruption of the endothelium and exposure of TF in the subendothelium initiate the extrinsic pathway. To activate factors IX and X into IXa and Xa, respectively, TF attaches to active factor VIIa to create a complex. Factor XII, prekallikrein, and high-molecular-weight kininogen in the blood are exposed to an artificial surface, activating the intrinsic pathway. A conformational shift in factor XII causes a little amount of factor XIIa to be produced, which then activates PK to kallikrein with reciprocal activation of factor XII to XIIa. Factor XI generates factor XIIa as a result, which then activates factor XI to factor XIa, converting factor IX to factor IXa. At the point where factor Xa is produced, both paths meet. Prothrombin (factor II) is changed into thrombin (factor IIa) by factor Xa. In turn, thrombin assists in the release of factor VIII from the von Willebrand factor and activates it into factor VIIa, activates platelets by disabling phospholipids that bind factor IXa, and activates factor XIII into factor XIIIa, which aids in clot stabilisation by cross-linking fibrin monomers. A tenase complex made up of factor IXa, factor VIIa, calcium and phospholipids attract a lot of factor X to activate it. In turn, prothrombin is transformed into thrombin with the aid of factor Xa, calcium and phospholipids in the prothrombinase complex. Then, fibrinogen is divided into monomers by the assistance of thrombin. Since the intrinsic pathway of the coagulation cascade cannot be properly triggered when factor VIII and factor IX are insufficient or dysfunctional, the process of clot formation is inadequate[6]. The presence of spontaneous bleeding, which varies in frequency and severity depending on the level of factor present at the plasma level, is a symptom of haemophilia, which is characterized by a lack of coagulation factors that causes a decrease in haemostasis.

- Mild deficiency (5-40% FVIII activity): It usually only presents with bleeding after surgical procedures.
- Moderate deficiency (1 to 5% FVIII activity).
- Severe deficiency (<1% FVIII activity): More frequently occurring spontaneous bleeding, which primarily affects the joints, is one of its defining characteristics. It can manifest as early as conception and displays a severe bleeding characteristic[7].

Muscle and joint haemorrhages, notably in the knees, elbows and ankles, are the clinical hallmarks of HA. The typical initial symptoms of acute hemarthroses are mild discomfort and a minor restriction in joint motion, which are thereafter followed by pain, joint swelling and cutaneous warmth. Joint haemorrhage typically results in a severe limitation of motion if left untreated. Sadly, the pathologic processes go on even after the bleeding stops because inflammation damages the blood-filled joints, causing synovitis, which raises the risk of recurrent hemarthroses in the same joints (the so-called target joints). The narrowing of the joint space as a result of cartilage loss, the growth of bone cysts, and motion restriction that results in lifelong impairment is the last stage of this vicious cycle that causes hemophilic arthropathy[8].

Joints that bear weight develop warmth, tenderness and pain, which trigger synovial hypertrophy, cartilage degradation and secondary osteoarthritis. Calf muscle hematomas that are left untreated can increase pressure and eventually lead to ischemia, necrosis, fibrosis and later Achilles tendon contraction and shortening. Massive intrauterine bleeding leading

Table 1: An overview of oral manifestations of haemophilia[1-4,8-18]

Author	Key focus area	Findings	Conclusion
Shilpa Padar Shastry *et al*[4], 2014	Review of hemophilia A with emphasis on its oral manifestations, investigations, and dental management.	Hemophilia A, which occurs due to deficiency of factor VIII, is the most common of the three, accounting for 80-85% of the cases.	The close cooperation between hematologists, general physicians, oral physicians and surgeons, and general dentists will help to provide utmost care and appropriate treatment for patients with hemophilia A, avoiding all unfavorable consequences.
Ruta Zaliuniene *et al*[9], 2014	Overview of the oral health aspects in hemophilia patients.	Main consequences of bleeding episodes in hemophilic patients are: hemarthrosis 70-80%, muscle/soft tissue bleeding 10-20%. Bleeding affects joints with predominant sequence: knee (45%), elbow (30%) and ankle (15%).	The population's share of people with congenital hemorrhagic diatheses is quite minimal. Due to the fact that the majority of dentists lack the necessary experience to manage oral issues in such patients, treating these patients presents a challenge.
Katayoun Salem *et al*[13], 2018	Assessment of the oral and dental health status in children and adolescents with hemophilia in Rasht, Iran.	The mean age of the subjects was 10.49±4.21 years in the case group and 10.5±4.07 years in the control group. 92.5% of the patients exhibited factor VIII deficiency and the most frequent blood group was A (34%).	92.5% of the patients with hemophilia had factor VIII deficiency and the rest had deficiencies of factors VII and IX. Prevention of dental problems is the main principle in oral care and might result in the avoidance of emergency events.
Ricardo Martínez-Rider *et al*[14], 2017	Clinical case report on dental management of child with incidentally detected hemophilia.	An 8.10-year-old boy without history of significant bleeding events reported to clinic complaining of lack of eruption of both permanent upper central incisors, vestibular squared incision over the gingiva with flap apical reposition, to expose the incisal third of both incisor crowns.	The patient underwent an 8-hour intravenous infusion of tranexamic acid (250 mg), vitamin K (5 mg), and normal saline to control the bleeding; at the end of this period, the haemorrhage was eventually stopped, and the patient was released.
Yanji Qu *et al*[3], 2014	Review on studies providing data of the prevalence of hemophilia or its subtypes.	The overall weighted prevalence of hemophilia was 3.6 per 100,000 and the prevalence among males was 5.5 per 100,000.	Based on the prevalence of haemophilia in mainland China identified by our study, 49,339 haemophiliacs are thought to reside there.
Connie H. Miller [et al][2], 2021	Application of tools in understanding the genetic causes of haemophilia in women and girls.	Coagulation parameters, F8 or F9 sequencing, F8 inversion testing, multiplex ligation-dependent probe amplification, karyotyping and X chromosome inactivation studies performed on the patient and parents.	Homozygous females with two abnormal alleles will have the same phenotype as hemizygous males, while heterozygous females are usually protected by the presence of a normal allele on their second X chromosome.
Xavier Frachon *et al*[15], 2005	To evaluate the effectiveness of a protocol combining general management through the injection of factor concentrates or DDAVP and local hemostasis using biological glue and gelatin packing, a retrospective study of 55 dental extractions performed during 19 interventions in 16 patients with haemophilia A or B was conducted.	4 of the 6 incidences of postoperative haemorrhage took place following the compression period. In 2 cases, injecting an antihemophilic factor concentrate was necessary in addition to repeating the local hemostasic procedures. Following the injection of the factor concentrate and the reapplication of the compression in the remaining 4 cases, the patients' conditions returned to normal.	A combination of an injection of coagulation factor concentrate or DDAVP, and use of an effective local hemostatic technique can, in most cases, prevent the onset of excessive, postsurgical bleeding.
M. Franchini *et al*[8], 2005	In a retrospective study conducted at three Italian haemophilia centres over a ten-year period, data on the oral health of patients with congenital hemorrhagic diseases was assessed.	Between 1993 and 2003, 247 patients with inherited bleeding disorders underwent 534 dental procedures including 133 periodontal treatments, 41 conservative dentistry procedures, 72 endodontic treatments and 288 oral surgery procedures.	A total of 10 bleeding issues (1.9%) were noted, the majority of which included individuals with severe or moderate haemophilia A who required multiple teeth extractions. Therefore, it has been demonstrated that their protocol of management for patients with genetic bleeding predisposition having oral therapy or surgery is successful in reducing hemorrhagic complications.

Gary Benson *et al*[1], 2018	Reviews on creating treatment regimens for people with haemophilia, covering the complete spectrum from clinical care for a newborn who has just been diagnosed to that for an elderly patient with several concomitant conditions.	Treatment options for managing bleeds in patients with mild/ moderate haemophilia who have developed inhibitors are recombinant activated factor VII (FVIIa, NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) or, if antibodies are directed against exogenous FVIII only, DDAVP.	Management strategies consider not only the vast differences in hemophiliac patients' needs, but also risks of inhibitor development and approaches to optimally engage patients.
Martha Cecilia Elizondo Rojas *et al*[10], 2022	Reviewing considerations in the dental office in the management of the hemophiliac patient.	In order to control or avoid bleeding, haemophilia A or B patients must receive intravenous infusions of replacement clotting factors. Since it is used most frequently after bleeding has started—in other words, in reaction to a hemorrhagic event—this replacement strategy is known as the "on demand" treatment.	The recommendations state that patients with early childhood easy bruising, spontaneous bleeding, and severe bleeding after trauma or surgery should have haemophilia suspected. Practise recommendations are required to enhance the diagnosis procedure and level of care.
Sara Israels *et al*[16], 2006	Reviews on preoperative systemic precautions and intraoperative hemostatic measures.	Techniques for managing postoperative bleeding episodes such as reapplication of pressure packs, packing or repacking sockets with Gelfoam, reinjection of local anesthetic with epinephrine, use of astringents are recommended.	Studies conducted in the last ten years have revealed a surprising level of intricacy related to the hemostatic process. Blood loss at the site of damage is immediately stopped by a finely orchestrated action of cellular and soluble components.
Waldemar Reich *et al*[17], 2009	Prospective assessment to determine the incidence of postoperative bleeding after oral surgery under local anaesthesia performed in outpatients with haemostatic disorders within a 5-year period.	One hundred twenty-one (70 males, 51 females) out of 2,056 outpatients with different haemostatic disorders (acquired or hereditary) were included. Postoperative bleeding was observed in 12 patients (9.9%). In three cases, inpatient treatment became necessary.	Treatment modalities such as Collagen vlies, primary suture, fibrin glue with appropriate operative technique enabled effective wound management.
Naveen Kumar J *et al*[18], 2007	Prescription of a simple protocol to diagnose bleeding disorders and a modified scheme for endodontic and periodontal therapy in a hemophiliac patient.	A prolonged activated partial thromboplastin time (APTT), normal prothrombin time (PT), normal bleeding time (BT), and low Factor VIIIC are the main diagnostic laboratory findings in haemophilia. Since even the APTT may be normal in mild cases, factor VIII assays are typically necessary.	Endodontic therapy may typically be performed under antifibrinolytic cover in all patients other than severe haemophiliacs. Avoiding instrumentation via the periapex is crucial in endodontic therapy. Replacement of LA and Factor VIII to a level of between 50 and 75% is necessary for periodontal surgery. Postoperative factor level maintenance is case-dependent, as expected.

DDAVP: 1-deamino-8-arginine vasopressin

to stillbirth and newborn cerebral bleeding are possible symptoms of severe cases. After trauma or minor surgical operations, there is a propensity for quick bruising and severe haemorrhage. Additionally, spontaneous middle ear bleeding, epistaxis, bleeding into joints that results in hemarthrosis, and bleeding into soft tissues are all possible. Haemophilia pseudotumors are tumor-like structures caused by tissue bleeding[4].

Multiple sites of bleeding are a hallmark of haemophilia, which usually takes the form of gingival and post-extraction haemorrhages in the mouth. Depending on the degree of severity of their haemophilia, patients may also experience several oral bleeding incidents throughout their lifetime. Bleeding episodes are less common in mild haemophilia and more common in severe haemophilia, followed by moderate haemophilia. Oral bleeding can also be brought on by iatrogenic causes and poor oral hygiene. Oral ulcerations and ecchymosis affecting the lips and tongue are frequent in toddlers[4].

Dental caries and gingivitis/periodontitis are the two main oral conditions that haemophiliac individuals have, just like the general population. It is probable that congenital coagulation problems are risk factors for dental caries, gingivitis, periodontitis and ensuing alveolar bone loss since these patients are reluctant to take necessary precautions against common bleeds[9].

The initial step is to identify the patients based on their clinical and family histories, risk factors for the disease and laboratory results. The main goal is to give patients dental treatment and care recommendations that will help them avoid the most common dental illnesses, like dental caries and periodontal disorders. Due to their incapacity to

practice proper oral hygiene, hemophilic patients are more prone to periodontal disorders than the general population. Additionally, the gingival sulcus is home to a variety of aerobic and anaerobic microbes that cause periodontal degeneration. The patient becomes aware of the necessity of routine visits for professional prophylaxis, examinations and treatment as well as the prevention of these organisms from producing gingival irritation[4].

Spontaneous mucosal bleeding, episodic, protracted, spontaneous or traumatic gingival bleeding are all very common. Additionally, there are hemophilia-related pseudotumors and hemarthrosis of the temporomandibular joint. Haemophilia patients must receive care that is focused on comprehensive care. In order to control or avoid bleeding, HA or HB patients must receive intravenous infusions of replacement clotting factors. This replacement approach is known as the "on demand" treatment because it is used the most frequently when bleeding has already started, *i.e.*, when the factor is used in reaction to a hemorrhagic episode. As a preventative step, treatment can be given on a regular basis without having to wait for a bleeding event to happen; this is known as prophylaxis. This plan is regarded as best practice in individuals with severe haemophilia, according to certain scientific research. Similarly, it is believed that replacing the deficient clotting factor is the best strategy to treat haemophilia so that the blood can coagulate normally. Blood plasma-derived clotting factor concentrates and recombinant clotting factor concentrates are the two primary varieties[10].

It is important to take into account the patient's level of haemophilia. If surgery, serious injury or teeth extractions are avoided, mild haemophilia may not be discovered until adolescence. As a result, a dentist might occasionally be the one to identify a patient's haemophilia. According to research, 30% of mild instances were only discovered after a major oral bleeding episode. To treat patients with hemostasis issues, the dentist needs to have a foundational understanding. The essential aim is to gather accurate clinical history so that you can use this information to create a proper treatment plan with the patient's treating physician. It is crucial to involve the patient in their care and emphasize the fact that with good oral hygiene and preventative measures, the dentist's involvement will be minimal, lowering the likelihood of any potential bleeding issues. To deliver thorough and high-quality dental care, there should be close communication between the dentist and the patient's medical team. Avoiding unintentional harm to the oral mucosa is crucial when performing any procedure in the mouth. Usage of saliva collector, impression removal, placement of x-ray film, especially in the sublingual region, use of a gum shield to protect soft tissues during reconstructive treatment, and application of soft yellow kerosene like petroleum jelly can all help prevent injury. Due to the abundance of expanded capillaries on the surface of the thinner regions of the gingiva, patients may present with bouts of spontaneous bleeding during teeth brushing, food abrasion or periodontal disease. Haematologists and dentists working together results in successful dental care for haemophiliac patients. Before and potentially after more extensive treatments like scaling and root planning, it could be necessary to raise the factor level to ensure proper coverage.

Using local anaesthesia for dental treatment is crucial. Factor replacement is necessary for lower alveolar blocks because they run the risk of hematoma formation in the retromolar or pterygoid spaces, which could limit the airway and cause bleeding into the muscles that surround them due to rich vasculature and blind injection. The only procedures that can necessitate hospitalization are oral surgery, periodontal surgery, and any dental procedure requiring anaesthesia with inferior alveolar nerve block and lingual infiltration anaesthesia. There are no limitations on the kind of local anaesthetic agent that can be employed, albeit those that contain vasoconstrictors may offer more local hemostasis. Most dental discomfort can be managed with a mild painkiller like paracetamol. Since acetylsalicylic acid prevents platelet aggregation, it shouldn't be utilized. Non-steroidal anti-inflammatory medicines (NSAIDs) have an impact on platelet aggregation, hence the patient's haematologist should be consulted before using any NSAIDs. Without the necessity for factor replacement, buccal infiltration can be used to anaesthetize the entire upper teeth as well as the anterior lower dentition and premolars. It is advised to use Articaine as a local anaesthetic, and various studies have demonstrated that inferior alveolar blocks can be avoided in favour of buccal infiltration of the jaw[10]. An overview of oral manifestations of haemophilia based on key focus areas has been mentioned in Table 1[1-4,8-18].

CONCLUSION

Hemophilia is an X-linked recessive inherited disorder. It is a member of the class of hereditary diseases brought on by a shortage of one or more coagulation factors. Patients with a history of spontaneous bleeding, especially into the joints, muscles and soft tissues, or prolonged bleeding after trauma or surgery should be suspected of having haemophilia. A family history of bleeding disorders should be carefully elicited because haemophilia runs in families. Patients with a bleeding disease require

dental management in collaboration with a haematologist.

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Original Article

Effect of different pneumoperitoneum pressures in laparoscopic cholecystectomy on levels of transaminases and GGT, randomized clinical trial

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ABSTRACT

Objectives: Laparoscopic cholecystectomy (LC) has changed the past history of gallstones treatment. Pneumoperitoneum with 12 mmHg significantly affects the hepatic and gastric microcirculation causing splanchnic ischemia. The present study assessed the effect of different pneumoperitoneum pressures during LC on liver enzymes.
Design: Randomized clinical trial
Setting: Tertiary university hospitals
Subjects: Patients having symptomatic cholelithiasis and indicated for cholecystectomy (recurrent biliary colic and cholecystitis)
Interventions: The study was conducted at Kafrelsheikh University hospital from June 2018 to June 2019. Two groups were randomly arranged with patients having cholelithiasis. Group I had LC with 10 mmHg pneumoperitoneum, while group II was at 14 mmHg pneumoperitoneum. The laboratory tests were performed preoperatively and 24 hours after surgery to assess the enzyme level differences.
Main outcome measures: Serum levels of aspartate aminotransferase (AST), alanine transaminase (ALT) and gamma-glutamyl transferase (GGT).
Results: A significant increase was noted after 24 hours of surgery in the serum levels of AST, ALT and GGT ($P<0.001$ in all). The AST, ALT and GGT levels were significantly higher in group II than group I.
Conclusion: The increased levels of serum liver enzymes after the performance of laparoscopic cholecystectomy are caused by a transient decrease in splanchnic blood flow. It is advised to use a lower pneumoperitoneum (10 mmHg).

KEY WORDS: laparoscopic cholecystectomy, LC complications, liver function tests, pneumoperitoneum

INTRODUCTION

Laparoscopy rapidly gained widespread acceptance and has been proved to have fewer adverse effects than open surgeries. Laparoscopy has multiple benefits, such as the short hospital stay time, low postoperative pain, early work return and good cosmetic results[1]. For decades, laparoscopic cholecystectomy (LC) had been the standard performed operation for the management of cholelithiasis, now being one of the most commonly performed operations[2].

Despite being the gold standard, there are some concerns about the adverse effects of pneumoperitoneum used in LC. It was found that pneumoperitoneum affects the hepatic function in healthy patients[3]. Pneumoperitoneum causes a transient decrease in the hepatic blood flow. The duration and pressure of this pneumoperitoneum were proved to affect the level of hepatic ischemia that was caused by the elevated liver enzymes[4].

However, it seems that these changes are out of significant clinical importance; these are transient effects and would be rapidly reversed to normal; we are faced in practice by patients with compensated chronic liver diseases that might deteriorate secondary

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to operative ischemic insult. Our aim is the evaluation of post LC changes in liver function tests (LFTs) with the low-pressure pneumoperitoneum (10mm Hg) versus the standard pneumoperitoneum (14mm Hg) and determination of its applicability.

SUBJECTS AND METHODS

Study population

The study is a randomized controlled study conducted between June 2018 and June 2019 on 141 patients with cholelithiasis who were admitted at the Department of Surgery, Kafrelsheikh University Hospital.

The study included patients having symptomatic cholelithiasis and indicated for cholecystectomy (recurrent biliary colic and cholecystitis) aged from 20 to 75 years of either sex with physical status I and II according to the American Society of Anesthesiologists. Written informed consent was obtained from each participant. Patients who were diagnosed during pregnancy, patients with acute cholecystitis, common bile duct (CBD) stones, gall stone pancreatitis, liver disease patients, and those having elevated levels of liver enzymes prior to the surgery were excluded. The patient characteristics, complete history, laboratory and imaging parameters were the basics of the evaluation.

The sample size calculation of each group was performed by Sealed Envelope Ltd. 2012. Power calculator for continuous outcome superiority trial, considering the difference in LFTs in a previous publication[5] with consideration of the power of study as 80% and level of significance as 5%.

Randomization

Randomization was performed by block randomization using Microsoft Excel 2016. In Group I, referred to as the low-pressure LC group, patients had laparoscopy at pneumoperitoneum of 10 mm Hg, while in group II, referred to as the standard-pressure LC group, patients had a laparoscopy with pneumoperitoneum of 14 mm Hg. The allocation was concealed by the opaque sealed envelope technique. The randomization was done by a person who was not part of the research or the surgery team. A nurse out of the study opened the envelopes out of the operating room before the surgery. During the postoperative care, until the 7th day (the final results), all patients and nurses were blinded about the group type. We analyzed the data of the groups at the end of the study after being decoded.

The ethical committee of the hospital approved the protocol of the study. We explained the operation to the patients and obtained written consent before enrollment in the study.

Preoperative evaluation

Good history taking with a complete physical examination was performed for all patients. All needed laboratory and imaging investigations were done, including complete blood count, liver function tests (alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin, gamma-glutamyl transferase (GGT)), blood glucose level, renal function tests (urea and creatinine), coagulation profile, albumin level, abdominal ultrasonography for all patients, computed tomography and magnetic resonance cholangiopancreatography if needed for exclusion of CBD stones.

Operative technique

Laparoscopically well-trained consultant surgeons with similar experience performed the operations. The LC was performed for patients of group I after creating 10 mmHg of pneumoperitoneum. The insufflation pressure, in the beginning, was at 10mm Hg and was maintained by an automatic insufflator. The four ports were inserted after head elevation and tilting of the patient to the left side; two 10 mm ports (supraumbilical and epigastric regions) and two 5 mm ports (right lateral and in subcostal region two fingers below midclavicular area). Calot's triangle was identified and dissected, showing the critical view of safety. The cystic duct and the cystic artery were divided after clipping of them. Removal of the gall bladder from the liver bed was performed by using the electrocautery, with the exclusion of the patients who needed excessive burn of gall bladder bed to control bleeding. The same technique was performed in group II at 14 mmHg of pneumoperitoneum. Cholecystectomy was performed under general anesthesia using the same protocol and medications for all patients; intravenous anesthesia was inducted, then continuous volatile anesthesia under mechanical ventilation. We paid attention not to use drugs that interfere with the liver's enzymatic activity. There was no performance of intraoperative cholangiography and manipulation of the biliary system.

The same drugs and infusions were administrated to all patients with the exclusion of hepatotoxic drugs like paracetamol. Assessment of the LFTs was performed by measuring the serum level of ALT, AST and GGT before the operation, at 24 hours after surgery and on the 7th day in the same laboratory with the same autoanalyzer. Operative time was calculated, and intraoperative complications and adverse events were recorded. We defined serious adverse events as life-threatening situations in which more hospital stay time than the ordinary time may be required or situations in which a significant or persistent disability has resulted. A scale of 1 to 10 was used to assess the

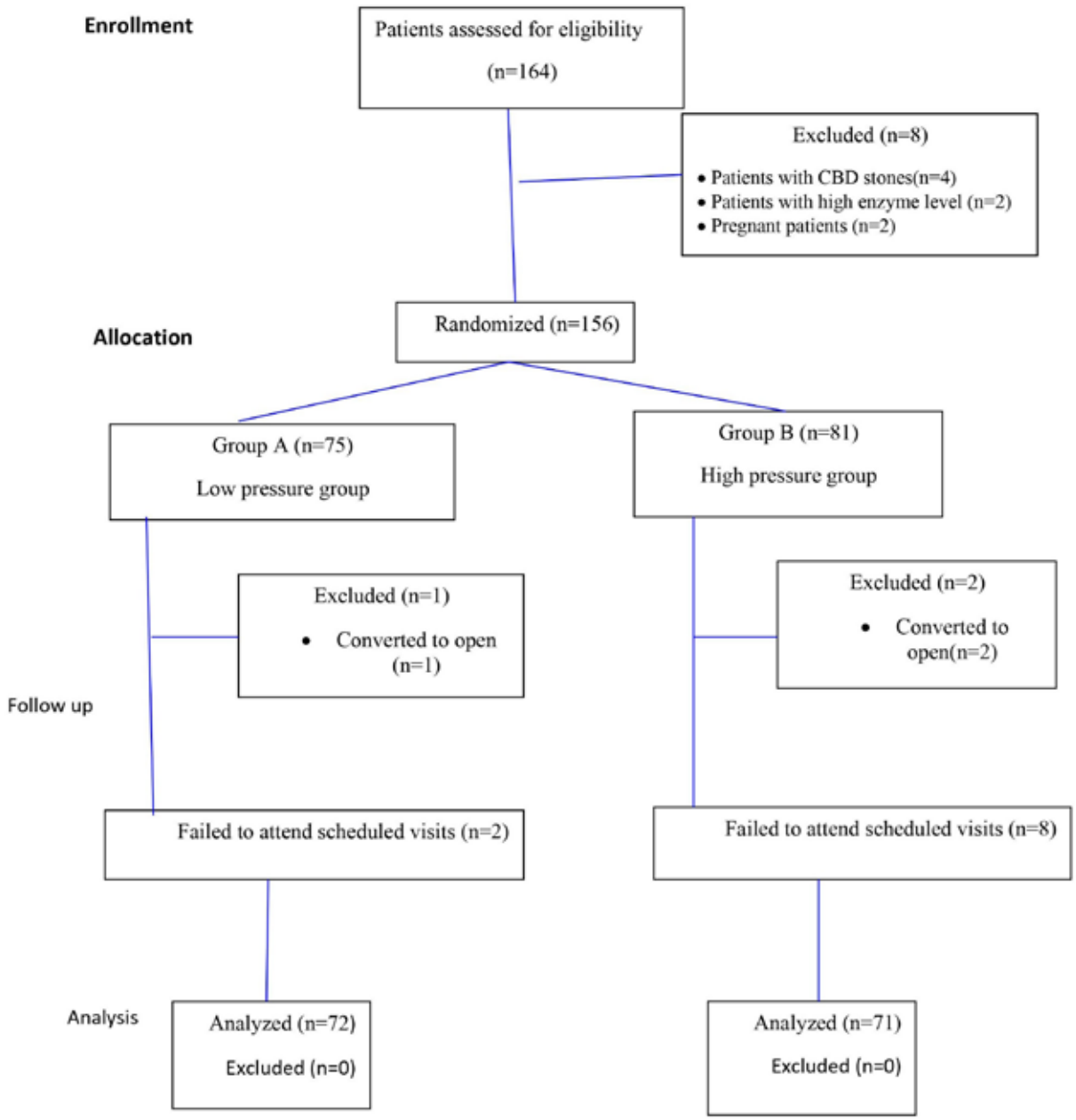

Figure 1: Consort flow diagram

level of the surgeon's comfort with dissection using four parameters (easy port insertion, visibility, port manipulation and easy dissection). The conversion rate to an open procedure was noted, and the number of cases in which the pneumoperitoneum was escalated to the normal pressure. The time until the back to normal daily activities after LC was recorded on the 7th day of operation.

Statistical analysis

Data were analyzed using the SPSS software package version 20.0 (Prentice Hall, Chicago, IL, USA). Qualitative data were described using numbers and percentages. Analysis of preoperative and postoperative means of enzymes levels was performed by paired t-test, while comparison of the means between the two groups was done by an unpaired t-test. Comparison between the two groups regarding categorical variables was done using the Chi-square (X^2) test. A *P* value of <0.05 was considered to be statistically significant. Per protocol analysis of adverse effects was performed.

RESULTS

A total of 164 patients were evaluated for LC from the outpatient clinic. Eight patients were

excluded from the study; four had CBD stones, two had preoperative elevated liver enzymes, and another two were pregnant women. The remaining 156 patients were allocated into two groups using the closed envelop method. Group I included 75 patients for whom LC was performed at 10 mmHg pneumoperitoneum and 14 mmHg pneumoperitoneum for 81 patients in group II.

Table 1: Demographic and perioperative characteristics of the patients

Demographic and Perioperative Characteristics of the patients	Group I (n=72)	Group II (n=71)
Age (in years) mean (SD)	37.66(10.85)	40.54(11.16)
Gender (male: female)	13:59	11:60
ASA (I/II)	42/27	49/23
Mean BMI(SD) (kg/m^2)	27.11(3.32)	27.5±4.34
Operative time (in minutes) mean (SD)	66.8(8.6)	57.7(10.4)
ALT (IU/L) mean (SD)	23.2(13.42)	26.47(11.93)
AST (IU/L) mean (SD)	23.75(10.74)	28.34(13.75)
GGT (IU/L) mean (SD)	39.06(25.74)	41.97(35.77)

ASA: American Society of Anesthesiologists; BMI: body mass index; ALT: alanine transaminase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase.

We excluded three patients from the study, one in Group I and two in Group II due to conversion to open cholecystectomy; two of them had intraoperative bleeding, and one had cystic duct injury by the clip at the junction of the cystic duct with the CBD. Ten patients were lost during follow up 2 in group I and 8 in group II leaving 143 patients, 72 in group I and 71 in group II who represented the population of the present study (Figure 1).

Both the groups were comparable regarding the patient's age, gender and body mass index (BMI). The two groups had no significant difference regarding the operative time (P>0.05). Also, preoperative LFTs and GGT showed no significant difference between both groups (Table 1). There were no postoperative morbidity or mortality issues in any of the patients included in the study. There was no need for any other medication outside of the used anesthetic protocol. There was no significance regarding the duration of hospital stay.

Table 3: Surgeon comfort during laparoscopic cholecystectomy performed at low pressure (10 mm Hg) and standard pressure (14 mm Hg) in mean (SD) (on a scale of 1-5) surgeon comfort

Parameters	LPPLC (n=72)	SPPLC (n=71)	*P*
Ease of port insertion	3.75±1.2	4.3±2.1	0.06
Visibility of the field	3.83±1.69	4.45±0.9	0.01*
Manipulation of instruments	4.2±1.32	4.44±1.21	0.26
Ease of dissection	3.96±1.26	4.32±0.96	0.058

SPPLC: standard pressure laparoscopic cholecystectomy; LPPLC: low pressure laparoscopic cholecystectomy.

There was a significant difference between the preoperative mean value of AST, ALT and GGT and 24 hours after surgery. The AST, ALT and GGT levels in group II were significantly higher than in group I (P=0.05, 0.001 and 0.01, respectively). These enzymes were back to normal values on the 7th day in the two groups (Table 2).

There was no significant difference regarding the surgeon's comfort level except with the field visibility in the standard pressure laparoscopic cholecystectomy (SPPLC) group. The comfort level was calculated for ease of ports insertion, visibility, instruments manipulation and ease of dissection (Table 3). Thermal injury of the common bile duct was experienced in one patient in SPPLC group, causing a minor leak, and was managed by inserting an endoscopic stent by endoscopic retrograde cholangiopancreatography (Table 4). On the 7th day of follow-up, the normal daily activities were continued.

Table 2: Postoperative changes in liver function tests after laparoscopic cholecystectomy performed at low pressure (10 mm) and standard pressure (14 mm Hg)

Parameters	Preoperative	*P**	Postoperative (24 h)	*P**	Postoperative (7days)	*P**	*P#*
Aspartate transaminase (AST) (IU/L)		0.06		0.05		0.8	
Group I	23.75(10.74)		41.93(25.74)		36.5(8.21)		<0.001
Group II	26.34(13.75)		50.12(25.26)	0.001	35.93(10.79)		<0.001
Alanine transaminase (ALT) (IU/L)		0.13				0.7	
Group I	23.2(13.42)		37.12(20.68)	0.01	25.95(16.52)		<0.001
Group II	26.47(11.93)		48.49(19.53)		25.42(13.38)		<0.001
Gamma-glutamyl transferase GGT (IU/L)		0.19				0.19	
Group I	39.06(25.74)		49.1(30.36)		40.01(23.64)		<0.001
Group II	41.97(35.77)		63.79(39.23)		43.86(32.67)		<0.001

*P value: t-test between the two groups.
#P value: Paired sample t-test between preoperative and 24-h postoperative period (intragroup variation analysis)

Table 4: Adverse events in both groups.

Parameters	LPPLC (n=72)	SPPLC (n=71)
Bleeding	3	2
Bile duct injury (n)	0	1
Gut injury (n)	0	0
Surgical site infection (n)	2	1
Drain placement (n)	1	1

SPPLC: standard pressure laparoscopic cholecystectomy; LPPLC: low pressure laparoscopic cholecystectomy.

DISCUSSION

Cholecystectomy has been the standard procedure in the treatment of benign gallbladder conditions. Nowadays, laparoscopic cholecystectomy is the commonly performed method[6-8]. Some adverse effects could result from the increased intra-abdominal pressure like the laparoscopic pneumoperitoneum[9-11].

Many studies have proven the marked rise of the serum liver enzymes level after laparoscopy, and this is taught to be the cause of the impaired liver and splanchnic perfusion[12-16]. Hepatic hypoperfusion induced by the pneumoperitoneum during laparoscopy as the portal venous pressure (7-10 mm Hg) is lower than the standard insufflation pressure (15 mm Hg) during laparoscopic cholecystectomy; the intraoperative portal venous flow could be decreased by the pneumoperitoneum causing liver enzymes elevation. Hepatic hypoperfusion at abdominal pressures higher than 6 mm Hg was described in a previous experimental study[17]. Eleftheriadis *et al* found a reduction in the microcirculation of the liver with 12 mm Hg pressure in laparoscopic cholecystectomy, while after the desufflation, there was an abrupt elevation[18].

Our study was conducted for evaluation of liver enzyme changes after different pressures of pneumoperitoneum in LC and knew the applicability and feasibility of the pneumoperitoneum in patients with BMI below 30k/m^2.

The physiological changes caused by abdominal pressure were reduced without any effect on the outcome of surgery when the pneumoperitoneum pressure was in a low range (8-10 mmHg). Performing LC with low-pressure pneumoperitoneum did not affect the operative time in the present research; there was no significant difference between the two groups regarding the operative time, 66.8(8.6) minutes in the low-pressure group and 57.7(10.4) in a high-pressure group (P=0.1). Hence, we recommend using low-pressure pneumoperitoneum, especially in low BMI patients and patients with borderline liver enzymes.

In agreement with our finding, Gurusamy *et al*[19] reported in their Cochrane database of systematic reviews that the operative time was only two minutes longer in the low-pressure group, without clinical significance or effect on the hospital stay.

In the present study, there was a significant elevation in the mean value of AST, ALT and GGT after 24 hours of LC in comparison to the preoperative values. Group II had higher levels of AST, ALT and GGT than group I (P=0.05, 0.04 and 0.03, respectively).

Jakimowicz *et al* found a portal venous flow reduction (53%) at 14 mm Hg of intraabdominal pressure. Reduction of these adverse effects is possible by gasless or low-pressure laparoscopic procedures as abdominal hypertension causes hepatocytes ischemia[20,21]. Morino *et al* found that the significance of the elevated levels of AST and ALT was higher if the operative time was more than 60 minutes after the investigation of the pneumoperitoneum time at constant pressure[22].

Under our results, Eryılmaz *et al*[23] applied the same technique using 14 and 10 mm Hg pneumoperitoneum pressure, and they found that AST and ALT levels were elevated in the 1st postoperative hour after 14 mmHg pneumoperitoneum in the surgery that caused a reduction in the blood flow to the liver; they concluded that pneumoperitoneum at 10 mmHg is better than 14 mmHg during laparoscopic cholecystectomy. Atila K *et al*[1] attributed the subclinical hepatic dysfunction after LC to the negative effects of hepatic blood flow by the pneumoperitoneum.

CONCLUSION

Elevated liver enzymes after laparoscopic cholecystectomy is caused by a transient reduction in splanchnic blood flow. Pneumoperitoneum at lower levels (10 mmHg) has a less harmful effect, and it is better to be adopted than 14 mmHg pneumoperitoneum without a significant increase in the operative time.

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Original Article

Investigation of key genes involved in MAPK/ERK and PI3K/AKT pathways in familial aggregation of hematological malignancies

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ABSTRACT

Objective: Investigating the key genes RAF1, BRAF and PIK3CA involved in MAPK/ERK and PI3K/AKT pathways in familial hematological malignancies
Design: Cross sectional study
Setting: Institute Paoli Calmette of Marseille, Faculty of Medicine of Sousse
Subjects: 107 patients belonging to 92 independent families (17 Tunisian and 75 French) diagnosed with hematological malignancies and associated cancer forms.
Intervention: A mutational analysis of RAF1, BRAF and PIK3CA genes involved in MAPK/ERK and PI3K/AKT pathways in 100 familial cases of blood cancer
Main outcome measure: Genes variations
Results: The RAF1 c.1669-36C>T detected in 31% of our cases have been associated with low gene expression in several tissues and have been described in many cancer forms. The BRAF c.1315-11T>G intronic variant in one patient diagnosed with Hodgkin's lymphoma may weaken the authentic acceptor-splicing site of the exon 11 by 34%, which is in favor of a probably deleterious effect. The BRAF c.1992+16G>C variant shows a high fixation index which could be important for appropriate anticancer drug selection. No PIK3CA variations were found.
Conclusion: We report some variants with potential deleterious effect that could be considered in the genetic background of familial hematological malignancies.

KEY WORDS: BRAF, familial cases, hematological malignancies, RAF1, PIK3CA

INTRODUCTION

Familial hematological malignancies (FHM) aggregations have been described in literature as rare events. Recent studies hypothesize that these pathologies are underdiagnosed. The recognition of inherited predisposition of hematological malignancies may lead to anticipated diagnosis in families with high risk and provide them with a better prognosis.

Several genes have been previously investigated related to FHM, specially those involved in the mitogen-activated protein kinase pathway (MAPK/ERK) and the lipid kinase phoshoinositide-3-kinase signaling pathway (PI3K/AKT) in several forms of cancer and particularly in hematological malignancies. Both pathways shown in Figure 1 play an important role in cell signaling, assuring prominent cellular processes such as growth, proliferation and apoptosis[1].

Alterations of genes coding the signaling cascade proteins in MAPK/ERK and PI3K/AKT pathways lead to human cancer and developmental disorders[2-4]. Among these genes, RAF1 (previously known as CRAF), BRAF and PIK3CA were reported as major features of tumorigenesis and malignant progression when disrupted.

The RAF1 and BRAF are key effector genes in the MAPK/ERK pathway, leading to the phosphorylation and translocation of ERK into the nucleus via the

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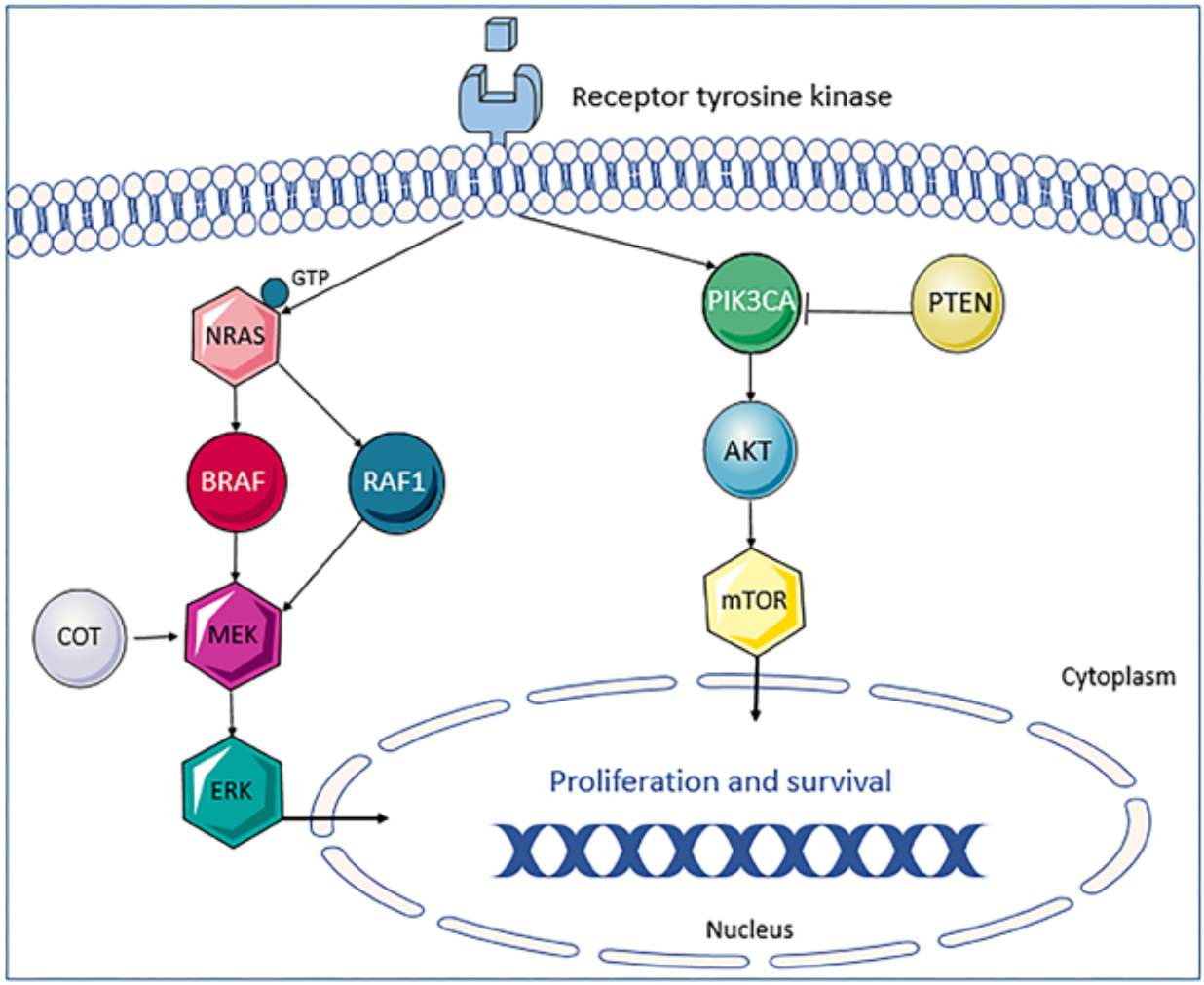

Fig 1: MAPK/ERK and PIK3CA/AKT signaling pathways.

MEK protein[5]. The MAPK/ERK is the most described pathway in association with human cancer, and genes playing signaling roles in this pathway are widely targeted for cancer therapy[6].

The BRAF gene is located on chromosome 7q34; it encodes a protein kinase, B-Raf. Most mutations of this gene induce constitutional activation of the protein kinase and are found in diverse cancer forms[7-8] including mainly solid tumors, particularly melanoma[9], thyroid[10] and colon cancer[11].

Interestingly, BRAF mutations have also been reported in hematological malignancies, including chronic lymphocytic leukemia[12], hairy cell leukemia[13] and de novo acute myeloid leukemia[14].

The RAF1 gene is located on chromosome 3p25; it encodes for a MAP3 kinase. Somatic mutations of this gene were less described in cancer compared to BRAF[15]. This gene is altered in only 1.07% of all cancers[16], and most of the described mutations occur in the CR2 domain (cysteine-rich domain), which may hamper the kinase activation. Mutations may lead to drug resistance in melanoma and lung cancers which make the RAF1 gene study of a clinical interest[17,18].

RAF1 mutations have been invoked in several forms of hematological malignancies. However, a few number of germline mutations within the RAF1 oncogene were reported. S427G and I448V mutations induced leukemic transformation in acute myeloid leukemia[19-21].

The PIK3CA gene encodes a phosphatidyl inositol 3-kinase (PI3K) that activates AKT through phosphorylation which leads to numerous downstream effects via the activation or the inhibition of multiple proteins involved in cell motility, adhesion, angiogenesis, metabolism, apoptosis and regulation of growth and proliferation[22]. The most common alterations in the PI3K pathway involve PIK3CA oncogene[23], in which most mutations occur in hotspot regions including exons 9 and 20 with respective frequencies of < 5% and 20% of all mutations[24].

Table 1: List of variants detected in the cohort of patients

Gene	Variant	SNP ID	Number of patients	Gnomad frequency	Clinical significance	References
RAF1	c.1193+124T>C	rs2290160	1	0.23342	Benign	No citations
RAF1	c.1194-179C>G	rs2596831	2	0.43543	Benign	No citations
RAF1	c.1371-45C>T	rs3730275	2	0.01277	Likely Benign	No citations
RAF1	c.1-38G>A	rs774065972	8	0.00002	Uncertain Significance	No citations
RAF1	c.1669-36C>T	rs3729931	31	0.35988	Benign	[39–45]
RAF1	c.1804-11_1804-7dupCTTTG	rs727503382	1	0.000004	Uncertain Significance	No citations
RAF1	c.582-31T>C	rs748106451	1	0.000004	Likely Benign	No citations
RAF1	c.990+107C>A	rs5746222	1	0.00477	Likely Benign	No citations
RAF1	c.991-42T>C	rs5746226	1	0.01099	Likely Benign	No citations
RAF1	p.(Ala42Ile)	rs876657965	1	ND	Likely Benign	No citations
RAF1	p.(Pro30Ser)	rs765857063	1	0.000004	Likely Benign	No citations
RAF1	p.(Thr303Thr)	rs5746219	1	0.00029	Likely Benign	No citations
RAF1	p.(Thr638Met)	rs730881007	1	0.00005	Benign	No citations
BRAF	c.1177+146G>A	rs1267632	2	0.02984	Benign	No citations
BRAF	c.1315-105C>G	rs71645971	2	0.00309	Likely Benign	No citations
BRAF	c.1315-11T>G	-	1	ND	Likely Pathogenic	No citations
BRAF	c.1992+16G>C	rs3789806	1	0.20919	Benign	[46]
BRAF	c.712-61G>C	-	1	ND	Likely Benign	No citations
BRAF	p.(Gly643Gly)	rs9648696	32	0.21180	Benign	[47]
PIK3CA	p.(His1060His)	rs748925418	1	0.000008	Benign	No citations

Transcript isoforms adopted in this study: RAF1: NM_002880.4, BRAF: NM_004333.6, PIK3CA: NM_006218.4
ND: not described

Deregulation in PI3K signaling contributes to a spectrum of human diseases including several forms of cancers[25] such as breast cancer[26], colon cancer[27], bladder cancer[28] and several forms of hematological malignancies[29]. In fact, several mutations were reported in acute myeloid leukemia[30] and diffuse large B cell lymphoma[31]. Since PI3K is largely studied in association with cancer, it constitutes one of the most prominent oncoproteins for therapeutic targeting[32]. A recent study showed that silencing the PIK3CA gene in childhood leukemia may lead to better response to chemotherapy[33].

The involvement of the MAPK/ERK and PI3K/AKT pathways components, mainly BRAF, RAF1 and PIK3CA, in several forms of cancer and specifically blood cancer, makes them potential candidate genes in familial hematological malignancies. This justifies the importance of investigating the mutational status of these genes for the first time in the context of hematological malignancies.

SUBJECTS AND METHODS

Patients

This is a cross-sectional study. 107 patients belonging to 92 independent families were analyzed: 17 Tunisian and 75 French families recruited via a French national cooperative network focusing on familial hematological malignancies and the GenHem INSERM/DGRS Franco-Tunisian project. The studied cohort consists of 89 patients belonging to 75 familial forms of hematological malignancies (at least two cases of hematological malignancies with or without solid tumors in first, second or third degree relatives), 17 patients from 17 families with aggregation of tumors (including one case of hematological malignancy in first, second or third degree relatives), and 1 patient who had a multiple primitive tumor with hematological malignancy but without family history.

Informed consent was obtained from the patients, relevant family members (healthy relatives) or their legal guardian as required by the Helsinki Declaration.

DNA extraction

Genomic DNA extraction was performed on peripheral blood cells obtained during complete remission as defined by standard protocols. The EZ1DNA tissue kit (Qiagen, Hilden, Germany) was used for DNA extraction according to the manufacturer's instructions. DNA was extracted from paraffin-embedded sections when no peripheral blood was available[34,35]. After DNA quality evaluation, only 100 from 107 DNA samples will be considered for our mutational analysis.

Sequencing

The entire coding regions and their adjacent introns of genes, RAF1 (NM_002880.4) and BRAF (NM_004333.6), and the two hotspot exons 9 and 20 of the PIK3CA gene (NM_006218.4), were amplified and sequenced. Purified PCR products were sequenced using the BigDye Terminator cycle sequencing ready reaction Kit v1.1 (Applied Biosystems—Foster City,

Table 2: Hematological malignancies and other tumors observed in our group of patients

No	Hematological malignancies	Other tumors	Number of patients
1	Hodgkin lymphoma (HL) + Non-Hodgkin's lymphoma (NHL)		1
2	Hodgkin lymphoma (HL) + Small intestine lymphoma		1
3	Chronic lymphocytic leukemia (CLL) + Chronic myelogenous leukemia (CML)	Breast cancer	1
4	Non-Hodgkin's lymphoma (NHL) + Myeloma		1
5	Chronic myelogenous leukemia (CML)	Breast cancer	1
6	Hodgkin lymphoma (HL)	Breast cancer	1
7	Acute myeloid leukemia (AML)	Ovarian cancer	1
8	Chronic lymphocytic leukemia (CLL)	Breast cancer	1
9	Chronic myelogenous leukemia (CML)	Breast cancer + Kidney cancer	1
10	Non-Hodgkin's lymphoma (NHL)	Thyroid cancer	2
12	Non-Hodgkin's lymphoma (NHL)	Melanoma	1
13	Non-Hodgkin's lymphoma (NHL)	Multiple primary neurological tumors + Bladder cancer	1
14	Non-Hodgkin's lymphoma (NHL)	Breast cancer	1
15	Monoclonal gammopathy of undetermined significance (MGUS)	Breast cancer	1
16	Myeloma	Breast cancer	1
17	Thrombocythemia	Breast cancer	1
18	Hodgkin lymphoma (HL)		20
19	Acute lymphoblastic leukemia (ALL)		4
20	Acute myeloid leukemia (AML)		6
21	Chronic lymphocytic leukemia (CLL)		8
22	Chronic myelogenous leukemia (CML)		1
23	Non-Hodgkin's lymphoma (NHL)		17
24	Lymphoma		3
26	Myeloma		4
27	Plasma cell myeloma (multiple myeloma)		1
28	Plasmacytoma		1
29	Myelodysplastic syndromes (MDS)		3
30	Waldenstrom lymphoma		1
31	Familial hematological malignancies (FHM)	Breast cancer + Thyroid cancer	2
32	Familial hematological malignancies (FHM)	kidney cancer + Ichtyosis	1
33	Familial hematological malignancies (FHM)	Glioblastoma	1
34	Familial hematological malignancies (FHM)	Colon cancer	2
35	Familial hematological malignancies (FHM)	Breast cancer	11
36	Familial hematological malignancies (FHM)	Oligodendroglioma	2
37	Familial hematological malignancies (FHM)	Lung cancer	2
	Total number of case		107

Major types of cancer observed in our group of patients	Number of patients (%), n=107
Non-Hodgkin's lymphoma (NHL)	24 (22.4)
Hodgkin lymphoma (HL)	23 (21.5)
Breast cancer	22 (20.6)

USA) and loaded onto an ABI Prism 3500 sequencer (Applied Biosystems). The SeqScape software program v2.5 (Applied Biosystems) was used to search for new variants in sequencing products. Primers sequences are listed in the supplementary Table 1.

Mutational analysis

Allelic frequencies of the obtained variants were compared to those in general population as presented in the Genome Aggregation Database (gnomAD), (URL: https://gnomad.broadinstitute.org/)[36]. The PolyPhen-2 program was used to predict the impact of the obtained variants on the structure and function of encoded proteins[37]. The impact of intronic variants on splicing were evaluated using MaxEntScan score[38].

RESULTS

Patients

A total of 81 French and 26 Tunisian familial cases of hematological malignancy were recruited, including chronic or acute, lymphoid or myeloid leukemia, Hodgkin's or non-Hodgkin's lymphomas, and

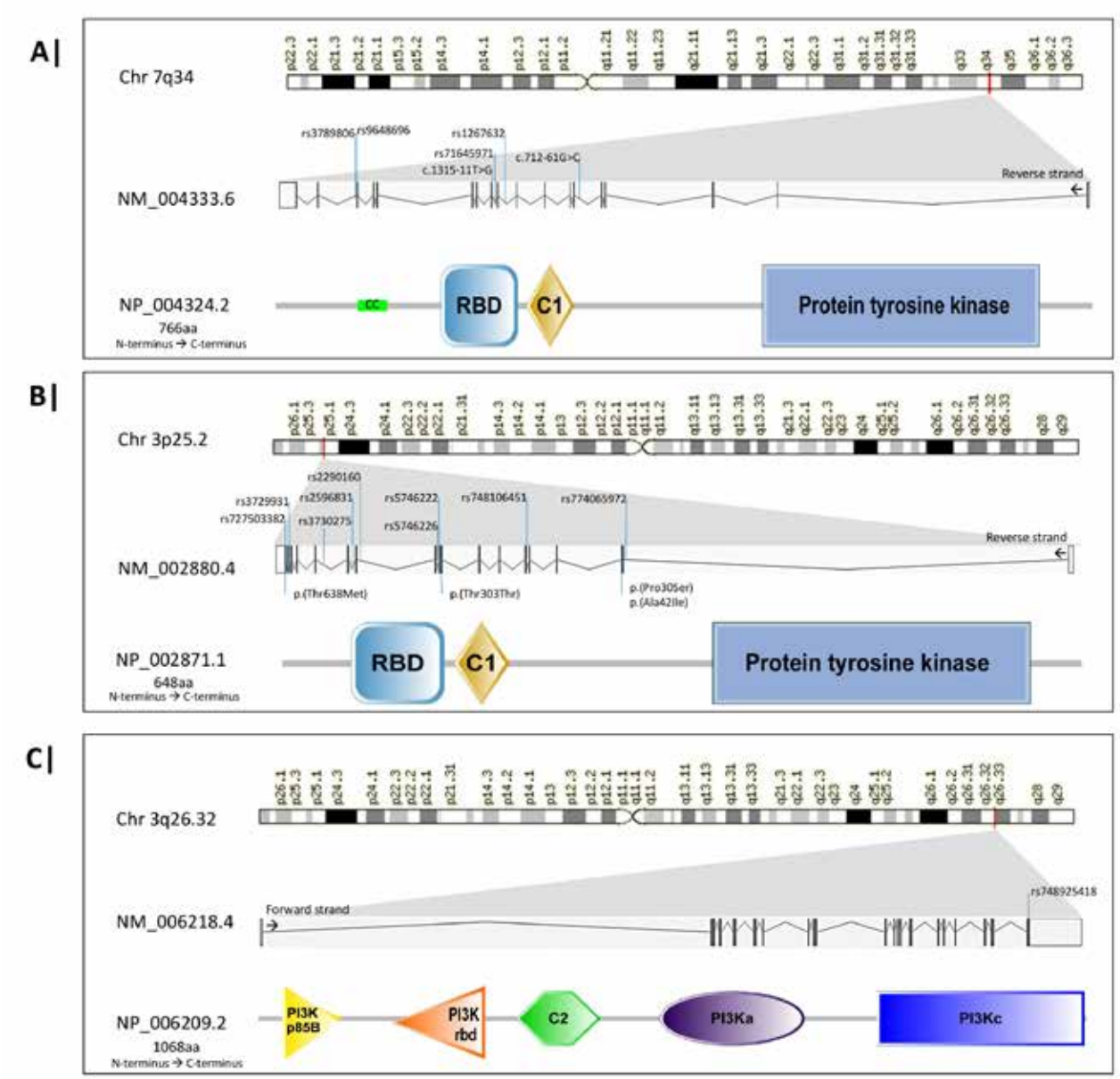

Fig 2: Illustration of the chromosomal position, transcript and protein of A/-BRAF, B/-RAF1 and C/-PIK3CA. The detected variants are indicated. Protein domains: CC: Coiled coil region, RBD: Raf-like Ras-binding domain, C1: Phorbol esters/diacylglycerol binding domain, PI3K_p85B domain: Region of p110 PI3K (Phosphatidylinositol 3-kinases) that binds the p85 subunit, PI3K_rbd domain: Ras-binding domain, C2 domain: Ca2+ binding motif, PI3Ka and PI3Kc domains: Phosphatidylinositol 3-kinase(PI3-kinase).

myeloproliferative or myelodysplastic syndromes with associated solid tumors (Table 2). The predominant forms of hematological malignancies were non-Hodgkin's lymphoma (22.4%) and Hodgkin's lymphoma (21.5%). Associated solid tumors were also noted in patients, notably, breast cancer in 20.5% of cases. Among all the recruited patients, 19 (17.76%) had two forms of cancer (hematological malignancies and solid tumor) and four of them (3.74%) had two forms of hematological malignancies.

Sequencing results

Sequencing of the 18 and 16 coding exons and their adjacent introns of BRAF and RAF1 genes respectively detected 19 different variants listed in Table 1 and shown in Figure 2.

Among these variants, only 3 were previously reported; rs3729931, rs3789806 and rs9648696[39-47]. We classified the variants following the consensus ACMG recommendations[48]. Accordingly, 16 among all the detected variants were noted as benign or

likely benign, 2 were of uncertain significance and only one variant detected in BRAF (c.1315-11T>G) was classified as likely pathogenic in one Tunisian patients diagnosed with Hodgkin's disease. The MaxEntScan score calculated for this latter variant has shown a decrease by 34.7% (3.07 vs 4.7). This variant probably alters the acceptor-splicing site of exon 11 in the BRAF gene.

The sequencing of PIK3CA hotspot exons 9 and 20 has revealed one synonymous variant (c.3180C>T; p.(His1060His); rs748925418) in one patient diagnosed with acute myeloid leukemia and ovarian cancer (Table 1).

DISCUSSION

Here we target for the first-time key genes BRAF, RAF1 and PIK3CA involved in MAPK/ERK and PI3K/AKT signaling pathways in familial context of hematological malignancies. Gene alterations involved in these two pathways have been previously described in several forms of cancer and sporadic forms of blood cancer. Thus, a group of French and Tunisian patients with various forms of FHM was recruited. The predominant forms of hematological malignancy observed in the recruited patients were Hodgkin's lymphoma and Non-Hodgkin's lymphoma, which represent two of the most frequent hematological malignancies worldwide[49].

Among all the solid tumors that co-segregate with FHM, breast cancer was observed in 20.5% of patients. This relatively high frequency of breast cancer in our cohort comparing to the prevalence of this solid tumors worldwide, is the result of our recruiting procedure of patients. In fact, familial forms of hematological malignancies were searched in relatives of patients diagnosed with breast cancer. Lower frequencies of other forms of cancer were observed including lung cancer, glioblastoma, colon cancer, melanoma and thyroid cancer.

Mutation investigation was performed by Sanger sequencing of the entire coding exons and adjacent introns of BRAF and RAF1 genes and the two hotspot exons of PIK3CA gene (exons 9 and 20). The RAF1 gene plays a central role in the MAP kinase pathway. Through our mutational analysis, we detected 13 different variations (Table 1). The c.1669-36C>T variant (rs3729931) located in exon 15 of RAF1 gene, is more likely benign. It was previously reported in association with hematological and cardiovascular traits[40,42-45], gastric cancer[39] and with colorectal cancer-specific mortality among patients diagnosed with rectal cancer[41]. The T allele in c.1669-36C>T variant is associated with low expression of the RAF1 in several tissues; therefore, it was considered as an expression quantitative trait locus gene[39]. In our cohort, this variant was detected in 31% of cases.

The c.1804-11_1804-7dupCTTTG (rs727503382) revealed in one patient diagnosed with Hodgkin lymphoma is located in the acceptor splicing site of the RAF1 exon 17. However, according to bioinformatics prediction tools, this variant has no deleterious effect on splicing (MaxEntScan score: 10.56 Vs 8.45). Another variant of RAF1 gene was detected in the 5'UTR region: c.1-38G>A (rs774065972). The effect of this variant on the gene expression is unknown. Thus, it was classified as a variant of uncertain significance.

A rare missense mutation (gnomAD: 0.00004776) was also found in RAF1: p.(Thr638Met) (rs730881007) in only one case with myeloma belonging to the French population. This new variant is located in a conserved position downstream the "Protein Tyrosine Kinase domain" of the protein. In silico analysis of this variant through PolyPhen-2 has shown no impact on the protein function. Thus, it was classified as benign.

Like RAF1, the serine/threonine kinase BRAF has a prominent role in regulating the MAP kinase/ERK signaling pathway. The most common mutation reported in BRAF gene V600E was not detected in our analyzed cohort, but we revealed 6 genetic variations, among which 5 were intronic.

The BRAF c.1315-11T>G variant was detected in one Tunisian patient diagnosed with Hodgkin's lymphoma. This novel variant weakens the authentic acceptor-splicing site of the exon 11 of BRAF gene. The MaxEnt Scan score for this variant is reduced by 34.7% (3.07 vs 4.7) which is in favor of a probably deleterious effect.

The BRAF intronic variant c.1992+16G>C (rs3789806) is likely benign, however, it was previously reported as a highly differentiated genetic variant with a fixation index (FST) value of 0.50 and 0.52 when compared in African Vs European and American vs European populations respectively[46]. Variants with high FST index reflect a considerable degree of genetic differentiation and imply an important drug response variability among different populations and ethnicities. These variants are important for appropriate anticancer drug selection[50].

The BRAF p.Gly643Gly (rs9648696) was previously identified in 6 among 15 cell lines of ovarian cancer, but was classified as a benign variant[47]. This variant is frequent in the general population according to the gnomAD database (21.2%: 59743/282062) and was detected in 32 patients of our cohort.

Among the 19 variants found in BRAF and RAF1 genes in our cohort with FHM, three presented a clinical significance as reported in literature; rs3729931 in RAF1 gene and c.1315-11T>G and rs3789806 in BRAF gene.

As for PIK3CA, the sequencing of the two hotspot exons (exons 9 and 20) did not reveal any mutation, except for one synonymous variant p.(His1060His) detected in exon 20. This result does not exclude the implication of PIK3CA in FHM. The rest of the gene's exons should be investigated for mutations.

CONCLUSION

Despite the important number of studies targeting genetic predisposition to FHM, few predisposing genes have so far been identified. The insufficient knowledge of the physiopathology of hematologic malignancies and their heterogeneities do not allow adequate choice of candidate genes.

According to our findings RAF1, BRAF and PIK3CA genes are not directly involved in the tumorigenesis in patients with FHM, but some variants could be considered as predisposing factor. These variants may contribute to the background of predisposing factor in familial hematological malignancies. The sequencing of these genes in a larger group of patients would offer further insights in their implication. Since MAPK/ERK and PI3K/AKT pathways were highly reported in pathogenesis of blood cancer, other genes involved in these two pathways should be investigated.

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Conflict of interest: The authors declare that they have no conflicts of interest to report regarding the present study.

Author contributions: Walid Sabri Hamadou, Rahma Mani, Nouha Bouali and Sawsen Besbes: created the study concept, abstracted data, writing the manuscript, Rym el Abed and Zohra Soua: research project director, scientific advisor.

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Original Article

Does the addition of oral dydrogesterone to vaginal progesterone gel in luteal phase support affect IVF-ICSI results?

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ABSTRACT

Objective: The aim of this study was to examine the pregnancy outcomes and live birth rates of 90 mg vaginal progesterone gel given alone protocol and 90 mg vaginal progesterone gel given together with 10 mg oral dydrogesterone protocol to provide luteal phase support in women undergoing in vitro fertilization- intracytoplasmic sperm injection (IVF-ICSI).
Design: A retrospective cohort study
Setting: Department of Obstetrics and Gynecology, University of Health Sciences Tepecik Training and Research Hospital, IVF Unit, Izmir, Turkey
Subjects: Between January 2018 - June 2020, women aged 18-40 years old who underwent ICSI treatment (fresh cycles) were included in the study.
Intervention: Clinical and laboratory parameters
Main outcome measures: Ongoing pregnancy and live birth rate
Results: A total of 291 patients who met our criteria were included in the study. For luteal phase support, 49.1% (n=143) of the patients used 90 mg vaginal progesterone gel alone, 50.9% (n=148) used vaginal progesterone gel combined with 10 mg oral dydrogesterone. Although the vaginal progesterone gel combined with oral dydrogesterone group is numerically higher in terms of pregnancy outcomes, this difference between the groups was not significant in terms of pregnancy per started cycle (27.9% vs 35.1%), ongoing pregnancy per started cycle (17.4% vs. 25.6%), ongoing pregnancy per embryo transfer (14.4% vs 19.5%) and live birth per embryo transfer (13.2% vs 18%).
Conclusions: In this study, it was found that adding short-term oral dydrogesterone to the vaginal progesterone gel for luteal phase support did not significantly affect pregnancy outcomes.

KEY WORDS: infertility, intracytoplasmic sperm injection, in vitro fertilization, luteal phase support, oral dydrogesterone, vaginal progesterone gel

INTRODUCTION

A successful pregnancy depends on synchronization between endometrial development and embryo quality in both natural and stimulated cycles[1]. The luteal phase results in the formation of the corpus luteum, which secretes estradiol (E2) and progesterone (P). Endometrial preparation, which begins in the proliferative phase, continues throughout the luteal phase. The main role of the corpus luteum is to secrete progesterone in the midluteal phase and thereby induce secretory transformation of the endometrium for blastocyst implantation. A functional and receptive endometrium during the luteal phase is essential for implantation[2].

Progesterone is the critical hormone in the formation of endometrial receptivity[2]. Gonadotropin-releasing hormone (GnRH) analogues and antagonists used during controlled ovarian hyperstimulation

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(COH) have a negative effect on endogenous luteinizing hormone (LH). Because of this LH suppression, corpus luteum cannot produce an optimal level of progesterone[3]. In addition, estrogen and progesterone levels secondary to ovarian hyperstimulation after COH may impair receptivity by affecting endometrial morphology[4]. Insufficient uterine receptivity is responsible for approximately 60% of implantation failure[5]. For all these reasons, in vitro fertilization (IVF) protocols require progesterone support in the luteal phase, and supporting the luteal phase with progesterone increases implantation and pregnancy rates[7,8].

Although the necessity of luteal phase support in IVF is accepted as indisputable; the type, dose and mode of administration of progesterone administered are controversial. Therefore, in this study, 90 mg vaginal progesterone gel given alone protocol and 90 mg vaginal progesterone gel given together with 10 mg oral dydrogesterone protocol on in vitro fertilization- intracytoplasmic sperm injection (IVF-ICSI) clinical outcomes was investigated.

SUBJECTS AND METHODS

Study design

This retrospective study was conducted at Department of Obstetrics and Gynecology, University of Health Sciences Tepecik Training and Research Hospital, IVF Unit from January 2018 - June 2020. It was approved by the local ethics committee (approval number: 2019/ 14-32, approval date: 09/10/2019) and was undertaken in accordance with the Declaration of Helsinki of 1964 (revised in 2008). Women who underwent fertility treatment in IVF unit from January 2018 to June 2020 were identified from the hospital database.

Study participants

Women aged 18-40 years old undergoing ICSI treatment (fresh cycles) for tubal factor, unexplained infertility and anovulation (polycystic ovary syndrome), who had normal endometrial thickness (8-12 mm) on the day of embryo transfer, who had no demonstrable endometrial pathology, who had presence of both ovaries, who have normal karyotype and who used GnRH antagonists for controlled ovarian stimulation were included in the study.

Patients with frozen cycles, patients who underwent conventional IVF technique (without ICSI method), diminished ovarian reserve and male factor cases, patients with uterine anomaly (patients with abnormal hysterosalpingography), and patients whose information could not be reached and/or whose information was incomplete were excluded from the study.

On the 12th day after embryo transfer, β-hCG was measured from peripheral venous blood. β-hCG <30 was defined as chemical pregnancy (negative pregnancy) and β-hCG ≥30 was defined as positive pregnancy, pregnancy loss before 12 weeks was defined as abortion, pregnancy continuing after 12 weeks was defined as ongoing pregnancy, births weighing ≥500 grams were defined as live birth.

COH and IVF-ET protocols

Antagonist protocol was given to all women included in the study. Ovarian stimulation was started with 150-300 units gonadotropin on the second or third day of the cycle, considering the number of antral folicules, women's age and body mass index (BMI).

Ovarian follicular development was monitored using transvaginal ultrasonography from the 5th day of stimulation. Antagonists (Cetrorelix ® 0.25 mg, Merc-Serono, Halle (Kantstrasse), Germany) are added to the stimulation protocol when the leading follicle diameter reached ≥13mm. When the three follicles reached a maximum diameter of 17 mm, 250μg of choriogonadotropin alfa (Ovitrelle ®; Merc-Serono, Modugno (Bari), Italy) was injected subcutaneously. Oocytes were retrieved transvaginally under ultrasonography-guidance 35-36 hours after hCG injection. Subsequently oocytes were cultivated in medium and 3-4 hours later, ICSI was performed.

Luteal phase support was started on the day of oocyte pick-up (OPU) with 90 mg vaginal progesterone gel (Crinone 8% ®, Merc-Serono, Watford (Hertfordshire), United Kingdom) or 90 mg vaginal progesterone gel combined with oral 10 mg dydrogesterone (Duphastone ®, Abbott, Chicago (Illinois), United States of America). Dydrogesterone was discontinued in those whose pregnancy test was positive and luteal phase support was continued with micronized vaginal progesterone gel until the 12th week of gestation.

Statistical analysis

Statistical Package for the Social Sciences 22.0 version (IBM Corporation, Armonk, New York, US) package program was used for the analysis of the data. Descriptive statistics of the data were given as mean ± (SD) or median (min-max). Qualitative data were calculated as percentages. Normality distribution of the data was evaluated by Shapiro-Wilk test and Q-Q graphs. Student T test was used in case of normal distribution of variables. Mann-Whitney U test was used for the comparison of parameters that did not show normal distribution. Chi-square test was used to evaluate categorical variables and the odds ratio (95% CI) calculations were made. The *P*-value <0.05 is considered significant.

Table 1: Demographic and medical characteristics of women involved in the study

Demographic and medical characteristics	Vaginal progesterone gel (n=143)	Vaginal progesterone gel combined with oral dydrogesterone (n=148)	*P*-value
Age (years) median (min-max)	31 (22-40)	30 (23-40)	0.915
Advanced age ≥35 (years) (n, %)	48 (33.5%)	50 (33.8%)	0.968
Male age (years) median (min-max)	35.5±5	35.4±5.2	0.555
BMI (kg/m^2) (mean±SD)	23.2±3	23.6±3	0.321
Infertility factor (n, %)			0.804
Anovulation (PCOS)	69 (48.2%)	72 (48.6%)	
Unexplained	57 (39.8%)	55 (37.2%)	
Tubal factor	17 (12%)	21 (14.2%)	
Basal FSH (IU/L) (mean±SD)	9.13±4.06	8.89±2.75	0.772
Basal E2 (pg/ml) (mean±SD)	49.48±42.45	47.75±24.60	0.533
Antral follicle count (mean±SD)	9.5±2.61	10.1±2.41	0.117

BMI: body mass index; PCOS: polycystic ovary syndrome; FSH: follicle-stimulating hormone; E2: estradiol

RESULTS

A total of 291 patients who met our criteria were included in the study. For luteal phase support, 49.1% (n=143) of the patients used vaginal progesterone gel alone, 50.9% (n=148) used vaginal progesterone gel combined with oral dydrogesterone.

Demographic and medical characteristics of the patients were analyzed in Table 1. There was no significant difference between the two groups in terms of female age, advanced female age (≥35 years), male age, BMI, basal follicle stimulating hormone (FSH) and basal E2 values and antral follicle counts. The two groups were statistically similar in terms of infertility factors.

The treatment characteristics of the patients were analyzed in Table 2. Accordingly, no significant difference was observed between the groups in terms of peak E2 (E2 measured on the day of hCG injection) and peak progesterone (P measured on the day of hCG injection) levels, total dose of FSH administration and total days of FSH administration. The group using vaginal progesterone alone was found to be significantly higher in terms of the E2 level measured on the day of OPU (*P*=0.010). The E2 level measured on the day of OPU was significantly higher in the group using vaginal progesterone gel alone (*P*=0.010). The groups were statistically similar in terms of endometrium thickness on transfer days and oocyte count retrieved in the OPU.

Pregnancy results of the patients were analyzed in Table 3. Although the vaginal progesterone gel combined with oral dydrogesterone group is numerically higher in terms of pregnancy outcomes, this difference between the groups was not significant in terms of pregnancy per started cycle (27.9% vs 35.1% and [OR 1.39, 95% CI 0.85-2.29; *P*=0.188]), ongoing pregnancy per started cycle (17.4% vs. 25.6% and [OR 1.63, 95% CI 0.92-2.88; *P*=0.089]), ongoing pregnancy per embryo transfer (14.4% vs 19.5% and [OR 1.44, 95% CI 0.83-2.51; *P*=0.192]) and live birth per embryo transfer (13.2% vs 18% and [OR 1.44, 95% CI 0.81-2.54; *P*=0.315]).

DISCUSSION

In this study, it was found that adding short-term oral dydrogesterone to the vaginal progesterone gel for luteal phase support did not significantly affect pregnancy outcomes. When the clinical parameters, response to treatment and pregnancy results of 291 patients who underwent IVF-ICSI were examined; there were no significant differences observed between the groups in terms of pregnancy per started

Table 2: Treatment characteristics of women involved in the study

Treatment characteristics	Vaginal progesterone gel (n=143)	Vaginal progesterone gel combined with oral dydrogesterone (n=148)	*P*-value
Days of FSH administration (day) (mean±SD)	8.3±1.5	8.5±1.5	0.101
Total dose of FSH administration (IU) (mean±SD)	2092±514	2205±482	0.334
Peak E2 = hCG injection day E2 level (pg/ml) (mean±SD)	1847.1±1271.1	1737.7±968.6	0.795
Peak P = hCG injection day progesterone level (ng/ml) (mean±SD)	1.14±0.71	1.27±0.73	0.058
E2 level on OPU day (pg/ml) (mean±SD)	1163.4±934.6	798.8±379.9	0.010
Endometrium thickness on transfer day (mm) (mean±SD)	10.26±6.1	11±6.9	0.656
Oocyte count retrieved in the OPU (mean±SD)	9.2±6.3	8.9±5	0.662

FSH: follicle-stimulating hormone; E2: estradiol; P: progesterone; OPU: oocyte pick-up

Table 3: Pregnancy results of women participating in the study

Pregnancy results	Vaginal progesterone gel (n=143)	Vaginal progesterone gel combined with oral dydrogesterone (n=148) (reference group)	OR (95% CI)	*P*-value
Pregnancy per started cycle (%)	27.9 (40/143)	35.1 (52/148)	1.39 (0.85-2.29)	0.188
Ongoing pregnancy per started cycle (%)	17.4 (25/143)	25.6 (38/148)	1.63 (0.92-2.88)	0.089
Ongoing pregnancy per embryo transfer (%)	14.4 (25/173)	19.5 (38/194)	1.44 (0.83-2.51)	0.192
Live birth per embryo transfer (%)	13.2 (23/173)	18 (35/194)	1.44 (0.81-2.54)	0.315

cycle (27.9% vs 35.1% and [OR 1.39, 95% CI 0.85-2.29; *P*=0.188]), ongoing pregnancy per started cycle (17.4% vs. 25.6% and [OR 1.63, 95% CI 0.92-2.88; *P*=0.089]), ongoing pregnancy per embryo transfer (14.4% vs 19.5% and [OR 1.44, 95% CI 0.83-2.51; *P*=0.192]) and live birth per embryo transfer (13.2% vs 18% and [OR 1.44, 95% CI 0.81-2.54; *P*=0.315]). To our knowledge, this is the first study to compare the use of vaginal progesterone gel alone versus vaginal progesterone gel combined with oral dydrogesterone for luteal phase support.

Human reproduction begins with the fertilization of an oocyte, following a series of molecular events, on the sixth day, with blastocyst development and attachment of the embryonic pole to the endometrium at the implantation window. During the implantation process, the blastocyst approaches the surface of the endometrium, attaches tightly and invades the endometrium. The synchronization and sensitization of the endometrium to implantation parallel to the development of healthy embryos is the most critical step in the development and continuation of pregnancy. Progesterone is the critical hormone in the formation of the endometrial receptivity[9]. A low progesterone level reduces implantation, so support of the luteal phase is essential[10,11]. Although there are many clinical studies on luteal phase support, there is no consensus on the type, dose and method of administration of progesterone administered[8]. When using progesterone for luteal phase support, the mode of administration and dose should be the most convenient and tolerable for the patient, as well as providing a high pregnancy rate.

Ganesh *et al* published prospective reviews of 1363 patients who underwent conventional IVF and IVF-ICSI[12]. In this study, three different protocols were applied to the patient groups, including 10 mg oral dydrogesterone twice a day, 90 mg vaginal progesterone gel once a day and 200 mg vaginal micronized progesterone capsule three times a day. Similar to our study, no significant difference was observed between the groups in terms of clinical pregnancy rate and ongoing pregnancy rate. In this study, live birth rates were not investigated. Similar to our study, maternal age, endometrial thickness and ovarian responses (total number of oocytes at OPU time) were similar between the groups.

Tomic *et al* divided 831 patients undergoing conventional IVF and IVF-ICSI into two groups according to the protocol of 10 mg oral dydrogesterone twice a day and 90 mg vaginal progesterone gel once a day and followed prospectively[13]. Similar to our study, no significant difference was observed between the groups in terms of clinical pregnancy rate and ongoing pregnancy rate. In this study, live birth rates were not investigated. Similar to our study, maternal age, endometrial thickness and ovarian responses (total number of oocytes at OPU time) were similar between the groups.

Griesinger *et al* divided 980 patients undergoing conventional IVF and IVF-ICSI into two groups according to 10 mg oral dydrogesterone three doses a day and 90 mg vaginal progesterone gel once a day and evaluated prospectively[14]. Similar to our study, no significant difference was observed between the groups in terms of clinical pregnancy rate, ongoing pregnancy rate and live birth rate. Yang *et al* examined the data of the same study included from China in their study. Accordingly, there was no significant difference between the groups in terms of clinical pregnancy rate, ongoing pregnancy rate and live birth rate[15]. These results are similar to our study.

Ozer *et al* examined 134 patients in frozen transfer by dividing them into groups of 90 mg vaginal progesterone gel one day and 10 mg oral dydrogesterone three doses a day[16]. Similar to our study, no significant difference was observed between the groups in terms of clinical pregnancy rate and ongoing pregnancy rate. In this study, live birth rates were not investigated. Similar to our study, maternal age, endometrial thickness and ovarian responses (total number of oocytes at OPU time) were similar between the groups.

Vuong *et al* investigated the data of 1364 patients in prospectively and analyzed 400 mg micronized vaginal progesterone twice a day + 10 mg oral dydrogesterone twice a day group and 400 mg micronized vaginal progesterone twice a day group[17]. In this study, live birth rates were 46.3% in the progesterone + dydrogesterone group, while it was 41.3% in the

progesterone-only group. A statistically significantly lower rate of miscarriage at <12 weeks was observed in the progesterone + dydrogesterone group versus the progesterone group (3.4% vs. 6.6%). The results of this study differ from our study. However, when looked in detail, the biggest difference is seen in patient selection criteria and progesterone usage form. Differently, our study includes only fresh transfers made with the ICSI technique, and the infertility indications of our patients are in a narrower area. In addition, our progesterone usage form and doses are different. In this study, dydrogesterone support was continued until the 7th gestational week. All these differences may have led to different results.

The limitations of our study are: it is a retrospective study and the number of our patients is limited. Our strengths are our patient selection criteria with strict narrow indications and minimizing the differences between groups by selecting only the patients who underwent IVF with the ICSI technique.

CONCLUSION

In conclusion, we can say that concomitant use of oral dydrogesterone with vaginal progesterone gel until pregnancy test is positive did not improve pregnancy status and live birth rates compared to using vaginal progesterone gel alone. Although the results pave the way for new studies, randomized controlled prospective and multicenter studies are needed to determine the optimal luteal phase support protocol.

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Conflict of Interest: The authors have no conflicts of interest to declare.

Authors' Contribution: Onur Burak Cegilli, Ebru Sahin Gulec and Burak Bayraktar contributed to conception and design of the study. Can Kose and Ahmet Demir organized the database. All the authors wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Original Article

Efficacy of Sacubitril-Valsartan on heart failure with preserved ejection fraction and atrial fibrillation in female patients

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ABSTRACT

Objective: We compared the clinical efficacy of sacubitril-valsartan versus valsartan alone on heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation in female patients.
Design: Retrospective study
Setting: Suzhou Ninth Hospital Affiliated to Soochow University
Subjects: A total of 60 female patients with HFpEF and atrial fibrillation were enrolled.
Interventions: Participants were randomly assigned into sacubitril-valsartan group and valsartan group. The average follow-up time was 6 months.
Main outcome measures: Six-minute walking test (6MWT) and admission frequency during the period were recorded. Other parameters including cardiac natriuretic peptide precursor (NT-proBNP), left ventricular ejection fraction, soluble ST2 (sST-2) level and echocardiographic measures of cardiac function and remodeling were determined.
Results: After six months of treatment, 6MWT scores were significantly higher in the sacubitril-valsartan group compared with the control group. The NT-proBNP level of sacubitril-valsartan group was significantly lower compared with that of the valsartan group. Left atrial volume index significantly decreased after sacubitril-valsartan treatment compared with the level in the valsartan group. The sST-2 level of sacubitril-valsartan group was remarkably lower compared with the level of the valsartan group. The number of hospital visits in the observation group was significantly lower compared with that in the control group.
Conclusion: Sacubitril-valsartan might help improve clinical prognosis of HFpEF with atrial fibrillation in female patients.

KEY WORDS: female atrial fibrillation, heart failure, preserved ejection fraction, Sacubitril-valsartan

INTRODUCTION

Cardiovascular diseases are major causes of deaths globally. Most cardiovascular diseases progress into heart failure and cause cardiac death. Heart failure with preserved ejection fraction (HFpEF) is a type of heart failure characterized by diastolic dysfunction but with left ventricular ejection fraction (LVEF) ≥50%. Prevalence of HFpEF has been increasing in recent years. Epidemiological studies report that HFpEF accounts for over 50% of all heart failure patient cases[1]. HFpEF is characterized by a preserved LVEF ≥50% with diastolic dysfunction, and is associated with high morbidity and mortality[2]. However, current treatment options are sub-optimal. Studies report that cardiac remodeling is one of the major processes that contribute to HFpEF[3]. HFpEF has a higher incidence of atrial fibrillation (AF)/flutter with more female and older patients compared with heart failure with reduced ejection fraction (HFrEF)[4]. However, current treatment strategies

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are not effective in reducing morbidity or mortality rate in HFpEF patients. Sacubitril-valsartan combination was reported to significantly reduce death from cardiovascular causes and to improve HFrEF patient outcomes (cardiovascular death or hospitalization for heart failure) in previous clinical trials[5], and was recommended in many treatment guidelines[4,6-7]. Sacubitril-valsartan acts on the dual systems — neprilysin and renin-angiotensin-aldosterone systems. Sacubitril inhibits neprilysin and suppresses degradation of brain natriuretic peptide (BNP). In addition, valsartan inhibits the renin-angiotensin-aldosterone system through angiotensin II receptor antagonist action, promoting vasodilation and urinary sodium excretion.

The previous PARAMOUNT trials reported that sacubitril-valsartan reduced NT-proBNP level, the size of the left atrium and improved New York Heart Association (NYHA) grading in HFpEF patients[8]. Findings from the PARAGON-HF subgroup showed that sacubitril-valsartan is more effective in women and patients with LVEF from 45 to 57%[9]. This study explored the role of sacubitril-valsartan in clinical prognosis of HFpEF with AF in female patients.

SUBJECTS AND METHODS

Study design

This study was a randomized, active-comparator trial. The study was approved by the ethical committee of Suzhou Ninth People's Hospital. All patients signed informed consent forms before enrollment. A total of 60 female patients diagnosed with HFpEF and AF aged 50-79 (66±9.3) years old who were admitted to the Department of Cardiology, Suzhou Ninth People's Hospital from March 2018 to March 2020 were included in this study. The study inclusion criteria were: 1) female patients above 50 years of age with AF and EF ≥50%; 2) NYHA class II-IV symptoms (dyspnoea on exertion or nocturnal, reduced exercise tolerance and fatigue, lethargy etc); 3) NT-ProBNP greater than 900pg/ml; 4) history of usage of diuretics to control heart failure symptoms within 30 days before enrollment; 5) history of structural heart disease, left atrial enlargement and/or left ventricular hypertrophy within 6 months before enrollment. Exclusion criteria: patients with previous LVEF <50%; report of myocardial infarction, CABG or any event that may reduce LVEF within 6 months before enrollment; systolic blood pressure <110 mmHg or >180 mmHg before enrollment; abnormal serum potassium and

Table 1: Comparison of baseline information between Sacubitril-valsartan and valsartan group

Characteristic	Sacubitril-valsartan (n=30)	Valsartan (n=30)	t/χ2*	*P*
General characteristics				
Age (Year)	67±8	65±11	0.827	0.411
HR (beats/min)	91.77±23.8	85.67±14.0	1.209	0.232
Blood pressure (mmHg)				
Systolic	125±13	119±15	1.310	0.195
Diastolic	74±7	71±9	1.918	0.060
6MWT (m)	325.1±48.6	346.8±65.0	1.466	0.148
LVEF (%)	54.67±2.82	55.43±4.01	-0.856	0.396
LAVI (ml/m^2)	37.74±3.37	36.57±3.25	-1.324	0.191
LVDd (mm)	54.42±4.05	53.63±4.07	0.751	0.456
NT-proBNP (pg/ml)	1634.78±119.24	1583.57±124.48	1.627	0.109
sST2 (ng/L)	1299.17±301.39	1180.10±387.25	1.329	0.189
eGFR (ml/min)	86.53±15.31	85.57±16.34	1.055	0.092
Comorbidities				
CHD (n, %)	14(46.7)	10(33.3)	1.111	0.292
Hypertension (n, %)	6(20.0)	7(23.3)	0.098	0.754
SDHVD (n, %)	6(20.0)	9(30.0)	0.800	0.371
Other (n, %)	4(13.3)	4(13.3)	0.000	1.000
Treatment				
Aspirin (n, %)	14(46.7)	9(30.0)	1.763	0.184
P2Y12 inhibitor (n, %)	4(13.3)	7(23.3)	1.002	0.317
Nitrates (n, %)	4(13.3)	5(16.6)	0.131	0.718
Statin (n, %)	13(43.3)	10(33.3)	0.635	0.426
ACEI/ARB (n, %)	6(20.0)	5(16.6)	0.111	0.739
β-AR blocker (n, %)	12(40.0)	9(30.0)	0.659	0.589

HR: heart rate; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection fraction; LAVI: left atrial volume index; LVDd: left ventricular end diastolic diameter; sST2: soluble suppression of tumorigenicity-2; 6MWT: six-minute walk test; CHD: coronary heart disease; SDHVD: senile degenerative heart valvular disease

Table 2: Comparison of NT-proBNP, LVEF and 6MWT between Sacubitril-valsartan and valsartan group

Groups	NT-proBNP (pg/ml)		LVEF (%)		6MWT	
	Baseline	After 6 months	Baseline	After 6 months	Baseline	After 6 months
Sacubitril-valsartan (n=30)	1634.78±119.23	394.51±67.29[ab]	54.67±2.82	56.50±4.53	325.1±48.6	429.0±57.6[ab]
Valsartan (n=30)	1583.57±124.48	652.85±71.73[a]	55.43±4.01	55.90±4.83	346.8±65.0	377.4±46.0[ab]

[a]Compared with the baseline, [a]$P<0.05$.
[b]Compared with valsartan group after 6 months treatment, [b]$P<0.05$.

eGFR <30 mL/min/1.73m^2 before enrollment, or eGFR reduced >35% compared with the baseline.

Study procedure

Diuretics and vasodilators were used to improve clinical symptoms of patients. All patients received anticoagulation therapy. In addition, β-blockers were administered orally. Dosages of β-blockers were adjusted based on the patient's heart rate. The heart rate was controlled to a value <80/min at rest time and <110/min during moderate exercise. A participant will usually be assigned to the treatment group or the control group at random. The treatment group was administered with sacubitril-valsartan, with a starting dose of 50 mg/time, twice a day. The dose was then gradually titrated to achieve the patient's maximum tolerable dose. The control group was administered with 80 mg/d of valsartan which was then gradually titrated to the patient's maximum tolerable dose. A 6-month follow-up was carried out for each patient. Patients were followed up by home-visit, call consultations to patients or family members, outpatient records and electronic medical records system, etc. General characteristics, past histories, blood test, therapeutic drugs, echocardiography data and total admissions were recorded before and after following up.

Statistical analysis

Data were analyzed using SPSS 22.0 statistical software. Quantitative data were expressed as mean ± standard deviation (x ± s). Intergroup comparisons were performed using independent samples t-test, whereas categorical data were compared using chi-square test. $P<0.05$ indicated that the difference was statistically significant.

RESULTS

The baseline information (including age, cause of heart failure, medication status, baseline of blood pressure, heart rate, 6-min walking distance test (6MWT)), blood test (including eGFR, NT-proBNP, sST2) and echocardiographic data (including LVEF, left atrial volume index (LAVI) and LVDd) showed no significant difference between the two groups before treatment ($P>0.05$, Table 1).

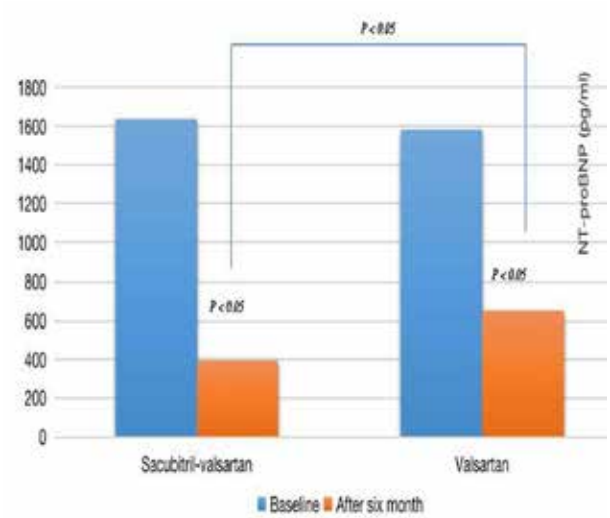

Fig. 1: Comparison of NT-proBNP between Sacubitril-valsartan and valsartan group.

The NT-proBNP level after treatment in the two groups was lower compared with the level before treatment ($P<0.05$). Furthermore, at the end of follow-up, the NT-proBNP level of the observation group was significantly lower compared with the level of the control group (394.51±67.29 pg/ml vs. 652.85±71.73

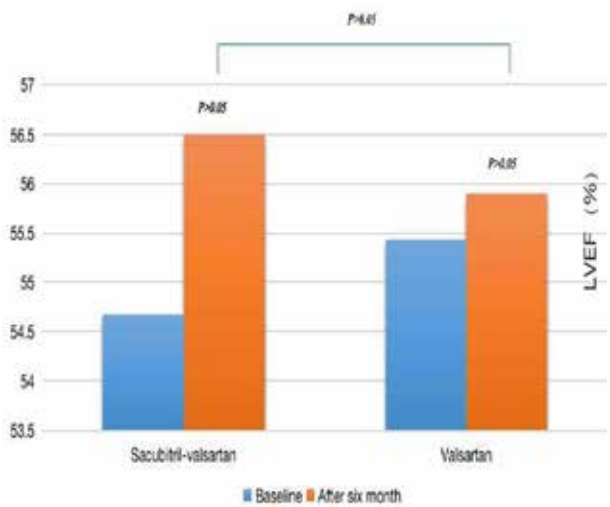

Fig. 2: Comparison of LVEF between Sacubitril-valsartan and valsartan group.

Table 3: Changes in LAVI, LVESVI and sST-2 in the two groups

Groups	LAVI		LVDd		sST-2	
	Baseline	After 6 months	Baseline	After 6 months	Baseline	After 6 months
Sacubitril-valsartan (n=30)	37.74±3.37	32.70±3.07[ab]	54.42±4.05	53.73±6.08	1299.17±301.39	688.57±326.21[ab]
Valsartan (n=30)	36.57±3.25	34.40±1.81	53.63±4.07	53.59±5.43	1180.10±387.25	850.37±233.80[a]

[a]Compared with the baseline, [a]$P<0.05$.
[b]Compared with valsartan group after 6 months treatment, [b]$P<0.05$.

pg/ml, $P<0.001$, Fig.1). LVEF did not improve after treatment in both groups compared with pre-treatment level ($P>0.05$, Fig.2). 6MWT levels showed significant increase after treatment in the two groups ($P<0.05$). Notably, 6MWT levels were remarkably higher in sacubitril-valsartan group compared with the levels in the valsartan group (429.0±57.6m vs. 377.4±46.0 m, $P<0.001$, Fig.3, Table 2).

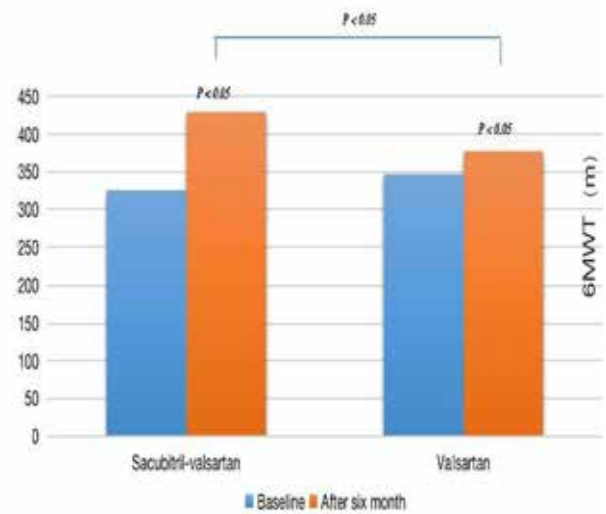

Fig. 3: Comparison of 6MWT between Sacubitril-valsartan and valsartan group.

Analysis of LAVI level and LVDd showed no significant difference between the two groups at baseline. After treatment, lower levels of LAVI and sST-2 were observed compared to the level before treatment in the sacubitril-valsartan group [(37.74±3.37 vs 32.70±3.07, $P<0.05$), (1299.17±301.39 vs 688.57±326.21, $P<0.05$), respectively]. Notably, the decreases of LAVI and sST-2 levels were even more in sacubitril-valsartan group compared with that of the valsartan group after treatment [(32.70±3.07 vs 34.40±1.81, $P<0.05$), (688.57±326.21 vs 850.37±233.80, $P<0.05$), respectively], as shown in Table 3.

The number of re-hospitalized patients in the sacubitril-valsartan group was dramatically lower compared with the number of re-hospitalized patients in the valsartan group (2.30±0.95 vs 3.53±1.48, $P<0.05$; Table 4).

Table 4: Comparison of readmission times between the two groups

Groups	No. of rehospitalizations
Sacubitril-valsartan(n=30)	2.30±0.95[a]
valsartan(n=30)	3.53±1.48

[a]Compared with the valsartan group, P<0.05.

DISCUSSION

Previous studies report that HFpEF mainly affects elderly female patients. Most HFpEF patients have atrial fibrillation, especially in old age and in females. AF is independently associated with greater exertional intolerance, natriuretic peptide elevation and left atrial remodeling in HFpEF. Atrial fibrillation is characterized by reduction of atrial ejection fraction, as well as diastolic heart failure[10]. In the study, sacubitril-valsartan significantly reduced the number of re-hospitalizations and improved 6MWT in female patients with HFpEF and AF.

Baseline NT-proBNP is a good predictor of hospitalization and death in patients diagnosed with heart failure. Previous studies report that NT-proBNP is an effective biomarker for determination of severity and prognosis of heart failure[11,12]. Studies reported that NT-proBNP levels after treatment is directly correlated with prognosis of patients[13]. In this study, the NT-proBNP level of the two groups of patients decreased significantly after treatment compared with baseline levels. This finding indicates that the clinical conditions of patients improved after standard treatment. The sacubitril-valsartan group showed a significant decrease in NT-proBNP level compared with the control. This finding implies that sacubitril-valsartan is more effective in improving the cardiac function of female patients with HFpEF and atrial fibrillation compared with administration of valsartan alone. Recent studies reported that HFpEF patients treated with sacubitril-valsartan showed a marked decrease in NT-proBNP levels, which is consistent with the findings of our study[8].

The 6MWT is a sub-maximal exercise test, which is used for short-term prognosis of patients, and is used by clinicians to study cardiac function[14-17]. 6MWT can evaluate reserve function, exercise endurance of

patients with chronic heart failure (CHF) and efficacy of drug treatment[18]. Recently, the American College of Cardiology/American Heart Association and the European Heart Association adopted 6MWT as an indicator of cardiac function assessment in their respective guidelines of heart failure, and approved its use in CHF assessment[19,20]. The results of this study showed that the 6MWT scores of the two groups after treatment were significantly higher compared with baseline scores. The sacubitril-valsartan group showed higher 6MWT scores compared with the control group. These findings showed that sacubitril-valsartan was effective in women with HFpEF and atrial fibrillation, and their exercise tolerance was significantly improved. The PARAMOUNT clinical trial[8] reports that neprilysin inhibotor LCZ696 reduced N-end brain natriuretic hormone (NT-proBNP) levels, and left atrium size in patients with HFpEF, which is consistent with the findings of this study.

The LVEF in both groups had not changed conspicuously after treatment in our study. Studies reported that increased 6MWT and LVEF is only consistent after a follow-up period >6 months group, implying that increase in exercise tolerance occurs before improvement of LVEF[21]. Left atrium volume is a recently proposed ultrasound index to accurately reflect ventricular diastolic function. The size of the left atrium is affected by several factors such as pressure load, volume load and myocardial dynamics. The size of the left atrium is correlated with the state of the atrioventricular pressure difference. When the left ventricular systolic function is normal, increase in the left atrium can be used to determine the impairment of the left ventricular diastolic function and increase in left ventricular filling pressure[22]. The 2007 ESC diagnosis consensus reports that LAVI calculated based on body surface area is an independent predictor of diastolic dysfunction[23]. LAVI is an indicator of normal left ventricular ejection fraction, heart failure and cardiovascular risk[24]. When the LAVI value >26ml/m^2, it is considered as an independent predictor of diastolic insufficiency, which is better compared with the left atrial area or left atrial dimension[25,26]. In this study, the LAVI of the observation group was significantly lower after treatment compared with the baseline. This finding shows that sacubitril-valsartan improves the diastolic function of female patients with HFpEF and atrial fibrillation.

In this study, sST2 was significantly lower after treatment compared with the level before treatment in both groups. In addition, sST2 level in the observation group was significantly lower compared with the sST2 level in the valsartan group. Expression levels of sST2 and ST2L increase with pressure and volume overload of the heart. sST2 exerts its activity by combining with the specific ligand IL-33[27]. Studies report that ST2L/IL-33 complex is a mechanical activation system that protects the heart against several conditions, such as anti-myocardial fibrosis, anti-cardiomyocyte hypertrophy, reduction of cell necrosis and improvement of left ventricular function and survival. Under anaerobic conditions, myocardial cell apoptosis occurs leading to low IL-33 levels, therefore, there is a high affinity in serum free sST2. These proteins can then be used as a decoy receptors, thus competing with ST2L binding sites of IL-33, resulting in inhibition of IL-33 / ST2L signal pathway, further weakening heart protection[28]. sST2 combines with IL-33 to cause imbalance of Th1/Th2 ratio, which affects immune function and inflammatory cytokine release, therefore, progress of cardiac remodeling is accelerated[29]. Studies report that the level of soluble ST2 is correlated with occurrence of heart failure and all-cause mortality[30]. In this study, the observation group showed significantly lower sST2 levels after treatment with sacubitril-valsartan compared with the levels in the control group. This finding implies that sacubitril-valsartan inhibits cardiac fibrosis, slows down or even inhibits cardiac remodeling in female patients with HFpEF and atrial fibrillation, thus delaying heart failure and reducing all-cause mortality in patients with heart failure.

CONCLUSION

The findings of this study provide a basis for treatment of female patients with HFpEF associated with atrial fibrillation. Sacubitril-valsartan may be useful in treating patients with HFpEF associated with atrial fibrillation in the terms of activity endurance and diastolic function. However, due to the small sample size in the single-center study, these data should be interpreted cautiously until confirmed by suitably-powered clinical trials. Therefore, further studies should be conducted using larger sample sizes to validate these findings and probing possible mechanisms.

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Case Report

Cutaneous sarcoidosis of a 31-year-old female: A case report

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology. Cutaneous sarcoidosis is seen in up to one-third of patients with systemic sarcoidosis and may be the first or the only clinical sign of the disease. It is characterized by the presence of non-caseating 'naked' granulomas in the affected tissue. We report a case of cutaneous sarcoidosis without systemic involvement. Lesions mimicked various other common dermatologic conditions. In this case, we describe the clinical and histopathological findings of cutaneous sarcoidosis.

KEY WORDS: angiotensin converting enzyme (ACE), cutaneous sarcoidosis, granuloma, lupus miliaris disseminatus faciei (LMDF)

INTRODUCTION

Sarcoidosis is a chronic granulomatous disease that affects multiple organ systems in the body. It is characterized by the formation of non-caseating epithelioid granulomas. The most common organs that are affected by sarcoidosis are the lungs, intrathoracic lymph nodes, eyes and skin[1]. The prevalence of sarcoidosis per 100,000 cases ranges from 0.04 to 64 cases[1]. In patients with systemic sarcoidosis, 20-35% of them can have cutaneous manifestations; however, cutaneous sarcoidosis can also occur without systemic disease in about 25% of cases[2]. Management of sarcoidosis is done by a multidisciplinary team. We report a case of cutaneous sarcoidosis without systemic involvement. Lesions mimicked various other common dermatologic conditions. In this case, we describe the clinical and histopathological findings of cutaneous sarcoidosis.

CASE REPORT

A 31-year-old female Ethiopian patient presented with multiple asymptomatic lesions of 3 months duration over the face. There was no history of fever, weight loss or night sweats. There was also no joint pain, cough, eye complaints or any other systemic symptoms. Family history was not significant. Moreover, there was no significant drug history. General physical and systemic examinations were normal. Dermatologic examination revealed multiple brownish papules all over the face, measuring 1-3 mm, mainly periorbital, perioral and involving the forehead (Fig 1). Some of the papules were coalescent together forming a plaque (Fig 2). Lesions were non-tender. Palms, soles, hair nail and mucosal areas were uninvolved. Ophthalmologic examination was normal. Chest X-ray was also unremarkable. The biopsy specimen shows nodular granulomatous dermatitis (Fig 3). The nodules are scattered throughout the dermis and formed by epithelioid histocytes, multinucleated giant cells and a thin rim of lymphocytes around them. The overlying epidermis is unremarkable (Fig 4). PAS, Giemsa, modified Zeil Nelson stains and polarization are negative.

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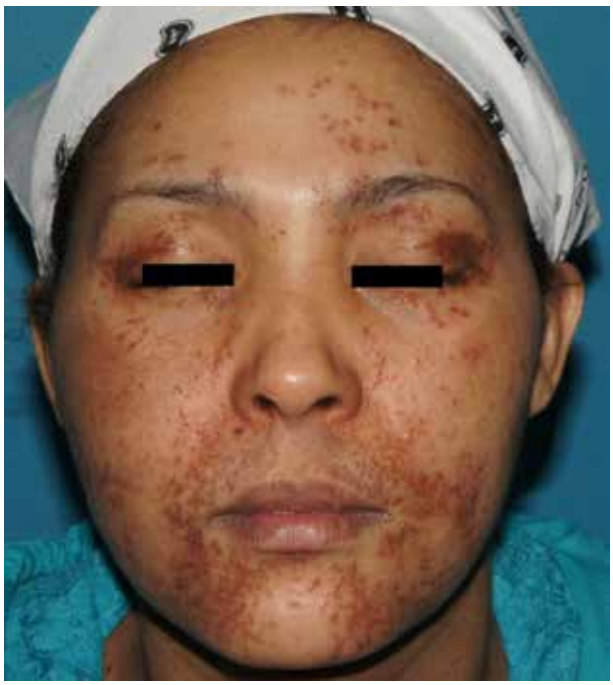

Fig 1: Tiny papular lesions on the face

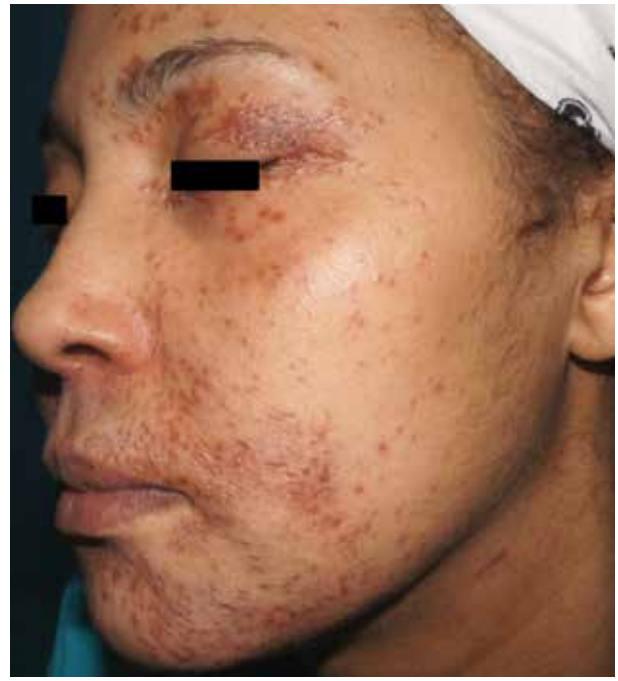

Fig 2: Grouped papules over the eye forming plaque

DISCUSSION

The skin is the second most common organ affected by sarcoidosis, and approximately 25-30% of sarcoidosis cases had skin manifestations. The highest incidence of cutaneous sarcoidosis occurs in Black American females[3]. Cutaneous sarcoidosis lesions could occur in any area of the skin, and more commonly involve previously manipulated areas as in tattoos and scars[3]. The diagnosis is based on clinical manifestations by appropriate history taking, physical examination, radiological and histopathological findings, and, finally, exclusion of other granulomatous diseases[4]. Our patient presented to us only with cutaneous manifestation. Moreover, the patient was not complaining of any constitutional symptoms or lymphadenopathy involvement. Histopathology report revealed sarcoidal granulomas. Laboratory investigations show that the level of serum angiotensin converting enzyme (ACE) was normal. Serum ACE levels are neither diagnostic nor predictors of systemic involvement, yet they may be useful for predicting disease progression[5].

Cutaneous sarcoidosis has to be differentiated from a similar clinical entity like lupus miliaris disseminatus faciei (LMDF) which is an uncommon, chronic, inflammatory dermatosis characterized

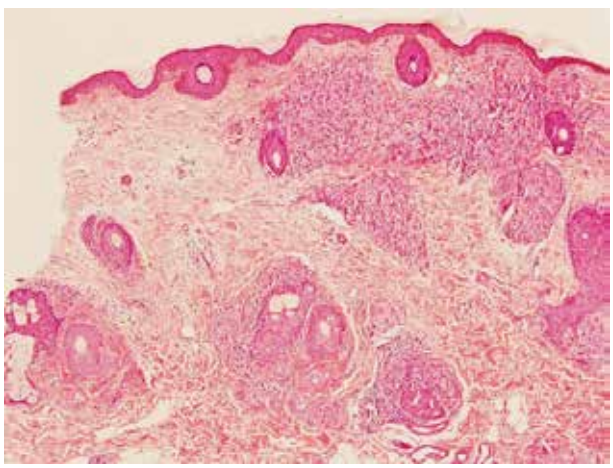

Fig 3: Low power showing nodular noncaseating granulomas involving the full thickness of the dermis

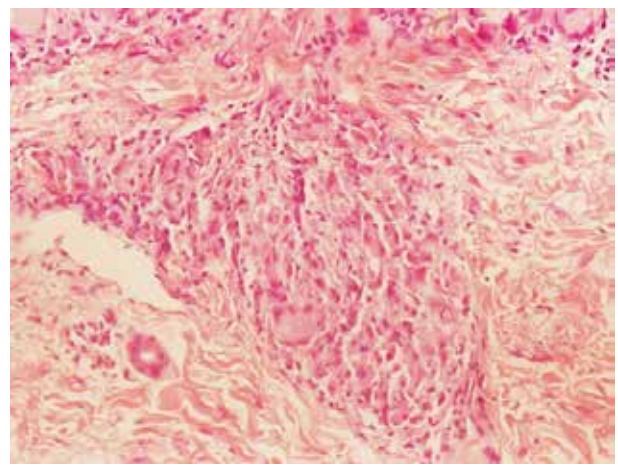

Fig 4: High power showing the granuloma predominantly composed of epithelioid cells, with Langhan's giant cells and sparse lymphocytic infiltrate (naked granulomas)

by red-to-yellow or yellow-brown papules of the central face[6]. Cutaneous sarcoidosis can be differentiated histopathologically from LMDF by the presence of noncaseating granuloma without inflammatory cells, known as naked granuloma, as it is diagnostic of sarcoidosis[3]. On the other hand, LMDF is characterized by the formation of caseating granuloma[6]. Additionally, the bright erythematous papules in cutaneous sarcoidosis rather than the apple jelly red-brown colored lesions as in LMDF[3,6].

CONCLUSION

Sarcoidosis is a disease with multiple organ's involvement. Cutaneous manifestations of sarcoidosis are different and non-specific. The diagnosis is confirmed by the presence of non-caseating epithelioid granulomas in histological findings.

ACKNOWLEDGMENT

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Case Report

Mastitis after port site extravasation of taxane-based chemotherapy: case report

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ABSTRACT

Drug extravasation is one of the uncommon complications of port catheter use. The incidence of drug extravasation in the literature is 0.01 - 7%. Depending on the extent of tissue damage and the cytotoxic effect of the drug, edema, cellulitis and even necrosis may occur in the breast or chest wall. We present a 38-year-old female patient with metastatic lung cancer who developed mastitis during paclitaxel-carboplatin chemotherapy received via the port catheter. Diffuse hyperemia, inflammation and blisters developed on the right breast. Daily paraffin antiseptic closure was applied to the wound and empirical antibiotic was given. After 21 days, local inflammatory signs resolved and only scar tissue remains on the skin of breast.

KEY WORDS: extra-vasation, mastitis, paclitaxel

INTRODUCTION

Unintentional leakage of a chemotherapeutic agent is a rare complication during cancer treatment. Results depend on the type of chemotherapeutic agents, extravasation amount and location. Chemotherapeutics can be classified according to potential of tissue damage after extravasation. Vesicant drugs can induce formation of blisters and can cause inflammation (cellulitis) and/or tissue necrosis[1].

The management of extravasation depends on clinical picture from conservative options to major surgical interventions[2,3]. Herein, we report a 38-year-old woman who developed mastitis after paclitaxel-carboplatin extravasation from a port.

CASE REPORT

A 38-year-old female patient was diagnosed with metastatic lung adenocarcinoma in 2014. She had no other known disease. She received 6 cycles of paclitaxel carboplatin chemotherapy in 2014. In 2017, she received radiotherapy for local recurrence in the left lung. Due to progression in 2017, six more cycles of gemcitabine were given. PET-CT in 2019 revealed metastasis in the L2 vertebra and a mass in the left ovary was observed. Stereotactic radiotherapy was performed for vertebral metastasis in May 2019. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed in November 2019 and the pathology result was lung cancer metastasis.

Paclitaxel-carboplatin was restarted in July 2021 due to recurrence. During the 2nd cycle of treatment, extravasation of the chemotherapeutic drug from the port resulted in diffuse hyperemia, inflammation and blister formation in the right breast. Infusion was stopped and the catheter system was washed with sterile saline.

Intravenous sulbactam-ampicillin was started empirically. A culture swab was taken from the wound before starting the antibiotic, revealing no growth. There were asymmetrical density increases in the right anterior chest wall on CT thorax, but no sign of catheter displacement/ fracture or thrombus formation in vascular structures (Figure 1).

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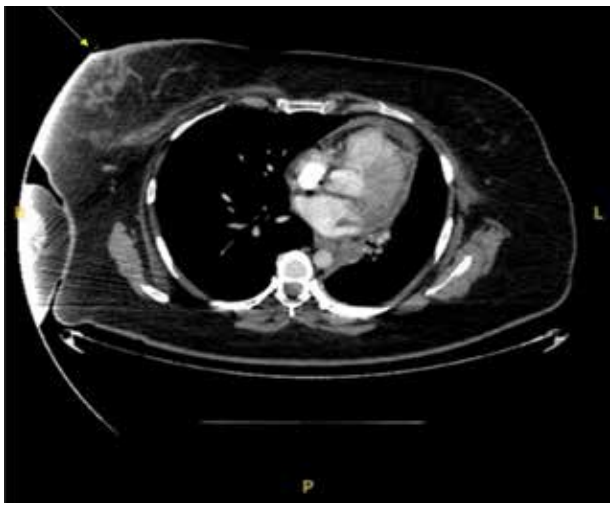

Figure 1: Asymmetrically increased density (yellow arrow) and edematous appearance of both breast tissue and the skin on thorax CT

Daily paraffin antiseptic dressing was applied to the wound. Intravenous antibiotic was continued for 7 days. Figure 2 shows the stages of recovery of the wound. After 21 days, local inflammatory signs disappeared and only scar tissue remained on the skin of breast (Figure 2).

DISCUSSION

Port catheter is an implanted vascular access device which is used for long-term chemotherapy protocols. However, there are early and delayed complications of these catheters. Early complications are due to iatrogenic injury such as pneumothorax, hemothorax, thoracic duct injury or arterial injury. Delayed complications include infection, extravasation, catheter thrombosis, catheter fracture with extravasation, or fracture with migration or embolization of catheter

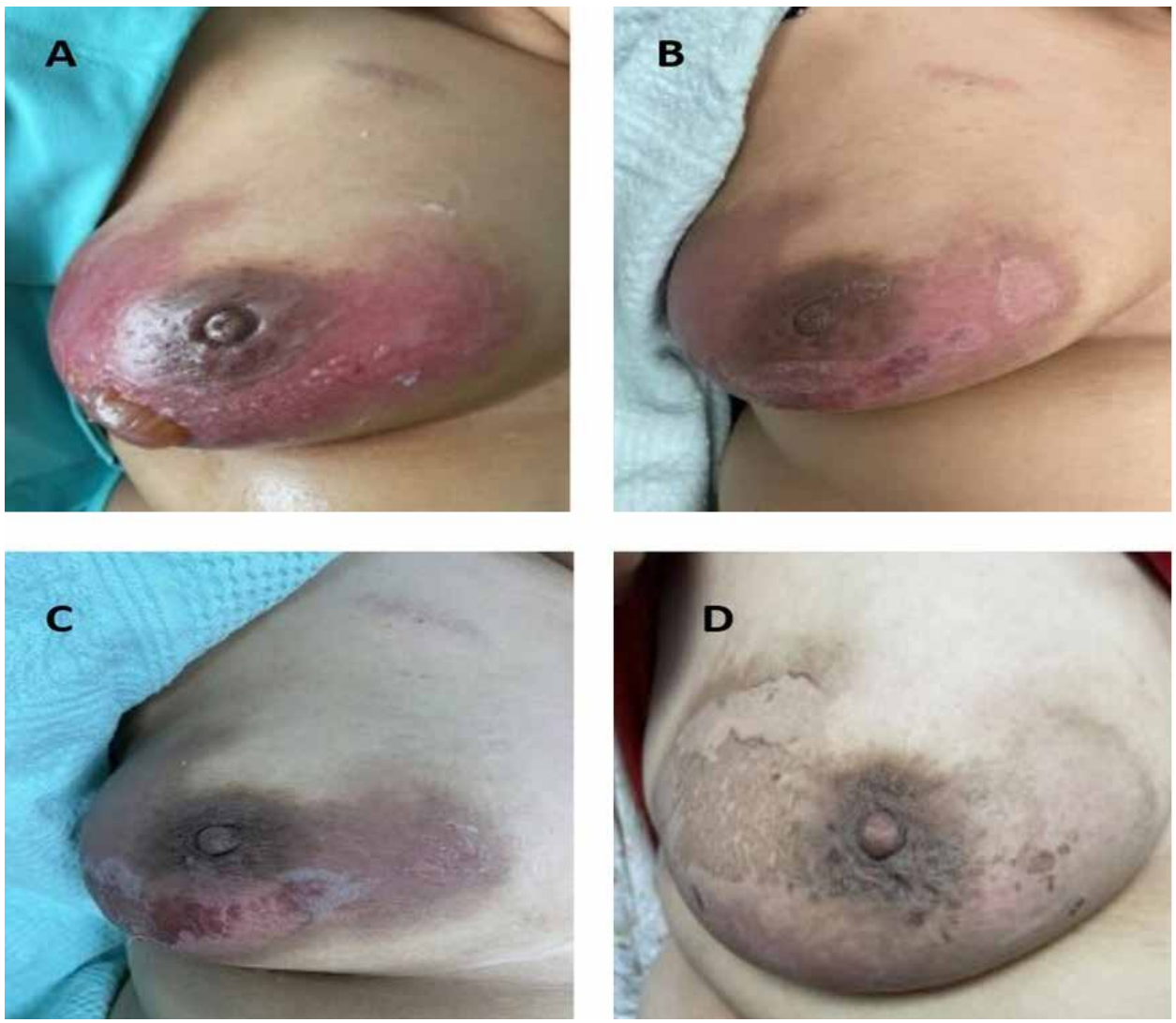

Figure 2: Blister formation and mastitis on 6th day after the drug extravasation (A) and regression/ complete resolution of inflammation (B to D)

material[4]. This case illustrates the destructive effect of paclitaxel/carboplatin extravasation on breast tissue.

The incidence of extravasation of chemotherapy is 0.01%-7% in the literature[1]. There are four mechanisms that cause drug extravasation. These are incomplete needle placement and needle dislodgment, thrombus or fibrin sheath formation, perforation of the superior vena cava and catheter fracture[5]. In case of catheter related extravasation, removal of the catheter is recommended in the literature. The integrity and working condition of the catheter were checked in this patient. After confirming that the clinical result was not related to the catheter, it was not removed during the follow-up period of the patient. In this patient, drug extravasation was due to needle dislodgment or incomplete placement.

Depending on the drug, signs may initiate as mild hyperemia and edema but may evolve to even necrosis in the following days. Extravasation reactions are classified as vesicant, irritant or non-vesicant. Irritant agents cause pain at the application site or along the vascular tracing. Vesicant drugs may cause different clinical pictures. These include erythema, blister development, edema, ulceration and tissue necrosis. Non-vesicant drugs rarely cause acute reactions and tissue necrosis. Paclitaxel-carboplatin chemotherapy protocol is classified as vesicant drug group that was given to our patient. Some chemotherapy drugs have specific antidotes which can be administrated to reduce local toxicity of vesicant drugs in case of extravasation[6]. In the literature, some rare chest wall necrosis cases were reported requiring reconstruction operations[7]. In this case, conservative treatment was sufficient for recovery of the patient.

Even if vesicant drug extravasation is an infrequent complication, it may cause irreversible clinical results. The European Oncology Nursing Society published a guideline for extravasation prevention, detection and management in 2007[8]. Nurses need to follow the current guidelines to be prepared for avoiding and managing these complications. Prevention of this complication can be achieved with only a well-trained caregiver.

CONCLUSION

Vesicant drug extravasation is seen rarely but may cause hazardous tissue destruction. Potential accidental extravasation should be managed appropriately according to type of drugs and more importantly, staff and/or patients should be trained in order to minimize patient and/or medication-related risk factors.

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Author contribution: Omer Cennet: data curation; supervision, editing; Dogukan Dogu: writing, investigation

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Case Report

A very rare lung tumor, inflammatory myofibroblastic tumor

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ABSTRACT

Inflammatory myofibroblastic tumors (IMT) are considered to be rare mesenchymal tumors which may most commonly originate from lungs, mesentery and omentum, usually seen within the first and second decade, very rare in adults. IMT's can also be named as xanthogranuloma, plasma cell granuloma, inflammatory pseudotumor, inflammatory myofibroblastic proliferation, fibrous plasma cell histiocytoma complex, histiocytoma and inflammatory fibrosarcoma. IMTs can be benign, may invade neighbouring structures, may cause malignant transformation, may present recurrence, and may even result in metastasis. Complete surgical excision of the mass if applicable, and is known to be preferred method for both diagnosis and treatment.
We report a case of pulmonary IMT with multiple lung metastasis in a middle aged man who had a previous history of testicular IMT.

KEY WORDS: CT, tumor, malignant, mesenchymal, pulmonary

INTRODUCTION

Inflammatory myofibroblastic tumors (IMT) are known to be rare mesenchymal tumors which may occur in almost every organ, most commonly in lungs, mesentery and omentum, usually seen between 0-20 years of age[1-4].

IMTs are extremely rare in adults, composing almost less than 1-2% of adult lung tumors[2,3]. IMTs, also named as xanthogranuloma, plasma cell granuloma, inflammatory pseudotumor, inflammatory myofibroblastic proliferation, plasma cell histiocytoma complex, fibrous histiocytoma and inflammatory fibrosarcoma, can be classified as benign tumors which may constitute myofibroblastic spindle cells, accompanied by an inflammatory infiltrate of plasma cells, lymphocytes and eosinophils[1,3,5].

A controversy has existed over whether IMT is a true neoplasm or a reactive lesion. They may be benign, may invade neighbouring structures, may show malignant transformation, may present recurrence, and may even cause metastasis, which may result in a wide spectrum of clinical presentations. Patients can be asymptomatic or present with hemoptysis, dyspnea, pleuritic pain, cough, constitutional symptoms and/or pneumonia[1,2,4].

In this article, we report a case of pulmonary IMT in a middle aged man who had orchiectomy due to a previous testicular IMT.

CASE REPORT

Our patient was a 43-year-old man with a history of left testicular IMT, who had visited medical oncology department with chief complaints of cough and hemoptysis. He had left orchiectomy in 2018 and was under follow-up for 3.5 years. Unfortunately, he had missed his routine controls in the pandemia during April 2020-July 2021. He had no recurrent mass in the orchiectomy zone and contralateral right testis in scrotal ultrasound. No metastatic mass lesion was observed in cranial computed tomography (CT). Nissen fundoplication due to massive gastro-osefageal reflux was performed in 2019 and had drainage stent catheter inserted from the distal osefagus through the gastric corpus. He also had complaints of chronic atrophic gastritis. No more recurrent mass and/or metastatic lymph nodes were observed in abdominopelvic CT.

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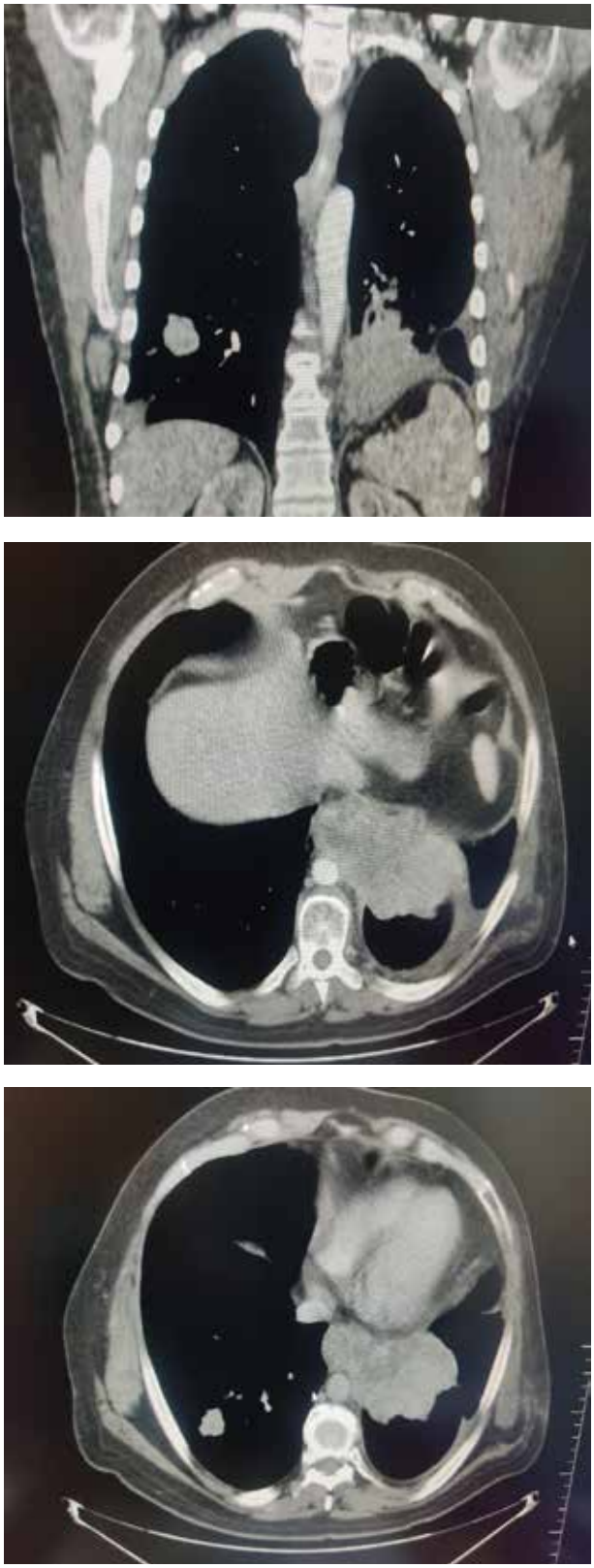

Figure 1 a, b, c: A left necrotic hypodense perihilar lung mass with left sided pleural effusion, a nodular metastatic lesion was visualized in the right lower lobe posterobasal segment, seen on contrast enhanced coronal-axial CT.

In the thorax CT, he had pericardal effusion about 2.5 cm in thickness and left pleural effusion. A huge hypodense necrotic mass about 10-12 cm in size was observed in the basis of left lung, protruding to the mediastinum with discrete interactions to the descending aorta and distal oesefagus, a subsegmental atelectasis was also seen as a satellite nodule in the neighbourhood (Figure 1 a,b,c).

A probably metastatic cavitary lesion was also visualized in the laterobazal segment of the same lung (Figure 2 a, b). Multiple parenchymal, pleural and subpleural nodular mass lesions were observed in both hemitoraxes with a maximum size of 30x13 mm (Figure 3 a, b).

Reticulonodular pattern and collaborating ground-glass appereance were presented in the posterobazal and superior segments of right lung with a milimetric partial thrombus in the right subsegmental pulmonary artery. Core biopsy and its samples can be insufficient for the exact diagnosis to our experience, so a wedge resection and subtotal excisional biopsy was performed for the lung mass. Histopathological diagnosis had approved primary pulmonary IMT. Wedge resection was preferred instead of lobectomy as he had pleural and pericardial effusion, protrusion of the mass to the mediastinum neighbouring thoracic aorta and osephagus, and multiple metastatic nodular lesions, which might also cause a prominent risk for total lingular collapse.

It was not a metastatic tumor of testicular IMT. Adjuvant 6 cure chemotherapy was planned and started as a therapeutic strategy for the patient, who showed a very good response to the treatment. Left basal metastatic cavitary lesion had almost completely disappeared, some metastatic nodules were also not visualized and remaining ones presented prominent reduction in their sizes.

In the laboratory analysis**,** he had 126 mg/dL glucose in serum with albumin level of 30 mg/dL. Alkalene phosphatase level of 143 mg/dL and CRP level of 59.09 mg/dL were examined. 1130 quantitative D-dimer level was measured. Other biochemical profile was almost normal: 13.200 white blood cell count with 9.8 g/dL Hb; 31.9% Htc were counted in the blood hemogram. 23.3 MCH and 30.6 MCHC with 76.1 MVC were observed. Neutrocytosis and lymphopenia were also defined in the complete blood count.

DISCUSSION

Lung IMTs are extremely rare, reported incidence of them is <1% of all lung tumors. They can be presented at any age, but are considered to have a dominancy for children and young adults[2,3,6]. IMTs may be expressed as low-grade malignant or benign

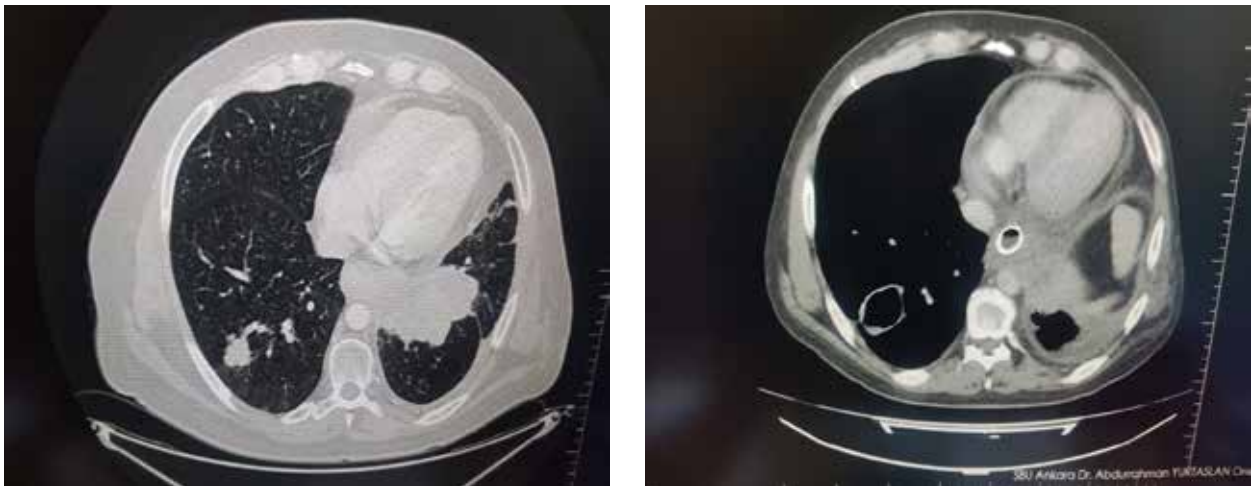

Figure 2 a, b: A right basal pulmonary cavitary lesion with left sided pulmonary mass, pericardial effusion and gastric drainage catheter (axial parenchymal and mediastinal lung CT windows)

tumor; spontaneous regression of them has been infrequently presented[1,4,7].

IMTs can be seen in various organs such as lung, spleen, liver, brain, larynx, urinary bladder, breast, testis, lymph nodes, salivary glands, soft tissues and skin. Most commonly involved localizations are lungs, abdominopelvic region and retroperitoneum. IMT usually affects a single organ, but multiple organ involvement is also possible, as seen in our patient consecutively, first in left testis then in the lung[1,3,5,8-10].

Radiographic findings showed a solitary peripheral lung nodule, usually visualized in lower lung lobes, within peripheral lung parenchyma and in subpleural locations in approximately 90% of cases[2-5]. IMTs appear as heterogeneous masses with variable contrast enhancement. On CT, calcifications, cavitations and lymphadenopathies are rare, pleural effusion and atelectasis are present in less than 10% of the cases[5-7]. PET/CT can also be a useful tool for discriminating benign IMT from malignant ones[4,5,11].

Diagnosis of IMT is difficult to identify and histopathological examination of the mass is usually needed[1-7]. Fine needle aspiration biopsy and bronchoscopic samples are almost insufficient for the exact diagnosis, therefore complete surgical excision of the mass if possible is known to be the method of choice, for both diagnosis and treatment[1,5,7,11]. Chemotherapy, radiotherapy and corticosteroid therapy for children are recommended for the patients with multifocal masses, insufficient resection, unresectable tumors and/or presence of contraindications for the surgery[1,2,6]. Prognosis mostly depends on the tumor size plus the quantity and quality of surgical intervention. Prognosis is excellent after radical resection if applicable. Patients should have routine long-term follow-

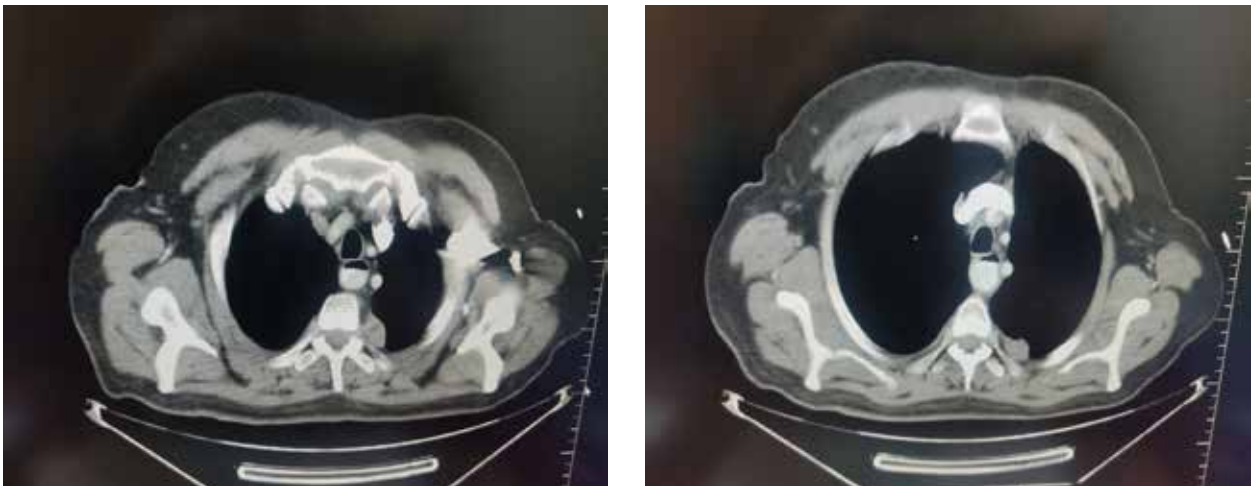

Figure 3 a, b: Left apical pleural and subpleural nodular metastatic lesions, seen on contrast enhanced axial CT scan.

up after surgery as recurrence could result even many years after the first diagnosis and the surgical excision[3,6,11,12].

Histologic examinations presented variable ratios of myofibroblastic type of spindle cells, which were arranged in a fibrous, myxoid or calcified stroma associated with an inflammation predominantly including plasma cells, lymphocytes and eosinophils throughout the tumor[4,6,8]. IMT includes three histological patterns. First is myxoid and rich vascular, resembling nodular fasciitis or granulation tissue. Second type is a more dense and compact proliferation of spindle cells with variable amounts of focal nodular lymphoid hyperplasia which looks like a collagenized fibromatosis. Third pattern is high sclero-hyalinized with slight cellular stroma that resembles a desmoid tumor[1-7,13]. In our case, second type (spindle cell proliferation with nodular lymphoid hyperplasia) seemed to be the histological pattern.

There are too many theories about the pathogenesis of IMT, proposing a couple of hypotheses such as infectious origin or an autoimmune mechanism, 30% of those cases are related with recurrent respiratory infections which are caused by nocardia, actinomycetes, mycoplasma, Epstein-Barr and human herpes virus etc[5,11,13].

Immunohistochemistry indicates a reactivity for smooth muscle actin and vimentin; approximately half of the patients present an overexpression of ALK protein which is a tyrosine kinase oncogen located on chromosome 2p23, leading a cytogenetic translocation with cellular proliferation. Several studies have demonstrated that these chromosomal abnormalities, tyrosine-kinase oncogen locus and/or DNA aneuploidy in IMT are correlated with local recurrence and tumor aggressiveness, which has concluded that IMT is a real tumoral process rather than an inflammatory reactive lesion[8-14].

IMT has a clonal proliferation of myofibroblasts with ALK-1 overexpression, majority of them are ALK tropomyosin (TPM)-4, ALK-TPM3, ALK–clathrin heavy polypeptide (ALK-CLTC) and ALK–5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (ALK-ATIC)[8,9,12-14].

In our patient, lung IMT also predicted overexpression of ALK that was depicted by immunohistochemistry.

Pathological differential diagnosis involves malignant lymphoma, organized pneumonia and solitary fibrous tumor. The low mitotic index, the mode of tumor growth, the negativity of CD34 and the polyclonality of lymphoid markers usually overcome most of those possible diagnosis. Other possible differential diagnosis can be angiomyofibroblastoma, desmoid fibromatosis, leiomyoma, fibrosarcoma, malignant fibrous histiocytoma, plasmacytoma, pseudolymphoma, sclerosing hemangioma, sarcomatoid carcinoma of the lung and nodular chronic pneumonitis[1-7,12-14].

If such a patient is seen in the future, we recommend to apply surgical excision of the mass by wedge resection and/or segmentectomy or lobectomy both for diagnosis and treatment. Adjuvant chemotherapy and radiotherapy should be applied in the next step to standardize the therapy.

CONCLUSION

Pulmonary IMT is known to be a rare benign tumor. However, risk of recurrence and distant metastasis will almost require a complete surgical approach. A routine prolonged follow-up is also essential. Clinical and radiological manifestations are almost non specific. Only histopathologic examination can confirm the real diagnosis.

To our experience, this case might be the first in the relevant literature that presented a pulmonary IMT following a testicular IMT with cavitary, nodular and pleural metastasis in the lungs. After diagnostic and therapeutic surgical excision of the pulmonary mass, adjuvant chemotherapy was planned and started for the lung metastasis.

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Author contribution: Hasan Aydin: patient analysis, writing and editing, figure and figure legends design, image interpretation; Ozge Tanisman: visualization, study formal analysis, image interpretation and reference styling; Halil Ibrahim Sara: detailed patient information concept analysis, writing skills.

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Case Report

Is the platelet rich plasma an effective treatment for wound dehiscence in biliary atresia: A case report

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ABSTRACT

Biliary atresia is the most important cause of jaundice in infants. Currently, the gold standard for surgery is Kasai portoenterostomy. Due to malnutrition, patients with biliary atresia are at risk for wound dehiscence. This case report aimed to discuss the platelet rich plasma treatment applied to a patient that was operated on for biliary atresia and who had wound dehiscence three times in the postoperative 5-17-29th days.

KEY WORDS: biliary atresia, platelet rich plasma, wound dehiscence

INTRODUCTION

Biliary atresia (BA) is the most important cause of jaundice, which appears in the first weeks of life and it's characterized by inflammation and obliteration in the biliary system, requiring urgent surgery[1]. Although significant advances have been made in biliary atresia surgery and follow-up since Kasai, we still face some difficulties such as cholangitis, failure of Kasai portoenterostomy (PE), portal hypertension, cirrhosis management, ascites, esophageal varices, surgical site infection and wound dehiscence[1-3]. Cholestasis or complications of portal hypertension, such as ascites and esophageal varices, are at the crucial risk factor for malnutrition[4]. It has been reported that the risk of wound infection and wound dehiscence are increased due to the development of growth factor resistance secondary to malnutrition, especially in malnourished patients[4,5]. Herein, we aimed to report the wound healing process of a malnourished infant who developed wound dehiscence three times after Kasai PE.

CASE REPORT

A 63-day-old boy was referred to our institute due to jaundice and pale stool. The patient's weight was 3.5 kg (<3 percentile). The patient with prolonged jaundice and direct bilirubin dominance in laboratory tests was evaluated in terms of biliary pathologies. At admission, direct bilirubin 5.45 mg/dL (R: 0-0.2 mg/dL), ALT 181 U/L (R: 0-50 U/L), AST 409 U/L (R: 0-50 U/L), GGT 323 U/L (R: 3-22 U/L), PLT 402*10^3/µl (R: 130-400*10^3/µl). Coagulation parameters were unremarkable. The CMV test was reported as IgM +ve. The CMV PCR test was +ve with 5,000,000 IU/mL (R: 227- 2,270,000 IU/mL). In hepatobiliary ultrasonography, it was reported that the gallbladder was fibrotic and atresia, and the triangular cord thickness was 4 mm. Two days after admission, the patient underwent diagnostic laparoscopic cholangiography. After the diagnosis was confirmed, Kasai PE was performed through right subcostal incision. Macroscopically, the liver appearance was cirrhotic. Liver biopsy was obtained. Liver pathology specimen reported grade 3 cirrhotic findings (according to the ISHAK modified HAI score)[6]. Wound is closed in layers after the drain is placed. The patient was fed when bowel function returned. At the postoperative period, the patient was monitored for electrolytes, and liver tests and third generation cephalosporin + metronidazole + steroid treatments were started. On the 5th postoperative day, wound dehiscence developed (Fig 1). The patient underwent surgery. Wound debridement and wound closure were

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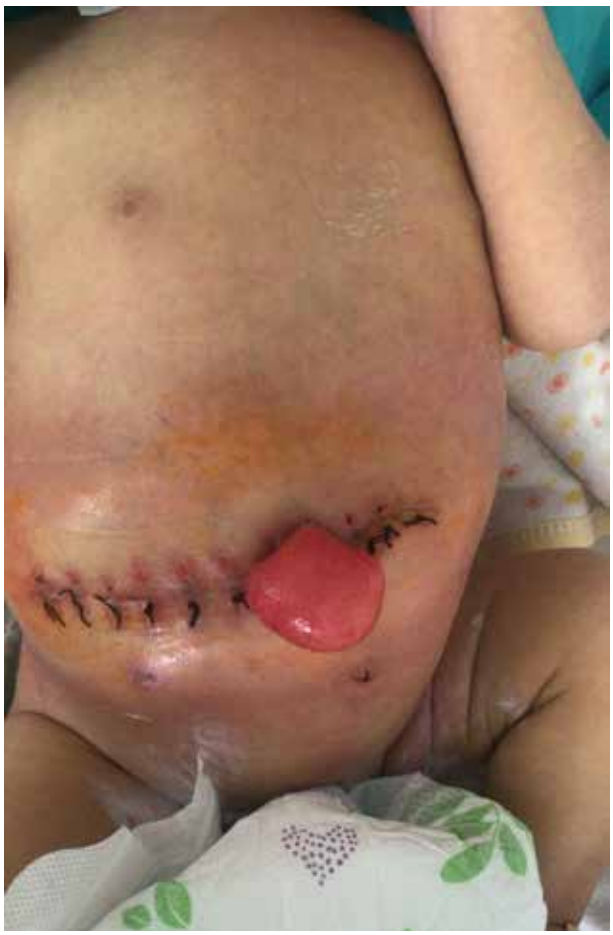

Fig 1: Clearly seen wound dehiscence

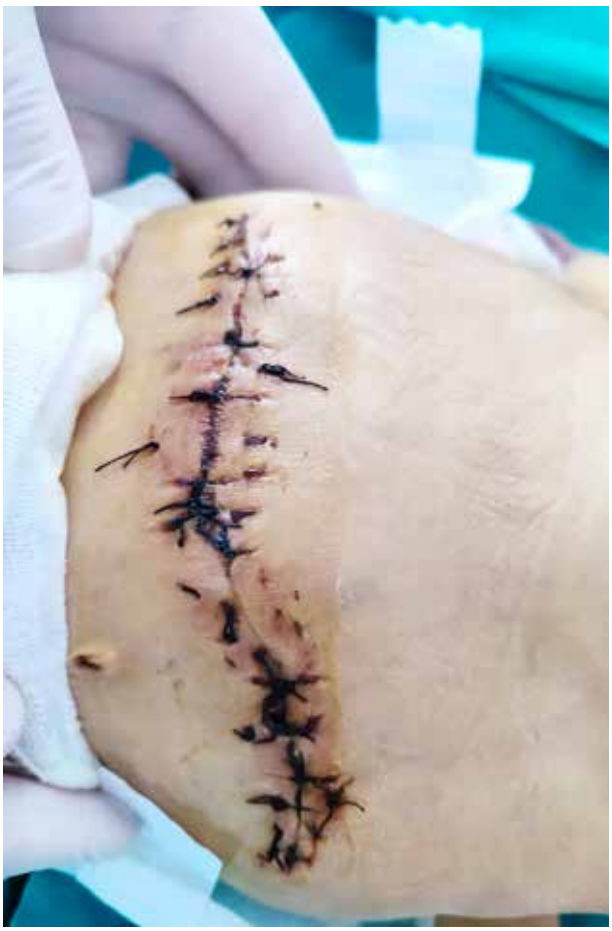

Fig 2: Wound after treatment with platelet rich plasma (PRP)

performed. In this patient, who already had poor wound healing due to malnutrition, the patient was simplified with a chloral hydrate drug to reduce wound tension. The steroid dose was reduced to 0.5 mg/kg/day in order to reduce the steroid immunosuppressive effects and to maximize wound healing. Despite these treatments, wound dehiscence developed two more times on the 17th and 29th postoperative days and wound debridement and wound closure were performed again. In the third wound dehiscence, the patient also underwent laparotomy. However, there was no significant adhesion between the intestines. During this time, a bilioenteric fistula had developed and unfortunately ascites were starting to become a nuisance. After the third wound dehiscence, it was decided to inject platelet rich plasma (PRP) into the wound site of the patient who had already developed growth factor resistance due to malnutrition in order to accelerate wound healing. We injected PRP into the wound on the 1st and 8th days (once a week). After 10 days of PRP treatment, the patient's wound site showed significant improvement (Fig 2).

DISCUSSION

Biliary atresia (BA) remains one of the most challenging conditions in pediatric surgery practice from diagnosis to surgical technique[2]. Although an important role has been played in surgical technique today, difficulties in diagnosis continue. It is obvious that cytokines play a crucial role in the pathophysiology of this inflammatory disease and the healing process[1,7].

Children with BA are at risk for malnutrition for a multitude of reasons, involving poor oral intake and intolerance of enteral feedings, fat malabsorption, growth factors resistance and abnormal nutrient metabolism[8]. Yang *et al* and Sultan *et al* have reported in their studies that patients with BA have hypermetabolic metabolism, requiring 150% of predicted energy needs, which may be worsened by infections, bleeding and circulating proinflammatory cytokines[9,10]. Unfortunately, the inflammatory process and cytokine storm already existing in its pathophysiology and the surgical stress on top of it significantly affect the nutritional intolerances of the patients in the postoperative period[1]. In another

unpublished study, we observed that BA patients in our clinic could not get enough nutrition due to malnutrition, abdominal distention, wound infection, ascites, etc., and therefore they lost a significant amount of weight. However, we believe that malnutrition is an important factor in the development of wound infection and dehiscence in patients with BA.

In patients with BA, the role of corticosteroids is controversial. However, many studies reported the beneficial effects of the steroids such as choleretic and decreased inflammation and scarring at the anastomosis site[11,12]. In our high-volume center, we also use steroids for the treatment of BA. Although Davenport *et al* reported that they did not observe the side effects of steroids in biliary atresia patients, Moore *et al* noted in their study that intravenous steroid administration poses a risk for wound infection[11,13]. In this patient, after wound dehiscence, we significantly reduced the steroid dose and continued treatment at a dose of 0.5 mg/kg/day.

In some studies, increased intra-abdominal pressure has been reported to cause wound dehiscence[14]. Therefore, we preferred to put the patient to sleep by using chloral hydrate medication from time to time to calm down our patient who has constant crying attacks.

With this patient, the development of wound site infection and wound evisceration for the third time, despite the initiation of chloral hydrate medication to reduce intra-abdominal pressure, IV antibiotic treatment, reduction of steroid dose and daily wound dressing prompted us to seek an alternative treatment method.

Optimal wound healing includes debridement, infection control and wound dressing[15]. When these actions fail and wound healing is impaired, however, additional therapies such as PRP may be considered. The prominent growth factors of PRP include platelet-derived growth factor, transforming growth factor β, vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor and fibroblast growth factor[16]. Several pathways were noted describing the mechanism of action[17]. So, with this patient, we have performed 1 ml PRP treatment once a week, as described in the literature by some researchers[18]. We observed significant wound healing after the 6th day of treatment. On the 10th day, there was excellent healing in the wound.

CONCLUSION

In conclusion, surgical site infection and wound dehiscence are more common in malnourished patients. In such a case, PRP can be considered. Randomized controlled trials are needed to evaluate the safety and efficacy of PRP in patients with biliary atresia.

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Authors contribution: Mustafa Azizoglu: Study conception and design, data acquisition, analysis and data interpretation and manuscript submission; Bahattin Aydogdu: analysis and data interpretation, drafting of the manuscript and critical revision; Mehmet Hanifi Okur: drafting of the manuscript and critical revision

Conflict of interest: The authors report no conflicts of interest.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Comparative analysis of salivary cytokine profiles and oral microbial composition in caries-active and caries-free children

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AIM
This study aimed to evaluate salivary cytokine levels and the prevalence of cariogenic bacterial species in children with active dental caries compared to caries-free peers.

METHODS
This cross-sectional study involved forty randomly selected children aged 7-9 years, who were divided into caries-active or caries-free groups. DNA was extracted from supragingival plaque using the DNeasy kit and analysed. Microbial profiling was conducted using HOMINGS 16S rRNA gene sequencing. Saliva samples were also collected and analysed using multiplex cytokine bead assays on the Luminex system to assess cytokine levels.

RESULTS
The caries-active group exhibited significantly higher relative abundance of genera Leptotrichia, Veillonella, and Kingella ($p < 0.05$). At the species level, Streptococcus sanguinis, Leptotrichia shahii, Streptococcus mutans, Leptotrichia sp. HOT_498, TM7[G-1] sp. HOT_346, Rothia dentocariosa were significantly enriched in the caries-active group. In females, IL-15 and IL-1β were significantly elevated in the caries-active group, with no cytokine differences observed in males or overall levels. The relative abundance of Leptotrichia shahii, Streptococcus mutans, Streptococcus sanguinis, TM7[G-1] sp. HOT_346, Abiotrophia defectiva, and Rothia dentocariosa significantly correlated with cytokines, including Aggrecan, BAFF, CD-40L, IL-1β, IL-5, IL-8, IL-11, IL-15, IL-17, IL-23, IL-28A, MIP-3α, Pentraxin 3, and TNF-α. In the caries-free group, only Leptotrichia hongkongensis showed a significant association with IL-10.

CONCLUSION
Distinct microbiome differences at both the genus and species levels were observed between caries-active and caries-free groups. Salivary cytokine levels were similar between the groups, except for higher IL-15 and IL-1β in females from the caries-active group. Correlations between bacteria and cytokines in the caries-active group highlight the need for further research on the microbiome-immune interaction in caries development.

CLINICAL SIGNIFICANCE
Microbiome profiles, cytokine levels, and their potential correlation in caries-active children suggest that further study and understanding of these factors could help identify individuals at higher risk for caries and guide preventive care.

Heterotopic hepatic tissue on gallbladder: A rare incidental finding

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J Clin Med Images Case Rep. 2024; 4(5): 1742.

INTRODUCTION
Heterotopic Hepatic Tissue (HHT) is an uncommon medical condition that occurs due to failure of embryological liver development. It can be encountered anywhere in the body and mainly on the gallbladder. HHT are often clinically silent, however they can pose a risk of complications such as torsion, malignant transformation and compression effect over the adjacent structures. We describe the case of hepatic choristoma that was discovered incidentally during laparoscopic cholecystectomy.

PRESENTATION OF CASE
A 38-year-old male patient otherwise healthy, presented with symptomatic gallbladder mural polyps. During procedure, a small lesion resembling liver tissue was noted attached to the gallbladder wall and both were resected successfully. Histopathologic examination revealed benign ectopic liver tissue.

DISCUSSION AND CONCLUSION
Hepatic choristomas are rare finding, typically detected during abdominal surgeries. Familiarity with this entity and its diverse presentations and potential complications is essential for improving patient outcomes. Once identified, surgical treatment should be considered as it may carry a risk of malignant transformation.

Safety of Using Tutoplast-Processed Fascia Lata in Rhinoplasty: A Systematic Review and Meta-Analysis

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OBJECTIVE
To evaluate the safety profile of using tutoplast-processed fascia lata (TPFL) as a graft material in patients undergoing both primary and revision rhinoplasty.

METHODS
PubMed, CENTRAL, Scopus, Web of Science, and EMBASE were searched. Eligible studies were evaluated for bias using the National Institutes of Health (NIH) assessment tool for cohort studies. Our safety outcomes included the incidence of graft resorption, infection, graft displacement, dorsal irregularity, overcorrected dorsal augmentation, and revision rates. Data were pooled as event rate (%) with a 95% confidence interval (CI) using STATA software.

RESULTS
Nine studies, comprising 827 patients, were included. Eight studies were evaluated with a low risk of bias, and one study had a moderate risk of bias. The pooled proportion analysis demonstrated a low graft resorption rate (event rate = 2.64%, 95% CI [0.69%, 5.62%]), infection rate (event rate = 0.30%, 95% CI [0.02%, 0.83%]), dorsal irregularity rate (event rate = 0.96%, 95% CI [0.09%, 2.51%]), graft displacement rate (event rate = 0.45%, 95% CI [0.07%, 1.12%]), overcorrected dorsal augmentation rate (event rate = 1.29%, 95% CI [0.39%, 2.65%]), and revision rate (event rate = 3.99%, 95% CI [1.82%, 6.90%]).

CONCLUSION
This meta-analysis of 827 patients demonstrated that TPFL has a favorable safety profile in both primary and revision rhinoplasty, with low complication and revision rates. TPFL, whether used alone or in combination with cartilage, is a viable graft option for dorsal augmentation and enhancing nasal dorsum contour.

Outcomes of Intermittent Hemodialysis vs. Continuous Kidney Replacement Therapy in Hemodynamically Stable Patients with Acute Kidney Injury: A Prospective, Observational, Multicenter Study

Ali AlSahow, Omar Alkandari, Yousif Bahbahani, Anas Alyousef, Bassam AlHelal, Heba AlRajab, Ahmed AlQallaf, Monther AlSharekh, Abdulrahman AlKandari, Gamal Nessim, Bassem Mashal, Ahmad Mazroue, Alaa Abdelmoteleb, Mohamed Elabbadi, Ali Abdelzaher, Emad Abdallah, Mohamed Abdellatif, Ziad ElHusseini, Ahmed Abdelrady

Med Princ Pract. 2025 Feb 4:1-17. doi: 10.1159/000543882. Online ahead of print.

INTRODUCTION
Continuous dialysis in hemodynamically stable patients with acute kidney injury (AKI) may impact outcomes differently than intermittent dialysis. We evaluated differences in patient and kidney outcomes between the two modalities.

METHODS
Clinical and 30-day outcome data for inpatients with AKI who were hemodynamically stable and not on ventilation and who received intermittent hemodialysis (IHD) or continuous kidney replacement therapy (CKRT) in public hospitals in Kuwait from January 1 to December 31, 2021, were prospectively collected.

RESULTS
We recruited 229 patients (age: 59.9 years; males, 60.3%; baseline eGFR, 56 ml/min). CKRT accounted for 72.9% of cases due to lack of access to water treatment. No statistically significant differences were observed between groups in terms of age, baseline eGFR, sex, comorbidities, cause of AKI, or fluid administration. Intensive care unit contributed 21% of cases, with no significant difference between groups. More IHD patients received diuretics (62.9% vs. 43.1% for CKRT, $p = 0.008$). At 30 days, 21.8% of patients had died. There was no statistically significant difference in mortality between groups (16.1% for IHD vs. 24% for CKRT, $p = 0.2$). Final eGFR was 53.2 ml/min, with no difference between groups. Complete kidney recovery was greater with CKRT (33.1% vs. 13.5%, $p = 0.009$). Baseline eGFR < 60 ml/min did not influence mortality or kidney recovery.

CONCLUSION
Compared with IHD, CKRT did not lower mortality at 30 days, which is similar to that of randomized trials; however, it was associated with better complete kidney recovery, which was reported in observational studies.

Strawberry Gallbladder: A Distinctive Type of Cholesterolosis, Case Report and Literature Review

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Strawberry gallbladder is a benign medical condition that refers to the surface appearance of the gallbladder mucosa. It occurs due to precipitations of lipids and macrophages in the lamina propria of the gallbladder wall.
We report the case of a 44-year-old female patient who presented to the emergency department with few days history of biliary colic. Investigations showed elevated AST, ALT and hypercholesteremia. Ultrasound abdomen demonstrated a mild fatty liver and multiple GB polyps. Laparoscopic cholecystectomy was performed. Histopathologic features were consistent with diffuse cholesterolosis.
Strawberry gallbladder is a distinctive type of cholecystosis. It is caused by irreversible alteration in the anatomic and morphologic aspects of the gallbladder lining. This entity is usually identified after surgery. Symptomatic patients with cholesterolosis will benefit from cholecystectomy.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2025; 57 (1): 54 - 62

International Conference on **Rural Medicine and Emergency Medical Services**
Mar 01, 2025
Canada, Vancouver
Organized by: Science Cite
Conference inquiry email: team@sciencecite.com

International Conference on Recent Advance in **Engineering and Technology**
Mar 01, 2025
Australia, Brisbane
Organized by: AFTER
Conference inquiry email: event@after.org.in

International Conference on **Pediatric Cardiology**
Mar 01, 2025
Canada, Toronto
Organized by: Research Plus
Conference inquiry email: info@researchplus.co

International Conference on **Clinical Nutrition**
Mar 03, 2025
Italy, Venice
Organized by: IIERD
Conference inquiry email: info@iierd.org

World Congress on Controversies in **Neurology**
Mar 03, 2025
South Korea, Daegu
Organized by: Sairap
Conference inquiry email: team@sairap.org

International Conference on **Stroke Rehabilitation and Cardiology**
Mar 04, 2025
United States, Dallas
Organized by: World Academics
Conference inquiry email: info@worldacademics.net

International Conference on **Gynecology, Obstetrics and Infertility**
Mar 04, 2025
United States, Philadelphia
Organized by: Research Leagues
Conference inquiry email: team@researchleagues.com

International Conference on **Infectious Disease Medicine, Infectious Diseases and Immunotherapy**
Mar 05, 2025
Italy, Milan
Organized by: IARF
Conference inquiry email: info@iarfconference.com

International Conference on Modern Research in **Biological, Pharmaceutical, Medical and Environmental Sciences**
Mar 05, 2025
United Arab Emirates, Abu Dhabi
Organized by: Science Leagues
Conference inquiry email: info@scienceleagues.com

International Conference on **Radiosurgery and Radiology**
Mar 05, 2025
United States, Philadelphia
Organized by: ISER
Conference inquiry email: info@iser.org.in

International Conference on **Pediatric Hematology and Pediatric Heart Diseases** (ICPHPHD-2025)
Mar 06, 2025
Kuwait, Kuwait city
Organized by: IITER
Conference inquiry email: info@iiter.org

International Conference on **Bacterial Diseases and Clinical Pathology**
Mar 07, 2025
Russia, Novosibirsk
Organized by: ISAR
Conference inquiry email: team@isar.org.in

International Conference on **Adolescent Medicine & Child Psychology**
Mar 07, 2025
Uzbekistan, Bukhara
Organized by: ITAR
Conference inquiry email: info@itar.in

International Conference on Emerging Focus in **Diabetes Research**
Mar 08, 2025
Bahamas, Lucaya
Organized by: Science Cite
Conference inquiry email: team@sciencecite.com

International Conference on **Medical Ethics Cases**
Mar 08, 2025
Kuwait, Kuwait city
Organized by: AFTER
Conference inquiry email: event@after.org.in

International Conference on **Adolescent Medicine & Child Psychology** (ICAMCP-2025)
Mar 08, 2025
Kuwait, Kuwait City
Organized by: AFTER
Conference inquiry email: event@after.org.in

International Conference on Emerging Focus in **Diabetes Research**
Mar 08, 2025
South Korea, Busan
Organized by: Scholars Forum
Conference inquiry email: conf@scholarsforum.org

World Congress on Controversies in **Neurology**
Mar 10, 2025
United States, California
Organized by: World Academics
Conference inquiry email: info@worldacademics.net

International Conference on **Clinical Cardiology, Heart Diseases**, Symptoms and Types
Mar 12, 2025
Saudi Arabia, Riyadh
Organized by: Science Society
Conference inquiry email: info@sciencesociety.co

International Conference on **Radiology, Medical Imaging and Radiotherapy**
Mar 13, 2025
Thailand, Bangkok
Organized by: Research Leagues
Conference inquiry email: team@researchleagues.com

International Conference on **Medical Health and Science**
Mar 13, 2025
China, Kunming
Organized by: Research Fora
Conference inquiry email: events@researchfora.net

International Conference on **Clinical Nutrition**
Mar 14, 2025
Spain, Granada
Organized by: AFTER
Conference inquiry email: event@after.org.in

International Conference on **Cardiology and Cardiac Surgery**
Mar 14, 2025
Indonesia, Bandung
Organized by: Science Society
Conference inquiry email: info@sciencesociety.co

International Conference on **Diabetes, Metabolic Syndrome and Obesity**
Mar 14, 2025
Thailand, Bangkok
Organized by: World Academics
Conference inquiry email: info@worldacademics.net

International Conference on **HIV/AIDS**
Mar 14, 2025
United Arab Emirates, Abu Dhabi
Organized by: Science Cite
Conference inquiry email: team@sciencecite.com

International Conference on **Pediatric Immunology and Pediatric Cardiology**
Mar 15, 2025
Australia, Brisbane
Organized by: Science Cite
Conference inquiry email: team@sciencecite.com

International Conference on **Stroke Rehabilitation and Cardiology**
Mar 18, 2025
United States, Los Angeles
Organized by: ITAR
Conference inquiry email: info@itar.in

World **Cardiology** and Cardiologist Conference
Mar 19, 2025
United Kingdom, Edinburgh
Organized by: Science Cite
Conference inquiry email: team@sciencecite.com

World Conference on **Liquid Biopsy & Biomarkers**
Mar 19, 2025
Saudi Arabia, Dammam
Organized by: Research Leagues
Conference inquiry email: team@researchleagues.com

International Conference on **Non-Infectious Diseases and Vaccination**
Mar 21, 2025
United States, San Francisco
Organized by: Science Society
Conference inquiry email: info@sciencesociety.co

International Conference on **Women Gynecology, Childbirth and Reproductive Medicine**
(ICWGCRM-2025)
Mar 21, 2025
Kuwait, Al Jahra
Organized by: Science Society
Conference inquiry email: info@sciencesociety.co

International Conference on **Cancer Biology and Pathology**
Mar 21, 2025
Germany, Berlin
Organized by: AFTER
Conference inquiry email: event@after.org.in

International Conference on Emerging **Infectious Diseases**
Mar 21, 2025
United Arab Emirates, Abu Dhabi
Organized by: Sairap
Conference inquiry email: team@sairap.org

International Conference on **Clinical Endocrinology and Diabetes**
Mar 22, 2025
Turkey, Bursa
Organized by: IIRST
Conference inquiry email: info@iirst.com

International Conference on **Stroke Rehabilitation and Cardiology**
Mar 25, 2025
Japan, Tokyo
Organized by: Science Cite
Conference inquiry email: team@sciencecite.com

International Conference on **Stroke Rehabilitation and Cardiology**
Mar 25, 2025
Iraq, Najaf
Organized by: Research Plus
Conference inquiry email: info@researchplus.co

International Conference on **Gynecology, Obstetrics and Infertility**
Mar 25, 2025
United Arab Emirates, Al Ain
Organized by: Research Foundation
Conference inquiry email: info@researchfoundation.net

International Conference on **Clinical Gynecology and Women Oncology**
Mar 26, 2025
South Korea, Seoul
Organized by: Science Cite
Conference inquiry email: team@sciencecite.com

International Conference on **Pediatric Endocrinology and Diabetes**
Mar 28, 2025
Saudi Arabia, Dammam
Organized by: IITER
Conference inquiry email: info@iiter.org

International Conference on **Clinical Pathology** and Diagnostic Techniques
Mar 28, 2025
United Kingdom, Birmingham
Organized by: IARF
Conference inquiry email: info@iarfconference.com

International Conference on **Clinical Endocrinology and Diabetes**
Mar 29, 2025
United Kingdom, Bradford
Organized by: Research Fora
Conference inquiry email: events@researchfora.net

International Conference on **Pediatric Cardiology**
Mar 29, 2025
United States, Seattle
Organized by: Research Foundation
Conference inquiry email: info@researchfoundation.net

International Conference on **Hypertension & Healthcare**
Mar 29, 2025
Tokyo, Japan
Organized by: ISER
Conference inquiry email: info@iser.org.in

International Conference on **Medical and Health Sciences**
Apr 01, 2025
United Kingdom, Edinburgh
Organized by: Scienceplus
Conference inquiry email: papers.scienceplus@gmail.com

International Conference on **Positive Psychology and Mental Health**
Apr 01, 2025
India, Bangalore
Organized by: IIERD
Conference inquiry email: papers.iistem@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Apr 02, 2025
United Arab Emirates, Abu Dhabi
Organized by: by Academics world
Conference inquiry email: info@academicsworld.org

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Apr 04, 2025
United States, Santa Clara, California
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Conference on **Epidemiology & Public Health**
Apr 04, 2025
Malaysia, Petaling Jaya
Organized by: Meeting Fora
Conference inquiry email: info@meetingfora.com

International Conference on **Laboratory Medicine & Pathology**
Apr 04, 2025
Australia, Perth
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Medical and Health Sciences**
Apr 05, 2025
United States, Boston, Massachusetts
Organized by: Science plus
Conference inquiry email: papers.scienceplus@gmail.com

International Conference on **Pediatrics, Perinatology and Child Health**
Apr 05, 2025
United States, New Orleans, Louisiana
Organized by: Research Era
Conference inquiry email: info.researcheraconference@gmail.com

International Conference on **Obesity Medicine**
Apr 06, 2025
Japan, Saitama
Organized by: United Research
Conference inquiry email: info.unitedresearch@gmail.com

2nd **Pediatric Haematology Oncology** Conference in Kuwait
Apr 07, 2025
Kuwait, Four Seasons Hotel
Organized by: Kuwait Association of Paediatricians

Global Summit on **Pediatrics and Child Health Care**
Apr 07, 2025
Spain, Valencia
Organized by: PEDIATRICS 2025
Conference inquiry email: pediatrics2025@researchconnects.org

International Conference on **Nutrition & Health**
Apr 09, 2025
United Arab Emirates, Abu Dhabi
Organized by: Conference Online
Conference inquiry email: info.conferenceonline@gmail.com

11th International Conference on **Physical Medicine & Rehabilitation**
Apr 10, 2025
United Arab Emirates, Dubai
Organized by: Physical Medicine 2025
Conference inquiry email: meevents@memeetings.com

International Conference on **Digital Health and Telemedicine**
Apr 11, 2025
United States, Atlanta, Georgia
Organized by: United Science Research Society
Conference inquiry email: info.usrsociety@gmail.com

5th Jahra **Internal Medicine** Day
Apr 12, 2025
Kuwait, Waldorf Astoria Hotel
Organized by: New Al-Jahra Hospital

The Second Edition of the Empowering **Women's Health** Conference
Apr 12, 2025
United States, Dubai
Organized by: Conference Coordinator
Conference inquiry email: reham_a@medvarsity.com

International Conference on **Mental Health and Psychiatry**
Apr 12, 2025
Saudi Arabia, Abha
Organized by: All Conference Series
Conference inquiry email: info.allconferenceseries@gmail.com

International World Research Congress on **Dentistry and Oral Health**
Apr 13, 2025
United States, El Paso, Texas
Organized by: Biofora
Conference inquiry email: info@biofora.org

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Apr 4, 2025
Saudi Arabia, Medina
Organized by: Wrfer
Conference inquiry email: contact.wrfer@gmail.com

The Miami International **Child & Adolescent Mental Health** (MICAMH)
Apr 14, 2025
United States, Florida
Organized by: FIU
Conference inquiry email: MICAMHsubmissions@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Apr 16, 2025
United States, New York
Organized by: Academics world
Conference inquiry email: info@academicsworld.org

International Conference on **Medical and Health Sciences**
Apr 16, 2025
Australia, Sydney
Organized by: Academics conference
Conference inquiry email: papers.academicsconference@gmail.com

International Conference on **Medical and Health Sciences**
Apr 16, 2025
Qatar, Doha
Organized by: Inder science
Conference inquiry email-Id: info.inderscience.org@gmail.com

International Conference on **Epidemiology & Public Health**
Apr 18, 2025
United States, San Antonio, Texas
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

International Conference on **Clinical Neuropharmacology, Neuroscience and Medicine**
Apr 18, 2025
Hungary, Miskolc
Organized by: Science Guru
Conference inquiry email: info.scienceguru@gmail.com

International Conference on **Epidemiology & Public Health**
Apr 19, 2025
United States, Phoenix, Arizona
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

Research International Conference on **Medical, Medicine and Health Science**
Apr 20, 2025
Italy, Rome
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Apr 21, 2025
Turkey, Istanbul
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Conference on **Medical and Health Sciences**
Apr 22, 2025
South Korea, Seoul
Organized by: ISERD
Conference inquiry email: info@iserd.co

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Apr 24, 2025
Italy, Rome
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Apr 25, 2025
South Africa, Johannesburg
Organized by: Academics world
Conference inquiry email: info@academicsworld.org

International Conference on Advances in **Health and Medical Science**
Apr 25, 2025
United Arab Emirates, Dubai
Organized by: SAARD
Conference inquiry email: info.saard.org@gmail.com

International Conference on Recent Advancement in **Medical Education, Nursing and Health Sciences**
Apr 26, 2025
United Arab Emirates, Dubai
Organized by: IRF conference
Conference inquiry email: info.irfconference@gmail.com

International Conference on Advances in **Medical Science and Health care**
Apr 26, 2025
Japan, Tokyo
Organized by: Academics era
Conference inquiry email: info@academicsera.com

Research International Conference on **Medical, Medicine and Health Science**
Apr 27, 2025
Singapore, Singapore
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Conference on **Epidemiology and Public Health**
Apr 27, 2025
United States, Texas
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Psychology and Mental Health**
Apr 27, 2025
Egypt, Elmohndseen
Organized by: Research Era
Conference inquiry email: info.researcheraconference@gmail.com

World Congress on **Women's Health Reproduction and Fertility**
Apr 27, 2025
United States, Wilmington, Delaware
Organized by: Japanese Society for Academic Research and Publication
Conference inquiry email: info.jsarap@gmail.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Apr 30, 2025
Canada, Ottawa
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Conference on **Tissue Science and Regenerative Medicine**
Apr 30, 2025
Saudi Arabia, Mecca
Organized by: Japanese Society for Academic Research and Publication
Conference inquiry email: info.jsarap@gmail.com

International Conferences on **Medical and Health Science**
May 01, 2025
United Arab Emirates, Dubai
Organized by: Theires
Conference inquiry email: info@theires.org

International conference on **Medical Health Science, Pharmacology & Bio Technology**
May 01, 2025
United States, New York
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
May 02, 2025
Maldives, Male
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

11th Amiri **Diabetes** Conference
May 02-03, 2025
Kuwait, Waldorf Astoria
Organized by: Amiri Hospital

International Conference on **Nutrition & Health**
May 03, 2025
China, Shanghai
Organized by: ASAR
Conference inquiry email: papers.asar@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
May 03, 2025
Germany, Berlin
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
May 05, 2025
Sweden, Stockholm
Organized by: Academics world
Conference inquiry email: info@academicsworld.org

International Conference on **Dental and Oral Health**
May 05, 2025
India, Pune, Maharashtra
Organized by: United Research
Conference inquiry email: info.unitedresearch@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
May 06, 2025
Turkey, Antalya
Organized by: WRFER
Conference inquiry email: contact.wrfer@gmail.com

International Conference on **Pediatrics and Child Health**
May 06, 2025
India, Mumbai, Maharashtra
Organized by: United Research
Conference inquiry email: info.unitedresearch@gmail.com

International Research Conference on **COVID-19** and its Impact on Mental Health
May 07, 2025
Japan, Tokyo
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Conferences on **Medical and Health Science**
May 08, 2025
Uzbekistan, Tashkent
Organized by: Theires
Conference inquiry email: info@theires.org

International Conference on **Mental Health and Wellbeing**
May 08, 2025
United States, New York
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
May 09, 2025
Qatar, Doha
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Conference on **Public Health and Epidemiology**
May 09, 2025
United States, New York
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

11th International Conference and Expo on **Physiotherapies, Physical Rehabilitation and Sports Medicine** (Physical Therapy 2025)
May 12, 2025
Canada, Toronto
Organized by: Kind Congress
Conference inquiry email: sportsmedicinecongress@medicalscienceconference.com

International Conference on **Food, Nutrition, Health & Lifestyle**
May 15, 2025
Switzerland, Geneva
Organized by: Biofora

International Conference on Recent Advancement in **Medical Education, Nursing and Health Sciences**
May 16, 2025
Australia, Melbourne
Organized by: IRF conference

International Conference on **Pathology and Laboratory Medicine**
May 17, 2025
Canada, Vancouver
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

Global Summit on **Stem Cell & Regenerative Medicine**
May 18, 2025
Italy, Turin
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Youth Mental Health**
May 19, 2025
Singapore, Singapore
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
May 20, 2025
United States, Las Vegas, Nevada
Organized by: WRFER
Conference inquiry email: contact.wrfer@gmail.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
May 21, 2025
Thailand, Bangkok
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

3rd International Summit on **Public Health and Preventive Medicine**
May 22, 2025
Netherlands, Amsterdam
Organized by: Spectrum Conferences
Conference inquiry email: isphpm2025@spectrumconferences.com

International Research Conference on **COVID-19** and its Impact on Mental Health
May 22, 2025
India, New Delhi
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Conference on Recent Advancement in **Medical Education, Nursing and Health Sciences**
May 25, 2025
United States, Santa Clara, California
Organized by: IRF conference
Conference inquiry email: info.irfconference@gmail.com

International Conference on **Medical and Health Sciences**
May 26, 2025
Jordan, Amman
Organized by: Inderscience
Conference inquiry email: info.inderscience.org@gmail.com

Global Summit on **Stem Cell & Regenerative Medicine**
May 29, 2025
United States, San Jose, California
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Internal Medicine and Hospital Management**
May 30, 2025
France, Toulouse
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Mental Health and Treatment**
May 31, 2025
United Kingdom Liverpool
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Public Health and Nutrition**
May 31, 2025
Germany, Frankfurt
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International World Research Congress on **Dentistry and Oral Health**
May 31, 2025
Spain, Palma
Organized by: Biofora
Conference inquiry email: info@biofora.org

International Conference on **Medical and Health Sciences**
Jun 05, 2025
Turkey, Istanbul
Organized by: Academics conference
Conference inquiry email: papers.academicsconference@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Jun 06, 2025
Lebanon, Byblos
Organized by: Academics world
Conference inquiry email: info@academicsworld.org

International Research Conference on **COVID-19** and its Impact on Mental Health
Jun 06, 2025
Thailand, Pattaya
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Conference on **Pathology and Laboratory Medicine**
Jun 08, 2025
Denmark, Aarhus
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Jun 09, 2025
Taiwan, Taipei
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Jun 12, 2025
Egypt, Suez
Organized by: Academics world
Conference inquiry email: info@academicsworld.org

International Symposium on **Public Health and Epidemiology**
Jun 12, 2025
Italy, Rome
Organized by: Conference coordinator
Conference inquiry email: publichealth@scsmeetings.com

International Conferences on Advances in **Nursing Science, Medical and Health Care**
Jun 15, 2025
Saudi Arabia, Medina
Organized by: Theires
Conference inquiry email: info@theires.org

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jun 17, 2025
United States, Cambridge, Massachusetts
Organized by: WRFER
Conference inquiry email: contact.wrfer@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Jun 17, 2025
Switzerland, Bern
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Conference on **Medical & Health Science**
Jun 18, 2025
United Kingdom, London
Organized by: Research fora
Conference inquiry email: info@researchfora.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jun 19, 2025
Ireland, Dublin
Organized by: WRFER
Conference inquiry email: contact.wrfer@gmail.com

International Research Conference on **COVID-19** and its Impact on Mental Health
Jun 19, 2025
United Kingdom, Oxford
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Jun 20, 2025
South Korea, Seoul
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Congress on **Physical Activity and Public Health**
Jun 20, 2025
Netherlands, Utrecht
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

International Conference on **Climate Change and Human Health** Impacts
Jun 21, 2025
United Arab Emirates, Dubai
Organized by: International Society for Environment and Climate Change
Conference inquiry email: info.isfecc@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Jun 23, 2025
Spain, Barcelona
Organized by: WRFER
Conference inquiry email: contact.wrfer@gmail.com

23rd International Conference on **Artificial Intelligence in Medicine** (AIME 2025)
Jun 23, 2025
Italy, Pavia
Organized by: Aime25
Conference inquiry email: info@hotelmoderno.it

International Research Conference on **COVID-19** and its Impact on Mental Health
Jun 28, 2025
Canada, Toronto
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

WHO-Facts Sheet

1. Ageing and health
2. Palliative care
3. Preterm birth
4. Trachoma
5. Zika virus

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2025; 57 (1): 63 - 72

1. Ageing and health

KEY FACTS

- All countries face major challenges to ensure that their health and social systems are ready to make the most of this demographic shift.
- In 2050, 80% of older people will be living in low- and middle-income countries.
- The pace of population ageing is much faster than in the past.
- In 2020, the number of people aged 60 years and older outnumbered children younger than 5 years.
- Between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22%.

Overview

People worldwide are living longer. Today most people can expect to live into their sixties and beyond. Every country in the world is experiencing growth in both the size and the proportion of older persons in the population.

By 2030, 1 in 6 people in the world will be aged 60 years or over. At this time the share of the population aged 60 years and over will increase from 1 billion in 2020 to 1.4 billion. By 2050, the world's population of people aged 60 years and older will double (2.1 billion). The number of persons aged 80 years or older is expected to triple between 2020 and 2050 to reach 426 million.

While this shift in distribution of a country's population towards older ages – known as population ageing – started in high-income countries (for example in Japan 30% of the population is already over 60 years old), it is now low- and middle-income countries that are experiencing the greatest change. By 2050, two-thirds of the world's population over 60 years will live in low- and middle-income countries.

Ageing explained

At the biological level, ageing results from the impact of the accumulation of a wide variety of molecular and cellular damage over time. This leads to a gradual decrease in physical and mental capacity, a growing risk of disease and ultimately death. These changes are neither linear nor consistent, and they are only loosely associated with a person's age in years. The diversity seen in older age is not random. Beyond biological changes, ageing is often associated with other life transitions such as retirement, relocation to more appropriate housing and the death of friends and partners.

Common health conditions associated with ageing

Common conditions in older age include hearing loss, cataracts and refractive errors, back and neck pain and osteoarthritis, chronic obstructive pulmonary disease, diabetes, depression and dementia. As people age, they are more likely to experience several conditions at the same time.

Older age is also characterized by the emergence of several complex health states commonly called geriatric syndromes. They are often the consequence of multiple underlying factors and include frailty, urinary incontinence, falls, delirium and pressure ulcers.

Factors influencing healthy ageing

A longer life brings with it opportunities, not only for older people and their families, but also for societies as a whole. Additional years provide the chance to

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pursue new activities such as further education, a new career or a long-neglected passion. Older people also contribute in many ways to their families and communities. Yet the extent of these opportunities and contributions depends heavily on one factor: health.

Evidence suggests that the proportion of life in good health has remained broadly constant, implying that the additional years are in poor health. If people can experience these extra years of life in good health and if they live in a supportive environment, their ability to do the things they value will be little different from that of a younger person. If these added years are dominated by declines in physical and mental capacity, the implications for older people and for society are more negative.

Although some of the variations in older people's health are genetic, most is due to people's physical and social environments – including their homes, neighbourhoods, and communities, as well as their personal characteristics – such as their sex, ethnicity, or socioeconomic status. The environments that people live in as children – or even as developing fetuses – combined with their personal characteristics, have long-term effects on how they age.

Physical and social environments can affect health directly or through barriers or incentives that affect opportunities, decisions and health behaviour. Maintaining healthy behaviours throughout life, particularly eating a balanced diet, engaging in regular physical activity and refraining from tobacco use, all contribute to reducing the risk of non-communicable diseases, improving physical and mental capacity and delaying care dependency.

Supportive physical and social environments also enable people to do what is important to them, despite losses in capacity. The availability of safe and accessible public buildings and transport, and places that are easy to walk around, are examples of supportive environments. In developing a public-health response to ageing, it is important not just to consider individual and environmental approaches that ameliorate the losses associated with older age, but also those that may reinforce recovery, adaptation and psychosocial growth.

Challenges in responding to population ageing

There is no typical older person. Some 80-year-olds have physical and mental capacities similar to many 30-year-olds. Other people experience significant declines in capacities at much younger ages. A comprehensive public health response must address this wide range of older people's experiences and needs.

The diversity seen in older age is not random. A large part arises from people's physical and social environments and the impact of these environments on their opportunities and health behaviour. The relationship we have with our environments is skewed by personal characteristics such as the family we were born into, our sex and our ethnicity, leading to inequalities in health.

Older people are often assumed to be frail or dependent and a burden to society. Public health professionals, and society as a whole, need to address these and other ageist attitudes, which can lead to discrimination, affect the way policies are developed and the opportunities older people have to experience healthy aging.

Globalization, technological developments (e.g., in transport and communication), urbanization, migration and changing gender norms are influencing the lives of older people in direct and indirect ways. A public health response must take stock of these current and projected trends and frame policies accordingly.

WHO response

The United Nations (UN) General Assembly declared 2021–2030 the UN Decade of Healthy Ageing and asked WHO to lead the implementation. The UN Decade of Healthy Ageing is a global collaboration bringing together governments, civil society, international agencies, professionals, academia, the media and the private sector for 10 years of concerted, catalytic and collaborative action to foster longer and healthier lives.

The Decade builds on the WHO Global Strategy and Action Plan and the United Nations Madrid International Plan of Action on Ageing and supports the realization of the United Nations Agenda 2030 on Sustainable Development and the Sustainable Development Goals.

The UN Decade of Healthy Ageing (2021–2030) seeks to reduce health inequities and improve the lives of older people, their families and communities through collective action in four areas: changing how we think, feel and act towards age and ageism; developing communities in ways that foster the abilities of older people; delivering person-centred integrated care and primary health services responsive to older people; and providing older people who need it with access to quality long-term care.

2. Palliative care

KEY FACTS

- Palliative care improves the quality of life of patients and that of their families who are facing challenges associated with life-threatening illness, whether physical, psychological, social or spiritual. The quality of life of caregivers improves as well.

- Each year, an estimated 56.8 million people, including 25.7 million in the last year of life, are in need of palliative care.
- Worldwide, only about 14% of people who need palliative care currently receive it.
- Unnecessarily restrictive regulations for morphine and other essential controlled palliative medicines deny access to adequate palliative care.
- Adequate national policies, programmes, resources, and training on palliative care among health professionals are urgently needed in order to improve access.
- The global need for palliative care will continue to grow as a result of the ageing of populations and the rising burden of noncommunicable diseases and some communicable diseases.
- Early delivery of palliative care reduces unnecessary hospital admissions and the use of health services.
- Palliative care involves a range of services delivered by a range of professionals that all have equally important roles to play – including physicians, nursing, support workers, paramedics, pharmacists, physiotherapists and volunteers — in support of the patient and their family.

Palliative care is an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual.

Addressing suffering involves taking care of issues beyond physical symptoms. Palliative care uses a team approach to support patients and their caregivers. This includes addressing practical needs and providing bereavement counselling. It offers a support system to help patients live as actively as possible until death.

Palliative care is explicitly recognized under the human right to health. It should be provided through person-centered and integrated health services that pay special attention to the specific needs and preferences of individuals.

Palliative care is required for a wide range of diseases. The majority of adults in need of palliative care have chronic diseases such as cardiovascular diseases (38.5%), cancer (34%), chronic respiratory diseases (10.3%), AIDS (5.7%) and diabetes (4.6%). Many other conditions may require palliative care, including kidney failure, chronic liver disease, multiple sclerosis, Parkinson's disease, rheumatoid arthritis, neurological disease, dementia, congenital anomalies and drug-resistant tuberculosis.

Pain and difficulty in breathing are two of the most frequent and serious symptoms experienced by patients in need of palliative care. For example, 80% of patients with AIDS or cancer, and 67% of patients with cardiovascular disease or chronic obstructive pulmonary disease will experience moderate to severe pain at the end of their lives. Opioids are essential for managing pain.

Opioids can also alleviate other common distressing physical symptoms including breathlessness. Controlling such symptoms at an early stage is an ethical duty to relieve suffering and to respect a person's dignity.

Insufficient access to palliative care

Each year an estimated 56.8 million people are in need of palliative care, most of whom live in low- and middle-income countries. For children, 98% of those needing palliative care live in low- and middle-income countries with almost half of them living in Africa.

Worldwide, a number of significant barriers must be overcome to address the unmet need for palliative care:

- national health policies and systems often do not include palliative care at all;
- training on palliative care for health professionals is often limited or non-existent; and
- population access to opioid pain relief is inadequate and fails to meet international conventions on access to essential medicines.

According to a WHO survey relating to noncommunicable diseases conducted among 194 Member States in 2019: funding for palliative care was available in 68% of countries and only 40% of countries reported that the services reached at least half of patients in need *(1).*

The International Narcotics Control Board found that in 2018, 79 per cent of the world's population, mainly people in low- and middle-income countries, consumed only 13 per cent of the total amount of morphine used for the management of pain and suffering, or 1 per cent of the 388 tons of morphine manufactured worldwide. Although that was an improvement over 2014, when 80 per cent of the world's population consumed only 9.5 per cent of the morphine used for the management of pain and suffering, the disparity in the consumption of narcotic drugs for palliative care between low- and middle-income countries and high-income countries continues to be a matter of concern *(2).*

Other barriers to palliative care include:

- lack of awareness among policy-makers, health professionals and the public about what palliative care is, and the benefits it can offer patients and health systems;
- cultural and social barriers, such as beliefs about death and dying;

- misconceptions about palliative care, such as that it is only for patients with cancer, or for the last weeks of life; and
- misconceptions that improving access to opioid analgesia will lead to increased substance abuse.

What can countries do?

National health systems are responsible for including palliative care in the continuum of care for people with chronic and life-threatening conditions, linking it to prevention, early detection and treatment programmes. This includes, as a minimum, the following components:

- health system policies that integrate palliative care services into the structure and financing of national health-care systems at all levels of care;
- policies for strengthening and expanding human resources, including training of existing health professionals, embedding palliative care into the core curricula of all new health professionals, as well as educating volunteers and the public; and
- a medicines policy which ensures the availability of essential medicines for managing symptoms, in particular opioid analgesics for the relief of pain and respiratory distress.

Palliative care is most effective when considered early in the course of the illness. Early palliative care not only improves quality of life for patients but also reduces unnecessary hospitalizations and use of health-care services.

Palliative care needs to be provided in accordance with the principles of universal health coverage. All people, irrespective of income, disease type or age, should have access to a nationally- determined set of basic health services, including palliative care. Financial and social protection systems need to take into account the human right to palliative care for poor and marginalized population groups.

As part of multidisciplinary teams, the nursing workforce should be trained in palliative care skills, especially those who work with patients with serious illness.

Specialist palliative care is one component of palliative care service delivery. But a sustainable, quality and accessible palliative care system needs to be integrated into primary health care, community and home-based care, as well as supporting care providers such as family and community volunteers. Providing palliative care should be considered an ethical duty for health professionals.

WHO response

Palliative care medicines, including those for pain relief, are included in WHO Essential Medicines List and the WHO Essential Medicines List for Children. Palliative care is recognized in key global mandates and strategies on universal health coverage, noncommunicable diseases, and people-centred and integrated health services. WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents were released in 2019 *(3)*.

In 2014, the first ever global resolution on palliative care, World Health Assembly resolution WHA67.19, called upon WHO and Member States to improve access to palliative care as a core component of health systems, with an emphasis on primary health care and community/home-based care. WHO's work to strengthen palliative care focuses on the following areas:

- integrating palliative care into all relevant global disease control and health system plans;
- assessing the development of palliative care services;
- developing guidelines and tools on integrated palliative care across disease groups and levels of care, addressing ethical issues related to the provision of comprehensive palliative care;
- supporting Member States in improving access to palliative care medicines through improved national regulations and delivery systems;
- a special focus on palliative care for people living with HIV, including development of guidelines;
- promoting increased access to palliative care for children (in collaboration with UNICEF);
- monitoring global palliative care access and evaluating progress made in palliative care programmes;
- developing indicators for evaluating palliative care services;
- encouraging adequate resources for palliative care programmes and research, especially in resource-limited countries; and
- building evidence of models of palliative care that are effective in low- and middle-income settings.

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3. Preterm birth

KEY FACTS

- An estimated 13.4 million babies were born preterm in 2020 (before 37 completed weeks of gestation) (1).
- Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 900 000 deaths in 2019 (2).
- Three-quarters of these deaths could be prevented with current, cost-effective interventions.
- Across countries, the rate of preterm birth ranges from 4–16% of babies born in 2020.

Overview

Preterm is defined as babies born alive before 37 weeks of pregnancy are completed. There are sub-categories of preterm birth, based on gestational age:

- extremely preterm (less than 28 weeks)
- very preterm (28 to less than 32 weeks)
- moderate to late preterm (32 to 37 weeks).

Babies may be born preterm because of spontaneous preterm labour or because there is a medical indication to plan an induction of labour or caesarean birth early.

An estimated 13.4 million babies were born too early in 2020. That is more than 1 in 10 babies. Approximately 900 000 children die in 2019 of complications of preterm birth *(1)*. Many survivors face a lifetime of disability, including learning disabilities and visual and hearing problems.

Globally, prematurity is the leading cause of death in children under the age of 5 years. Inequalities in survival rates around the world are stark. In low-income settings, half of the babies born at or below 32 weeks (2 months early) die due to a lack of feasible, cost-effective care such as warmth, breastfeeding support and basic care for infections and breathing difficulties. In high-income countries, almost all these babies survive. Suboptimal use of technology in middle-income settings is causing an increased burden of disability among preterm babies who survive the neonatal period.

Why does preterm birth happen?

Preterm birth occurs for a variety of reasons. Most preterm births happen spontaneously, but some are due to medical reasons such as infections, or other pregnancy complications that require early induction of labour or caesarean birth.

More research is needed to determine the causes and mechanisms of preterm birth. Causes include multiple pregnancies, infections and chronic conditions such as diabetes and high blood pressure; however, often no cause is identified. There could also be a genetic influence.

Where and when does preterm birth happen?

The majority of preterm births occur in southern Asia and sub-Saharan Africa, but preterm birth is truly a global problem. There is a dramatic difference in survival of premature babies depending on where they are born. For example, more than 90% of extremely preterm babies (less than 28 weeks) born in low-income countries die within the first few days of life, yet less than 10% of extremely preterm babies die in high-income settings.

The solution

Preventing deaths and complications from preterm birth starts with a healthy pregnancy. WHO's antenatal care guidelines include key interventions to help prevent preterm birth, such as counselling on healthy diet, optimal nutrition, and tobacco and substance use; fetal measurements including use of early ultrasound to help determine gestational age and detect multiple pregnancies; and a minimum of 8 contacts with health professionals throughout pregnancy – starting before 12 weeks – to identify and manage risk factors such as infections.

If a woman experiences preterm labour or is at risk of preterm childbirth, treatments are available to help protect the preterm baby from future neurological impairment as well as difficulties with breathing and infection. These include antenatal steroids and tocolytic treatments to delay labour and antibiotics for preterm prolabour rupture of membranes (PPROM).

In 2022, WHO also published new recommendations on the care of the preterm infant. These reflect new evidence that simple interventions such as kangaroo mother care immediately after birth, early initiation of breastfeeding, use of continuous positive airway pressure (CPAP) and medicines such as caffeine for breathing problems can substantially reduce mortality in preterm and low birthweight babies.

WHO guidance stresses the need to ensure the mother and family take the pivotal role in their baby's care. Mothers and newborns should remain together from birth and not be separated unless the baby is critically ill. The recommendations further call for improvements in family support including education and counselling, peer support and home visits by trained health-care providers.

WHO response

WHO is committed to reducing the health problems and lives lost as a result of preterm birth, including working with Member States and partners to implement Every newborn: an action plan to end preventable deaths, adopted in May 2014 in the framework of the UN Secretary-General's Global strategy for women's and children's health; and strengthening the availability and quality of data on preterm births.

WHO regularly updates clinical guidelines for the management of pregnancy and mothers with preterm labour or at risk of preterm birth, and guidelines on the care of preterm and low birth weight babies.

WHO also supports countries to implement WHO's guidelines, aimed at reducing the risk of negative pregnancy outcomes, including preterm births, and ensuring a positive pregnancy and postnatal experience for all women and their infants. This includes developing and updating tools to improve health-care providers' skills, knowledge and behaviours, and assess the quality of care provided to mothers at risk of preterm delivery and preterm babies.

WHO also undertakes research to improve care for women and preterm newborns in low- and middle-income countries, including the WHO ACTION Trials (Antenatal Corticosteroids for Improving Outcomes in preterm Newborns); the nutritional management of growth faltering in early infancy trial; and an implementation research trial to scale-up immediate kangaroo mother care (KMC). WHO works with partners around the world to conduct research into the causes of preterm birth and provides updated analyses of global preterm birth levels and trends every 3 to 5 years.

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4. Trachoma

KEY FACTS

- Trachoma is a disease of the eye caused by infection with the bacterium *Chlamydia trachomatis*.
- It is a public health problem in 38 countries and is responsible for the blindness or visual impairment of about 1.9 million people.
- Blindness from trachoma is irreversible.
- Based on April 2024 data, 103 million people live in trachoma endemic areas and are at risk of trachoma blindness.
- Infection spreads through personal contact (via hands, clothes, bedding or hard surfaces) and by flies that have been in contact with discharge from the eyes or nose of an infected person. With repeated episodes of infection over many years, the eyelashes may be drawn in so that they rub on the surface of the eye. This causes pain and may permanently damage the cornea.
- In 2023, 130 746 people received surgical treatment for advanced stage of the disease, and 32.9 million people were treated with antibiotics. Global antibiotic coverage in 2023 was 29%.

Overview

Trachoma is the leading infectious cause of blindness worldwide. It is caused by an obligate intracellular bacterium called *Chlamydia trachomatis*. The infection is transmitted by direct or indirect transfer of eye and nose discharges of infected people, particularly young children who harbour the principal reservoir of infection. These discharges can be spread by particular species of flies.

Symptoms and transmission

In areas where trachoma is endemic, active (inflammatory) trachoma is common among preschool-aged children, with prevalence rates which can be as high as 60–90%. Infection becomes less frequent and shorter in duration with increasing age. Infection is usually acquired when living in close proximity to others with active disease, and the family is the main setting for transmission. An individual's immune system can clear a single episode of infection, but in endemic communities re-acquisition of the organism occurs frequently.

After years of repeated infection, the inside of the eyelid can become so severely scarred (trachomatous conjunctival scarring) that it turns inwards and causes the eyelashes to rub against the eyeball (trachomatous trichiasis), resulting in constant pain and light intolerance. This and other alterations of the eye can lead to scarring of the cornea. Left untreated, this condition leads to the formation of irreversible opacities, with resulting visual impairment or blindness. The age at which this occurs depends on several factors including local transmission intensity. In very highly endemic communities it can occur in childhood, though onset of visual impairment between the ages of 30 and 40 years is more typical.

Visual impairment or blindness results in a worsening of the life experience of affected individuals

and their families, who are normally already amongst the poorest of the poor. Women are blinded up to 4 times as often as men, probably due to their close contact with infected children and their resulting greater frequency of infection episodes.

Environmental factors associated with more intense transmission of *C. trachomatis* include:

- inadequate hygiene
- crowded households
- inadequate access to water
- inadequate access to and use of sanitation.

Distribution

Trachoma is hyperendemic in many of the poorest and most rural areas of Africa, Central and South America, Asia, Australia and the Middle East.

It is responsible for the blindness or visual impairment of about 1.9 million people. It causes about 1.4% of all blindness worldwide.

Overall, Africa remains the most affected continent and the one with the most intensive control efforts.

As of 21 October 2024, 21 countries – Benin, Cambodia, China, Gambia, Islamic Republic of Iran, Lao People's Democratic Republic, Ghana, India, Iraq, Malawi, Mali, Mexico, Morocco, Myanmar, Nepal, Oman, Pakistan, Saudi Arabia, Togo, Vanuatu and Viet Nam – had been validated by WHO as having eliminated trachoma as a public health problem.

Economic impact

The burden of trachoma on affected individuals and communities is enormous. The economic cost in terms of lost productivity from blindness and visual impairment is estimated at US$ 2.9–5.3 billion annually, increasing to US$ 8 billion when trichiasis is included.

Prevention and control

Elimination programmes in endemic countries are being implemented using the WHO-recommended SAFE strategy. This consists of:

- Surgery to treat the blinding stage (trachomatous trichiasis);
- Antibiotics to clear infection, particularly mass drug administration of the antibiotic azithromycin, which is donated by the manufacturer to elimination programmes, through the International Trachoma Initiative;
- Facial cleanliness; and
- Environmental improvement, particularly improving access to water and sanitation.

Most endemic countries have agreed to accelerate the implementation of this strategy to achieve elimination targets.

Data reported to WHO by Member States for 2023 show that 130 746 people with trachomatous trichiasis were provided with corrective surgery in that year, and 32.9 million people in endemic communities were treated with antibiotics to eliminate trachoma. In 2019, when COVID-19 did not affect programmes' ability to undertake community-based work, 92 622 people with trachomatous trichiasis were provided with corrective surgery, and 95.2 million people were treated with antibiotics.

Elimination efforts need to continue to ensure that we reach the target set by World Health Assembly resolution WHA 51.11, which is elimination of trachoma as a public health problem *(1)*. Particularly important will be the full engagement of multiple actors involved in water, sanitation and socioeconomic development.

WHO response

WHO adopted the SAFE strategy in 1993. WHO's mandate is to provide leadership and coordination to international efforts aiming to eliminate trachoma as a public health problem, and to report on progress towards that target.

In 1996, WHO launched the WHO Alliance for the Global Elimination of Trachoma by 2020. The Alliance is a partnership which supports implementation of the SAFE strategy by Member States, and the strengthening of national capacity through epidemiological surveys, monitoring, surveillance, project evaluation, and resource mobilization.

The World Health Assembly adopted resolution WHA51.11 in 1998, targeting the global elimination of trachoma as a public health problem with 2020 as the target date. The neglected tropical diseases road map 2021–2030, endorsed by the World Health Assembly in 2020 through its decision 73(33), sets 2030 as the new target date for global elimination.

Notes

(1) Elimination of trachoma as a public health problem is defined as: (i) a prevalence of trachomatous trichiasis "unknown to the health system" of <0.2% in adults aged ≥15 years (approximately 1 case per 1000 total population), and (ii) a prevalence of trachomatous inflammation—follicular in children aged 1–9 years of less than 5%, sustained for at least two years in the absence of ongoing antibiotic mass treatment, in each formerly endemic district; plus (iii) the existence of a system able to identify and manage incident trachomatous trichiasis cases, using defined strategies, with evidence of appropriate financial resources to implement those strategies.

5. Zika virus

KEY FACTS

- Zika virus is transmitted primarily by Aedes mosquitoes, which bite mostly during the day.
- Most people with Zika virus infection do not develop symptoms; those who do typically have symptoms including rash, fever, conjunctivitis, muscle and joint pain, malaise and headache that last for 2–7 days.
- Zika virus infection during pregnancy can cause infants to be born with microcephaly and other congenital malformations as well as preterm birth and miscarriage.
- Zika virus infection is associated with Guillain-Barré syndrome, neuropathy and myelitis in adults and children.
- In February 2016, WHO declared Zika-related microcephaly a Public Health Emergency of International Concern (PHEIC), and the causal link between the Zika virus and congenital malformations was confirmed. WHO declared the end of the PHEIC in November of the same year.
- Although cases of Zika virus disease declined from 2017 onwards globally, transmission persists at low levels in several countries in the Americas and other endemic regions.

Overview

Zika virus is a mosquito-borne virus first identified in Uganda in 1947 in a Rhesus macaque monkey followed by evidence of infection and disease in humans in other African countries in the 1950s.

From the 1960s to 1980s, sporadic human infections were detected across Africa and Asia. However, since 2007 outbreaks of Zika virus disease have been recorded in Africa, the Americas, Asia and the Pacific.

In outbreaks over the last decade Zika virus infection was found to be associated with increased incidence of Guillain-Barré syndrome. When Zika virus emerged in the Americas, with a large epidemic in Brazil in 2015, an association between Zika virus infection and microcephaly (smaller than normal head size) was first described; there were similar findings in French Polynesia upon retrospective review. From February to November 2016, WHO declared a Public Health Emergency of International Concern (PHEIC) regarding microcephaly, other neurological disorders and Zika virus, and the causal link between Zika virus and congenital malformations was soon confirmed *(1,2)*. Outbreaks of Zika virus disease were identified throughout most of the Americas and in other regions with established *Aedes aegypti* mosquitos. Infections were detected in travellers from active transmission areas and sexual transmission was confirmed as an alternate route of Zika virus infection.

Cases of Zika virus disease globally declined from 2017 onwards; however, Zika virus transmission persists at low levels in several countries in the Americas and in other endemic regions. In addition, the first local mosquito-transmitted Zika virus disease cases were reported in Europe in 2019 and Zika virus outbreak activity was detected in India in 2021. To date, a total of 89 countries and territories have reported evidence of mosquito transmitted Zika virus infection; however, surveillance remains limited globally.

Symptoms

Most people infected with Zika virus do not develop symptoms. Among those who do, they typically start 3–14 days after infection, are generally mild including rash, fever, conjunctivitis, muscle and joint pain, malaise and headache, and usually last for 2–7 days. These symptoms are common to other arboviral and non-arboviral diseases; thus, the diagnosis of Zika virus infection requires laboratory confirmation.

Complications

Zika virus infection during pregnancy is a cause of microcephaly and other congenital malformations in the infant, including limb contractures, high muscle tone, eye abnormalities and hearing loss. These clinical features are collectively referred to as congenital Zika syndrome.

The risk of congenital malformations following infection in pregnancy remains unknown; an estimated 5–15% of infants born to women infected with Zika virus during pregnancy have evidence of Zika-related complications *(3)*. Congenital malformations occur following both symptomatic and asymptomatic infection. Zika infection in pregnancy can also cause complications such as fetal loss, stillbirth and preterm birth.

Zika virus infection can also cause Guillain-Barré syndrome, neuropathy and myelitis, particularly in adults and older children.

Research is ongoing to investigate the risk and effects of Zika virus infection on pregnancy outcomes, strategies for prevention and control, and effects of infection on other neurological disorders in children and adults.

Transmission

Zika virus is primarily transmitted by infected mosquitoes of the *Aedes* (*Stegomyia*) genus, mainly *Aedes aegypti*, in tropical and subtropical regions. *Aedes* mosquitoes usually bite during the day. These mosquitoes also transmit dengue, chikungunya and urban yellow fever.

Zika virus is also transmitted from mother to fetus during pregnancy, as well as through sexual contact, transfusion of blood and blood products, and possibly through organ transplantation.

Diagnosis

Infection with Zika virus may be suspected based on symptoms of persons living in or visiting areas with Zika virus transmission and/or *Aedes* mosquito vectors. A diagnosis of Zika virus infection can only be confirmed by laboratory tests of blood or other body fluids, and it must be differentiated from cross-reactive related flaviviruses such as dengue virus, to which the patient may have been exposed or previously vaccinated.

Treatment

There is no specific treatment available for Zika virus infection or disease. People with symptoms such as rash, fever or joint pain should get plenty of rest, drink fluids, and treat symptoms with antipyretics and/or analgesics. Nonsteroidal anti-inflammatory drugs should be avoided until dengue virus infections are ruled out because of bleeding risk. If symptoms worsen, patients should seek medical care and advice.

Pregnant women living in areas with Zika transmission or who develop symptoms of Zika virus infection should seek medical attention for laboratory testing, information, counselling and other clinical care.

Prevention

No vaccine is yet available for the prevention or treatment of Zika virus infection. Development of a Zika vaccine remains an active area of research.

Mosquito bites

Protection against mosquito bites during the day and early evening is a key measure to prevent Zika virus infection, especially among pregnant women, women of reproductive age and young children.

Personal protection measures include wearing clothing (preferably light-coloured) that covers as much of the body as possible; using physical barriers such as window screens and closed doors and windows; and applying insect repellent to skin or clothing that contains DEET, IR3535 or icaridin according to the product label instructions.

Young children and pregnant women should sleep under mosquito nets if sleeping during the day or early evening. Travellers and those living in affected areas should take the same basic precautions described above to protect themselves from mosquito bites.

Aedes mosquitoes breed in small collections of water around homes, schools and work sites. It is important to eliminate these mosquito breeding sites, including covering water storage containers, removing standing water in flowerpots, and cleaning up trash and used tires. Community initiatives are essential to support local government and public health programs to reduce mosquito breeding sites. Health authorities may also advise use of larvicides and insecticides to reduce mosquito populations and disease spread.

Prevention of sexual transmission

For regions with active transmission of Zika virus, all people with Zika virus infection and their sexual partners (particularly pregnant women) should receive information about the risks of sexual transmission of Zika virus.

WHO recommends that sexually active men and women be counselled and offered a full range of contraceptive methods to be able to make an informed choice about whether and when to become pregnant in order to prevent possible adverse pregnancy and fetal outcomes.

Women who have had unprotected sex and do not wish to become pregnant due to concerns about Zika virus infection should have ready access to emergency contraceptive services and counselling. Pregnant women should practice safer sex (including correct and consistent use of condoms) or abstain from sexual activity for at least the entire duration of pregnancy.

For regions with no active transmission of Zika virus, WHO recommends practicing safer sex or abstinence for a period of three months for men and two months for women who are returning from areas of active Zika virus transmission to prevent infection of their sex partners. Sexual partners of pregnant women living in or returning from areas where local transmission of Zika virus occurs should practice safer sex or abstain from sexual activity throughout pregnancy.

WHO response

WHO supports countries to conduct surveillance and control of arboviruses through the implementation of the Global Arbovirus Initiative, which is aligned with and expands upon recommendations laid out in the Zika Strategic Response Plan.

WHO responds to Zika in the following ways:

- supporting countries in the confirmation of outbreaks through its collaborating network of laboratories;
- providing technical support and guidance to countries for the effective management of mosquito-borne disease outbreaks;
- reviewing the development of new tools, including insecticide products and application technologies;

- formulating evidence-based strategies, policies, and outbreak management plans;
- providing technical support and guidance to countries for the effective management of cases and outbreaks;
- supporting countries to improve their reporting systems;
- providing training on clinical management, diagnosis and vector control at the regional level with some of its collaborating centres; and
- publishing guidelines and handbooks on epidemiological surveillance, laboratory, clinical case management and vector control for Member States.

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