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Editorial

The Mystery of COVID-19: More Questions Emerge

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New coronavirus, with the other name of SARS-Cov-2, first emerged in China's Wuhan city of Hubei province in December 2019. The virus causes a disease varying from asymptomatic course to acute respiratory distress syndrome or multiple organ failure. The disease caused by this virus discovered in 2019 named Coronavirus Disease-19 (COVID-19), and then, a global epidemic (pandemic) has been declared on March 11, 2020, byWorld Health Organization (WHO).[1,2] Since COVID-19 cases have similar symptoms, clinical and laboratory findings with SARS-Cov and MERS-Cov patients, previously performed studies thought to be a pathfinder to define the pathogenesis of the disease.[2,3] However, there are still some unsolved issues for the various aspects of COVID-19, although more than six months passed from the appearance of the first case in China. Of course, scientists have been studying the coronavirus to spread reliable life-saving information, as well as combating dangerous misunderstandings. Here are some of the most important questions to solve the mystery of COVID-19.

Where the virus comes from?

Knowing how coronavirus infections evolve and spread may provide insights improved tracing of emerging coronavirus infections. Also, this may give some hints for effective treatments in the future. Researchers still are not sure how the coronavirus across the human from bats. In the case of previous SARS-Cov infection, the weasel-like civet blamed as the most likely intermediate animal host. For the SARS-Cov-2, researchers have suggested that civets, pigs, snakes, or possibly pangolins were an intermediary host. On the other hand, it is also possible that the virus passed straight from bats to humans, or this virus is a hybrid of bat and pangolin viruses.[4] However, currently available data do not support any of these ideas.

How many people got really infected with SARS-Cov-2?

People who infected with SARS-Cov-2 but did not get sick and had no symptoms have been

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one of the most confounding factors to determine actual numbers of infected individuals. Also, some people develop quite mild or atypical symptoms or who were accepted as asymptomatic until they demonstrate the unexpected manifestations of COVID-19. Additionally, many asymptomatic cases went unnoticed because diagnostic testing is only performed on cases with typical symptoms. So all these suggest that the absence of symptoms does not mean the absence of infection, and the actual number of cases is much higher than reported by officials. Indeed, The Centers for Disease Control and Prevention proclaimed that the exact number of COVID-19 cases in the U.S., including asymptomatic cases, maybe ten times higher than what has been reported by the government at the end of June 2020.[5] There was again some confusion about the nature of asymptomatic spread. Therefore, knowing the actual prevalence of the cases, including the asymptomatic ones, is important to understand how the virus spreads, and if asymptomatic cases have developed efficient immunity against reinfection.

Do we gain long-term immunity against SARS-Cov-2?

Previous coronaviruses like SARS and MERS, antibodies seemed to last for a year or more after peaking within months of infection. But studies performed so far showed that antibodies against SARS-CoV-2 remain high for two to three months after infection, but then typically begin to wane.[6] Several studies also demonstrated that higher antibody titers are associated with more severe clinical cases.[7-10] Although higher antibody titers have been seen in critically ill patients, it is not clear whether these antibody responses lead to pulmonary pathology. On the other hand, a study from Mount Sinai Hospital in New York mentioned that longer or more severe cases did not necessarily produce more antibodies than mild or asymptomatic ones.[11] Long-term protection is provided by the induction of long-lived plasma cells and memory B cells. Still, no one is certain about the prospects for long-term humoral immunity and the specific levels of antibodies required for full immune protection. But there is a great interest to understand the lifespan of B cell memory responses to SARS-CoV-2 since this is essential to develop vaccination strategies.[12] This is also critical for controlling the pandemic since it will enable officials to lift social-distancing restrictions for people who have already recovered from COVID-19.

Would vaccine work?

By now, 140 candidate coronavirus vaccines are in preclinical evaluation. Twenty-three of them are already being tested in clinical trials.[13] First data from animal studies and early-stage human trials mainly test safety, and no trial-limiting safety concerns were reported in association with candidate vaccines. Also, multiple research groups have conducted challenge trials in which animals or humans received the candidate vaccine and were then exposed to SARS-Cov-2, to examine whether the candidate vaccine can prevent infection. Studies in macaque monkeys demonstrated that vaccines might efficiently prevent lung infection resulting in pneumonia, but not block infection elsewhere in the body, such as the nose.[14] These initial results suggest that the COVID-19 vaccine may prevent severe diseases but not protect from the viral spread. Experimental COVID-19 vaccine being developed by the Pfizer and the BioNTech triggered immune responses in healthy patients, whereas this vaccine led to fever and other mild side effects, especially at higher doses.[15] But, it is needed to conduct large studies with substantial follow-up time that aim to test vaccine efficacy. Also, future studies will need to include a more diverse group, such as pregnant women, participants from different ethnicity, elderly people.

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Review Article

Diabetes Mellitus and the Lungs

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This paper is dedicated to the memory of Professor Doctor Nihat Ozyardimci, born in 1st March 1937 and passed away in 18th July 2018, who devoted his life to scientific studies and patient care in chest diseases and tuberculosis. He was one of the distinguished leaders in this field in Turkey.

Abstract

Diabetes mellitus is a chronic disease characterized by hyperglycemia causing damage to the vascular system. The lungs with a large vascular network are also predisposed to diabetes' vascular damage. Diabetes may lead to pulmonary parenchymal damage besides alterations in the vascular system and the alveolar-capillary membrane. Symptoms and damage caused by diabetes are usually underdiagnosed because of the large pulmonary reserves. Pulmonary involvement in diabetes is an area that draws attention in recent years. This attention increases especially with the new Coronavirus disease-2019 (COVID-19) pandemic when worse prognosis is detected in diabetics. In this review, possible mechanisms leading to pulmonary involvement and pulmonary function abnormalities in diabetes, interaction between COVID-19 and diabetes concerning lungs and the basic effects of antidiabetic drugs on the lungs are discussed in the view of the literature.

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Introduction

Diabetes mellitus is a chronic disease characterized by hyperglycemia. According to International Diabetes Federation (IDF) approximately 463 million people are diabetic worldwide currently and diabetes increases the risk of early death. IDF estimated 4.2 million deaths due to diabetes and it's complications in 2019.[1] Diabetes mellitus leads to chronic complications and damages the vascular system, heart, eyes, kidneys and nerves that significantly contribute to morbidity and mortality. The lungs are also predisposed to diabetes' vascular damage, since they have a large vascular network. The alveolar capillary network is the largest microvascular organ with a surface area of 140 m^2. Symptoms and disability caused by diabetes develop later in the lungs compared to other organs, because of the larger pulmonary reserves.[2-5] Pulmonary involvement in diabetes is an area that draws attention in recent years. Nowadays, with the new Coronavirus disease-2019 (COVID-19) pandemic, this attention rises prominently due to the worse prognosis reported in diabetics. In this review, possible involvement mechanisms and functional abnormalities in the lungs in diabetes, interaction between COVID-19 and diabetes concerning lungs and the basic effects of antidiabetic drugs on the lungs are discussed in the view of the literature.

How can diabetes mellitus affect the lungs?

There are some possible mechanisms concerning pulmonary involvement in diabetes.

Chronic inflammation

Diabetes leads to chronic low-grade inflammation which is associated with increased levels of inflammatory mediators, such as C-reactive protein (CRP) and interleukin (IL)-6, that may affect the lungs. Inflammation can cause impaired lung function. Type 2 diabetics with inadequate glycemic control are shown to have lower forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) compared to subjects with adequate control, which might be a result of inflammation aggravated with poor glycemic control.[5,6] Studies conducted in patients with type 2 diabetes mellitus demonstrated that hs-CRP associates negatively with lung function.[6,7]

Insulin resistance and hyperinsulinemia

Insulin resistance, especially seen in type 2 diabetes, contributes to increased insulin levels which leads to increased airway smooth muscle (ASM) mass and contractility that decreases muscle strength in the long run. Increased respiratory smooth muscle mass also leads to airway hypersensitivity and activation of epithelial mesenchymal trophic unit leading to airway remodeling.[8-10] Insulin resistance is also thought to affect lung volume and mechanical function via mediators such as leptin. Serum leptin levels are shown to be inversely related to FEV1.[5,11,12] High glucose concentrations in the airways lead to enhanced responsiveness of ASM to contractile agents. Different studies have shown that hyperglycemia and insulin resistance are closely related to idiopathic pulmonary fibrosis and chronic obstructive pulmonary diseases.[3,4]

Advanced glycation end products

Because of prolonged hyperglycemia and glucotoxicity, activation of nonenzymatic glycosylation of lung collagen and elastin by advanced glycation end products (AGEs) results in reduced lung elasticity. Nonenzymatic glycosylation of collagen in the lungs makes it less susceptible to proteolysis which accumulates in lung connective tissue and chest wall.[5,13] Collagen accumulation leads to increased stiffness of both lung parenchyma and chest wall and restrictive functional defects occur. When elastic recoil capacity of the lung is lost, this situation leads to dynamic collapse of small airways during exhalation. AGEs may initiate adaptive immune reactions and reactive oxygen species (ROS) production, which leads to microvascular damages and structural changes like thickening of alveolar epithelial basal laminae. These changes and damages impair lung function.[7] AGE receptors are commonly found in membranes and cytoplasms of pneumocytes and macrophages in the lungs. When the AGE receptors are stimulated inflammatory response, cytokine production and endothelial vascular permeability increase and lungs' vascular network is damaged.[4]

Autonomic neuropathy

Autonomic neuropathy seen as a complication of diabetes leads to neuroadrenergic denervation of the lungs and respiratory muscles. Neuropathic as well as myopathic changes of respiratory muscles can impair the ventilatory pump efficiency which may contribute to functional defects in the lungs.[4,5]

Pulmonary infections

In healthy individuals, the glucose concentration in the respiratory tract is lower than blood glucose at a rate of 1/12. Normal range of blood glucose is 70-100 mg/dL. When blood glucose exceeds 120 mg/dL, the airway glucose concentration increases and creates a favorable environment for bacterial growth. Besides, chronic hyperglycemia impairs neutrophil function leading to defects in phagocytosis. All of these defects can facilitate development of pulmonary infections and lung damage in diabetics.[4,14]

Pulmonary involvement in new Coronavirus disease-2019

Diabetes mellitus leads to inflammation, increased proinflammatory cytokine production and endothelial dysfunction. These facts are also reported in COVID-19 caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 mostly affects the lungs and is often manifested by severe acute respiratory syndrome. In diabetics, SARS-CoV-2 infection often impairs glycemic control. Immune response is disrupted due to hyperglycemia and viral replication cannot be controlled. IL-6, CRP, ferritin and D-dimer serum levels are shown to be higher in diabetic patients with COVID-19 compared to non-diabetics. These findings may explain the higher cytokine release and tendency to thrombosis in diabetics. The large vascular network in the lungs involved with thrombosis together with cytokine storm may explain the negative prognosis tendency seen in diabetics with COVID-19. In these patients, pneumonia is often more refractory to medical treatments and oxygen support and intensive care monitoring are more frequently required, leading to poor prognosis and increased mortality.[15-18]

Histopathological changes

Diabetes can cause an injury in the pulmonary microcirculation by increasing vessel wall thickness, similar to vascular injuries seen in other organs. Diabetic alveolar epithelial cells and endothelial capillary basal lamina are shown to be thicker compared to controls. The degree of thickening was shown to correlate significantly with the thickness of basal laminas in renal tubules and muscle capillaries, but not with patient's or diabetes' age.[5,19]

What are the respiratory function abnormalities seen in diabetes?

Reduced diffusion capacity of lungs for carbonmonoxide

Diffusion capacity of lungs for carbonmonoxide (DLCO) can be easily measured by lung function tests. DLCO depends on alveolar-capillary membrane conductance and pulmonary capillary blood volume. Diabetes is frequently associated with histopathological alterations such as the thickening of the pulmonary capillary basal lamina and alveolar epithelium both contributing to reduced gas diffusion velocity through the alveolar-capillary membrane.[5,20] A reduction in the permeability of the alveolar-capillary basement membrane was detected in diabetic patients even without any evidence for DLCO reduction.[21] Reduction of DLCO in diabetic patients was shown to correlate with other vascular complications of diabetes, like retinopathy and nephropathy.[22] Affected pulmonary vasculature may lead to redistribution of pulmonary circulation, leading to ventilation/perfusion mismatch, which impaires gas exchange. DLCO changes in diabetic patients can also be due to the autonomic nervous system dysfunction, seen in diabetes as a complication. Reduced DLCO and cardiac autonomic dysfunction are found to be significantly associated which can be determined by heart rate variability measurement.[23] Lung capillary blood volume was reported to be decreased in patients with type 1 diabetes.[24]

Lung volume reductions

Diabetes may lead to parenchymal damages as well as alterations in the pulmonary vascular system and the alveolar-capillary membrane.[25] Inflammatory changes in hyperglycemia can cause pulmonary fibrosis. In a study in which FVB mice with streptozotocin induced type 1 diabetes

were examined, alveolar septal thickening, inflammatory cell infiltration and marked fibrosis in the interstitium of the lungs were detected. These changes were accompanied by an increase in the markers associated with fibrosis like connective tissue growth factor and fibronectin. Besides an increase in the expression of mRNA of the inflammation and coagulation markers like PAI-1 and tumor necrosis factor (TNF)-α were detected. Lung fibrosis with specific nodular pattern are also reported in diabetic patients.[3,5,22] Lung volume reductions due to anatomic lung abnormalities in patients with diabetes can partly explain the pulmonary function defects. Tests demonstrating lung mechanical function include dynamic breathing changes in lung elasticity, airflow resistance, and maximal forced spirometric pulmonary function tests (PFT). In practice, PFTs are influenced by different factors like aging, loss of muscle strength from any cause and obesity. Studies evaluating spirometric PFTs in patients with diabetes have conflicting results some showing decrease in PFTs in diabetics, some not.[20,24,27-30]

Bronchomotor tone and control of ventilation

Diabetics are shown to have disorders in bronchomotor tone and control of ventilation due to autonomic neuropathy which can cause functional impairment of the respiratory system through damage to the bronchial neuroadrenergic innervation. Defects in bronchial neuroadrenergic innervation can change the ventilatory response to central and peripheral stimuli. While chemosensibility to hypoxia is shown to be depressed in diabetic patients with autonomic neuropathy[31], there are conflicting results regarding chemosensibility to hypercapnia. The ventilatory response to hypercapnia is reported to be reduced, normal or increased in different diabetic populations with autonomic neuropathy.[32,33] This heterogenity may be due to differences in the patterns of the autonomic nervous system disturbance, degrees of dysautonomia and intensities of stimuli.[34] Dysfunction of autonomic innervation and reduction of peripheral and central chemosensibility may be involved in altered perception of breathlessness -which is generally the main symptom- and abnormality in the ventilatory response to exercise.[5]

Respiratory muscle function

Respiratory muscle function defects may lead to reduced lung volumes, leading to restrictive functional impairment. The respiratory muscle strength is reported to be weakened in diabetics.[35] In a study conducted in type 2 diabetics, reduction in respiratory muscle strength was found to be inversely correlated with the degree of glycemic control and more prevalent in those with diabetic microvascular complications.[36] In a study conducted in type 2 diabetics, restrictive pulmonary function was found to be related to glucose metabolism, and presence of nephropathy was shown to increase the risk of restrictive lung disease.[37]

What are the possible effects of antidiabetic agents on the lungs?

All antidiabetic agents control hyperglycemia via different mechanisms, some of them decreasing insulin resistance. Control of glycemic parameters and metabolic control is important in preventing or delaying diabetes related vascular complications. Some antidiabetic agent groups are thought to have positive effects on possible pulmonary outcomes via different actions, mainly through anti-inflammatory effects. Metformin inhibits the release of proinflammatory cytokines and activation of nuclear factor-κB (NF-κB)[38], reduces CRP.[39] Glibenclamide is an inhibitor of IL-1β in pancreatic islets.[40] Thiazolidinediones are agonists for the peroxisome proliferator-activated receptor-γ (PPAR-γ). They have potent anti-inflammatory effects in the lungs[41] by inhibiting NF-κB-mediated inflammatory pathways and reducing levels of TNF-α and IL-6.[42] Glucagon like peptide 1 analogs stimulate vasodilation and bronchodilation. Dipeptidylpeptidase 4 inhibitors inhibit AGE and receptor (RAGE) gene expressions and proinflammatory pathways.[43,44]

Insulin has anti-inflammatory effects by suppressing the production of ROS and inhibiting proinflammatory transcription factors like NF-κB, activator protein-1, and early growth response-1. Besides some concerns also exist regarding the potential for pulmonary hazard with chronic use of inhaled insulin due to immunogenic and growth-promoting properties. Inhaled insulin has the potential to induce a concentration-

dependent ASM contraction via prostaglandins.[4,45,46]

It seems necessary to conduct more clinical studies evaluating the effects of antidiabetic treatment options on the lungs to clarify the specific pulmonary effects of antidiabetic agents, other than glycemic control.

Conclusion

Diabetes mellitus is a chronic disease that may lead to chronic micro and macrovascular complications. The lungs are the largest microvascular organs with their huge alveolar capillary network. This property makes lungs vulnerable to the harmful effects of diabetes mellitus. Because of the larger pulmonary reserves, symptoms and disability from diabetes may not be diagnosed until subclinical pulmonary dysfunction becomes overt with accompanying situations like aging, smoking, cardiopulmonary diseases and infections like SARS-CoV-2. Periodic monitoring of the respiratory function in patients with diabetes is important by keeping in mind the possible presence of an assault of diabetes mellitus on pulmonary vasculature and parenchyme. Providing good glycemic control and controlling hyperinsulinemia by reducing insulin resistance will allow to reduce or prevent lung-related problems in diabetic patients.

Conflict of interest

The author declared that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Review Article

Current Approaches to The Basic Aspects of Osteoporosis

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Abstract

Osteoporosis is a systemic skeletal disorder characterized by an imbalanced bone turnover leading to low bone mass and bone microarchitecture disruption that increase the risk of fractures. It is the most common metabolic bone disorder seen in the World due to prolongation of life. In this review, the basic aspects for the evaluation, diagnosis, treatment and follow-up of osteoporosis is discussed in the view of the literature.

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Introduction

Osteoporosis is the most common metabolic bone disorder encountered in the World with the prolongation of human life and aging. In recent decades, it has become an important public health problem, since almost 50% of women and 22% of men have fractures after the age of 50 years. Besides approximately 9 million osteoporotic fractures are reported annually in the World. Osteoporosis is defined as a systemic skeletal disease characterized by an imbalance in bone turnover that results in low bone mass and disruption of bone microarchitecture with increased bone fragility and fracture risk. Osteoporotic fractures, also known as fragility fractures, are the fractures that occur as a result of a person's fall from his/her height or less than height, without trauma, at or slower than walking speed. The bones with the highest risk of osteoporosis related fractures are the femur, vertebra, wrist, humerus and pelvis. [1,2-4]

Osteoporosis can be seen because of primary and secondary causes (*Table 1*). Being postmenopausal (Type 1) and aging (Type 2) are primary causes. Aging in men, menopause in addition to aging in women increase the frequency of osteoporosis. The female to male ratio in primary osteoporosis is 5.7 to 4.[5] Secondary causes should be screened especially

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Table 1. *Secondary causes of osteoporosis*

Lifestyle related	**Medications**	**Endocrine diseases**
Inadequate calcium and protein intake	Glucocorticoids	Hypogonadism
Vitamin D deficiency	Anticoagulants (heparin, warfarin)	Glucocorticoid excess
Vitamin A excess	Anticonvulsants	Hyperparathyroidism
Immobilization	Proton pump inhibitors	Hyperthyroidism
Insufficient physical activity	Selective serotonin reuptake inhibitors	Hyperprolactinemia
Very low body mass index	Lithium	Diabetes mellitus
Smoking	Thiazolidinedione	
Alcohol consumption	High dose levothyroxine	**Collagen tissue diseases**
	Aromatase inhibitors	Rheumatoid arthritis
Gastrointestinal diseases	Gonadotropin-releasing hormone	Ankylosing spondylitis
Postgastrectomy syndrome	Medroxyprogesterone	
Primary biliary cirrhosis	Aluminum	**Other**
Inflammatory bowel disease	Cyclosporin A	Kidney failure
Hemochromatosis	Tacrolimus	Chronic obstructive
	Methotrexate	pulmonary disease
Hematological diseases		Homocysistinuria
Multiple myeloma		
Lymphoproliferative diseases		

in premenopausal women and men younger than 50 years of age with osteopenia or osteoporosis. Primary causes may also be accompanied by secondary causes in postmenopausal women and older men, so possible secondary causes should be screened in differential diagnosis at any age.[2,3]

Diagnosis

Although osteoporosis is the most common metabolic bone disease, only approximately 20% can be diagnosed and treated. The purpose of diagnosing osteoporosis is to identify patients at high risk for bone fragility and to start treatment to prevent fractures. To diagnose and treat current cases screening of osteoporosis is important (*Table 2*).[2,3] Detailed history and physical examination, laboratory evaluation, bone mineral density measurement and vertebral imaging are important for the diagnosis of osteoporosis. Medical history should be questioned carefully and main clinical findings should be examined detailly in all cases. Difficulty in walking is seen in hip fractures. Fractures lead to chronic pain, difficulty in mobilization, dependence on someone else and depression. Increase in mortality rates due to fractures is also reported.[2,3] Routine laboratory tests should be evaluated, and other tests for secondary causes should be conducted if necessary (*Table 3*). 25-hydroxy (OH) vitamin D level measurement and exclusion of osteomalacia is important. Bone mineral density (BMD) measurement cannot distinguish osteoporosis from osteomalacia, in both cases BMD is reduced.[2,3] Bone turnover markers are the substances that occur in the blood and urine during the bone cycle. They can be measured in plasma, urine, or serum and their levels reflect osteoblastic (bone formation) or osteoclastic (bone resorption) activity. Although bone turnover markers are thought to be helpful in determining the risk of fracture and monitoring the treatment, they are not routinely used in the diagnosis of osteoporosis. Serum procollagen type I N propeptide (s-PINP) can be used as a bone production marker and serum type I collagen C-terminal telopeptide cross-links (s-CTX) as a bone resorbtion marker if measured by standardized methods.[2-4]

Bone mineral density measurement

The most commonly used gold standard method for measuring bone density is dual energy X ray absorptiometry (DXA) because of its availability for clinical use, easy application and low radiation exposure. This method evaluates the L1 to L4 vertebrae in the spine and the femur. It should not be used in pregnant women as it creates low dose radiation exposure. DXA measures BMD areally and shows the amount of bone mineral in grams per square centimeter (BMD=gr/cm^2). The fracture risk of any region in the skeletal system is determined by the BMD measurement of that region. In a standard patient, lumbar spine and hip measurements are taken with DXA. Radius measurement is rarely used in cases such as primary hyperparathyroidism, morbid obesity and the presence of prosthesis and kyphoscoliosis in

Table 2. *Candidates for screening in terms of osteoporosis*

Women over 65 and men over 70 years of age (regardless of risk factors)
Postmenopausal and perimenopausal women <65 years of age and men aged 50-69, in the presence of one of the risk factors stated below
• Fragility fracture • The presence of fractures in direct radiographs • Glucocorticoid usage (≥5 mg/day prednisolone or equivalent, >3 months) • Smoking • Alcohol consumption • Body mass index <20 kg/m² or major weight loss • Rheumatoid arthritis • A history of disease associated with osteoporosis • Drug usage with high-risk for osteoporosis
Women or men <50 years of age in the presence of one of the risk factors stated below
• Hypogonadism or early menopause • Presence of one of the secondary causes of osteoporosis • Fragility fracture • The presence of fractures in direct radiographs • Glucocorticoid usage (≥5 mg/day prednisolone or equivalent, >3 months) • Smoking • Alcohol consumption • Body mass index <20 kg/m² or major weight loss • Rheumatoid arthritis • A history of disease associated with osteoporosis • Drug usage with high-risk for osteoporosis

which hip or vertebra measurements cannot be made.[2,3,6,7]

DXA measurement gives T- and Z-scores other than BMD values. T-score is the standard deviation of the person's measured bone mass compared to the mean peak bone mass of the young adult reference population of the same sex. Z-score, on the other hand, shows the difference between the bone mineral density of the measured region and average bone density value of the normal population of the same age in terms of standard deviation (SD).

The World Health Organization recommends using the T-score for postmenopausal women and men aged 50 years or older for the diagnosis of osteoporosis, and the Z-score in children, premenopausal women and men younger than 50 years of age.[2,3,6] In postmenopausal women and men aged 50 years or older, T-score greater than or equal to -1.0 SD is normal. Osteopenia is diagnosed if the T-score is between -1 and -2.5 SD, osteoporosis if T-score less than or equal to -2.5 SD, and severe (established) osteoporosis if accompanied by one or more fragility fractures.

Table 3. *Evaluation of osteoporosis*

History	Age, gender, complaints, personal and family histories, osteoporosis and fracture-related conditions, concomitant diseases, drugs used, smoking, alcohol, nutrition and exercise habits
Clinical symptoms and findings	Back pain due to vertebral fractures, shortened height, spinal kyphosis, scoliosis, postural problems due to kyphosis and scoliosis, restrictive lung and heart function disorders, sleep disorders
Physical examination	Height, weight, body mass index, presence of kyphosis or scoliosis, findings related to secondary causes (Cushing, hyperthyroidism, arthritis etc.)
Laboratory tests	Serum calcium, phosphorus, 25OH vitamin D, parathormone, alkaline phosphatase, thyroid stimulating hormone, creatinine, alanine and aspartate aminotransferases and calcium in 24-hour urine
Imagings	Dual energy X ray absorptiometry (DXA), vertebral thoracolumbar X ray graphies

According to Z-score, premenopausal women, men younger than 50 years old, and children diagnosed as having a lower bone mass than expected according to their chronological age if Z-score is less than or equal to -2 SD and normal bone mass according to chronological age if Z-score is higher than -2 SD.[2,3] BMD values of DXA measurements are also used in treatment follow-up, but not T- or Z-scores, to evaluate the effectiveness of osteoporosis treatment.

Vertebral Imaging

Vertebral imaging is also important in the diagnosis and follow-up of osteoporosis. Lateral thoracolumbar vertebra X-ray radiography should be performed and evaluated in patients with osteoporosis and having high risk of fracture.[2,5] The main groups in which vertebral imaging is recommended are;

- Women aged ≥70 years and men ≥80 years with a total hip, femoral neck or vertebra T-score of ≤-1.0 SD,
- Women aged 65-69 years and men 70-79 years with a total hip, femoral neck or vertebra T-score of ≤-1.5 SD,
- Postmenopausal women and men ≥50 years with specific risk factors like;
  - Recently used or ongoing glucocorticoid therapy,
  - History of fragility fracture,
  - At least 2 cm shorter than the previous height during follow-up,
  - Height shortened by at least 4 cm according to height in twenties.

Vertebral fractures can be evaluated by visual semi-quantitative methods like thoracolumbar X ray graphies in which the area between the thoracic 4th vertebra and the lumbar 4th vertebra is examined. Fractures in vertebras can be wedge, concave or crushed collapse nature. Height of the vertebra is an important evaluation parameter as

Table 4. *FDA approved treatment options, their recomended dosages, mode of administrations, main side effects and usages in postmenopausal and male osteoporosis*

Drug	Recomended dose and route of administration	Main side effects	Usage in osteoporosis	
			Postmenopausal	Male
Bisphosphonates				
Alendronate	10 mg/day or 70 mg/week, oral	dyspepsia, abdominal pain, musculoskeletal pain	+	+
Ibandronate	2.5 mg/day or 150 mg/month, oral or 3 mg/3 months, intravenous	dyspepsia, abdominal pain, musculoskeletal pain, back pain, headache	+	-
Risedronate	5 mg/day or 35 mg/week or 150 mg/month, oral	rash, abdominal pain, dyspepsia, diarrhea, arthralgia	+	+
Zoledronate	5 mg/year, intravenous	fever, myalgia, hypotension, fatigue, nausea, vomiting, inflammation in the eyes, abdominal pain	+	+
Selective estrogen receptor modulators				
Raloxifene	60 mg/day, oral	arthralgia, leg cramps, flu-like syndrome, peripheral edema, hot flashes, venous thromboembolism	+	-
Calcitonin				
Calcitonin	100 IU/alternate day, subcutaneous or intramuscular or 200 IU/day, intranasal applying to 1 nostril alternatingly	injection site reaction, nausea, vomiting, abdominal pain, flushing, rhinitis, nasal irritation, dry nose, dizziness	+	-
Parathyroid hormone analog				
Teriparatide	20 mcg/day, subcutaneous	transient hypercalcemia, nausea, rhinitis, arthralgia, pain	+	+
Monoclonal antibody				
Denosumab	60 mg/6 month, subcutaneous	dermatitis, rash, bone and muscle pain, urinary infection	+	+

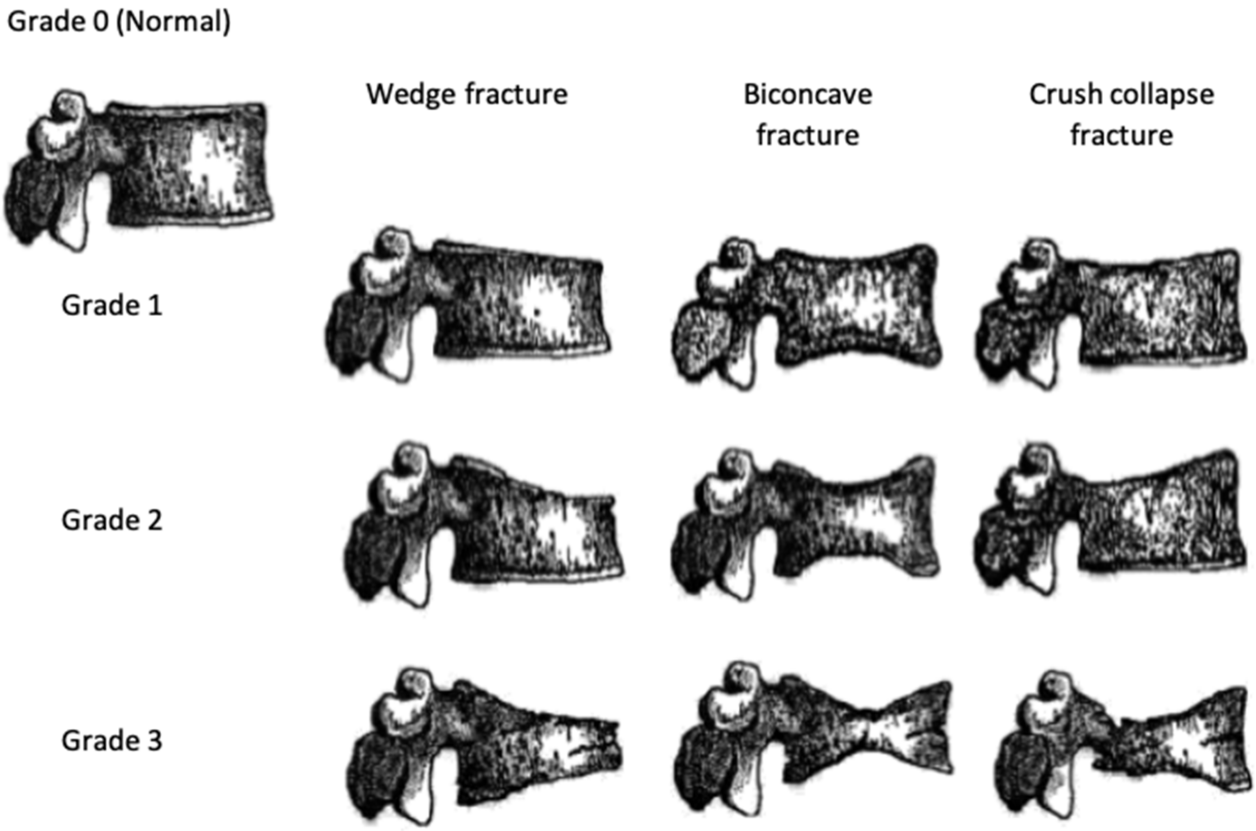

Figure 1. *Evaluation of vertebral fractures*[9]

well as type of the fracture. The vertebra is stated to be normal (Grade 0) if there is no vertebral height loss, mild (Grade 1) if <25% loss, moderate (Grade 2) if 26-40% loss, and severe (Grade 3) if more than 40% loss (*Figure* 1).[8,9] Women and men with vertebral fractures have an increased risk of developing new vertebral and femur fractures. Presence of a vertebral fracture in women increases the risk of a new vertebral fracture 5 times and a new hip fracture 2 times compared to ones without vertebral fracture.[2,10,11]

Treatment

Non-pharmacological approaches like having calcium-rich diet, exercise, exposure to sunlight for vitamin D production, quitting smoking and alcohol are the main treatment options for osteopenia and osteoporosis as well as measures taken to reduce the risk of trauma or fall.[2,3,12] Exercise in adulthood leads to higher BMD and better neuromuscular function causing lower risk of falls and fractures.[1]

Besides lifestyle changes, pharmacological treatment is given in patients with a vertebral, femoral neck or total hip T-score of -2.5 or below in DXA measurement with or without a concamitant fracture. In patients with osteopenia, drug treatment can be started if 10 years of hip fracture risk is calculated to be ≥3% or 10 years of major osteoporotic fracture risk is ≥20% with the fracture risk assessment (FRAX) tool which is validated in postmenopausal women and men aged >40 years.[2,12]

While making the treatment decision, each patient should be evaluated with her/his own characteristics, and other risk factors should be taken into consideration along with BMD. If there are conditions accompanying that may lead to secondary osteoporosis, they should be treated as well. Otherwise, the treatment efficacy of the drugs used for osteoporosis may be reduced. Testosterone replacement therapy is recommended for young male patients with hypogonadism with a serum total testosterone level below 200 ng/dL. Although estrogen replacement therapy should be given in hypogonad premenopausal women with estrogen deficiency, estrogen replacement is not recommended as the first-line therapy in the prevention or treatment of postmenopausal osteoporosis. In postmenopausal women, estrogen therapy is only recommended if there is a high risk of osteoporosis and other non-estrogen treatments are not suitable for the patient.[2,3,12,13]

There are different pharmacological treatment

options in osteoporosis. The main agents used are calcium, vitamin D, bisphosphonates, estrogen replacement therapy, selective estrogen receptor modulators, calcitonin, teriparatide, denosumab and strontium ranelate. Among them strontium ranelate which has both anabolic and antiresorbtive effects on bone has not been approved by American Food and Drug Administration (FDA) for the treatment of osteoporosis. Oral calcium 1000-1200 mg/day and oral vitamin D 800-1200 IU/day should be given to all patients, depending on their needs. Appropriate anabolic or antiresorptive treatment options should be given to the patient when necessary, taking into account factors such as the gender of the patient, the menopausal status, the effects of the drug and the potential for possible side effects (*Table 4*). Pharmacological treatment other than calcium and vitamin D should not be considered unless there is an ongoing bone loss or recurrent low-traumatic fractures in premenopausal women. If it is absolutely necessary, drug side effects, benefits and risks should be evaluated very well, and possible adverse effects and contraindications of drugs used in childbearing age on mother and baby should be carefully and detailly evaluated.[2,4,12,14,15]

In follow-up, all the patients with osteoporosis should be reassessed clinically to monitor compliance and side effects of drugs. Presence of height loss, new fractures and risk of falls should be evaluated at each visit which may alter patient management. BMD testing can be used for treatment monitoring as well as bone turnover markers if possible. It would be ideal if BMD testing could be done on the same DXA machine.[2,3,15] The fact that consecutive BMD measurement values have not changed or increased indicates that the treatment is effective.[2,3] BMD measurement with DXA should be repeated every 2 years in postmenopausal women and men over 70 years, once a year in patients under treatment, every 6 months in patients receiving teriparatide therapy, every 6 months or a year according to the physician's decision in patients with secondary osteoporosis.[2]

Conclusion

Osteoporosis, although the most common metabolic bone disorder, it is generally underdiagnosed. The purpose of diagnosing osteoporosis is to identify high risk patients and start treatment to prevent fractures. Unfortunately, quite low percentage of the patients are properly diagnosed and treated. For a proper approach, basic aspects for the evaluation, diagnosis, treatment and follow-up of osteoporosis should be known detailly and applied properly to the patients.

Conflict of Interest

The author declared that there is no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Original Article

Effectiveness and Reliability of Splenectomy in Chronic Immune Thrombocytopenia

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Abstract

Introduction: Splenectomy is markedly effective treatment modality at early period in adult chronic immune thrombocytopenia (ITP). Long-term outcomes are still controversial. The aim of this study was to determine long-term effectiveness and reliability of splenectomy in ITP and to identify factors influencing on long-term response.
Methods: The study included 100 ITP patients who underwent splenectomy in our general surgery department. Parameters including gender, age, platelet count, comorbid diseases, antiplatelet antibody positivity and long-term effect of medical treatment on response to splenectomy were considered.
Results: Owing to advances in treatment protocols, ITP has become a more benign disease and need for splenectomy has been decreased. However, splenectomy is a highly effective in second-line treatment.
Conclusions: Based on our results, it was seen that open or laparoscopic splenectomy with low morbidity and mortality rates is an appropriate treatment modality for long-term control of chronic ITP in cases requiring splenectomy. Age and postoperative platelet count were identified as significant prognostic and predictive factors for long-term response to splenectomy.

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Keywords: splenectomy, chronic immune thrombocytopenia, ITP

Introduction

Chronic immune thrombocytopenia (ITP) is an acquired disorder which develops due to reduction in lifespan of platelets as a result of early destruction in reticuloendothelial system, particularly in spleen, because of autoantibodies against platelets, and progresses with thrombocytopenia (platelet count <100x10^9/L). Based on severity of thrombocytopenia, it may often manifest with mucocutaneous bleeding and less frequently with visceral or life-threatening hemorrhages.[1,2] In addition, fatigue and decreased quality of life can be seen in symptomatic patients.

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In adults, annual incidence is 3.3/100,000 while prevalence is 9.5/100,000 for primary ITP indicating that is not an infrequent disease.[3-5] The ITP primarily involves women at childbearing age (female:male ratio=3:1). It is most commonly seen between 15 and 40 years of age. Its incidence as well as rate of diagnosis in asymptomatic patients has been increased over time.[2,6] Although investigations on pathophysiology of ITP have been intensified in recent years, its pathogenesis could not be fully elucidated. Major mechanisms addressed are abnormal anti-platelet antibodies, impaired megakaryopoiesis and T cell-mediated platelet damage and different mechanisms can play role in each patient.[7-9]

The ITP is a condition which may be life-threatening and annual risk for fatal bleeding ranges from 0.4% to 13% based on age.[2] Although peripheral platelet count is most important marker for bleeding risk, many studies has demonstrated inconsistent results at varying platelet counts. The degree of thrombocytopenia does not necessarily correlate with risk for bleeding. No bleeding is observed in some patient with severe thrombocytopenia while serious bleeding may occur in patients with milder thrombocytopenia. The need for treatment can vary among individuals and is determined by clinical presentation. Corticosteroids are first-line therapy in cases requiring treatment. The goal of treatment is to achieve safe platelet counts to prevent severe bleeding. Splenectomy may be considered as second-line treatment in cases refractory to corticosteroid therapy. Eighty percent of patients respond to splenectomy. The treatment response is persistent in 66% of responders and no additional treatment is required for at least 5 years. Partial or transient response is observed in those with incomplete response while 14% of patients are refractory and response will disappear over time.[1,2,10,11] Additional treatment options include intravenous immunoglobulin (IVIG), high-dose dexamethasone, azathioprine, interferon-alpha (IFN-α), vincristine and other immunomodulatory agents. In recent years, novel thrombopoietin (TPO) receptor antagonists have become an effective treatment option. However, their use is limited by severe adverse events such as rebound thrombocytopenia (10% reduction in platelet count compared to baseline), increased reticulin fiber in bone marrow and thrombotic complications after withdrawal of drug. As similar to other treatment modalities, decision and recommendation of splenectomy is an individualized process based on age, disease duration, comorbid conditions, effectiveness of steroid therapy, side effects and the patient's preference.[2,11]

Material and Methods

This retrospective study was conducted on 100 patients with available data who underwent splenectomy with diagnosis of ITP at General Surgery Department of Uludag University, School of Medicine between 1980 and 2004. We extracted data regarding age at presentation, platelet count at presentation, autoantibody positivity, scintigraphy and sonography results, comorbid conditions, hematological parameters, response to medical treatment, adverse events, splenectomy indication and time to splenectomy from patient files. We also assessed preoperative platelet count, vaccination status, preparation therapies at critical platelet counts, age at surgery, type of surgery, minimum and maximum platelet counts within 72 hours after surgery and postoperative morbidity and mortality. Early response was defined as response at month one after surgery while the response was classified as complete, partial and unresponsive. Third-line therapeutic interventions were identified in unresponsive patients and in those with partial response or relapse.

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 10.01 (SPPS Inc, 1989-1999). Following parameters were used for comparisons between groups: 1-Mean and standard deviation as descriptive statistics for quantitative variables; 2- Kaplan-Meier test for time to relapse and stability duration; 3-Chi-square test to compare rates; 4-Ordinal logistic regression analysis to assess effects of several factors on long-term outcomes and to identify critical age threshold. A p value <0.05 was considered as significant while a p value <0.01 as significant on highest degree.

Results

The study included 100 patients (22 men and 78 women) who underwent splenectomy with diagnosis of chronic ITP and had minimum follow-up of 12 months. Mean age at presentation was 34.1±1.4 years (15-79). The ITP diagnosis was made by symptoms of bleeding as mucocutaneous bleeding being most common while it was made incidentally by exclusion of all other factors causing thrombocytopenia. There was at least one systemic disorder (e.g. hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease) in 21 patients at time of presentation. Mean platelet count at presentation was 17,945±1,225x10^9/L and antiplatelet autoantibody was positive in 22 patients at time of presentation. All patients underwent bone marrow biopsy prior to splenectomy. Bone marrow biopsies resulted in normocellular bone marrow with increased megakaryocytes. Accessory spleen was detected in 2 patients on scintigraphy while splenomegaly in 2 patients on sonography.

Prednisolone as first-line treatment was given to all patients other than one patient declined medical treatment and 2 patients received danazol after declining steroid therapy. In addition to steroid therapy, IVIG was given to 11 patients with critical platelet counts. The splenectomy indications included refractoriness to steroid and other medical therapies in 47 patients, need for high-dose steroid therapy and adverse events related to long-term steroid use (Cushingoid appearance, uncontrolled hyperglycemia, neuropathy, myopathy, osteoporosis, gastric bleeding, lung abscess) in 51 patients and declination of medical therapy in 2 patients.

Mean time from medical therapy to splenectomy was 9.4±1.9 months (2-168) and all patients received pneumococcal and Hib vaccines at least 2 weeks before splenectomy. Mean preoperative platelet count was 83,887±6,574x10^9/L (14-330x10^9/L). Preoperative and perioperative platelet infusions were performed in patients with platelet count <50x10^9/L and IVIG was given to 22 patients before surgery. Mean postoperative 1st day platelet count was 362,849±25,665x10^9/L. Ecchymosis or subcutaneous hematoma was developed in 3 patients while pneumonia in 2 patients, superficial wound site infection in 1 patient, epistaxis in 1 patient and intra-abdominal abscess in one patient after surgery. One patient underwent surgery due to intra-abdominal bleeding on the postoperative hour 8. One patient died due to pneumonia developed on the day 7 after surgery.

Mean follow-up after splenectomy was 70.4 ± 4.9 months (12-284). The patient with partial response, relapse or no response received steroid and third-line treatment regimens. No splenectomy-related infection, sepsis or life-threatening abnormality was observed at long-term. All cases showed early response with complete response in 87 patients and partial response in 12 patients. One patient died. Mean time to relapse was 29.5±9.5 months (1-156). Of 18 patients with relapse, complete response was achieved in 10 and partial response in 7 patients. One patient was unresponsive. To assess effectiveness and reliability of splenectomy at early and late period, the effects of age, gender, autoantibody positivity, response to medical treatment, time to splenectomy and postoperative platelet counts were addressed with literature data.

Mean age at presentation was 33.2±3.6 years whereas mean platelet count was 22,288±20,055x10^9/L; mean preoperative platelet count was 85,077±20,055x10^9/L; mean age was 35±4 years at time of surgery. Eleven relapses were observed within first year while no relapse was observed at period of 12-24 months (*Table 1*).

Low-dose steroid trial was performed in all patients with relapse or those requiring treatment despite partial remission; however, only 5 patients responded to low-dose steroid therapy (0.5 mg/kg/day), all of which achieved complete response. Dose escalation was required in 9 patients and complete response could not been achieved.

Table 1: Number of cases and time of relapse

Time of relapse	0-12 Months	12-24 Months	24-36 Months	36-48 Months	48-60 Months	>60 Months
Number of cases	11	0	3	1	1	2

Multi-drug therapy was given to 11 patients while 2 patients shifted to azathioprine and partial response persistent in both patients. The refractory patient was lost during follow-up. At long-term, there was complete response in 85 patients, partial response in 13 patients and no response in one patient. In 72 patients, postoperative platelet count remained above 150,055x10^9/L and none required medical treatment.

Patients responsive to splenectomy were significantly younger and critical age threshold was estimated to be 37 years in ordinal logistic regression test. It was found that long-term response had highly significant association with age, postoperative platelet count and presence of comorbid disease ($p<0.01$). No significant association was found for response to steroid, presence of autoantibody and time from medical treatment to splenectomy ($p>0.05$). Table 2 presents distribution of patients according to parameters evaluated and rates of early and late responses. One month after the operation, the response is considered an early response and the response was defined as complete response (CR), partial response (PR) and unresponsive (UR). The response 12 months after the operation was accepted as a late response (*Table 2*).

Discussion

Although chronic ITP is a condition which can be difficult to control, surgical team as well as hematologists are involved the treatment of ITP. Since spleen plays role in both antibody formation and platelet destruction, the destruction is reduced via splenectomy by removing major organ where antibody-coated platelets are up-taken and destructed. Another effective mechanism is that splenectomy allows a significant reduction in total lymphoid mass (25% of which is at spleen) where anti-platelet antibody is generated. Thus, splenectomy remains to be valid therapeutic option in second-line treatment in cases refractory to immunosuppressive treatment or those requiring high doses of steroids.[12,14]

The ITP can affect individuals from all ages; however, it is more commonly seen between puberty and 50 years of age. It is generally seen after 40 years of age and has peak about 30 years of age.[13] It predominantly affects women at childbearing age. In the literature, female: male ratio varies from 1.7 to 3.0. In our study, female: male ratio was found as 3.5.

The signs and symptoms are highly variable ranging from mild mucosal bleeding to serious hemorrhages such as intracranial bleeding.

Table 2: Response and variables influencing on response

		Early Response			Relapse	Late period		
		CR	PR	Death		CR	PR	UR
Age	≤37y n:64	59	5	0	7	59	4	1
	>37y n: 36	28	7	1	5	26	9	0
Gender	Female n: 78	70	7	1	13	68	9	0
	Male n: 22	17	5	0	5	17	4	1
Postoperative platelet count	<300 X10^9/L n: 50	38	11	1	11	37	11	1
	≥300 X10^9/L n: 50	49	1	0	7	48	2	0
Comorbidity	Exist n: 21	15	5	1	3	14	6	0
	None n: 79	72	7	0	15	71	7	1
Response to steroid therapy	Responsive n: 51	46	5	0	12	41	9	1
	Refractory n: 47	39	7	1	6	43	3	0
Time from medical treatment to splenectomy	<6 months n: 64	56	7	1	11	56	7	0
	≥6 months n: 36	31	5	0	7	29	6	1
Autoantibody positivity	Positive n: 22	20	2	0	3	18	4	0
	Negative n: 78	67	10	1	15	67	9	1

CR: complete response, PR: partial response, UR: unresponsive

Although hemorrhage is rarely seen in general unless there is severe thrombocytopenia, degree of thrombocytopenia does not necessarily correlate with risk for bleeding. Based on previous studies, risk for bleeding is lower in ITP patients when compared to patients with thrombocytopenia and hypo-regenerative bone marrow. This is explained by the fact that, in ITP, circulating platelets are younger; thus, more active in hemostasis. In our study, the patients most commonly presented with mucocutaneous bleeding; followed by those diagnosed incidentally. In Western studies, patients were most commonly diagnosed incidentally, which can be explained by sociocultural level of society and development level of healthcare systems.[2,4,15] Despite development level of medicine today, ITP diagnosis can only be made by excluding other causes and factors leading thrombocytopenia. In our study, in addition to other screenings tests, autoantibody screening and bone marrow aspiration were performed in all patients and autoantibody positivity was detected in 22 patients. Sonography evaluation and scintigraphy scan must be performed in all patients scheduled for surgery. Splenomegaly is observed in 3% of patients on sonography while accessory spleen is seen in 2-13% of patients on scintigraphy. In our study, splenomegaly was detected in 2 patients by sonography while accessory spleen in 2 patients by scintigraphy. Failure to identify accessory spleen during surgery is major cause of unresponsiveness to surgical treatment.[1,11,16,17] Thus, screening accessory spleen before surgery will improve success of surgical treatment.

In general, complete remission rate ranges from 53% to 75% by initial treatment with steroids.[18] In our study, all patients underwent splenectomy were refractory to steroid therapy or experienced relapse following steroid. In the treatment of ITP, role of splenectomy is based on more than 80 years of experience and it is only treatment option with known curative effects in majority of patients although different remission rates were reported in different series. In the literature, response rate for splenectomy is 80-85% in early period and 50-80% in late period[1,2,11,14,15]; in our study, response rate was 87% and 85%, respectively. Available data indicate that splenectomy achieves complete and persistent response in two-third of ITP patients refractory to initial treatment. In a meta-analysis including 2,623 patients, complete response was achieved in 65% while partial response in 22% of cases after splenectomy.[19] In addition, remission was persistent in almost all cases achieved response with splenectomy.

Although there are different opinions about timing of splenectomy, in a consensus report published in 2019, it is recommended to delay splenectomy for 12 or 24 months due to likelihood of remission and stabilization after diagnosis.[20] However, splenectomy before 12 months can be considered in cases in which severe and symptomatic thrombocytopenia persist despite initial steroid therapy and are at higher risk for bleeding. The time from medical therapy to splenectomy differs among different clinics and studies; and it was found as 9.42±1.91 months (2-168) in our study. However, it was found that time from medical treatment to splenectomy had no significant effect on outcome.[1,2,21]

Although splenectomy-related morbidity and mortality rates vary according to factors such as surgical technique employed, age, preoperative platelet count, they have been reported as 9-12% and 0.2-1% in different series, respectively.[19] In recent years, in parallel to advances in minimally invasive surgery, it has become a more preferable method with minimal morbidity and shorter length of hospital stay. In a review including 3,000 splenectomy cases, morbidity and mortality rates were found to be lower in laparoscopy group compared to laparotomy group (morbidity; 9.6% vs. 12.9% and mortality; 0.2% vs. 1%). The complete response is observed within first two weeks after splenectomy and platelet count can increase immediately after splenectomy in some cases.[22] In our study, 93 patients underwent conventional splenectomy while 7 patients underwent laparoscopic splenectomy. In recent years, laparoscopic splenectomy was performed in more cases due to increased experience; thus, splenectomy-related morbidity and mortality rates were markedly decreased. By improved surgical experience, laparoscopic splenectomy has become choice of surgical method by taking patient characteristics into account.

Major complications include surgical complications and infections in splenectomy. During follow-up, 6 patients died due to ITP and treatments related to ITP, including 2 patients with bleeding and 4 patients with infection.[2] In another study, 27 of 245 patients (11%) died

during study period and cause of death was ITP-related hemorrhage in 3 patients (1.2%), post-splenectomy sepsis in one patient (0.4%). Remaining deaths were found to be unrelated with ITP or treatment.[1,23] To minimize risk for infection after splenectomy, patients should be vaccinated against Streptococcus pneumoniae, Hemophilus influenzae and Neisseria meningitidis at least two weeks before surgery.

Varying relapse rates have been reported following splenectomy and relapse is generally seen within first years with decreased likelihood of relapse over time.[1,2,14,15] Although relapse is more commonly seen in emergent splenectomy in particular, accessory spleen is detected in 10-18% of the patients refractory to splenectomy or experience relapse after splenectomy. In our study, no accessory spleen was detected on scintigraphy in 18 patients with relapse.[24,25] Mean time to relapse was 29,556±9 months (1-156) and relapse developed within first year in 11 patients.

Splenectomy decision or recommendation is an individualized process, which is affected by patient age, comorbid conditions and psychology and sociocultural level of patients. Splenectomy decision is challenging in all aspects; thus, patients who will benefit from splenectomy, extent of expected benefit and risks should be identified before surgery.[1,2] Although many studies investigated predictive and prognostic factors for splenectomy in ITP, only age at splenectomy was found as positive prognostic factor in some studies.[14,26,27] In our study, effects of gender, comorbid condition, age at splenectomy, time from medical treatment to splenectomy, presentation, preoperative and postoperative platelet counts, steroid response and autoantibody positivity were evaluated at long-term after splenectomy. It was found that age at splenectomy and postoperative platelet count had highly significant positive effect on outcome while presence of comorbid condition had highly significant negative effect on outcome. Age <37 years and postoperative platelet count >300x10^9/L were determined as major positive prognostic and predictive factors.

Conclusion

In conclusion, chronic ITP is the hematological disorder in which feasibility of both medical and surgical treatments have been studied most intensively. In current treatment algorithm, steroid therapy is first choice; however, splenectomy is the only curative treatment with complete response rates of 87% and 85% at early and late period in patients with insufficient response to steroid therapy. Age and postoperative platelet count are major prognostic and predictive factors for long-term outcomes.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Original Article

Effects of Cigarette Smoking on Total and Salivary Cortisol Levels

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Abstract

Introduction: Although there are some studies regarding the effects of cigarette smoking on serum total cortisol (TC) and salivary cortisol (SaC) levels, the results are still not conclusive. For this purpose, we aimed to determine the effects of cigarette smoking on TC and SaC levels in a small sample of healthy volunteers.
Methods: Twenty-five (12 females and 13 males) smokers with a mean age of 42.6±15 years and 25 (12 females and 13 males) age- and gender-matched healthy non-smokers (mean age: 40.8±14.5 years) were enrolled in the study. Hypothalamic-pituitary-adrenal (HPA) axis was evaluated by baseline TC and SaC levels, and TC and SaC responses to standard dose (250 μg) ACTH stimulation test. TC and SaC levels were obtained under baseline and stimulated conditions.
Results: Although mean TC and SaC levels were higher in smokers versus non-smokers, a statistically significant difference was not found between the two groups.
Conclusion: TC and SaC levels were not statistically different between smokers and non-smokers. Further studies with a larger sample size are needed to draw definitive conclusions.

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Keywords: Smoking, serum total cortisol, salivary cortisol, ACTH stimulation test

Introduction

Cortisol is a stress hormone which may be influenced by cigarette smoking. Cigarette smoking can interfere with steroid hormone release, binding, transport, storage, metabolism, and clearance, resulting in changes in circulating hormone concentrations.[1,2] It is known that smoking is associated with moderately elevated cortisol levels.[2] Several studies have reported the stimulating effects of acute doses of nicotine delivered by cigarette smoking on the hypothalamic-pituitary-adrenal (HPA) axis.[2-4] Nicotine has a stimulatory effect on HPA axis

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activity with increased plasma cortisol and urinary 17-hydroxycorticosteroid levels detected following cigarette smoking.[2] Nicotine probably stimulates hypothalamic cholinergic receptors, leading to a release of corticotropin-releasing hormone (CRH). Nicotine also stimulates adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary with a subsequent cortisol release from the adrenal cortex. Additionally, nicotine induces vasopressin secretion which can lead to ACTH release.[4] It is also known that total cortisol (TC) levels increase within the first 20 minutes after cigarette smoking.[5] On the other hand, acute tobacco abstinence was shown to cause a reduction in TC.[6]

Cortisol levels can be measured in plasma, urine, and saliva. Salivary cortisol (SaC) directly diffuses along the capillaries to target tissues and it is a biomarker of serum free cortisol (FC) level. Sampling of saliva is easy and painless. SaC, as a surrogate biomarker of FC has been increasingly used in scientific studies.[7-10] There are controversial data in literature regarding the effect of cigarette smoking on SaC. In one study, SaC levels were increased in current smokers compared with nonsmokers.[11] Cessation of cigarette smoking results in a reduction of SaC levels.[12] In a study by Wong et al., SaC levels were significantly lower during the abstinent session versus the non-abstinent session in the same population.[13] However, in some other studies it was concluded that SaC levels were not affected by cigarette smoking.[14-16] As previously mentioned, evidence for an association of smoking with SaC are mixed. For this purpose, we aimed to investigate SaC levels of cigarette smokers and non-smokers in a population of healthy volunteers.

Methods

Twenty-five healthy smokers (12 females and 13 males) with a mean age of 42.6±15 years, and 25 age- and sex-matched (12 females and 13 males) healthy non-smoker (mean age: 40.8±14.5 years) controls were enrolled in the study. The duration of cigarette smoking was estimated by pack-years (number of packs of cigarettes smoked per day x years smoked per person). This study was part of another study investigating the HPA function of healthy people at our hospital. The study was approved by the Local Ethics Committee and informed consent was obtained from all volunteers. Exclusion criteria included a diagnosis of diabetes mellitus, malignancy, history of corticosteroid exposure, oral contraceptive use, and also the presence of any condition that could affect functioning of the HPA axis.

ACTH stimulation tests: Tests were performed between 08:00-09:00 a.m., after an overnight fast. Blood and saliva samples for TC and SaC were obtained before and at 30, 60, 90 minutes after administration of 250 μg synthetic ACTH.[17] Samples were centrifuged, aliquoted and stored at -80 °C until analysis.

Salivary samples: Sixty minutes before the test, individuals were not allowed to smoke, eat, drink liquids or brush their teeth. Saliva samples were collected by using oral swabs (Salimetrics®).[18] Salivary cortisol was measured using a commercially available high-sensitivity enzyme immunoassay (EI) kit (Salimetrics® Inc, State College, PA, USA) according to the manufacturer's instructions.[9]

Serum TC: Serum TC levels were measured by radioimmunoassay (RIA) method (Immunotech; Prague, Czech Republic).

Statistical analyses

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS for Windows, version 15; Chicago; IL). Since the data were distributed homogenously, statistical analyses were performed by parametric tests. The results were presented as mean and standard deviation (SD). Comparisons between two groups of data were done by paired t-test. Statistical significance was set at a p-value less than 0.05.

Results

Demographic and smoking status of the study subjects are shown in Table 1. Mean duration of smoking was 14±14 (median: 9, min: 1, max: 45) years for the study sample and 13.3±16 (median:7, min: 1, max: 45) and 15.5±10.4 (median: 15, min: 25, max: 30) years respectively for females and males. Baseline, peak and delta hormone levels of the smoker and non-smoker groups are summarized in Table 2.

Although mean TC and SaC levels at baseline and 30, 60 and 90 minutes after ACTH stimulation

Table 1: Demographic characteristics of the subjects.

Group	Age (years)	
Smokers (n=25)	44.8±15.5 (F, n=12) 40.5±15 (M, n=13)	42.6±15
Non- smokers (n=25)	44.5±14.4 (F, n=12) 36.8±14 (M, n=13)	40.8±14.5
p Value		0.89

Table 2: Baseline, peak and delta hormone levels of the subjects during 250 µg ACTH stimulation test.

		Baseline (Mean, SD)	Peak (Mean, SD)	Delta (Mean, SD)	p value
TC (µg/dL)	**Smokers**	11.8±7	34.8±11.4	23±12.4	*<0.01*
	Non-smokers	8.9±4.6	31.2±9.3	22.3±11.8	*<0.01*
	p value	0.09	0.22	0.82	
SaC (µg/dL)	**Smokers**	0.53±0.54	2.55±1	2±0.98	*<0.01*
	Non-smokers	0.51±0.40	2.34±0.78	1.81±0.73	*<0.01*
	p value	0.89	0.43	0.35	

TC= Total cortisol, SaC= Salivary Cortisol

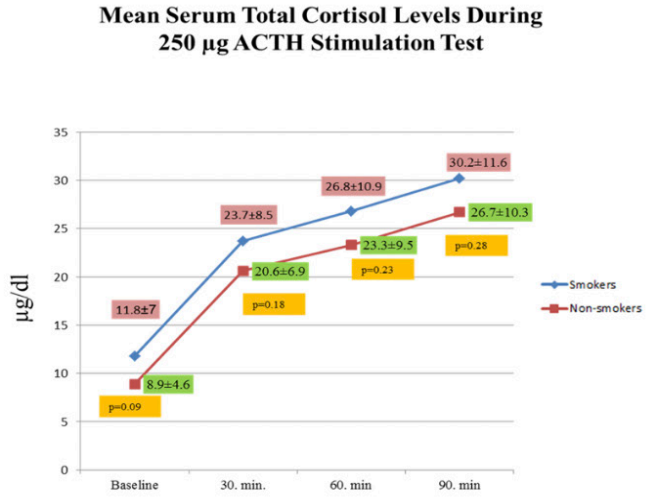

Figure 1a. TC levels at baseline and 30, 60 and 90 minutes after ACTH stimulation test

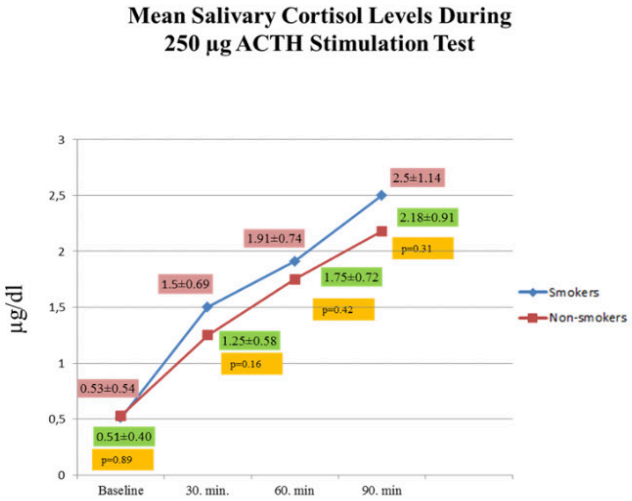

Figure 1b. SaC levels at baseline and 30, 60 and 90 minutes after ACTH stimulation test

test were higher among smokers, a statistically significant difference was not found between the two groups (*Figures 1a and 1b*). As shown in Figure 2, baseline and stimulated SaC levels were also similar among males, females and overall.

Discussion

In any investigation on the effects of smoking on cortisol, consideration should be given to the type of method used for cortisol measurement (TC, FC or SaC) while interpreting the results.

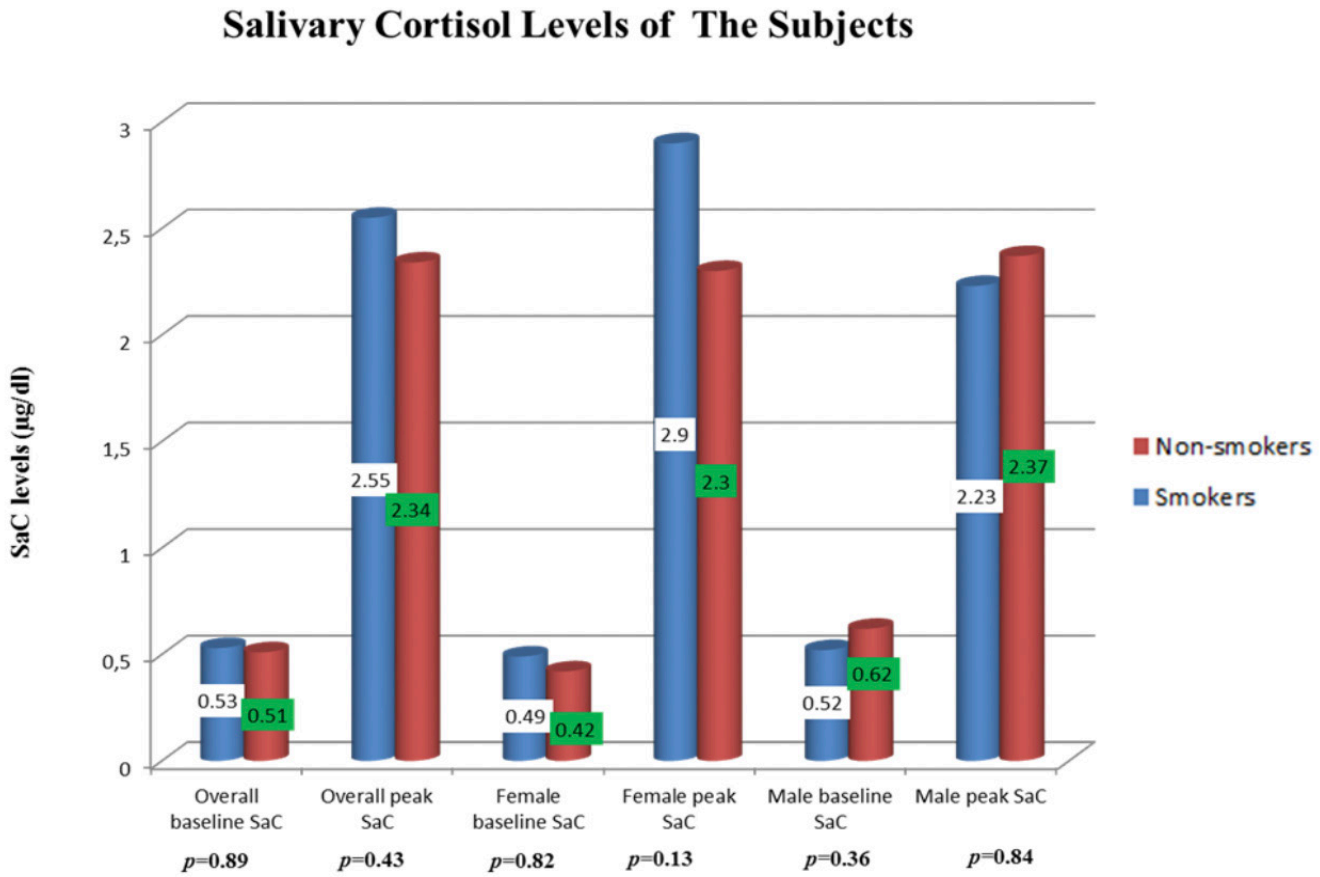

Figure 2: Salivary cortisol levels of the subjects overall and in female and male groups.

This is because it is known that the biologically active fraction of cortisol is FC and it should be the primary fraction to be measured since it is not affected by cortisol-binding proteins. However, FC measurement is a cumbersome and time-consuming method that is dependent on laboratory and technician. However, when SaC is directly measured using the EI method, it is not affected by cortisol-binding proteins or any factors that could have an impact on these proteins.

In our study, TC and SaC levels of the subjects were not statistically different between smoking and non-smoking groups. Studies comparing smokers and non-smokers using TC showed that TC was generally higher among smokers.[2,5,11] However, Handa et al.[19] found lower morning TC values in a group of middle-aged male smokers.19 In our study, baseline and stimulated TC values did not differ between sexes. We also found that SaC levels were not different between smokers and non-smokers in the present study. Considering that SaC reflects biologically active FC, we may suggest that smoking does not have any effect on FC levels. Consistent with our findings, in their study Yeh and Barbieri[20] showed that urinary cortisol levels which reflected FC were not different between 10 smokers and 15 non-smokers. Contrastingly, Kirschbaum et al. reported higher SaC levels in smokers than in non-smokers in two studies.[21,22] In a new study published in 2019, examining cortisol secretion and sleep continuity in smokers and non-smokers, a marked difference was observed between SaC values of 38 regular smokers and 39 non-smokers (0.73± 0.58 µg/dL versus 0.47± 0.26 µg/dL, respectively).[23] In the present study, we did not find any difference between SaC levels between smokers and non-smokers at baseline and following ACTH stimulation. This finding suggests that several ingredients found in cigarettes including nicotine do not have a local effect on SaC. Also, it suggests that smoking does not have an additional impact on the HPA axis. In conclusion, we believe that it might be more appropriate to utilize SaC to assess FC in future studies that examine the HPA axis in relation to smoking status.

Conclusion

Although there were only 25 smokers in our study, we found that cigarette smoking did not

have an effect on TC and SaC levels. Further studies with a larger sample size are needed to draw definitive conclusions.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Note: This study was partly reported as a poster presentation at the European Congress of Endocrinology (ECE) held between May 16-20, 2015 in Dublin, Republic of Ireland.

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Case Report

Development of Pancytopenia After Single Low-Dose Methotrexate Therapy in Patients with Chronic Kidney Disease: a Review of the Literature

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Abstract

Methotrexate (MTX) is widely used in the treatment of both rheumatoid arthritis (RA) and psoriatic arthritis (PA) with a side effect of pancytopenia. However, very few cases of severe pancytopenia caused by low-dose MTX therapy have been described in chronic kidney disease. Pancytopenia occurred after using a single dose of MTX in our three patients with chronic kidney dysfunction. While one patient died due to sepsis and multiple organ failure, the others recovered. The severity of MTX-induced pancytopenia in our cases was likely related to the underlying kidney disease. These cases suggest that uremic patients may develop severe fatal bone marrow toxicity even with a single dose of MTX. Therefore, complete blood count monitoring after MTX treatment in this population would be beneficial.

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Keywords: *Chronic kidney disease, methotrexate, psoriatic arthritis, rheumatoid arthritis, pancytopenia*

Introduction

Methotrexate (MTX), a classical antifolate, has gained wide acceptance due to its efficacy in a variety of inflammatory rheumatological disorders, including rheumathoid arthritis (RA) and psoriatic arthritis (PA).[1,2] Although MTX at doses as low as 5-25 mg per week is the first-line therapy for RA, inter- and intra-patient variability in the response to treatment with the contribution of variability in concentrations of active polyglutamate metabolites can affect clinical efficacy and toxicity.[3] The absence of neutropenia or agranulocytosis episodes with MTX treatment at a dose of 7.5 mg per week for two years in patients with RA over 65 years of age indicates that this treatment is safe even in the elderly.[4] However, rare adverse hematological side effects associated with low-dose MTX, including fatal pancytopenia, are an increased cause of concern in patients with rheumatological disorders and renal dysfunction.[3,5] Herein, three patients with chronic kidney disease (CKD) who developed pancytopenia after a single oral or intramuscular dose of MTX are presented.

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Case Report

Case 1. The first case was a 58-year-old woman with a history of chronic hypertension and kidney dysfunction. She had RA for 30 years. Serum creatinine level was 1.4 mg/dL and creatinine clearance was 43 mL/min. MTX was prescribed because of insufficient effect of steroids on increased joint pain, and a single dose of 12.5 mg was administered orally. Abdominal pain, chest discomfort, vomiting, and skin rush developed 5 days after administration of single-dose MTX. Petechial lesions on her pretibial area and ecchymosis on anterior aspect of left knee were remarkable. Laboratory findings at admission included severe pancytopenia: white blood cells 1,200 cells/μL with 160 cells/μL neutrophils, platelets 8,800 cells/μL and hemoglobin 9.1 g/dL. A bone marrow aspiration revealed erythroid hyperplasia with megaloblastic maturation and relative preponderance of eosinophils in the granulocytic series without atypical or blastic cells, as well as marked suppression of the megakaryocytic series. The patient was diagnosed as having MTX-induced pancytopenia and myelosuppression. She was treated with folinic acid and granulocyte colony stimulating factor. Two units of red blood cells and two units of platelets were replaced. On the 13th day of her hospitalization, she recovered completely and was discharged.

Case 2. The second case was a 43-year-old male patient with psoriasis and PA for 20 years. He had been on hemodialysis treatment for 3 months due to end-stage renal disease. MTX was prescribed because of a diffuse psoriatic eruption, and a single dose of 12.5 mg was administered orally. 7 days after the use of MTX, the patient applied with complaints of diarrhea, anorexia, chills, fever and not feeling well for two days. In his physical examination, blood pressure was 100/60 mmHg, pulse rate was 110 beats/min, body temperature was 38.5 °C, and respiratory rate was 20/min. Laboratory findings at the admission showed pancytopenia with a hemoglobin level of 5.9 g/dL, a white blood cell count of 3,100 cells/μL with 590 cells/μL neutrophils, and a platelet count of 31,300 cells/μL. The patient was diagnosed as having MTX-induced pancytopenia and neutropenicsepsis. He was treated with amikacin, cephapirin, folinic acid and granulocyte colony stimulating factor. After two days, his white blood cell dropped to 400 cells/μL without neutrophils. Then, the patient's need for inotropic agent and blood product transfusion continued. Eventually, the patient died with multiple organ failure due to sepsis.

Case 3. The third case was a 22-year-old woman patient with psoriasis for 20 years. She had been on hemodialysis treatment for 13 years due to end-stage renal disease. A dermotologist started a single dose of 10 mg intramuscular MTX therapy per week for active psoriatic lesions. Five days later, she admitted to the emergency room of our center with complaints of fever, vomiting, nausea, diarrhea, epistaxis and stomatitis. In her physical examination, blood pressure was 100/60 mmHg, pulse rate was 107 beats/min, body temperature was 39.5 °C, and she had multiple oral mucosites. Laboratory analysis revealed the following: pancytopenia, with a hemoglobin level of 5.5 g/dL, a white blood cell count of 1,810 cells/μL with 390 cells/μL neutrophils, and a platelet count of 72,000 cells/μL. The patient was diagnosed as having MTX-induced pancytopenia and neutropenic sepsis. She was treated with meropenem, fungostatin gargling, folinic acid and granulocyte colony stimulating factor. Due to the deepening of pancytopenia, 12 units of fresh frozen plasma, 10 units of platelet concentrate and two units of red blood cell support were required. On the 12th day of treatment, the patient's blood values improved. She was discharged on the 21st day after admission.

Discussion

Long-term weekly low-dose MTX therapy has proven to be highly effective in RA and other rheumatic diseases. Although myelosuppression is major dose-limiting side effect of high-dose MTX, low-dose MTX therapy can infrequently cause significant side effects such as hepatotoxicity, pulmonary damage and myelosuppression.[6] Low-dose weekly therapy in RA can lead hematologic toxicity associated with macrocytic red blood cells due to folate depletion.[7] Occasionally, anemia, leukopenia or thrombocytopenia can occur even without significant reduction in other cell lines.6 But, the development of pancytopenia is a more

severe complication after low-dose MTX use.[8-11]

A literature search found a total of 70 cases with pancytopenia related to low-dose MTX therapy in RA patients between 1980 to 1995 years.[12] In most patients, the mean weekly MTX dose was 7.5-10 mg and the mean cumulative dose was 675 mg (range: 10-4,800). 12 (17.1%) patients died, 10 of 12 patients had renal dysfunction and 9 had concomitant infection. The toxicity data from long-term prospective studies involving 511 patients treated with MTX for at least 13 weeks found an estimated incidence of pancytopenia of 1.4% (n=7).[12] In a prospective follow-up study assessed the frequency of MTX-induced pancytopenia in 157 patients with psoriasis, an overall incidence of pancytopenia was 11%.[2] In other study, the rate of pancytopenia was lower in 284 RA patients who received weekly oral low-dose MTX therapy (n=4, 1.4%).[13] The cumulative dose of MTX ranged from 15 mg to 760 mg at the time of pancytopenia. In another study, the prevalence of cytopenia was 2.38% (n=10) in 420 patients with RA, and only 1 patient had pancytopenia.14 Serum creatinine values of three patients with cytopenia were higher than 1.2 mg/dL. Patients with cytopenia received MTX at a weekly dose of 2.5-8 mg for a mean of 60 months (range: 10-119).[14] Intriguingly, no correlation was found between the total MTX dose and the severity of side effects.[2] In case series of Sosin et al.[15], MTX doses and durations of four cases with myelosuppression were 17.5 mg for 2 months, 5 mg for 6 months, 5 mg for 10 years and 10 mg for 7 months. Similarly, one of Calvo-Romero's[16] 2 patients who developed MTX-related pancytopenia used 15 mg of MTX for 10 days and the other used 1,030 mg of MTX for 23 months. A total of five patients of around 2,500 patients of RA who prescribed MTX between January 1996 to September 2005 developed MTX-induced pancytopenia, and the cumulative dose of MTX of patients varied from 25 mg to 2.1 g.[17] Several patients developed fatal pancytopenia even after the minimal cumulative dose of MTX as low as 10 mg, and may occur at any time during treatment.[12] In another report, the minimal single MTX dose leading to fatal neutropenia in patients with chronic uraemia had been reported to be 2.5 mg per week.[18]

After starting MTX therapy, pancytopenia may occur suddenly within 1-2 months with a possible idiosyncratic reaction or years later due to dose-dependent cumulative effect.[19] Myelosuppression can be due to impaired MTX excretion and/or accumulation of its metabolites intracellularly. Numerous riskfactors for MTX-induced pancytopenia include impaired renal function, hypoalbuminemia, low folate levels, concurrent infection, advanced age, multiple drugs usage and lack of folate supplementation.[20] Previous studies have shown association of cytopenia with C677T and 1298AA polymorphism.[21,22]

Considering the literature data, it is clear that presence of renal dysfunction is the most important risk factor of MTX toxicity including hematological effects.[5,12,23] Renal impairment rates in patients with pancytopenia in different series have been reported between 30.4% and 54.3%.[12,24,25] Approximately 35% of MTX is bound to plasma proteins. It is mainly cleared through the kidneys and is excreted 80% to 90% of the absorbed amount is excreted in the urine unchanged within 48 hours by glomerular filtration and active tubular secretion, mostly within the first 8 hours.[1,3,5] Therefore, impaired renal excretion of MTX and prolonged exposure to the drug increase the risk of myelosuppression and other toxicities. If occurrence of an acute disease or addition or change of a non-steroidal anti-inflammatory drug (NSAID) impair renal function or MTX is taken daily instead of weekly, low-dose MTX is more likely to cause myelosuppression.[6] High-dose MTX related-kidney damage, which can occur due to precipitation of MTX crystals and tubular damage, is very rare with chronic low-dose therapy. In a study of twenty-one RA patients receiving a standard 7.5 mg dose of weekly MTX and concomitant NSAID therapy, no differences in area under the serum concentration versus time curve (AUC), time to maximal MTX concentration (Tmax), or maximal MTX concentration achieved post-dosing (Cmax) were observed over a 2 year period. Creatinine clearance decreased significantly after 6 months of treatment.[26]

When the cases with CKD published in the literature are evaluated, it is seen that after multiple doses or prolonged use of MTX, patients develop bicytopenia or pancytopenia (*Table 1*).[5,23,27-38] However, similar to our cases, pancytopenia has rarely been reported after a single dose of MTX (*Table 2*).[18,40-42] 16 (7 females, 43.8%) of 24 patients with CKD who developed bicytopenia or pancytopenia received multiple MTX doses, while

8 (4 females, 50%) received a single dose of MTX. Median ages [54 (range: 22-68) vs. 60 (range: 21-76) years, respectively], gender distributions and dialysis modalities between singledose and multiple-dose MTX groups were comparable. One of our patients was stage 3 CKD, 17 out of 24 patients were on maintenance hemodialysis and 6 were on peritoneal dialysis. Depletion of folate prior to the initiation of MTX and the lack of folate supplementation may have contributed to bone marrow toxicity in some patients.[27] If the mean corpuscular volume (MCV) is above 94 fl during MTX treatment, hematological toxicities may be predicted in some patients. Co-administration of MTX with low-dose oral folic acid (5 mg/day) can sometimes reduce the incidence of myelosuppression. However, leukopenia may occur despite folic acid or folinic acid supplements in uremic patients receiving long-term low-dose MTX, and folate supplement may not reduce the risk of hematological toxicity and the possibility of discontinuation of treatment.[28,39] None of those receiving a single dose of MTX received folic acid or calcium folinate supplements before treatment. Only 6 of those receiving multiple doses of MTX received pre-treatment supplement. None of our patients used folic acid before MTX.

In patients with MTX-induced pancytopenia, oral mucositis and fever are the common symptoms at presentation, similar to our cases (*Tables 1 and 2*). These symptoms should alert the clinician to suspect neutropenia. Non-survivor uremic patients with pancytopenia had lower nadir leukocyte counts and higher MTX levels than those of survivors. The highest methotrexate level leads to more severe bone marrow toxicity and the lowest leukocyte count and may worsen the prognosis.[32] The median cumulative MTX dose in multiple-dose MTX group was statistically insignificantly higher than that of single dose MTX group [15 (range: 7.5-100) vs. 7.5 (range: 2.5-25) mg, respectively, p=0.053]. However, the cumulative dose of 3 patients was not reported. After developing MTX toxicity, 12 of 24 patients had MTX concentration measured at different times. Different toxicity reference values have been reported in the literature (>0.1, >0.01 or >0.02 μmol/L). In some patients, the MTX concentration was very high (range: 0.06-0.53 μmol/L)1[8,31-33,37,38,41], while in others it was measured normal (0.005 μmol/L)[29] or slightly high (range: 0.02-0.03 μmol/L).[34,36,40,42] In our cases, MTX level could not be measured. Really, myelosuppression may become evident in the setting of prolonged elevated serum levels of MTX. Mortality rates of single dose (n=3, 37.5%) and multiple-dose (n=4, 25%) MTX groups were similar. The main cause of death in pancytopenic patients with CKD was sepsis and multiple organ failure. In analysis of 25 cases with MTX-induced pancytopenia between 1999 and 2004, the severity of pancytopenia correlated with MTX dose. 32% (n=8) of the patients had impaired renal function, and the mortality rate was 28%.[24]

Currently, MTX use is controversial in dialysis patients, even at a low dose. Stage 2 CKD is not associated with increased toxicity.[43] A significant reduction of MTX clearance is observed in patients with stage 3 CKD. However, no prediction for the individual patient is possible due to the wide variation in pharmacokinetics.[44] Peritoneal dialysis, conventional hemodialysis, hemoperfusion and plasmapheresis have been reported to have little effect on the removal of polyglutamated MTX metabolites within cells in MTX intoxication.[5,18,29,45,46] Hemodialysis and hemoperfusion methods can effectively remove approximately 50% of MTX that binds to proteins. However, with a post-dialysis rebound, MTX concentration returns to 90-100% of its level prior to the procedure.[29] While plasma MTX concentrations can be reduced by 26% by plasma exchange or exchange transfusion, hemodiafiltration can decrease its concentrations by 82% over 3 days.[36] Diskin et al[33] reported that the clearance of MTX on peritoneal dialysis was less effective than that on hemodialysis. In contrast, high flux hemodialysis reduced plasma MTX concentrations by 75.5% within 4-12 hours.[47] In another study, serum levels of MTX have been shown to be efficiently reduced by high-flux hemodialysis dialyzers of 92.1±10.3 mL/min.[48] Intensive-cycler peritoneal dialysis and high-flux hemodialysis are potential options for effective removal of MTX.[49] However, the possibility of removing the drug in the case of toxicity may still be limited.[50] We did not change the current dialysis treatment modalities in both of our patients. In the presence of advanced renal failure and dialysis patients, even at low doses, MTX has a higher risk of toxicity due to higher plasma levels and longer half-lives. MTX can be detected even up

Table 1. The characteristics of patients with chronic kidney disease (CKD) who developed pancytopenia after single dose methotrexate (MTX)

Ref.	Age, sex	CKD stage (duration) and co-morbidities	MTX Endication	MTX (Dose/duration/cumulative dose)	Folic Acid	Clinical findings	WBC/PNL (cells/µL)	Outcomes
27	49, M	Stage 5-HD, DM, HT	Myositis	IV weekly/2 doses/-	No	pharyngitis, oral mucositis, loose stools, fever, normal platelet	900/330	Improved
27	52, M	Stage 5-HD, DM, HT	Myositis	2.5 mg/wk, IM, then 5 mg/wk/-/-	Yes	pneumonia, sepsis	2,200/-	Improved
27	61, F	Stage 5-HD, DM, HT	Psoriasis, PA	2.5 mg/wk, PO, single dose, stop due to nausea and ~1 month later; 2.5 mg/wk, IM/2 doses/7.5 mg	No	sore throat, fever, sepsis	50/0	Died
30	60, F	Stage 5-HD, DM, HT	RA	5 mg/wk, PO/2 doses/10 mg	No	diarrhea, buccal ulcerations (4 days after 2nd dose)	1,300/66	Improved
5	74, F	Stage 5-HD, amyloidosis	RA	5 mg/wk, PO/two doses/10 mg (interval of 5 days)	No	stomatitis with multiple ulcerations (1 day before 2nd dose), fever	1,700/306	Improved
23	64, M	Stage 5-PD	Psoriasis	-/-/35 mg	No	mouth ulceration, fever, oropharygeal ulceration, normal platelet, invasive pulmonary aspergillosis after resolution of neutropenia	300/0	Died
33	60, M	Stage 5-PD (14 months), HT, CAD, emphysema	RA	10 mg/wk, SC/2 doses/20 mg	No	nausea, hematemesis, stomatitis, anorexia, odynophagia, septic shock	700(300)/-	Died
28	33, F	Stage 5-PD (5 years), lupus nephritis	Intractable arthritis	5 mg/wk, PO/4 doses/25 mg	Yes	mucositis, tachycardia, general weakness, chest discomfort, respiratory distress, anemic appearance, leg edema	1,500/960, after 5 days 600/90	Improved
34	66, M	Stage 5-HD, HT	psoriasis, PA	5 mg/wk, PO/2 doses/10 mg	Yes	nausea, severe sore throat, low-grade fever, toxic erytrodermia, oral mucositis, buccal ulcerations, liver toxicity, oesophagal candidiasis	-/70	Improved
35	55, F	Stage 5-HD (7 years)	RA	7.5 mg/wk, PO/12 doses/90 mg	Yes	fever, general fatigue, multiple oral ulcers, erythroderma rash with cutaneous ulceration, carbuncles	630/-	Improved
37	76, M	Stage 5-HD (5 years), HT	Bullous pemphigoid	2.5 mg twice weekly, PO/3 doses/7.5 mg	Yes	pneumonia	550/-	Died
32	61, F	Stage 5-PD (6 years)	Intractable chronic eczema	7.5 mg/wk, PO/2 doses/15 mg	No	general malaise, stomatitis, fever, sepsis	30/-	Improved
38	21, F	Stage 5-HD (9 years), hypovolemic shock	Ectopic pregnancy	100 mg, IV	No	fever, sore throat, mouth, pruritis, diffuse maculopapular rash on face and body surface, oral thrush, mucositis, mild trismus	730/20	Improved
31	48, M	Stage 5-HD (5 years)	Bullous pemphigoid	10 mg/wk, PO/2 doses/10 mg	yes	acute shortness of breath, non-productive cough, fever, MTX pneumonitis	1,800/-	Improved
36	46, M	Stage 5-HD (12 years), glomerulonephritis	RA	-	No	epigastric pain, nausea, diarrhea, pneumatosis intestinalis	690/-	Improved
29	68, M	Stage 5-PD (3 years)	Granulomatosis with polyangiitis	7.5 mg, PO/2 doses/15 mg	No	odynophagia, asthenia, adynamia, bleeding from gums, oral ulcers, painful skin lesions, fever, necrotic lesions on the lower lip, ulcers on the cheeks, aphthae on the tongue, erythematous macules, mucosal membranes lesions, septic shock	1,300/182	Improved

WBC: leukocyte, PNL: neutrophil, F: female, M: male, HD: hemodialysis, PD: peritoneal dialysis, DM: diabetes mellitus, HT: hypertension, CAD: coronary artey disease, RA: rheumatoid arthritis, PA: psoriatic arthritis, IV: intravenously, IM: intramuscular, PO: orally, SC: subcutaneously.

Table 2. The characteristics of patients with chronic kidney disease (CKD) who developed pancytopenia after single dose methotrexate (MTX)

Ref.	Age, sex	CKD stage (duration) and co-morbidities	MTX endication	MTX dose	Clinical findings	WBC/PNL (cells/µL)	Outcomes
18	52, F	Stage 5-HD	RA	2.5 mg, PO	Fever, pharyngitis, stomatitis-oral ulcerations, rash, bacteremia, a large subdiaphragmatic abscess at autopsy	500/120	Died
18	47, F	Stage 5-HD, scleroderma, Raynaud's phenomenon, renovascular HT	polymyositis	2.5 mg, PO	Fever, pneumonitis, normal platelet	1,500/495	Improved
40	57, M	Stage 5-HD	RA	5 mg, PO	Fever, stomatitis with multiple ulcers, fatigue, sepsis, jaundice	100/-	Improved
41	56, M	Stage 5-HD (7 years), IgA nephropathy, chronic hepatitis C infection	Pustular psoriasis, PA	2.5 mg, PO	Fever, deranged liver function, paroxysmal supraventricular tachycardia, acute coronary syndrome	500/-	Died
42	68, M	Stage 5-PD, HT, nonischemic cardiomyopathy, pulmonary HT, wandering atrial pacemaker, mesenteric atherosclerosis	Refractory squamous cell carcinoma of the hands	25 mg, IL	Nausea, general malaise, shortness of breath, pustular hand lesions, mucositis, deranged liver function, fever	1,300(600)/-	Improved
*	58, F	Stage 3	RA	12.5 mg, PO	Abdominal pain, chest discomfort, vomiting, skin rush	1,200/160	Improved
*	43, M	Stage 5-HD (3 months)	Psoriasis, PA	12.5 mg, PO	Diarrhea, anorexia, chills, fever, sepsis, mucositis, hepatotoxicity	3,100/590	Died
*	22, F	Stage 5-HD (13 years)	Psoriasis	10 mg, IM	Fever, vomiting, nausea, diarrhea, epistaxis, stomatitis, sepsis	1,810/390	Improved

* present cases, WBC: leukocyte, PNL: neutrophil, F: female, M: male, HD: hemodialysis, PD: peritoneal dialysis, HT: hypertension, RA: rheumatoid arthritis, PA: psoriatic arthritis, PO: orally, IM: intramuscular, IL: intralesional.

to 3 weeks after taking small doses of 2.5 mg.[29] Therefore, it may not be appropriate to administer MTX therapy in patients with stage 4 and stage 5 CKD.

Conclusion

In our patients with renal dysfunction, MTX-induced pancytopenia developed within a few days after a single dose of MTX administration. Since the mechanisms of action and dose-response relationships are not fully elucidated, there is considerable heterogeneity in RA therapy with low dose MTX.[3] Recently, the 2016 update of European League Against Rheumatism recommendations for the management of RA suggests administering oral or subcutaneous MTX with short-term glucocorticoid initially, if tolerated, rapidly increasing the dose to 25-30 mg per week and evaluating the response to treatment within 8-12 weeks.[51] In patients with normal renal function, the recommended doses are within a range of 5 to 7.5 mg per week. This dose can be increased by steps of 2.5 to 5 mg, up to a maximal dose of 15 mg/week. However, in patients with renal dysfunction, if necessary, the initial weekly dose should be 2.5 mg, and the dose should be gradually increased by 2.5 mg per week by close monitoring of whole blood count. The maximal dose should not exceed 5-7.5 mg. Some nephrologists recommend applying 30% of the routine dosage.[52] The American College of Rheumatology (ACR) recommend that a routine complete blood count should be performed every four weeks during the first three months of therapy, every 8 to 12 weeks from three to six months, and every 8 to 12 weeks thereafter, depending upon the nature and/or severity of abnormalities noted during monitoring.[53] Folic acid (1 mg/day) or folinic acid (2.5 mg/week) supplement may be beneficial in all patients receiving MTX, especially those with MCV >100 fl. These low doses does not interfere with the beneficial effects of MTX.35 If bone marrow toxicity is suspected, MTX treatment should be terminated immediately and the patient's clinical findings should be closely monitored. In fact, if the estimated creatinine clearance is below 30 mL/min, it would be more appropriate to prefer alternative treatments due to the risk of life-threatening myelosuppression.

Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CASE REPORT

A Case Report of Cutaneous and Systemic Lupus Erythematosus After Bupropion Usage

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Abstract

Bupropion is a drug used to smoke cessation. Various complications have been reported after using this drug. In a 58-year-old female patient, skin findings and anti-Ro52 positivity developed after the use of this drug. Later, signs of vasculitis appeared under immunosuppressive therapy. The patient was diagnosed with cutaneous and systemic lupus erythematosus.

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Introduction

Approximately half of the patients with subacute cutaneous lupus erythematosus (SCLE) meet the 1997 American College of Rheumatology (ACR) classification criteria for systemic lupus erythematosus (SLE). However, subsequent studies have demonstrated that 10 to 15% of patients with SCLE develop severe central nervous system or kidney clinical symptoms due to SLE involvement.[1] There is a strong association between SCLE, human leukocyte antigen (HLA)-DR3, antibodies to Ro/SSA, and polymorphisms in the tumor necrosis factor (TNF)-alpha promoter gene. Anti-Ro/SSA antibody is positive in 80% of SCLE patients.[2,3] Many classes of drugs have been implicated in SCLE, including antihypertensive drugs, lipid-lowering agents, proton pump inhibitors, antifungal agents and TNF-alpha inhibitors.[4-8] Bupropion is a monocyclic antidepressant drug associated with phenylethylamines (amphetamines). The slow-release formula is used in the treatment of nicotine addiction. The most common side effects are dose-dependent seizures, abnormal liver function, and urticaria.[9-11] Herein we presented a case of cutaneous and systemic lupus erythematosus which is associated with bupropion usage.

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Case Report

A 58-year-old woman who was on 300 mg/day bupropion treatment for 4 days for smoke cessation complained of widespread muscle and joint pain, dry mouth, discoid rashes on hands, arms and legs. Prednisolone and azathioprine were started with the diagnosis of SCLE by skin biopsy. Azathioprine was discontinued because of leukopenia. The patient was referred to our center for further evaluations and treatment. In the initial physical examination, body temperature was 36.8^{0}C, blood pressure was 110/70 mmHg, respiratory sounds were coarse. There was bilateral hyperemic rash in the lower extremities and tenderness in her knees and ankles. In the laboratory tests the complete blood count (CBC) and urine analysis were unremarkable. Erythrocyte sedimentation rate (ESR) was 60 mm/hour. Viral serological tests for herpes simplex virus, Ebstein Barr virus, cytomegalovirus, hepatitis B, hepatitis C and human immunodeficiency virus (HIV) infections were negative. C-reactive protein (CRP) was 1.29 mg/dL and procalcitonin was negative. Complement levels were in normal ranges and direct-coombs test was negative. The anti-nuclear antibody (ANA) was positive at 1/100 titration end-point, anti-Ro52 was positive. Anti-histone, anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) were negative. Pathergy test was negative. Thorax computed tomography due to dyspnea and hypoxia did not have evidence of pulmonary embolism, but both lungs had ground-glass opacities, thickening of the interlobular septa, and occasionally enlargement of the small airways. In the pulmonary function tests and carbon monoxide diffusion test (DLCO), forced vital capacity (FVC) was 1,340 mL, and forced expiratory volume (FEV-1) was 1,030 mL and DLCO was low. It was considered that pulmonary findings were due to rheumatologic disease involvement. The ophthalmological examination revealed no vasculitis findings like uveitis.

Consequently, drug-related lupus-like syndrome associated with bupropion was considered with the complaints of discoid rashes, myalgia, arthralgia and laboratory findings of positive ANA and anti-Ro52 tests, and elevated ESR. She was discharged with a daily dose of 20 mg prednisolone. The patient was admitted with steroid-induced hyperglycemia 20 days after the discharge. Her serum glucose level was 350 mg/dL and HbA1C was 6.5%. A basal-bolus insulin therapy was started with a dose of 10 units insulin aspart at three times a day preprandially and 12 units of insulin glargine once as basal treatment. The patient was receiving 15 mg of prednisolone treatment daily. After 4 months, the patient was re-admitted to the hospital with the complaint of discharge from hyperemic necrotic lesions on the elbows and fingers, while prednisolone treatment continued. The patient was diagnosed with lupus-related vasculitis. The patient used 3 cycles of cychophamide and mycophenolate mofetil for 3 months. Then 4 doses of rituximab were given once a week at a dose of 375 mg/m^2. The discharge at the elbow completely resolved. However, two fingers of her left hand were amputated due to circulatory failure. Prednisolone and hydroxychloroquine were given as maintenance therapy. After 2 years, prednisolone treatment was discontinued. The clinically stable patient is still monitored only by hydroxychloroquine treatment.

Discussion

Certain drugs may trigger an autoimmune response; most often, these drugs induce autoantibodies, which may occur in a significant number of patients, but most of these patients do not develop signs of an autoantibody-associated disease. In some patients, a clinical syndrome with features similar to SLE may develop, which is defined as drug-induced lupus.[12] Drug-induced lupus has similarities to spontaneous SLE, but there are some differences in clinical and immunologic features and in the frequency of such features. It is important to know the differences between drug-induced SCLE and drug-induced SLE.[13] Although there were several systemic findings such as arthralgia and myalgia seen in SLE during this period, drug-induced lupus-like syndrome was primarily considered in our patient. Medications identified as definitely causing drug-induced lupus include procainamide, hydralazine, minocycline, diltiazem, penicillamine, isoniazid, quinidine and anti-TNF alpha therapy (most commonly with infliximab and etanercept), interferon-alfa and methyldopa.[14-16] The prognosis of drug-induced lupus is generally quite favorable in most case series and in our experience, with disease typically

resolving after drug withdrawal, even though treatment may be needed for up to several months in some patients.[17-19] Occasional patients require glucocorticoid therapy, but life-threatening disease is infrequent.[20]

Patients with drug-induced SCLE have anti-Ro/SSA antibodies, while patients with drug-induced SLE usually have antihiston antibodies. In our patient, the anti-histone was negative, but anti-Ro52 was positive. In our patient, SLE was diagnosed due to the development of vasculitis under immunosuppressive therapy. In 2004, Jumez et al.[21] reported the first cutaneous lupus erythematosus case that worsened with bupropion therapy, and then Cassis et al.[22] reported another SCLE case caused by bupropion. Recently, a case series of five patients with bupropion-related cutaneous lupus erythematosus have been reported.[23] It is stated in the literature that symptoms appear between 2 weeks and 3 months after the use of bupropion. As in our case, there is no case that starts in a short time. There are no cases of bupropion-induced or aggravated SLE in the literature. Naranjo algorithm score was determined 4 and it can be defined as possible drug adverse reaction. In the literature, SLE rash is more emphasized with active smoking. There are no data in the literature about the relationship between smoking cessation and lupus activation.

Vasculitis develops in approximately 11 to 20% of patients with SLE.[24] The most common form, occurring in 10% to 15% of cases, is urticarial vasculitis. Cutaneous vasculitis was found in 19% to 28% of patients with SLE. Vasculitis may also affect small arteries, possibly resulting in microinfarcts of the tips of the fingers, the toes, the cuticles of the nail folds (splinter hemorrhages), and the extensor surface of the forearm and shin.[25]

Conclusion

The diagnosis of drug-induced lupus should be considered primarily in patients who develop skin findings after the use of bupropion. However, these patients should also be evaluated for possible SCLE, especially if there are some antibody positivity such as anti-Ro52. The appearance of vasculitis findings in our patient during the period of immunosuppressive therapy supported the presence of SLE. As a result, the use of bupropion during smoking cessation therapy may increase disease activity or cause the disease to become evident, especially in patients with SLE.

Conflict of Interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Letter to Editor

Health & Safety and Public Health on Board Vessels During New Coronavirus Outbreak (2019-nCoV)

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Abstract

Passenger and cargo unit transportation and harvesting fish stock are the lifebloods of global economy. 90% of global trade by volume is carried on across the world by ships. 30 million passengers are transported on 272 cruise liner worldwide each year. Fish is an important source of protein for people. Estimated 2 million seamen who work on board vessels as seafarer and 27 million fishermen who work on commercial fishing vessels to capture fish stocks. The recent coronavirus pandemic disease (COVID-19) has shown that maritime and commercial fishing industry are a critical working environments and seafarers and fishermen are also a critical skills and professions. In this comment, the importance of marine medicine during COVID-19 pandemic and developing on maritime medicine and introduction of newly established departments in University of Health Sciences, Turkey are tried to be discussed.

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Keywords: *Maritime Medicine, Seafarer, Fisherman, new coronavirus, Ship, COVID-19*

Approximately 90% of global trade by volume is carried on across the world by ships. Additionally, apart from good and cargo transportations in maritime sector, an estimated 30 million passengers are transported on 272 cruise liner worldwide each year. Seafood is an important source for human being and fish is an important source of protein for mankind. Fishing has a tremendous economic importance, providing a major food source of all world population. Approximately 2 million seamen who work on board vessels and an estimated 27 million fishers who work on commercial fishing vessels to capture fish stocks.[1] The recent coronavirus epidemic disease (COVID-19) has shown that maritime and commercial fishing industry are a critical working environment and seafarers and fishermen are also a critical skills and professions. Turkey is a port, flag and coastal state.[2]

Transport by sea and commercial fishing which are the lifebloods of global economy, COVID-19 has shown the importance of maritime and commercial fishing industry. In this respect, continuous free movement of fishers and seafarer on working vessels and free passage across borders are taken as a basis even in COVID-19 pandemic.[3]

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Ships in general as a working environments, bring many seamen, fishers and passengers together in semi enclosed spaces such as cabins, messrooms, restaurants, bars, may facilitate transmission of respiratory diseases.[4] Many operational guides have been prepared by World Health Organization (WHO) after COVID-19. These guides are for any authority which is related to public health response to any event onboard ships and ports such as port and border health authorities (General Directorate of Border and Coastal Health), port authorities, harbor masters, ship operators and owners and also ship health officers, doctors and ship crew members.[5,6] The virus named as Novel Coronavirus (2019-nCoV), causes illness which was initially seen in Wuhan city, China, on 31 December 2019. Some confirmed cases of 2019-nCoV have been reported from ships as well during COVID-19 outbreak all over the world.[7] The coronavirus COVID-19 is affecting 213 countries and territories around the world. Two passenger cruise liners named Diamond Princess and MS Zaandam on international shipping trade by date 06 June 2020 were also affected.[8] This situation showed that seafarers, crew and passengers are at greater risk for severe consequences of 2019-nCoV disease. First cases were reported from cruise liner ship Diamond Princess which was in Japan. During 2019-nCoV outbreak cases reported not only from Diamond Princess but also from different types of ships such as RO-RO/Passenger. Ship named El. Venizelos is chartered to use as a hostel ship for workers and seafarers in Spain. Some Turkish workers and seafarers were also embarked on board in Turkey. Later ship started to sail for Spain. When the ship was on the way, 2019-nCoV spreaded worldwide. Spain was badly affected from 2019-nCoV. No permission was given to berth to the port for El. Venizelos due to the spread of 2019-nCoV in Spain. El. Venizelos started to return to Turkey. COVID-19 was first identified on board vessel El. Venizelos while ship was at sea en route. Ship came back to Turkey to leave Turkish seafarers and workers. Due to safety issues the master of the ship did not allow the crew and workers to disembark from the ship. Later the ship sailed for the next port of call which was in Greece. Two persons were disembarked from the ship for hospitalization. Greek authorities reported COVID-19 diagnosis in 121 personnel who were the crew and workers and the ship was quarantined. 65 cases out of total 121 cases were Turkish crew and workers. Personnel whose COVID-19 test results were positive, were quarantined in different cabins on board vessel as shown in figures (*Figures a and b*).[9-12] Crew and workers whose test results were negative, disembarked from the ship and placed to hotels ashore. Apart from this, 4 crew members with coronavirus symptoms who were working on Turkish aircraft carrier were disembarked for hospitalization from the ship in Turkey. Ship was trading regularly en route between Turkey and Italy. One out of four crew had a positive test result.[13]

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Figure a: Quarantine on board for seafarer

Figure b: Ship is lying in port

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