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INVITED REVIEW

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THROMBOTIC EVENTS IN INFLAMMATORY RHEUMATOLOGICAL DISEASES

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Abstract

Active inflammation is a prothrombotic state characterized by the activation of procoagulant mechanisms and endothelial cells. In fact, the correlation between antiphospholipid antibodies in systemic lupus erythematosus (SLE) and the predisposition to venous and arterial thrombosis is known. Thus, it appears that thrombotic events are associated with disease activity and/or inflammation in many inflammatory rheumatic diseases. The present study is a review of the main pathogenetic features and clinical aspects of thrombosis in inflammatory rheumatic diseases, SLE, rheumatoid arthritis, vasculitis, Sjögren's syndrome, and dermatomyositis/polymyositis, highlighting the appropriate therapeutic approaches in each case. Therefore, it appears that inflammatory rheumatological diseases are associated with an increased thrombotic risk and predisposition to arterial and venous thrombosis, greater than that in the general population.

Keywords: Thrombosis, autoimmune diseases, systemic erythematosus lupus, rheumatoid arthritis, vasculitis, Sjögren's syndrome

INTRODUCTION

Thrombosis is a multifactorial disease resulting from the confluence of inherited, acquired, and environmental risk factors. These factors may contribute to a part of Virchow's triad, which is used to explain the pathophysiology of venous thrombosis. This triad consists of impaired blood flow (stasis), hypercoagulability of blood components, and damage to the inner wall of blood vessels (endothelial damage) (1). Inflammation is a key feature of systemic autoimmune diseases. Many studies have been conducted to establish the relationship between inflammation and the hypercoagulable state or between inflammation and endothelial dysfunction.

Mechanisms linking inflammation and thrombosis: There are three main natural anticoagulation mechanisms: the tissue factor (TF) inhibitor, the heparin-antithrombin III pathway, and the protein C anticoagulant pathway (2). These mechanisms exert a strong anticoagulant effect under physiological conditions. However, inflammation can disrupt this balance and induce a predisposing state for thrombosis through several different mechanisms.

Active inflammation: It is a prothrombotic state characterized by upregulation of tumor necrosis factor-α (TNF-α) and endothelial cell activation. Upregulation of TNF-α is thought to increase serum TF levels, a natural procoagulant mechanism. In addition, endothelial cell activation promotes platelet activation, which is important for thrombus formation (3). In patients with rheumatoid arthritis (RA) and ankylosing spondylitis, inhibition of TNF-α decreased plasminogen activator inhibitor-1 (PAI-1) and

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decreased the PAI-1/t-perimeter area ratio (PA ratio). This means that TNF-α is probably involved in inhibiting the fibrinolytic system in patients with chronic rheumatic diseases.

TNF-α receptor (TNFR) subtypes may play an important role in thrombogenesis. TNFR1 is ubiquitously expressed, whereas TNFR2 is predominantly expressed in immune and endothelial cells. In a mouse study, the time to complete thrombotic arterial occlusion followed by vessel wall injury was accelerated in TNFR1-deficient mice but not in TNFR2-deficient or TNFR1/TNFR2-deficient mice when TNF-α was administered. This suggests that a TNF-α-induced hypercoagulable state requires TNFR2 (4).

As mentioned, there is an association between TNF-α inhibitors and thrombosis. TNF-α is an inflammatory cytokine involved in the pathogenesis of various inflammatory conditions. Although the exact relationship between TNF-α and thrombosis has not been fully elucidated, there are reports indicating that TNF-α inhibitors may increase the risk of thrombosis in some patients.

MATERIAL AND METHODS

Purpose of review: The aim of this review was to identify the clinical aspects of thrombosis in autoimmune rheumatic diseases, highlighting the possible pathogenic mechanisms, frequency of thrombotic events, and appropriate therapeutic approaches in each case.

Search strategy: We performed a literature search of English-language publications related to thrombotic phenomena in patients with inflammatory arthritis, vasculitis such as Behçet's syndrome (BS), anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, giant cell arteritis (GCA), primer Sjögren syndrome (pSS), and polymyositis (PM)/dermatomyositis (DM). The PubMed database was searched from 2000 to April 2023. All studies that included thrombosis in the context of autoimmune rheumatic diseases were collected. The terms were used as keywords in English "thrombosis or (thrombotic events) and (autoimmune diseases)", "thrombosis and (rheumatological diseases)", "(arterial and venous thrombosis) and (rheumatological diseases)", "thrombosis and (systematic erythematosus disease)", "thrombosis and lupus", "thrombosis and (RA)", "thrombosis and (Sjögren syndrome)", "thrombosis and polymyositis", "dermatomyositis and thrombosis", "pulmonary embolism (PE) and (systematic erythematosus disease)", "PE and lupus", "PE and (RA)", "PE and (Sjögren syndrome)", "PE and polymyositis", "PE and dermatomyositis", "venous thromboembolism (VTE) and (systematic erythematosus disease)", "VTE and lupus", "VTE and (RA)", "VTE and (Sjögren syndrome)", "VTE and polymyositis", "VTE and dermatomyositis", "deep venous thromboembolism (DVT) and (systematic erythematosus disease)", "DVT and lupus", "DVT and (RA)", "DVT and (Sjögren syndrome)", "DVT and polymyositis", "DVT and dermatomyositis", "thrombosis in vasculitis", "thrombosis and vasculitis", "Behçet".

Inclusion criteria: Articles published in English on thrombotic phenomena in adult patients with rheumatological diseases are included. The exclusion criteria included articles dealing with pregnancy-related thrombotic phenomena and postoperative outcomes. Articles published in English were selected, with particular emphasis on review articles, clinical patient studies, and published patient series with a review of the relevant literature. After reviewing the abstracts of a significant number of articles, the most representative ones were selected.

Description of studies: Data from each study were extracted by one investigator. The following information was systematically extracted: first author, year of publication, country where the study was conducted, total number of patients included (cases and controls), total number of thrombotic events observed in each rheumatological disease examined, and the total amount of control patient populations where available. Some studies included multiple patient populations with various rheumatic diseases. Therefore, data for each disease were extracted from these articles and analyzed separately.

RESULTS

Thrombosis in Systemic Lupus Erythematosus (SLE)

Arterial and venous thrombosis are well-known clinical entities in SLE, with a prevalence of >10%. This prevalence may even exceed 50% in high-risk patients (5). A 30-year study of patients with SLE found that 20% of patients f events during disease progression "20.3% 49 thrombotic events, relative risk 9.6 [95% confidence interval (CI) 4.1-27.4, p<0.0001]" (6). The incidence of thrombosis tends to increase during the first year. Possible reasons for this early higher incidence of thrombosis could be high levels of disease activity and circulating immune complexes, cytotoxic antibodies, or a more general inflammatory state. In a 10-year prospective study of patients with SLE, the most common causes of death were active SLE (26.5%), thrombosis (26.5%), and infection (25%), with thrombosis being the second most frequent. Bello et al. (7) showed that patients with SLE have a statistically significantly increased risk of DVT compared with the general population (relative risk 4.38). In fact, VTE cases concern younger patients than the general population, and the frequency of episodes is even higher in positive antiphospholipid antibodies (aPL).

Antiphospholipid antibodies: Thirty percent of SLE cases have positive aPL (8). aPL binds to plasma proteins with affinity for surface phospholipids. The most important recognized antigens are β2-GP (GP) and prothrombin. Anti-centromere antibodies (ACA), Anti-La antibodies (LA), and anti-β2-glycoprotein I antibodies have been confirmed to increase the risk of thrombosis from the very first studies in SLE (9). In Bello's et al. (7) study, the incidence of thromboembolic events in SLE patients with positive aPL was estimated to be 0.13 (n/N, 95% CI 0.07-0.21) and in SLE patients without positive aPL was 0.07 (n/N, 95% CI 0.04-0.10). aPL may be transiently positive. 50% of patients with SLE show positive aPL. To be considered significant, they should be persistently positive on at least two occasions, 12 weeks apart. Not all patients with aPL develop thrombosis, which could be explained by different phospholipids or different binding proteins. Several hypotheses have been proposed to explain the pathogenic effects of these auto antibodies and their role in the development of thrombosis. They attach to the negatively charged surface of phospholipids, which can cause platelet activation, interfere with coagulation inhibitors such as protein C, inhibit antithrombin and fibrinolysis, and initiate thrombus formation. They are related to both arterial and venous thrombosis. However, approximately 40% of adults with SLE who are not positive for aPL may develop thrombosis, which means that other clotting factors, such as homocysteine levels, protein C and S, ANCA, and neutrophil intracellular traps (NETs), play an important role in the manifestation of thrombosis (10).

The prevalence of LA and ACA titers for SLE is 28% and 42%, respectively. Of the abovementioned patients, 42% of LA-positive patients and 40% of ACA-positive subjects had a history of thrombosis. In contrast, the prevalence of thrombosis in patients without ACA or LA is only 10-18% (10).

Inflammatory disease activity-coagulation activation: Inflammation induces the expression of TF, an important step in the initiation of coagulation. Therefore, vasculitis mediated by immune complexes and chronic destruction of the vessels is caused. Consequently, inflammation of endothelial cells leads to thrombosis (10). Deposition of immune complexes on the vascular endothelium can lead to increased surface factor expression, increased thrombocytes, and activation of plasminogen inhibitor I. Thus, activation of the coagulation pathway is consequential. If vessel damage is present, vasoconstriction occurs as a critical initial response, causing a reduction in vessel diameter and slowing the flow of blood, which is the hemodynamic basis for subsequent hypercoagulable processes. Circulating blood cells and endothelial cells lining blood vessels generally do not express TF and are exposed to blood after vascular injury. At the same time, when the endothelium is damaged, the underlying collagen is exposed to circulating platelets, which activate the intrinsic coagulation pathway. Circulating platelets directly adhere to collagen via GP Ia/IIa surface receptors. This adhesion is further enhanced by von Willebrand factor (vWF) released by vascular endothelial cells and platelets. These interactions also activate platelets. Activated platelets release ADP, serotonin, platelet-activating factor, vWF, and thromboxane A2 into the plasma, which activates additional platelets. Fibrinogen binds to GP IIb/IIIa, which contributes to the aggregation of adjacent platelets, increasing the risk of thrombosis (8).

Neutrophil intracellular traps: Activated neutrophils may release NETs during a distinct form of cell death, termed NETosis. NETs are rich in bioactive molecules that promote thrombosis (including atherothrombosis), inflammation, and fibrosis. Thus, although neutrophils may not be present in chronic inflammatory lesions, their remnants may enhance the inflammatory response beyond their short lifetime in tissues (11). Neutrophils can cause pathological venous and arterial thrombosis or "immunothrombosis" by releasing NETs, which are networks of chromatin fibers released during neutrophil necrosis. NETs include histones, antimicrobial peptides, and oxidative enzymes such as neutrophil elastase and myeloperoxidase antibodies (MPO) (7). NETs trap erythrocytes and platelets and bind fibrinogen, fibronectin, vWF, and TF, thereby promoting thrombus formation and stabilization (11). Therefore, intervening NETs could be a potential target for anticoagulant therapy.

Anti-endothelial cell antibodies: Anti-endothelial cell antibodies (AECAs) are antibodies, parts of immunoglobulin A, G, or M, that bind to antigens through the F (ab) domain. AECAs are a heterogeneous group of autoantibodies that can react with different antigenic structures associated with endothelial cells, such as heparin-like compounds, DNA and DNA-histone complexes, ribosomal proteins PO and L6, elongation factor 1a, fibronectin and β2-GP I, thereby promoting the production of TF and leading to vascular damage (Figure 1). The presence of AECA has been associated with renal involvement, vascular lesions, pulmonary hypertension, ACA, and thrombosis in SLE (7).

ANCA is a class of autoantibodies responsible for causing systemic vascular inflammation by binding to target antigens on neutrophils. Several studies have shown that ANCA can activate neutrophils that adhere to the endothelium of blood vessels and release reactive oxygen species, nitric oxide (NO), and inflammatory cytokines [TNF-α, interleukin (IL)-1β, IL-8 and IL-12]. Toxic substances (serine proteases) and NETs, which result

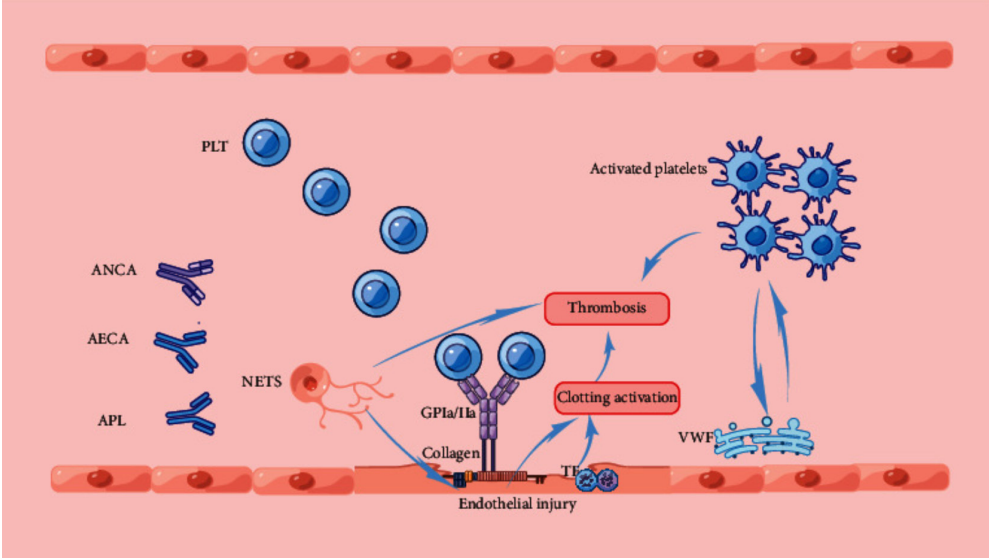

Figure 1. When endothelial cells are destroyed by autoantibodies (ANCA, AECA, aPL) and neutrophil extracellular traps, collagen and TF are exposed in the circulating blood, activating the coagulation cascade. Circulating platelets directly adhere to collagen via glycoprotein Ia/IIa surface receptors. This adhesion is further enhanced by the release of vWF from damaged vascular endothelium and activated platelets. These interactions further activate platelets, ultimately increasing platelet aggregation and thrombosis
ANCA: Anti-neutrophil cytoplasmic antibody, AECA: Anti-endothelial cell antibody, aPL: Antiphospholipid antibodies, vWF: von Willebrand factor

in vascular endothelial injury in small blood vessels and activate the coagulation pathway (7,12).

Protein C and S: Protein C, protein S, and antithrombin deficiencies are rare but carry a higher risk of venous thrombosis (10). Disorders of the protein C pathway in SLE have received much attention recently. Antithrombomodulin antibodies interfere with activated protein C (APC) and aPL interfere with the protein C pathway, leading to an increased risk of thrombosis (13). LA also increases APC resistance (APC-R). APC-R is defined as a reduced anticoagulant response in the protein C pathway. Hereditary APC-R caused by the factor V Leiden mutation is strongly associated with an increased risk of VTE. Although APC-R increases the risk of venous thrombosis, it remains unclear whether it increases the risk of arterial thrombosis (7).

Homocysteine levels: Plasma homocysteine levels are independent risk factors for atherosclerosis, arterial thrombosis, and possibly venous thrombosis. Elevated plasma homocysteine levels may occur because of vitamin B12, B6, or folate deficiency, chronic renal failure, hypothyroidism, certain malignancies, medications, and inherited enzyme abnormalities. The prothrombotic activities may be attributed either to a direct toxic effect on the endothelium or to indirect effects. Hyperhomocysteinemia is detected in approximately 15% of patients with lupus. The prevalence of hyperhomocysteinemia is significantly higher in patients with SLE and thrombosis. Elevated homocysteine levels were demonstrated in 27.3% of SLE patients with thrombosis compared with 16.9% of those without thrombosis (10).

Treatment strategies for thrombosis in patients with SLE: In recent decades, the treatment of SLE has shifted from the use of hydroxychloroquine, glucocorticosteroids (GC), and conventional immunosuppressive drugs to biological agents, among which golimumab is the first and only biological agent approved for the treatment of SLE to date. Because of the application of biological agents, the prognosis of patients with SLE has improved significantly. However, as patient survival has increased, the incidence of complications such as thrombosis has increased (7). Treatment strategies focus primarily on controlling disease activity while minimizing the accumulation of damage associated with active disease and drug-related adverse effects. Anticoagulants are used to treat thrombotic episodes. Concomitant initiation of heparin (either intravenous or subcutaneous) is recommended, and oral anticoagulants should be started at the same time (10). Heparin administration is usually continued for 3-5 days to achieve the corresponding therapeutic international normalised ratio range. If intravenous heparin is used, activated partial thromboplastin time (APTT) is used to monitor the response to establish effective heparinization. However, APTT may be prolonged in the presence of LA in the blood. Duration of treatment can be determined by

the presence of aPL, site of thrombosis, recurrence, and presence of precipitating factors. Derksen's study concluded that the probability of no recurrence in patients taking oral anticoagulants at eight years was 100%, whereas in patients who discontinued anticoagulants, the recurrence rate was 50% at 2 years and 78% at 8 years of follow-up (7).

Thrombosis in Antiphospholipid Syndrome

The exact incidence of antiphospholipid syndrome (APS) in the general population is not known. The prevalence of the syndrome is 40-50 cases per 100,000 people. The presence of aPL in the general population varies between 1% and 5%. However, only a minority of individuals with positive aPL will develop clinical manifestations of the syndrome. The clinical significance of the presence of aPL in the younger population, who have not developed vascular manifestations, is not known. In SLE, aPLs are frequently detected, with at least one aPL test positive in more than 30% of patients (14).

Thrombotic manifestations in APS: Venous thrombosis is more common than arterial thrombosis. Arterial thrombosis mainly involves the central nervous system (CNS) with manifestations of cerebrovascular events. Thrombosis can occur in any organ, be deep or superficial, affect the upper or lower limbs, the lungs, or be located in unusual places (intra-abdominal, etc.).

Thrombotic episodes in APS are recurrent and usually have the same distribution as the initial episode. Therefore, patients with venous thrombosis have recurrences from the venous system, whereas patients with arterial thrombosis have recurrences from the arterial circulation system. The heterogeneity in the clinical expression of the syndrome is due to a combination of vaso-occlusive events, characterized by PE, cerebrovascular strokes, and DVT. Even events from different organs were observed in the same patient, with the time window between the events varying from weeks to months or even years (15).

Therapeutic approach: The therapeutic approach is based on direct oral anticoagulants (DOACs), which remain the basis of treatment and secondary prevention. Although current evidence is insufficient to make recommendations, if the choice of anticoagulant falls within a DOAC, dabigatran may be preferred over the other anti-factor Xa Assay (Heparin Assay) DOAC (16).

Thrombosis in RA

A Swedish prospective nationwide follow-up study showed that Swedish patients with RA had an increased risk of DVT, which was consistently elevated for the first 10 years after diagnosis. The incidence rate of PE appears to be 6.38 within the first year after diagnosis and 1.53 within the first 1-5 years of follow-up, decreasing to 1.15 after 5 years. In fact, the risk of thromboembolism was found to be significantly increased in hospitalized patients with RA compared with healthy controls (relative risk: 2.25) and appears to be independent of classic risk factors for venous thromboembolic disease (17).

Pathophysiological mechanisms: RA results in the generation of autoreactive T and B cells, leading to immunosuppression. The presence of autoantibodies against citrullinated peptides and immunoglobulin G (rheumatoid factor) leads to the formation of immune complexes and abundant complement activation. A key inflammatory cascade is the overproduction of TNF-α and IL-6. Cataracts create excess fibrin, and the typical disease processes are due to the interaction of fibrin thrombi with the endothelial cells of the vessels. The etiology of thrombotic propensity in RA remains unclear due to various mechanisms and causative factors (18). The factors responsible for the thrombotic tendency of RA are presented below.

Endothelial damage: Recent studies have shown that the disruption of endothelial function in the early stages of the disease due to inflammation leads to endothelial cell activation, altered endothelial permeability, and increased leukocyte and platelet adhesion, which predisposes patients to thrombosis. Endothelial dysfunction is associated with inflammation because endothelial-derived coagulation factors vWF and PAI-1 are increased and may play an important role in both the course of RA and thrombosis (19). During inflammation, monocytes express transcellular adhesion molecules, which are induced by proinflammatory cytokines such as IL-1β, TNF-α, and C-reactive protein. Endothelial dysfunction not only leads to venous thrombosis but also promotes atherosclerosis and predisposes patients to arterial clots (20). Endothelial dysfunction not only leads to venous thrombosis but also affects arteries by accelerating atherosclerosis and promoting arterial thrombosis as well (21).

Hypercoagulability and inhibition of fibrinolysis: Inflammation modulates thrombotic responses by reducing anticoagulants and suppressing fibrinolysis (20). Natural anticoagulants reduce the thrombotic response but may be suppressed by inflammatory mediators. A transmembrane GP synthesized by vascular endothelial cells and distributed on the endothelial cell surface is thrombomodulin, which binds to thrombin and activates protein C. Prothrombotic activities are believed to exert a toxic effect on the endothelium and lead to decreased expression of thrombomodulin. Therefore, the protein C pathway is considered a major target. TNF-α factor specifically decreases thrombomodulin and the endothelial cell protein C receptor, both of which are needed for optimal activation of protein C. Therefore, APC and thus protein S, the other natural anticoagulant, are reduced, increasing the risk of VTE (18).

Thrombin-activated fibrinolysis inhibitor (TAFI) is a proenzyme that activates the fibrinolytic system after activation by factors such as thrombin/plasmin and thrombomodulin. TAFI has been found to be elevated in patients with RA compared with controls, particularly in patients with active inflammation. Therefore, a higher TAFI titer may cause a hypercoagulable state leading to VTE (20).

Viscosity and vascular stasis: Plasma hyperviscosity, which occurs during active joint disease (acute inflammation), is a major predisposing factor for VTE. Similarly, impaired venous blood flow and stasis caused by immobility during critically active disease also predispose patients to VTE (18). In addition, coagulation factor VIII, fibrinogen, and vWF are significantly elevated in inflammatory rheumatic diseases and are known to increase plasma viscosity, which is a risk factor for thrombosis (19).

Therefore, plasma hyperviscosity and venous stasis in patients with RA during acute inflammation are important factors influencing the formation of Virchow's triad, leading to thrombus formation (18). Simultaneously, the immobilization of the patient caused by joint disease further predisposes to DVT (19).

Antiphospholipid antibodies: The presence of positive aPL in patients with RA does not correlate with thrombosis or other clinical features of APS. LA is poorly described in patients with RA and VTE, and the literature is limited; however, it should be considered as a strong risk factor for VTE (18). In a review published in 2006 by Omair et al. (19), the prevalence of aPL antibodies in patients with RA was 22% in samples of no more than 200 patients, with some studies showing some association, but further investigation is needed.

Treatment of VTE in a patient with RA: The first goal of treatment in patients with RA is to relieve pain and reduce inflammation. The most effective drugs are non-steroidal anti-inflammatory drugs and GC (18).

GC is the mainstay of RA treatment. Efforts have been made to limit their use as bridging therapy or during flare-ups. Their chronic use is still significant but is decreasing over time. Their use increases the risk of VTE 2-3-fold in different patient populations while further increasing endothelial injury by decreasing NO levels and increasing adhesion molecule expression (19).

Pharmacological prophylaxis for VTE

Although patients with RA have a higher rate of spontaneous VTE than the general population, long-term systemic prophylactic anticoagulation is not recommended. However, patients with RA are often exposed to risk conditions for VTE that may require prophylactic anticoagulation. Patients with RA are often referred for total knee or hip replacement. This perioperative situation is generally accepted as a high-risk situation for VTE. However, patients with RA undergoing surgery have an increased risk, similar to that of the general population.

Surgery had the same risk of postoperative VTE (about 1.9%). The situation is different in hospitalized patients. Awareness of the risk of VTE and anticoagulation prophylaxis should be strongly considered in these cases, even if there are still no specific recommendations for the administration of prophylactic anticoagulation in patients with (18).

Therapeutic Approach for VTE in RA Setting

The main treatment for VTE is anticoagulation. In patients with suspected or confirmed VTE, anticoagulation should be initiated as soon as possible and before the results of diagnostic tests. The risk of VTE recurrence decreases rapidly once anticoagulation is initiated. Anticoagulation is preferably initiated using low molecular weight heparine or fondaparinux. Current guidelines recommend that after the first episode, patients need anticoagulation for 3 months. Novel oral anticoagulants are used primarily as first-line therapy because there is no need to perform laboratory testing of their efficacy. It is worth noting that NOACs have never been specifically evaluated in patients with RA; therefore, further studies are needed (18).

Vasculitis

A. Behçet's Syndrome

The pathophysiology of thrombosis in BS is not widely established, but the systemic inflammatory response appears to play an important role. However, it must be emphasized that inflammation and hemostasis are closely related and that the immune system plays a role in the thrombotic process. A generalized disruption of CD4+ lymphocytes, monocytes, and neutrophils and overproduction of Th1 cell-associated proinflammatory cytokines, such as interferon-gamma, TNF-α, IL-1, IL-6, IL-8, and IL-12, have been observed in BS. Th17 cells together with their cytokines, IL-17A, IL-22, TNF-α, also appear to be involved in the inflammatory process, as well as IL-21, which can promote Th1 and Th17 differentiation and suppression of T regulatory cells. All these prothrombotic factors promote thrombotic events in BS (22).

Coagulating mechanism: In BS, the coagulation system can promote inflammation and thrombosis through multiple factors, such as TF, thrombin, and protein C, with accompanying fibrinolysis disorder. Endothelial dysfunction, resulting from immune and inflammatory factors, appears to be a hallmark of

BS and plays a key role in the occurrence of thrombotic events. Decreased production of NO, an important marker of endothelial dysfunction, was observed in some patients with active BS. In addition, high levels of other markers of endothelial damage, such as circulating vWF and thrombomodulin, were found in patients with active BS. Increased levels of vascular endothelial growth factor, which is a marker of angiogenesis, and certain adhesion molecules, such as intercellular adhesion molecule-1 and E-selectin, produced by activated endothelial cells, have also been reported in patients with patients (22).

Venous thrombosis in BS: Thrombosis is the most common vascular event in patients with BS, with a prevalence ranging from 14% to 39%. Venous involvement is characteristically more common, accounting for 75% of all vascular complications. Venous thrombosis occurs more often in men with active disease in the early years, sometimes early after the occurrence of the disease, and tends to recur. DVT and superficial venous thrombosis of the lower extremities are the typical manifestations, but thrombosis can occur anywhere in the venous system and involve atypical sites such as the hepatic veins, superior and inferior vena cava, and brain sinus brain (22). Indeed, the prevalence of Budd-Chiari syndrome because of occlusion of the main hepatic veins, inferior vena cava, or both has an occurrence rate of 3.2% in Behçet's patients. Inferior vena cava thrombosis is often associated with hepatic vein thrombosis (16).

Arterial involvement in BS: Arterial involvement is present in 1 to 7% of patients. The most characteristic arterial manifestations in patients with BS are aneurysms, whereas arterial thrombosis is less frequent. These complications may remain asymptomatic or lead to life-threatening events such as acute myocardial infarction, stroke, mesenteric thrombosis, intermittent claudication, or gangrene of the lower extremities. Arterial occlusions and venous thrombi sometimes coexist in the same patient and may be associated with aneurysms. Thus, the co-existence of thrombosis and aneurysms is a peculiar feature of BS (22).

Treatment: Currently, the management of vascular thrombosis in patients with BS relies on immunosuppressive therapy to reduce vessel wall inflammation. Anti-inflammatory treatments are capable of promoting the rapid and effective regression of vascular lesions and preventing the expansion of thrombosis and its recurrence. European League Against Rheumatism recommendations suggest immunosuppressive therapy with agents such as GC, azathioprine (AZA), cyclophosphamide (CYC), or cyclosporine A (CsA). AZA and CsA along with low-dose GC are usually the first choice for treating DVT and superficial venous thrombosis. CYC is the recommended treatment in patients with BS with arterial involvement. Usually, anticoagulants alone are not recommended in patients with BS. In fact, it is only for CNS venous thrombosis that some recommend anticoagulation, with or without GC. As a general approach in daily practice, life-threatening conditions such as pulmonary artery aneurysms and Budd-Chiari syndrome are treated with more aggressive medical treatments, including cycles of CYC and glucocorticoids (23).

B. ANCA Vasculitis

Endothelial cell dysfunction is characteristic and is likely caused by the interaction between neutrophils (activated by TNF-α and ANCA) and endothelial cells, with subsequent massive oxidative stress ultimately leading to atherothrombotic complications. Activation of circulating factors such as factor VIII further drives the coagulation cascade. The cleavage of prothrombin to thrombin by factor Xa is a critical step leading to the conversion of fibrinogen to fibrin, which forms the bulk of the clot. Clot formation is usually followed by fibrinolysis, which is driven by the conversion of plasminogen to plasmin by the enzyme t-PA in the presence of fibrin, resulting in increased thrombotic activity (12).

Activation of neutrophils: An additional mechanism of neutrophil activation has been described, termed NETosis. Neutrophils are capable of releasing extracellular nucleic acids associated with histones and granule proteins capable of trapping bacterial agents. These NETs have also been implicated in thrombotic events and appear to be a potential bridge between autoimmunity and coagulation. In particular, ANCA-primed neutrophils degranulate and release NETs, which in turn contain MPO and proteinase 3, which act as autoantigens, thus creating a self-reinforcing process (12,22).

Venous thrombosis in ANCA-associated vasculitis: In recent years, evidence has emerged to support an increased incidence of venous thrombotic events in ANCA vasculitis. They were found to have an increased incidence of venous thromboembolism, especially during active disease, which was confirmed by subsequent studies (22).

Arterial involvement in ANCA-associated vasculitis: An increased incidence of arterial events in ANCA vasculitis has been reported. An increased risk of acute myocardial infarction was observed in a Swedish study, particularly in men aged >50 years at the time of diagnosis. Interestingly, this population had an increased risk of acute coronary events in both the early (within 5 years of diagnosis) and late (after 10 years of diagnosis) phases of the disease, suggesting that not only acute but also chronic inflammation may be involved in this process.

Immunothrombosis in the context of coronavirus disease-2019 and ANCA vasculitis: In the context of the ongoing coronavirus disease-2019 (COVID-19) pandemic, thrombotic events occurring due to endotheliitis have been associated with neutrophil activation, resulting in the formation of NETs. The literature studies ANCA vasculitis diagnosed shortly after COVID disease (12).

C. Large Vessel Vasculitis

Venous thrombosis has been poorly investigated. In temporal arteritis (GCA), the incidence rate of venous involvement is estimated to be 13.3/1000/year for VTE and 8.5/1000/year for DVT. In a retrospective study of 909 patients, an increased risk of VTE (both DVT and PE) was observed, particularly in the first year after diagnosis. In addition, in this population, the risk was higher in the first year after diagnosis, suggesting a possible role of inflammation in the pathogenesis of vascular events (22).

A recent prospective study evaluating almost 3500 patients with GCA reported an increased risk of thrombosis, especially in the first month after diagnosis (22).

A recently published comprehensive meta-analysis clearly showed that the use of antiplatelet/anticoagulant therapy is not effective for primary prophylaxis, whereas it could be beneficial as combination therapy with GC in established disease, without an increased risk of bleeding (22).

D. Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a multisystem necrotizing vasculitis of medium-sized arteries that is not associated with glomerulonephritis or ANCA positivity. The results regarding thrombotic events in PAN are conflicting. A study in 285 patients with PAN reported a much lower incidence of VTE compared with ANCA vasculitis, whereas a more recent Swedish population-based study suggested an increased risk of thrombotic events (24).

E. Henoch-Schönlein Purpura

Henoch-Schönlein purpura is a systemic vasculitis of the small vessels that mainly affects children. There are insufficient reports of thrombotic events (25).

F. Kawasaki Disease

Kawasaki disease is systemic vasculitis and represents the most common cause of acquired heart disease in childhood. Sometimes, despite appropriate treatment, coronary aneurysms occur, which could lead to vascular occlusion and consequently myocardial infarction (24).

Retroperitoneal Fibrosis

Retroperitoneal fibrosis is a rare fibroinflammatory disorder characterized by the presence of a retroperitoneal mass, which could be primary or secondary, mainly in neoplastic or infectious diseases. Venous thrombosis can be a symptom of compression of vessels in circular structures in the iliac or inferior vena cava (22).

Dermatomyositis/Polymyositis

The meta-analysis of Li et al. (26) demonstrated that inflammatory myositis is associated with an increased risk of VTE. In fact, an increased risk of VTE was associated not only with PM and DM. Systemic inflammation associated with PM/DM can induce a hypercoagulable state by activating the coagulation machinery, reducing natural anticoagulants, and suppressing fibrinolysis, which leads to thrombus formation. The findings of course, eh are limited because they are based on relatively small samples. A significant association between PM/DM and VTE risk was observed in Caucasians. This relationship cannot be assessed among other populations, such as Asians and Africans, because of a lack of relevant publications on VTE risk. More future studies are needed to determine whether this association is also significant among other populations of different origins (26).

A prospective study conducted in the British Columbia population showed, among 752 cases with inflammatory myopathies, an increased risk of VTE, DVT, and PE in PM and similarly in DM [incidence rate 8.14 (4.62 to 13.99), 6.16 (2.50 to 13.92) and 9.42 (4.59 to 18.70), respectively] and especially in the first year after the diagnosis of the disease, the highest rates of thrombosis were observed. There are plausible mechanisms that explain the increased risk of VTE events. Inflammatory arthritis can affect venous stasis by reducing mobility. Inflammation modulates thrombotic responses by increasing the expression of procoagulant factors such as TF, downregulating natural anticoagulants such as proteins C and S, and suppressing fibrinolysis, all of which lead to a hypercoagulable state. In addition, inflammation can affect the function of the endothelium in both arteries and veins and lead to vessel wall damage (27).

Sjögren's Syndrome

The study by Aviña-Zubieta et al. (21) confirmed the relationship of pSS in 1175 patients and the increased risk of venous thrombosis and specifically for PE, DVT, and VTE compared with the general population of British Columbia, Canada with rates of PE, DVT, and VTE in pSS cases respectively 4.07 (95% CI, 2.04-8.09), 2.80 (95% CI, 1.27-6.17), and 2.92 (95% CI, 1.66-5.16).

In another study conducted by the medical school of Hannover, Germany, the risk of cardiac and vascular events was studied in 312 patients diagnosed with pSS. Initially, it was found that 1/10 (28/312 i.e. 9%) of the patients experienced at least one episode of myocardial ischemia, cerebrovascular stroke, or peripheral arterial disease. It was found that pSS patients with thrombotic complications with CNS symptoms were younger than expected compared with the average age of onset in the German population, and indeed of all ischemic events, 21% of these cases had obvious symptoms of ischemic stroke (i.e. from 9% of all pSS patients). Involving CNS involvement compared with 6/28 (21.4%) vs. 23/284 (8.1%), p=0.021). In addition, almost one-fifth of pSS patients [specifically 61/312 cases (19.6%)] were affected by cardiac events as the risk of myocardial ischemia was significantly higher (28).

The most likely mechanism is that inflammation caused by lymphocytic infiltration contributes to the development of VTE because it activates procoagulant mechanisms, reduces the activity of natural anticoagulant mechanisms, and impairs the fibrinolytic system. This is also consistent with the fact that the risk was found to be higher during the period when the disease is most active and inflammation is less controlled, i.e., immediately after diagnosis (21).

At the same time, the increased concentration of autoantibodies has been implicated in a higher risk of cerebral infarction and venous thromboembolism in patients with pSS who carry higher titers of anti-SSA/Ro and anti-SSB/La antibodies. We observed a higher prevalence of anti-SSB/La positivity in patients with pSS and myocardial infraction (p=0.017). Nevertheless, the association of thrombotic phenomena with pSS is suggestive, as the association with atrial fibrillation or other risk factors was unsought. Knowledge about risk factors may help clinicians identify patients with pSS who are at risk of CVD (28).

DISCUSSION

Patients with inflammatory rheumatic diseases have an increased risk of developing mainly venous and arterial thrombosis. Arterial and venous thrombosis are a well-known clinical entity in SLE, with a prevalence of >10%, and the risk of thrombosis is increased among patients with higher titers of LA, ACA, and aPL. Inflammatory disease activity and activation of NETs by neutrophils further promote thrombosis. In APS, venous thrombosis is more frequent than arterial thrombosis. Arterial thrombosis mainly involves the CNS with manifestations of cerebrovascular events. Thrombosis can occur in any organ, be deep or superficial, affect the upper or lower limbs, the lungs, or be located in unusual places (intra-abdominal, etc.) (5,9,10,13).

Regarding the increased risk of thromboembolism in patients with SLE and ANCA-associated vasculitis, their risk appears to be significantly higher than that in other disease populations. ANCA vasculitis is associated with a greater likelihood of thromboembolism because of either the vasculitis itself through injury to the vessel or greater local edema and vascular narrowing in the context of vascular inflammation. The increased risk in SLE is likely a multifactorial issue, excluding renal involvement (such as nephrotic syndrome, which may increase hypercoagulability due to an imbalance in the excretion of antithrombotic factors), an increased concentration of aPL, and an overall inflammatory state such as and in all other autoimmune diseases.

RA appears to predispose patients to an increased risk of DVT and PE due to impaired endothelial function in the early stages of the disease due to a proinflammatory state, increased viscosity, vascular stasis, and impaired fibrinolysis, whereas arterial thrombosis has not been observed (18,19).

Regarding pSS, high rates of both venous thrombotic events were found compared with the general population, with twice the frequency of PE, DVT, and VTE in pSS patients than in the general population, as well as arterial thrombotic events, i.e., strokes, myocardial ischemia, and peripheral arterial disease (21,28).

DM/PM presents a high risk of DVT and PE, especially in the first year after the diagnosis of the disease (27).

A meta-analysis by Lee and Pope (3) showed a significantly increased risk of DVT in inflammatory rheumatic diseases, especially in the first year of disease onset (4). However, the true rates of DVT in rheumatic diseases and in the reviewed studies may be underestimated. Patient-reported symptoms may be vague and may even be misattribute to the rheumatologic disorder.

The reason for the increased thrombotic risk is the increased inflammatory activity of rheumatic diseases. Inflammation induces the expression of TF, an important step in the initiation of coagulation. Thus, vasculitis mediated by immune complexes and chronic destruction of the vessels is caused (10). At the same time, the activation of neutrophil extracellular traps (NETs), which are rich in bioactive molecules, promotes thrombosis (including atherothrombosis), inflammation, and fibrosis. Thus, although neutrophils may not be present in chronic inflammatory lesions, their remnants may enhance the inflammatory response beyond their short lifetime in tissues (11). In particular, about inflammatory joint diseases, the immobilization caused by inflammation and the need for surgical treatment, such as arthroplasty, increase the risk of deep vein thrombosis (13).

Ramagopalan et al. (29) examined the risk of venous thromboembolism in people admitted to hospital with a history of autoimmune rheumatic diseases, using the full National Hospital for England statistical episode data set from 1999 to 2008. Compared with controls, patients with various autoimmune rheumatic conditions showed statistically higher rates of thromboembolism. Specifically, the rates pooled were SLE 3.71 (95% CI; 3.43-4.02, p<0.001), pSS 2.02 (95% CI; 1.80-2.26, p<0.001), RA 1.75 (95% CI; 1.70-1.80, p<0.001), PAN 3.53 (95% CI; 2.76-4.44, p<0.0001, p<0.001) and ankylosing spondylitis 1.93 (95% CI; 1.74-2.14, p<0 .0001) (29).

The Swedish study by Zöller et al. (24) examined the risk of PE in patients with autoimmune diseases in Sweden. The MigMed2 database containing information on all registered residents of Sweden from 1964-2008 was used. The results showed that among rheumatological diseases, PAN [standardized infection ratio (SIR) 13.26, 95% CI; 9.33-18.29], PM/DM (SIR 16.44, 95% CI; 11.57-22.69), and SLE (SIR 10.23%, 95% CI; 8.31-12.45) were associated with a higher risk of PE (24). A particularly increased risk of thrombosis in autoimmune rheumatological diseases was observed in the present study, especially in DVT and especially in the first year of the onset of the disease, where the inflammatory activity is particularly intense. However, further and more extensive studies are needed to establish corresponding guidelines for the prevention and treatment of thrombotic events in rheumatological diseases.

CONCLUSION

Patients with inflammatory rheumatic diseases have an increased risk of developing venous and arterial thrombosis. Arterial and venous thrombosis are common clinical entities in SLE, with an increased risk of thrombosis in patients with higher LA, ACA, and aPL titres. RA appears to predispose patients to an increased risk of DVT and PE, whereas venous thrombosis predominates in pSS. Additionally, in PM/DM, there is a high risk of DVT and PE. These phenomena are observed in the first year after the onset of the disease, when the inflammatory process is more intense. However, further and more extensive studies are needed to establish corresponding guidelines for the prevention and treatment of thrombotic events in rheumatological diseases.

In this study, we investigated the risk of thrombotic events in patients with autoimmune rheumatological diseases, which is increased mainly in the first year of diagnosis of the disease with high rates of DVT and other venous and arterial thrombosis.

Authorship Contributions

Surgical and Medical Practices: A.S., S.T., Concept: A.S., S.T., Design: A.S., S.T., Data Collection or Processing: A.S., S.T., Analysis or Interpretation: A.S., S.T., Literature Search: A.S., S.T., Writing: A.S., S.T.

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

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LETTER TO THE EDITOR

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OCCUPATIONAL THERAPY IN CHRONIC RHEUMATIC DISEASES AND SCIENTIFIC INTEREST IN "OCCUPATIONAL THERAPY PUBLICATIONS IN TURKEY"

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To editor:

The profession of "Occupational Therapy" encourages individuals to achieve health and wellness by participating in meaningful occupations in daily life. It plays a critical role in primary healthcare services (1). Both healthy individuals and people with physical and cognitive impairments experience limitations in their daily and professional lives. The main goal of "Occupational Therapy" is for the individual to be self-sufficient and to fulfill his duties and responsibilities within his nuclear family or society (2). With developments in the field of health, the elderly population is increasing, and these people are accompanied by cognitive and psychiatric problems at different levels. Older people with cognitive/psychiatric disorders often experience various functional deficits in their daily lives that affect their independence, safety, and activity levels (3). In chronic rheumatic diseases, unwanted pain, swelling, and limitation of movement may develop in the musculoskeletal system. Even if many people do not develop a physical limitation, it causes limitations in psychological and social areas. Therefore, there is a need for a holistic perspective of "Occupational Therapy" in the rehabilitation of chronic rheumatic diseases (4,5).

Bibliometric analysis provides an objective perspective on scientific studies by providing statistical information about scientific articles, including author, institution, citation, country, article type, and year information etc. It enables the dissemination of publications' impact, productivity, quality, and collaboration indicators. We see that the volume of occupational therapy data has grown worldwide in the last decade, and scientific interest in these articles needs to increase in Turkey (6,7).

Bibliometric analysis of occupational therapy publication activity in Turkey provides a cross-sectional perspective on the developments in current research in rehabilitation science (8). On 14.12.2023, the keyword "Occupational Therapy" was written on the first line in the Web of Science (WoS) (9) database at all times, and a total of 42.613 documents were accessed. When only those in Turkey were marked in the countries section, 282 (0.6%) documents were obtained. According to the countries and regions, the top 5 list was as follows: 1st USA (15.498), 2nd England (4.920), 3rd Canada (3.835), 4th Australia (3.581), 5th Sweden (1.662) (Figure 1). Turkey ranks 26th among 169 countries.

Of these, 85.8% were research articles (n=242), 92 were review (n=26), 3.5% were meeting abstract (n=10) and 1.4% were proceeding paper (n=4). 33.3% (n=94) of the documents were open access, 90.7% of the documents were in English, and 9.3% were in Turkish. Looking at the years, 2021 was the year with the most articles published, with 54 (19.1%) articles, and there was a linear increase in articles on the subject of occupational therapy over the years.

According to the WoS category, 33.6% (n=95) of the articles were in the field of Rehabilitation, 10.6% (n=31) were in Medicine

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General Health, 9.9% were in Public Environmental Occupational Health, 7.8% were in Clinical Neurology, and 6.7% (n=19) were in Pediatrics. Hacettepe University ranked first in the affiliation list with a frequency of 40.7% (n=115) (Figure 2).

According to the citiation report, the number of citing articles was 2951 (self-citiations included), times cited was 3.067 (self-citiations included), average per tem= 10.88 and H index= 25 (Figure 3).

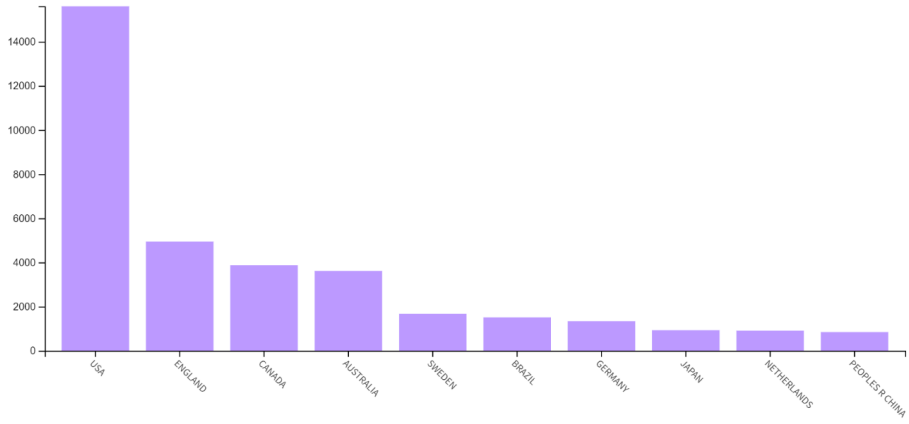

Figure 1. Bar chart of the countries

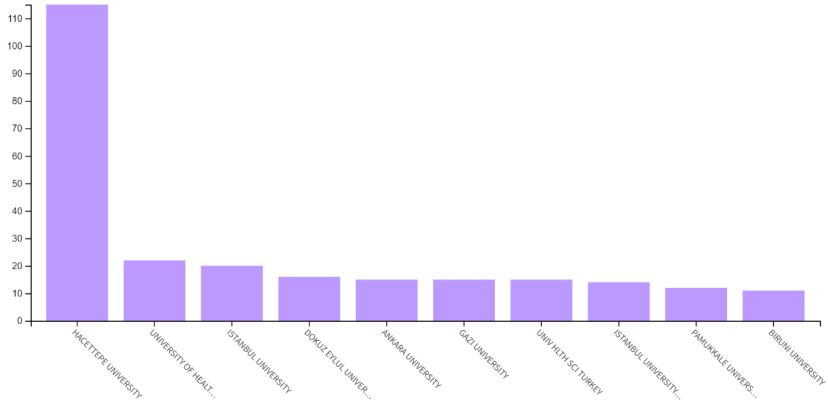

Figure 2. Bar chart of affiliations in Turkey

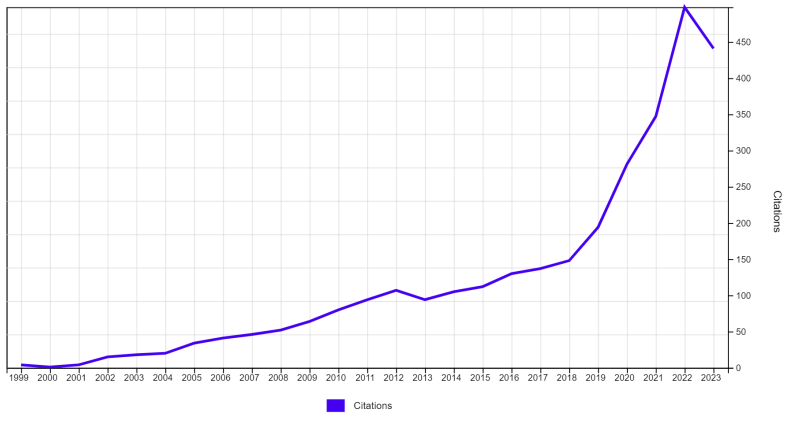

Figure 3. Times cited and publications over time

As can be seen, there is not enough scientific interest in the subject of occupational therapy in Turkey compared with other countries. After natural disasters such as floods, earthquakes, volcano eruptions, and hot wars, which started during the 2019 COVID-19 pandemic period and developed due to the climate crisis in 2023, the importance of people being able to both be self-sufficient individually and fulfill their duties and responsibilities as a part of society has become more important. During the disaster period, a multidisciplinary team must be formed to determine the situation of the disaster and list the needs. An occupational therapist should be included in this team (10).

The aim of the treatment of rheumatic disease is to control inflammation, prevent attacks, and protect joints. Occupational therapy approaches that target problems in the patient's daily routine, social and recreational activities, and professional life will benefit these patients, increase the functional capacity of the person, and contribute positively to the quality of life.

When we look at the core literature data about occupational therapy, we see that there are data in a multidisciplinary field such as rehabilitation, clinical neurology, internal medicine, psychiatry, and basic care services such as nursing, pediatrics, sports sciences, and orthopedics. Occupational therapists and physiotherapists are professional practitioners who perform assessments and treatments to improve, improve, or maintain the daily activities or professional lives of individuals, groups, or communities. The number of people in this field in Turkey is also insufficient.

Scientific research topics are affected by official health policies, countries' development levels, traditional beliefs and attitudes, individuals' needs, and environmental factors such as climate and geography. The articles written may also vary because of differences in the areas in which the authors and clinicians are experienced. In the field of occupational therapy, there is a need for qualitative research on the good management of individuals' needs, considering their subjective perspective.

Ethics

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ORIGINAL ARTICLE

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REAL-LIFE DATA IN RHEUMATOID ARTHRITIS PATIENTS USING BARICITINIB AT A SINGLE CENTER

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Abstract

Aim: Rheumatoid arthritis (RA) poses a significant health challenge and is characterized by chronic immune-mediated inflammation and potential joint damage. This study explores the real-life effectiveness of baricitinib, a Janus kinase inhibitor, in treating patients with RA. The goal of this study was to assess its impact on disease activity and factors influencing treatment outcomes.

Material and Methods: Ninety patients with RA diagnosed between September 2021 and 2023 at Necmettin Erbakan University Meram Medical Faculty Hospital were retrospectively analyzed. Baricitinib, prescribed during this period, was evaluated for its impact on C-reactive protein (CRP), Disease Activity Score-28 with CRP (DAS28/CRP), and overall treatment continuation rates. Demographic and clinical data, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) markers, were collected.

Results: Significant reductions in CRP and DAS28/CRP levels were observed over a 12-week follow-up after baricitinib use. Positive detection rates for RF and anti-CCP were 60% and 57.8%, respectively. Baricitinib demonstrated a high continuation rate (82%) at an average of 9.37 months. No significant differences were found in the continuation rates based on the prior use of conventional or biological disease-modifying anti-rheumatic drugs (DMARDs).

Conclusion: Comparisons with existing studies support the efficacy of baricitinib in improving disease activity. Our findings align with the literature, emphasizing positive outcomes in patients with prior DMARD experience. Unlike some studies reporting higher discontinuation risks, our results highlight a favorable safety profile. The study's limitations include a short follow-up period, which warrants further investigation with larger cohorts. In conclusion, baricitinib exhibits promising real-life effectiveness in RA treatment, emphasizing its role as a valuable therapeutic option.

Keywords: Real-life experience, baricitinib, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, multisystemic, immune-mediated disease that can lead to progressive joint damage. Left untreated, RA may result in loss of physical function. In addition, specific comorbidities such as nodules, interstitial lung disease, fatigue, depression, and cardiovascular disease may develop, contributing to increased mortality.

The goal of treatment is to achieve and maintain remission or low disease activity by initiating early disease-modifying anti-rheumatic drug (DMARD) therapy during the course of the disease. Traditional synthetic DMARDs (csDMARDs), primarily methotrexate (MTX), with or without low-dose glucocorticoids, have long been the cornerstone of treatment. Updated management guidelines from the European League Against

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Rheumatism (EULAR) recommend the addition of biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) to csDMARD therapy (1).

Janus kinases (JAKs) are key enzymes in the signaling pathways of numerous surface cytokine receptors, including those involved in inflammatory physiology. Janus kinase inhibitors (JAKi), a novel class of drugs, are small molecules designed for targeted therapy with rapid onset of action. Baricitinib, an oral selective inhibitor within the JAK family of protein tyrosine kinases, exhibits high potency and selectivity for JAK1 and JAK2. JAK enzymes phosphorylate and activate signal transducers and transcription activators (STATs) within the cell, modulating gene expression. Baricitinib acts by blocking cytokine signaling associated with RA through the JAK-STAT pathway, thereby reducing inflammation, cellular activation, and proliferation of key immune cells (2). Baricitinib is the first drug approved for treating RA in the JAKi class. As a selective inhibitor of JAK1 and JAK2, it modulates the signaling of various cytokines involved in the immune-inflammatory response. It has been approved for the treatment of moderately to severely active RA in adults in more than 40 countries, including European countries and the United States. Baricitinib has demonstrated efficacy in clinical trials encompassing all clinically relevant RA patient populations: those not using MTX, inadequate responders to MTX (MTX-IR), and inadequate responders to bDMARDs (3).

The primary objective of this study was to evaluate the real-life effectiveness of baricitinib treatment in patients with RA. Secondary objectives include assessing the impact of gender and positivity for markers such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), as well as evaluating the influence of concomitant use of DMARDs on drug persistence.

MATERIAL AND METHODS

Study Population

Between September 01, 2021, and September 01, 2023, patients diagnosed with RA who sought treatment at the Rheumatology Outpatient Clinic of Necmettin Erbakan University Meram Medical Faculty Hospital and were prescribed baricitinib were retrospectively screened. Ninety patients aged 18 years or older were included in the study. Participants had a history of prior treatment with cDMARDs and/or bDMARDs. Patients with additional inflammatory diseases, liver diseases, end-stage kidney disease, diabetic nephropathy, other autoimmune diseases, active infections, recent blood transfusions, or a history of anemia were excluded from the study. The study was approved by the Pharmaceutical and Non-Medical Device Research Ethics Committee (2023/4583).

Demographics and Clinical Data

Patients were diagnosed with RA on the basis of the 2010 American College of Rheumatology/EULAR criteria. The RF and anti-CCP results for all patients are available in the system. Initial and 12-week post-treatment C-reactive protein (CRP) values, as well as Disease Activity Score with 28 Joint Counts (DAS-28)/CRP values, were extracted by reviewing the records. These parameters were systematically analyzed to assess the inflammatory response and disease activity in patients with RA before and after a 12-week treatment period.

Statistical Analysis

Data analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant. The Kolmogorov-Smirnov test was used to assess the normality of the variables. All continuous data showed a nonnormal distribution. Results were expressed as mean (standard deviation) for continuous variables and as numbers and percentages for categorical variables. Pearson's chi-square test, Fisher's exact test, and Mann-Whitney U test were used for the comparison of findings between the two groups. Intra-group assessments were conducted using the Wilcoxon signed-rank test.

RESULTS

Ninety patients diagnosed with RA using baricitinib were included in the study. The demographic data of the patients are presented in Table 1. The rates of positive detection of RF and anti-CCP in our patients were 54 (60%) and 52 (57.8%), respectively.

A significant difference was found between the initial CRP values and the CRP values in the 12th week after the use of baricitinib in the patients included in the study ($p<0.01$). Additionally, the DAS-28/CRP values, which were 4.71 at the beginning, were found to be 2.42 at the end of the 12-week follow-up ($p<0.01$).

Table 1. Demographic data of patients treated with baricitinib

Variables	Values
Age (year old)	47.1 (±8.8)
Female gender, n (%)	95 (94.0)
RF, n (%) Negative Positive	 36 (40) 54 (60)
Anti-CCP, n (%) Negative Positive	 26 (28.9) 52 (57.8)

RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide

Out of the 90 patients who initiated baricitinib, treatment is ongoing for 74, while 16 have undergone a medication change due to ineffectiveness; no side effects necessitating discontinuation were observed. At the end of the 9.37-month duration of baricitinib use, the medication continuation rate was 82%.

When comparing patients using only conventional synthetic DMARDs (csDMARDs) and those using both bDMARDs and csDMARDs regarding medication continuation, no significant difference was found (p=0.951). Furthermore, when comparing patients based on the positivity or negativity of RF and anti-CCP for medication continuation, no significant difference was observed (p=0.564). See Table 2 for details.

DISCUSSION

In our study, we observed a significant reduction in CRP and DAS-28 levels in patients using baricitinib during the 12-week follow-up. Our retrospective study revealed that patients had prior experience with csDMARDs or bDMARDs. When comparing patients who had previously used both bDMARDs and csDMARDs with those who had only used csDMARDs, we did not find a significant difference in the continuation rates of baricitinib treatment.

Upon reviewing the literature, we encountered a study conducted by Yang et al. (2) in China, which included 231 patients with a mean age of 48.2 years, all of whom had previously used csDMARDs. This study focused on patients with moderate to severe active RA who showed resistance to MTX treatment. The DAS28-hsCRP values from baseline to weeks 12 and 24 demonstrated significant improvement with baricitinib treatment compared with the placebo group (2). In Takahashi et al. (4) involving 113 patients, a substantial decrease in the mean DAS28-CRP values was observed. Additionally, in the study conducted by Wu et al. (5), it was observed that 52.4% of patients achieved DAS28-CRP remission at 24 weeks. The results regarding the efficacy of baricitinib in these studies were similar to our findings.

In comparison with previous studies, Takahashi et al. (4) and Baldi et al. (6) reported continuation rates for baricitinib over 24 weeks as 86.5% and 69.3%, respectively (4,5). Additionally, Alten et al. (7) esreported a medication continuation rate of 87.6% during the 24-week follow-up, while Takagi et al. (8) and co-authors reported it as 73.35%, and Deprez et al. (9) and the team documented a baricitinib retention rate of 67% over the course of 54 weeks. In our study, the continuation rate for baricitinib use after an average of 9.37 months was found to be 82%. This rate is notably consistent with findings from other studies.

Upon reviewing the literature, Baldi et al. (6) conducted a study where they found no significant difference in the continuation of baricitinib treatment based on RF and/or anti-CCP positivity or negativity. Similarly, in our study, there was no significant relationship between the continuation of treatment and the seropositivity or seronegativity of patients, aligning with the findings of Baldi et al. (6).

In the study conducted by Baldi et al. (6), they observed that while the improvement in disease activity was greater in the group that had previously used only conventional csDMARDs, baricitinib was still effective in patients who had previously used bDMARDs. However, the analyses revealed that in patients with a history of bDMARD treatment, this situation was associated with a higher risk of treatment discontinuation (9). In contrast, our study did not reveal any significant differences.

Given the potential increased risk of serious cardiac events (e.g., myocardial infarction, stroke, venous thromboembolism, pulmonary embolism) associated with baricitinib, the Food and Drug Administration recommends conducting a thorough risk-benefit assessment for patients before initiating or continuing treatment (9). Similarly, the European Medicines Agency advises against the use of JAK inhibitors in patients with a high risk of major cardiovascular problems or those with a history of significant tobacco use unless there are suitable alternative treatments available (6).

Table 2. Factors affecting the continuation of baricitinib treatment

Variables	Medication usage continues	Medication has been changed	p
Previously administered medications Using csDMARD Using bDMARDs and/or csDMARDs	 41 (%55.4) 33 (44.6)	 9 (%56.3) 7 (%43.8)	**0.951***
Serology positivity Serology negativity	48 (%64.9) 26 (%35.1)	12 (75.0) 4 (25.0)	**0.564****

*Pearson chi-square, **Fisher's exact test, csDMARD: Conventional synthetic disease-modifying antirheumatic drug, bDMARD: Biologic disease-modifying antirheumatic drug

In our study, the average age of patients was 47.18 years,reflecting a preference for treatment in younger patients due to the increased risk of cardiovascular diseases and thromboembolism in older individuals. The limited number of patients and the retrospective nature of the study with an average follow-up of 9.37 months may have contributed to the absence of observed side effects necessitating the discontinuation of baricitinib. Treatment changes in our study were primarily driven by ineffectiveness rather than safety concerns. In our study, 82% of patients treated with baricitinib continued the treatment, indicating that eighteen percent of patients did not continue with the treatment. In the study conducted by Alten et al. (7), the discontinuation rate of baricitinib due to inadequate efficacy at 6 months was 12.4%. Similarly, in Takagi et al. (8), this rate was 10.10%, aligning with our findings.

Study Limitations

A significant limitation of our study is the short follow-up period, which consequently resulted in a limited number of patients. However, the study's major strength lies in presenting the efficacy of baricitinib treatment based on real-life data. This provides valuable insights into the clinical applicability and effectiveness of the treatment.

Although the efficacy of baricitinib has been demonstrated in patients who have previously used csDMARDs and/or bDMARDs, further research with additional analyses and larger patient groups is required to comprehensively assess side effects.

CONCLUSION

As a conclusion, this study underscores that the utilization of baricitinib constitutes an efficacious and secure alternative in the management of rheumatoid arthritis.

Ethics

Ethics Committee Approval: The study was approved by the Pharmaceutical and Non-Medical Device Research Ethics Committee (2023/4583).

Informed Consent: Retrospective study.

Authorship Contributions: Surgical and Medical Practices: B.E., A.K., Concept: B.E., A.K., Design: B.E., A.K., Data Collection or Processing: B.E., A.K., Analysis or Interpretation: B.E., A.K., Literature Search: B.E., A.K., Writing: B.E., A.K.

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ORIGINAL ARTICLE

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THE EFFECT OF TNF-ALPHA INHIBITORS USED IN RHEUMATOLOGIC DISEASES ON HEMATOLOGICAL PARAMETERS

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Abstract

Aim: Tumor necrosis factor (TNF) inhibitors are used in patients resistant to conventional treatments for rheumatologic diseases such as rheumatoid arthritis (RA) and spondyloarthropathy (SpA). Agents used for treating rheumatic diseases affect hematological parameters. In this study, we evaluated hematological parameters in patients with inflammatory rheumatic diseases who started anti-TNF treatment at our center.

Material and Methods: A total of 109 patients diagnosed with RA, SpA without psoriatic arthritis (PsA) and PsA who applied to the İnönü University Rheumatology Clinic and started TNF inhibitor treatment were included in the study. The patients' diagnoses, demographic data such as age and gender, and laboratory parameters (white blood cell, eosinophil, lymphocyte, monocyte, neutrophil counts, hemoglobin, platelet (PLT), mean platelet volume (MPV) ratio, neutrophil to lymphocyte ratio, monocyte/lymphocyte ratio and eosinophil/lymphocyte ratio) at the beginning of treatment and at the first month of treatment were recorded.

Results: The rheumatic inflammatory patients included in our study comprised 29 RA, 16 PsA, and 64 spondyloarthritis without PsA patients. Seventy-seven patients were female (70.6%), and 32 were male (29.4%), with a mean age of 46 (18-78). When all patients were evaluated together, a statistically significant decrease in white blood cell, neutrophil, and PLT counts, a statistically significant increase in hemoglobin, lymphocyte, and eosinophil counts, and a statistically significant decrease in neutrophil to lymphocyte and monocyte to lymphocyte ratios with an increase in MPV and mean platelet volume to platelet count were observed at the 1st month of treatment. No complications related to laboratory changes were observed, and no patient discontinued treatment.

Conclusion: Although there were changes in hematological parameters in patients receiving TNF inhibitor treatment in our study, we believe that regular hemogram monitoring should be performed at regular intervals in patients undergoing anti-TNF treatment, despite the absence of any complications in our study, as cases of severe cytopenia and eosinophilia have been reported in the literature following TNF inhibitor treatment.

Keywords: Spondyloarthritis, psoriatic arthritis, rheumatoid arthritis, hematological parameters, NLR ratio, anti-TNF agents

INTRODUCTION

Tumor necrosis factor-alpha (TNF-α) is a bell-shaped trimeric glycoprotein comprising 212 amino acids. It is primarily produced by monocytes and macrophages and exhibits a broad spectrum of biological effects (1). TNF-α plays crucial roles in natural or acquired immunity, cachexia, endotoxic shock, inflammation,

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tissue remodeling, infection and immunity, cytotoxicity, and apoptosis (1). Agents that inhibit TNF-α, such as anti-TNF agents, are used in rheumatic diseases resistant to conventional treatment, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and inflammatory bowel diseases (2). TNF-α blockade can be employed in pathologies associated with increased TNF-α expression. Anti-TNF drugs can be produced in the form of monoclonal antibodies or fusion proteins targeting this cytokine (1).

Various side effects of anti-TNF treatments have been reported in clinical applications, including injection site reactions, infusion reactions, infections, cytopenia, demyelinating diseases, heart failure, increased autoimmune diseases, pulmonary fibrosis, and liver toxicity (3). Although current guidelines do not mandate regular hemogram monitoring because hematological side effects were not reported shortly after the release of these drugs, non-malignant hematological side effects such as profound neutropenia, thrombocytopenia, pancytopenia, and hypercoagulable eosinophilia have been reported in the literature during treatment (4).

Furthermore, the specific parameters derived from the ratio of certain parameters in these blood count tests were correlated with various systemic disease clinics. Relationships between hematological indices, such as mean platelet volume to platelet count ratio (MPR), neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and eosinophil to lymphocyte ratio (ELR), and the survival of various malignancies have been demonstrated. Different cells play dominant roles in the pathogenesis of different rheumatic diseases; therefore, these cell ratios are expected to be associated with disease clinics in clinical practice. Recent studies have shown the relationship between these indices and the clinical symptoms and disease activities of various rheumatic diseases (5-7).

In our study, we aimed to evaluate the impact of anti-TNF treatments used for treating inflammatory rheumatic diseases on hematological parameters and the hematological indices derived from these parameters.

MATERIAL AND METHODS

Ethical approval for our study was obtained from the İnönü University Scientific Research and Publication Ethics Committee under protocol number 2019/243. Subsequently, we retrospectively analyzed the data of 109 patients diagnosed with RA, spondyloarthropathy without PsA (non-PSA SpA), and PsA who applied to the İnönü University Faculty of Medicine, Rheumatology Outpatient Clinic and initiated anti-TNF (infliximab, adalimumab, etanercept, certolizumab, and golimumab) treatment for the first time at our center.

Hemogram parameters of the patients at the initiation of anti-TNF treatment and at the 1st month after treatment were examined. Hemogram parameters included white blood cell count, eosinophil count, lymphocyte count, monocyte count, neutrophil count, hemoglobin level, PLT count, MPV, and ratios such as MPR, NLR, MLR, and ELR.

Statistical Analysis

Statistical analysis were performed using the SPSS 22 statistical program (IBM Corp., Armonk, N.Y., USA). Data are presented as mean ± standard deviation. Paired samples t-test was employed for the analysis of dependent variables, with $p<0.05$ considered statistically significant.

RESULTS

A total of 109 patients were included in our study. Of these, 77 were female (70.6%) and 32 were male (29.4%). Sixty-four patients were diagnosed with non-PSA SpA, 29 with RA, and 16 with PsA. The average age was 46 (18-78). Adalimumab was the most commonly initiated treatment in 46 patients (42.2%), followed by golimumab in 31 patients (28.4%), etanercept in 27 patients (24.8%), certolizumab in 3 patients (2.8%), and infliximab in 2 patients (1.8%). The baseline characteristics of the patients and the values of hematological parameters at the initiation of treatment and at the first month are presented in Table 1.

In our study, there were statistically significant decreases in white blood cell count, neutrophil count, PLT, and NLR and MLR ratios at the first month compared with baseline values for all treatment agents. In addition, there were statistically significant increases in hemoglobin, eosinophil count, lymphocyte count, MPV, and MPR values. In addition to these values, there was a statistically nonsignificant increase in monocyte count and ELR value (Table 1). Furthermore, all data were separately analyzed within disease subgroups (Table 2-4). In patients with RA, there was a statistically significant increase in eosinophil and lymphocyte counts and a statistically significant decrease in PLT. No statistically significant changes were observed in the other parameters (Table 2). In the non-PSA SpA group, there was a statistically significant increase in lymphocyte count and a statistically significant decrease in neutrophil and PLT. Consequently, an increase in the MPV/PLT ratio and a statistically significant decrease in the NLR and MLR ratios were observed (Table 3). In the PsA patient group, in addition to the changes observed in the non-PSA SpA group, a statistically significant decrease in white blood cell count was noted (Table 4).

Table 1. Changes in hematological parameters at the initiation and first month of anti-TNF treatment in all patients

Parameter	Baseline value (mean ± SD)	Post-treatment 1st month (mean ± SD)	p-value
Leukocyte (10^9/L)	8.29±2.13	7.89±1.82	0.027
Eosinophil (10^9/L)	0.17±0.28	0.21±0.15	0.020
Lymphocyte (10^9/L)	2.33±0.68	2.61±0.76	<0.001
Monocyte (10^9/L	0.67±0.21	0.67±0.20	0.968
Neutrophil (10^9/L)	5.00±1.90	4.34±1.64	<0.001
Hemoglobin (g/dL)	13.13±0.15	13.35±0.16	0.007
Platelet (10^{12}/L)	308.7±75.3	286.9±61.2	<0.001
MPV (fL)	10.45±0.89	10.54±0.84	0.037
MPV/platelet ratio	0.0362±0.01071	0.0388±0.01038	<0.001
NLR	2.38±1.38	1.91±1.40	<0.001
MLR	0.31±0.13	0.28±0.13	0.004
ELR	0.07±0.05	0.08±0.05	0.751

p-values were considered statistically significant if <0.05, TNF: Tumor necrosis factor, SD: Standard deviation, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio

Table 2. Changes in hematological parameters at the initiation and 1st month of anti-TNF treatment in patients with rheumatoid arthritis

Parameter	Baseline value (mean ± SD)	Post-treatment 1st month (mean ± SD)	p-value
Leukocyte (10^9/L)	8.05±2.39	8.02±2.30	0.923
Eosinophil (10^9/L)	0.16±0.12	0.23±0.18	0.005
Lymphocyte (10^9/L)	2.06±0.66	2.28±0.77	0.041
Monocyte (10^9/L)	0.70±0.22	0.70±0.23	0.899
Neutrophil (10^9/L)	4.97±2.23	4.73±2.33	0.540
Hemoglobin (g/dL)	12.46±0.27	12.63±0.30	0.391
Platelet (10^{12}/L)	321.03±84.24	304.65±64.51	0.071
MPV (fL)	10.45±1.00	10.45±0.82	1.000
MPV/platelet ratio	0.0349±0.0103	0.0360±0.0089	0.299
NLR	2.64±1.63	2.57±2.29	0.811
MLR	0.36±0.14	0.34±0.18	0.498
ELR	0.08±0.052	0.09±0.05	0.042

p-values were considered statistically significant if <0.05, TNF: Tumor necrosis factor, SD: Standard deviation, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio

DISCUSSION

Anti-TNF therapies have emerged as a significant treatment option for rheumatic diseases. Beyond their clinical effects, researchers are increasingly interested in their impact on bone marrow stem cells and, consequently, hematological parameters (8-10). TNF is known as a proinflammatory cytokine and can affect homeostasis in the bone marrow microenvironment. Depending on the cytokine microenvironment and its own concentration, TNF can exert stimulatory or inhibitory effects on the growth of hematopoietic progenitors. While TNF-α has been shown to have a stimulatory effect on granulocyte colony-stimulating factor, erythropoietin, and stem cell factor, it has been shown to have an inhibitory effect on granulocyte-macrophage colony-stimulating factor and interleukin (IL)-3 in other studies. In addition, various proinflammatory cytokines such as IL-1, IL-6, and IL-8 are known to be affected by TNF-α. Therefore, theoretically, inhibition of TNF-α may lead to bone marrow insufficiency by blocking stem cell differentiation (8). A correlation between TNF-α levels and the development

Table 3. Changes in hematological parameters at the initiation and 1st month of anti-TNF treatment in patients with spondyloarthritis without psoriatic arthritis

Parameter	Baseline value (mean ± SD)	Post-treatment 1st month (mean ± SD)	p-value
Leukocyte (10^9/L)	8.26±2.05	8.01±1.69	0.214
Eosinophil (10^9/L)	0.18±0.12	0.19±0.13	0.277
Lymphocyte (10^9/L)	2.44±0.70	2.77±0.75	<0.001
Monocyte (10^9/L)	0.63±0.19	0.66±0.19	0.260
Neutrophil (10^9/L)	4.94±1.83	4.31±1.35	0.002
Hemoglobin (g/dL)	13.34±0.21	13.52±0.21	0.050
Platelet (10^{12}/L)	306.00±74.98	282.96±62.13	<0.001
MPV (fL)	10.47±0.84	10.53±0.84	0.154
MPV/platelet ratio	0.0367±0.0113	0.0395±0.0113	0.002
NLR	2.26±1.35	1.70±0.85	<0.001
MLR	0.28±0.13	0.25±0.10	0.005
ELR	0.07±0.05	0.07±0.04	0.574

p-values were considered statistically significant if <0.05, TNF: Tumor necrosis factor, SD: Standard deviation, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio

Table 4. Changes in hematological parameters at the initiation and 1st month of anti-TNF treatment in patients with psoriatic arthritis

Parameter	Baseline value (mean ± SD)	Post-treatment (mean ± SD)	p-value
Leukocyte (10^9/L)	8.84±1.95	7.16±1.11	0.008
Eosinophil (10^9/L)	0.17±0.16	0.17±0.12	0.983
Lymphocyte (10^9/L)	2.37±0.55	2.53±0.63	0.283
Monocyte (10^9/L)	0.73±0.24	0.65±0.18	0.175
Neutrophil (10^9/L)	5.32±1.58	3.74±0.91	0.003
Hemoglobin (g/dL)	13.48±0.38	13.95±0.36	0.34
Platelet (10^{12}/L)	297.18±59.51	271.00±45.24	0.013
MPV (fL)	10.35±0.92	10.71±0.89	0.007
MPV/platelet ratio	0.0364±0.0088	0.0407±0.0079	0.018
NLR	2.35±0.93	1.57±0.52	0.004
MLR	0.32±0.10	0.26±0.08	0.049
ELR	0.07±0.06	0.07±0.05	0.759

p-values were considered statistically significant if <0.05, TNF: Tumor necrosis factor, SD: Standard deviation, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio

of neutropenia in patients receiving chemotherapy for acute leukemia was demonstrated in a study by Bruserud et al. (10).

Although rare, hematological side effects such as thrombocytopenia, neutropenia, pancytopenia, and aplastic anemia, which can sometimes result in death, have been reported in patients receiving anti-TNF treatment. In a post-marketing cohort study by Feltelius et al. (11), approximately half of the 17 patients receiving etanercept developed serious hematological reactions. However, another study by Miehsler et al. (12) reported a generally low incidence of hematological side effects in patients receiving infliximab. Cases of pancytopenia and aplastic anemia have been reported using both etanercept and infliximab (13-16). In another study by Yazdani et al. (17), 12% of 130 patients receiving anti-TNF treatment developed non-infection-related cytopenia, predominantly leukopenia, but these cytopenias were transient and did not require hematological monitoring. In our study, although there was a statistically significant decrease in white blood cell and neutrophil counts

in patients after anti-TNF treatment, no patient had leukopenia or neutropenia requiring discontinuation of the drug. However, despite the lack of clinical significance, there was a statistically significant increase in hemoglobin levels, possibly related to the suppression of inflammation.

Eosinophilia after anti-TNF treatment has also been reported. Cancelliere et al. (18) reported a case of subacute prurigo with marked eosinophilia after infliximab administration in an 80-year-old patient with RA. The relationship between TNF inhibition and eosinophilia was confirmed in this case because both prurigo and eosinophilia significantly improved after discontinuation of the drug but recurred when another TNF inhibitor, etanercept, was started (18). In our study, especially in patients with RA, there was a statistically significant increase in eosinophil count after treatment.

In recent years, the NLR and platelet-lymphocyte ratio (PLR) have been shown to be systemic inflammation markers associated with the prognosis of many cardiovascular diseases, malignancies, and chronic inflammatory diseases. Additionally, NLR and PLR are related to erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IL-6, and TNF-α (19-21). In a study evaluating NLR ratios after anti-TNF treatment in RA and AS patients, NLR was correlated with disease activity score 28 (DAS 28), ESR, and CRP in RA patients and with bath AS disease activity index, ESR, and CRP in AS patients (5). In another study examining NLR in patients with psoriasis and PsA, NLR was significantly correlated with PASI scores, and a high NLR ratio was found to be a predictor for the development of PsA in patients with psoriasis (7). In our study, although disease activities were not evaluated, NLR and MLR ratios, indicative of systemic inflammatory response, decreased after anti-TNF treatment, showing a negative correlation with the inflammatory process, and the MPV, indicative of platelet function activity, increased. Because of the increase in MPV and decrease in platelet count, MPR also increased. These results suggest that anti-TNF treatment agents are effective in suppressing inflammation.

Our study has limitations due to its retrospective nature, the small number of included patients, and the evaluation of only the first-month data of the patients. Although the clinical and laboratory activations of patients were not individually assessed at the beginning and after treatment, biological therapies were initiated during the active disease period. In addition, in our study, changes in the hemogram parameters induced by anti-TNF therapies were investigated; hence, the first-month hemogram parameters were evaluated without altering the current treatments of the patients.

CONCLUSION

In conclusion, patients receiving TNF-α inhibitors are closely monitored for diseases such as malignancy, hepatitis B, and tuberculosis; however, current guidelines do not provide clear information regarding hematological monitoring. Although our study did not reveal significant changes in hematological parameters after anti-TNF treatment that would necessitate discontinuation or cessation of treatment, serious hematological reactions such as severe leukopenia, neutropenia, thrombocytopenia, and eosinophilia have been reported in the literature after anti-TNF treatment. Therefore, prospective studies with a larger number of patients, evaluating disease activity scales, and having a longer follow-up period are required to comprehensively assess the efficacy and side effects of anti-TNF treatment agents in rheumatic diseases.

Ethics

Ethics Committee Approval: Ethical approval for our study was obtained from the İnönü University Scientific Research and Publication Ethics Committee under protocol number 2019/243.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: R.P.S., S.Y., Y.S.D., A.K., Concept: R.P.S., S.Y., Design: R.P.S., S.Y., Y.S.D., A.K., Data Collection or Processing: R.P.S., S.Y., Y.S.D., Analysis or Interpretation: R.P.S., S.Y., Literature Search: R.P.S., S.Y., A.K., Writing: R.P.S., S.Y., A.K.,

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MALIGNANCIES AND THEIR EFFECTS ON DISEASE COURSE IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Abstract

Objectives: Systemic sclerosis (SSc) is an inflammatory disease. Systemic inflammatory diseases increase the risk of malignancy. Malignancy prevalence has been reported previously as 3.6-10.7% in SSc. Standardized incidence ratios (SIRs) were calculated for lung cancer (4.9), skin cancer (4.2), hepatocellular carcinoma (3.3), hematological malignancies (2.3), esophageal cancer (15.9), and oropharyngeal carcinoma (9.6). Thus, the aim of this study was to document the prevalence of malignancies and their potential effect on disease course in patients with SSc with a 10-year follow-up.

Material and Methods: SSc patients from two territory hospitals diagnosed between 2010 and 2020 were included in the study. Demographical, clinical, and laboratory features were recorded. Cancer types and their effect on the features of SS were analyzed using suitable statistical methods.

Results: Five (3.4%) of 149 SSc patients (137 females and 12 males) had a cancer diagnosis, and their mean age was 54±6.4 years. All five were females, and the mean age of cancer diagnosis was 50±6.6 years. Two of them had breast cancer, one had ovarian cancer, one had soft tissue sarcoma, and the last one had basal cell carcinoma. Time to cancer diagnosis from SSc diagnosis was 6.6±5.5 (minimum-maximum: 2-14) years. Two of them died during the follow-up period. Three of SSc with concomitant cancer were diffuse cutaneous SSc and two cases were limited cutaneous SSc subtype. Only one patient had received cyclophosphamide treatment. Dysphagia and gastroesophageal reflux disease (GERD) are prevalent in patients with cancer.

Conclusion: This study shows that 3.4% of SSc patients have cancer risk. Dysphagia and other GERD symptoms are more prevalent in patients with concomitant cancer than in those without. Dysphagia and other GERD symptoms may be candidate surrogate markers of malignancy in patients with SSc.

Keywords: Scleroderma, sytemicsclerosis, malignancies, dysphagia, GERD

INTRODUCTION

Systemic sclerosis (SSc) is a chronic, multisystemic, autoimmune disease characterized by fibrosis of the skin and internal organs. It leads to changes in the skin, musculoskeletal system, lungs, heart, gastrointestinal system, and kidneys due to inflammation and fibrosis. The pathogenesis of SSc is thought to comprise a triad of abnormal autoimmune responses, small vessel vasculopathy, and increased fibrosis in tissues (1).

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Malignancies are an important part of the burden of comorbidities associated with rheumatic diseases (2). Increased cancer risk is associated with both basic immunological dysfunction and drug therapies. With the increase in effective treatments for SSc, mortality rates due to interstitial lung disease, pulmonary hypertension (PHT), and renal crisis are decreasing, whereas long follow-up periods increase the incidence of malignancy. Malignancy in SSc is frequently observed in patients with severe skin involvement and with anti-RNA polymerase III antibodies, one of the specific autoantibodies (3,4).

There are various rates in the literature regarding the prevalence of malignancy in patients with SSc (3.6-10.7%) (5). In a meta-analysis, the standardized incidence ratio (SIR) for all malignancies in patients with SSc was found to be 1.41 (6). It was observed that male patients had a higher SIR than female patients. However, contrary to what is known, there was no difference between the diffuse and limited types. In this meta-analysis, significant increases in the risk of lung, liver, and bladder cancers, non-Hodgkin's lymphoma, and leukemia were also observed. The increased risk for specific malignancies included lung cancer (SIR 4.9), skin cancer (SIR 4.2), hepatocellular carcinoma (SIR 3.3), hematological malignancies (SIR 2.3), esophageal carcinoma (SIR 15.9), and oropharyngeal carcinoma (SIR 9.6) (7,8).

In the literature, data on malignancy rates, malignancy types, and risk factors in patients with SSc are contradictory (9). Therefore, the aim of this study was to document the prevalence of malignancies in patients with SSc and their potential impact on the disease course with a 10-year follow-up.

MATERIAL AND METHODS

Before starting the study approval was obtained from the Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (approval number: 774, date: 29/05/2021). Between 2010 and 2020, patients with SSc diagnosed with International Classification of Diseases diagnosis code who applied to two centers were screened and identified. The SSc diagnoses of the patients were confirmed according to the "2013 The American College of Rheumatology (ACR)/The European Alliance of Associations for Rheumatology (EULAR) SSc classification criteria". Patients who did not fulfill the 2013 classification criteria according to their file records were excluded from the study. Patients were screened for malignancy diagnosis through the hospital information management systems of the two centers, follow-up files, "e-Nabız" of the patients (it is an application where health professionals can access health data collected from health institutions over the internet), and the Medulla doctor system. Patients diagnosed with malignancy at least 2 years after the diagnosis of SSc were included in the study. Patients without a diagnosis of malignancy were enrolled as the control group. Clinical characteristics were recorded from the patients' files, laboratory characteristics were recorded through the hospital systems, and computed tomography (CT) findings of patients with thoracic CT (interstitial lung disease or pleural effusion) and echocardiographic findings of patients with echocardiography were recorded. Interstitial lung disease and PHT were determined according to international definitions (10,11). Those with skin involvement on the proximal knee, elbow, and trunk were classified as having diffuse SSc. Other patients were classified as limited (12).

Statistical Analysis

All data were recorded and analyzed using Statistical Package for Social Sciences (SPSS) for Windows 25 software. The conformity of the variables to normal distribution was evaluated by the Kolmogorov-Smirnov and Shapiro-Wilk tests. The t-test was used for normally distributed data, and the Mann-Whitney U test was used for nonparametric data. Results are expressed as mean $\pm$ standard deviation for normally distributed data and median and minimum-maximum for non-normally distributed data. For categorical variables, results were presented as numbers and percentages. The chi-square test was used for categorical variables between proportions. p-values 0.05 were considered statistically significant.

RESULTS

According to 2013 ACR/EULAR SSc classification criteria, 149 patients with SSc (137 F/12 M) were identified. Of the patients, 45 had diffuse SSc, 89 had limited SSc, and 9 had sine scleroderma.

Malignancy was detected in 5 patients (3.36%). The mean age of the patients with malignancy was 54$\pm$6.4 years. All 5 patients were female. The mean age at diagnosis of malignancy was calculated as 50$\pm$6.6 years. Invasive ductal breast cancer was diagnosed in 2 patients, basal cell carcinoma of the skin in 1, ovarian adenocarcinoma in 1, and soft tissue sarcoma in 1. The interval between the diagnosis of SSc and malignancy was a minimum of 2 years and a maximum of 14 years (6.6$\pm$5.5). Two of the patients died. One was malignancy-related, and the other was due to other accompanying medical problems.

Three of the patients were followed up with a diagnosis of diffuse SSc and 2 with a diagnosis of limited SSc. Impairment in pulmonary function tests was detected in 2 patients, interstitial lung disease was detected in 3 patients on CT, and PHT was detected in 2 patients on echocardiography. One patient

had received pulse cyclophosphamide treatment, 2 patients had received rituximab treatment, 3 patients had received methotrexate treatment, 2 patients had received azathioprine treatment, and one patient had received D-penicillamine treatment.

When SSc patients with and without malignancy were compared, patients with malignancy had older age (54±6.4 vs. 50.3±14.2 and longer follow-up period (10.60±4.8 vs. 8.3±5.5), but no statistically significant difference was observed (p=0.43 and p=0.24, respectively). The proportion of patients with diffuse SSc was higher in the malignancy group, but not statistically significant (60% vs. 11% p=0.36). Dysphagia and gastroesophageal reflux disease (GERD) symptoms were significantly higher in patients with a diagnosis of malignancy (p=0.048 and p=0.038). Platelet count was found to be statistically significant in patients with malignancy (p=0.06), close to the significance level. No significant difference was observed in terms of other clinical and laboratory characteristics (Table 1 and 2).

The rate of malignancy development in diffuse and limited SSc patients was calculated as 6.3% in diffuse SSc patients and 2.1% in limited SSc patients [p=0.34, odds ratio=2.97 (0.48, 18.40)] (Figure 1).

DISCUSSION

The risk of malignancy is increased in systemic autoimmune rheumatic diseases. Although this increased risk has not been fully elucidated, it is thought to be the result of both the effects of chronic inflammation and tissue damage caused by autoimmunity on cancer risk and the inadequacy of drugs used for treating rheumatic diseases and impaired immunity against oncogenic viral infections (13).

Although there are different data in the literature regarding the risk of malignancy development in patients with SSc, the general opinion is that the rate of malignancy increases. The estimated SIR range from 1.5 to 5.1 compared with the general population (2). The malignancies with the highest reported increased risk are lung cancer and non-Hodgkin's lymphoma (8,14). An increased risk of oropharyngeal and esophageal cancer has also been reported in patients with scleroderma (14). In a review by Wooten (5), data from 5686 SSc patients were pooled and 358 (6.3%) malignancies were reported (based on data from 7 studies with malignancy rates ranging from 3.6% to 10.7%). The most commonly reported malignancies were pulmonary, breast, and gastrointestinal. The malignancy rate in our study was lower than that reported in these studies (3.4%). Lung cancer, the most commonly reported malignancy, was not observed in our patients. Breast cancer, which is the second most common malignancy, was detected in 2 of our patients.

Olesen et al. (15) showed that the risk of developing malignancy was approximately 1.5 times higher in patients with SSc than in the general population according to data obtained from patients diagnosed with SSc from 1977 to 2006 in the Danish

Table 1. The demographical and clinical features of SSc with cancers and without cancer

Mean ± SD or percent	Malignant (n=5)	Non-malignant (n=144)	p
Sex (females), n (%)	5 (100)	132 (91)	1
Mean age, years	54±6.4	50.3±14.2	0.43
Follow-up period, years	10.6±4.8	8.3±5.5	0.24
Death, %	2 (40)	17 (11)	0.24
Diffuse cutaneous SSc, n (%)	3 (60)	45 (31)	0.36
Digital ulcer, n (%)	1 (20)	53 (37)	0.75
Pitting scar, n (%)	3 (60)	61 (42)	0.75
Telangiectasia, n (%)	2 (40)	20 (14)	0.33
Dysphagia, n (%)	**4 (80)**	**47 (32)**	**0.048**
GERD symptoms, n (%)	**4 (80)**	**44 (30)**	**0.038**
Dyspnea, n (%)	4 (80)	97 (67)	0.93
HRCT abnormalities, n (%)	3 (60)	63 (44)	0.35
FVC %	82±23.1	76±18.6	0.64
PAP, mmHg‡	28±8.4	28±15.5	0.57

Statistically significant values are shown in bold, ‡PAP values were recorded by echocardiography, SSc: Systemic sclerosis, SD: Standard deviation, GERD: Gastroesophageal reflux disease, HRCT: High resolution computerized tomography, FVC: Forced vital capacity, PAP: Pulmonary artery pressure

Table 2. The laboratory features and medications of SSc with cancers and without cancer

Mean ± SD or percent	Malignant (n=5)	Non-malignant (n=144)	p
Hemoglobin, g/dL	13.2±0.9	12.7±1.5	0.53
Leukocyte, $10^3/mm^3$	6.4±1.8	8.4±2.9	0.11
Platelet, $10^3/mm^3$	238±37.8	295.5±96.7	0.06
ESR, mm/h	23±20	23±17	0.90
CRP, mg/dL	0.5±0.4	1.1±3.1	0.61
Creatinine, mg/dL	0.6±0.1	0.6±0.2	0.56
ANA positives, n (%)	4 (80)	118 (87)	0.93
Anti-Scl70 positives, n (%)	1 (20)	51 (39)	0.64
Anti-centromere positives, n (%)	0	29 (22)	0.58
Anti-Ro positives, n (%)	2 (40)	25 (19)	0.56
Cyclophosphamide, n (%)	1 (20)	43 (29)	1
Rituximab, n (%)	2 (40)	12 (8.3)	0.1
Mycophenolate mofetil, n (%)	1 (20)	19 (13)	0.51
Methotrexate, n (%)	3 (60)	39 (27)	0.27
Azathioprine, n (%)	2 (40)	78 (54)	0.86
D-penicillamine, n (%)	1 (20)	2 (1.4)	0.09

SSc: Systemic sclerosis, SD: Standard deviation, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: Anti-nuclear antibody

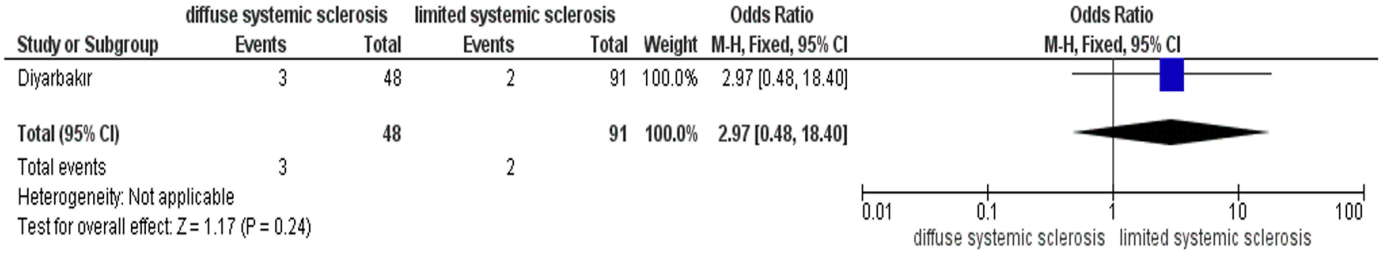

Figure 1. Malignancy risk ratio in patients with diffuse and limited SSc

national patient registry. In this study, the incidence of cancer was higher in men than in women (SIR 2.2 and 1.3, respectively). In general, male patients have a higher risk of malignancy (6). Only one review reported that older women have a higher risk of malignancy (5). In our study, all patients with malignancy were female, which may be due to the small number of male patients diagnosed with SSc.

Anti-RNA polymerase III SSc is associated with renal crisis (16). However, many studies have also found an association between anti-RNA polymerase III, an antibody specific for the diagnosis of SSc, and malignancy (4,17,18). Nikpour et al. (17) found that anti-RNA polymerase III antibodies were particularly associated with malignancy diagnosed within 5 years of the onset of SSc skin disease (13.3% vs. 3.9% in antibody positive patients). It was also found that these patients had a severe disease profile. In the study by Moinzadeh et al. (4), 2177 patients were screened and 7.1% had a history of cancer. When the autoantibody profile was evaluated, the prevalence of malignancy was calculated as 14.2% in anti-RNA polymerase III-positive patients, 6.3% in anti-Scl-70 antibody-positive patients, and 6.8% in anti-centromer antibody-positive patients, and the difference was significantly higher (4).

The occurrence of malignancy in rheumatological patients increases the burden of disease and negatively affects quality of life and life expectancy. It has been shown that 55% of deaths in SSc patients are directly related to SSc and 41% to non-SSc causes. The causes of non-SSc-related deaths based on the EUSTAR database are infections (13% of all deaths), neoplasia (13% of all deaths), and cardiovascular disease (12% of all deaths) (19). In

our study, the mortality rate was higher in patients diagnosed with malignancy (40% vs. 11%).

In a multicenter study conducted by Kaşifoğlu et al. (20) in which malignancy risk factors were evaluated in patients with SSc, 340 patients with SSc were screened and 25 patients (7%) were diagnosed with malignancy. 4 patients were diagnosed with bladder cancer, three with breast cancer, three with non-small-cell lung cancer, and three with hematological malignancy. When the data of patients with malignancy were compared with those of patients without malignancy, no statistically significant difference was found in demographic characteristics, organ involvement, autoimmune serology, cyclophosphamide use, and dose. However, higher doses of cyclophosphamide were used in patients with bladder cancer. In our study, GERD and dysphagia symptoms were reported more frequently in patients with malignancy. However, no significant difference was observed between the treatment options. In fact, we found that rituximab and mycophenolate mofetil, which are relatively safe, were preferred more in patients with malignancy. This is because malignancy patients have more aggressive disease. Cyclophosphamide, which is most commonly associated with the development of malignancy, was used in only one patient. This may be due to the clinician's anticipation of the risk of malignancy. In addition, we found that penicillamine treatment (although not widely used today) was used at a higher rate in patients with malignancy, although not statistically significant.

In another study by Sargin et al. (21) 153 patients were screened, and malignancy was detected in 7 patients. Malignancy was detected in three males and four females, and the mean age was 51.2 years. One lung cancer, 2 gastrointestinal system cancers, one myelodysplastic syndrome, two malignant melanomas (eye and skin), and one ovarian cancer were detected. Smoking, male gender, being diagnosed with diffuse SSc, and anti-Scl-70 positivity were reported as risk factors. In our study, we found a higher rate of malignancy in patients with diffuse SSc (6.3% vs. 2.1%). The odds ratio was calculated as 2.97 for the diffuse subtype.

Our study had some limitations. The number of patients with malignancy was low. Because the number of male SSc patients was low, we did not have a male patient diagnosed with malignancy. Risk factors could not be evaluated because our study was conducted through a retrospective file review. Our study included malignancies observed in a 10-year follow-up. In addition, the RNA polymerase III antibody, which was evaluated as a risk factor in most studies, was not evaluated in our patients.

CONCLUSION

The risk of cancer is increased in patients with SSc compared with the general population. It is important to perform age/gender appropriate malignancy screening in every case of clinical suspicion for early diagnosis and treatment in terms of a possible accompanying malignancy. However, routine screening of all patients is not recommended. Studies with larger case series are needed to determine malignancy screening recommendations and risk factors specific to SSc patients.

Ethics

Ethics Committee Approval: The study approval was obtained from the Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (approval number: 774, date: 29/05/2021).

Informed Consent: A study retrospective was designed.

Authorship Contributions

Surgical and Medical Practices: İ.G., M.A.B., L.A., R.Ç., Concept: İ.G., M.A.B., L.A., R.Ç., Design: İ.G., M.A.B., L.A., R.Ç., Data Collection or Processing: İ.G., M.A.B., Analysis or Interpretation: İ.G., R.Ç., Literature Search: İ.G., L.A., Writing: İ.G.

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IDIOPATHIC GRANULOMATOUS MASTITIS: MULTICENTER STUDY

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Abstract

Objectives: Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic inflammatory breast disease of unknown etiology. There is no standardized treatment because its etiology is still unclear. In this multicenter study, we presented the demographic, treatment, and follow-up characteristics of IGM cases monitored by rheumatology clinics.

Material and Methods: This retrospective study was conducted in 13 different rheumatology centers. A total of 108 patients with IGM were included in the study. Demographic and clinical data were retrospectively obtained from patient files.

Results: The most commonly administered drugs were, in order of frequency, corticosteroid (CS) (91.7%), methotrexate (MTX) (74.1%), antibiotics (63%), non-steroidal anti-inflammatory drugs (41.7%), azathioprine (AZA) (13.9%), colchicine (5.6%), and tumor necrosis factor (TNF) inhibitors (0.9%). The most commonly used form of immunosuppressive (IS) treatment was the MTX and CS combination 78 (72.2%). The ratio of patients receiving CS alone was 19 (17.6%). The ratio of patients who were operated on only and did not use IS drugs was 6.5%. The ratio of patients who received no treatment was 2.8%. Among the drugs used, MTX and CS alone use were independent risk factors for relapse; (p=0.027, p=0.011, respectively). The relapse rate was higher in patients receiving CS alone.

Conclusion: IS drugs including CS, MTX, AZA, and TNF inhibitors seem to be efficient for treating IGM. CS alone use is associated with relapse, and the use of other IS drugs such as MTX is particularly effective in reducing relapse in IGM.

Keywords: Granulomatous mastitis, rheumatology, immunosuppressive drugs, corticosteroid, methotrexate

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare, benign, chronic inflammatory breast disease of unknown etiology. IGM frequently affects women of reproductive age and is characterized by the presence of non-caseating granulomas confined to the breast lobule (1,2). The mass presents with clinical findings such as erythema, swelling, fistula, nipple retraction, nipple discharge, abscess, and enlarged lymph nodes, and radiological findings such as hypoechoic lesions, calcifications, and asymmetric density increase (3). Because IGM may clinically and radiologically mimic acute breast infections or malignancy and hence cause a delay in diagnosis, pathological detection and exclusion of other causes are required for a definitive diagnosis of IGM. Other causes that should be excluded include tuberculosis, sarcoidosis, mycotic/parasitic infections, and other infective and autoimmune causes of granulomatous inflammation, such as granulomatous polyangiitis (GPA) (3,4).

The etiology of IGM is not clearly known, but risk factors may include trauma, hormones [oral contraceptives (OCS), pregnancy and childbirth], breastfeeding (which may involve both trauma and hormones), high prolactin (PRL) levels, infections (especially *Corynebacterium*), and autoimmunity (5,6). In addition, there appear to be geographical and ethnic differences in the prevalence of IGM (5,6). This geographical diversity suggests that there may be an underlying unidentified infectious trigger or genetic predisposition involved. Although antibiotics, corticosteroids (CS), and surgical excision are the primary treatment options for IGM, there is no standardized treatment because its etiology is still unclear (7,8). In this multicenter study, we aimed to present the demographic, treatment, and follow-up characteristics of IGM cases monitored by rheumatology clinics.

MATERIAL AND METHODS

This retrospective study was conducted in 13 different rheumatology centers. Ethics committee approval was obtained from by Fırat University Non-interventional Research Ethics Committee (approval number: 9613, date: 06/07/2022).

The informed consent form was obtained from each participant. A total of 108 patients whose physical examination findings were compatible with IGM and whose breast biopsy specimens were diagnosed as non-caseating granuloma on histopathological evaluation were included in the study. Patients over 18 years of age with clinical and radiological findings compatible with IGM and histopathologically verified granulomatous mastitis were included in this study, whereas patients with less than 6 months of follow-up, patients with underlying infection, granulomatous diseases such as tuberculosis, sarcoidosis, GPA, and malignancy were excluded.

Demographic and clinical data were retrospectively obtained from patient files. Age, gender, age at diagnosis, smoking status, oral contraceptive use, pregnancy and breastfeeding status, history of trauma, presence of infection, and autoimmune disease were recorded for each patient. The clinical findings were as follows: unilateral/bilateral presentation, mass, presence of skin changes (erythema, nipple inversion, hardening), pain in the breast, fistulization to the skin, nipple discharge, ulceration, axillary lymphadenopathy (LAP), arthralgia, arthritis, erythema nodosum (EN), fever, and weight loss.

Erythrocyte sedimentation rate, C-reactive protein, PRL, anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, anti-double-stranded DNA antibodies, rheumatoid factor, angiotensin-converting enzyme, and complement levels were obtained from the medical records of the patients. The findings from imaging methods used in diagnosis [breast ultrasound (US), breast magnetic resonance (MR) imaging or mammography], culture results, and biopsy results were recorded. Breast imaging findings were recorded using the terminology defined in the American College of Radiology Breast Imaging Reporting and Data System (9).

Treatment options administered [antibiotics, CS, immunosuppressive (IS) drugs, or surgical intervention], drug doses for each patient, duration of treatment, disease course, and outcomes were investigated. The IS drugs used [CS, methotrexate (MTX), azathioprine (AZA), and tumor necrosis factor (TNF) inhibitors] were recorded. The dose of CS was indicated as methylprednisolone (MP) or equivalent.

Treatment efficacy was evaluated as clinical improvement and partial or complete remission. Improvement in symptoms, physical examination findings, and acute phase reactants at the first-month visit was classified as clinical improvement; at least 50% improvement in clinical and radiological findings at the 3rd or 6th-month visits was classified as partial remission; and complete improvement in clinical and radiological findings at the 6th-month visit was classified as complete remission. Partial response is defined as a decrease in each clinical feature of at least half. If there was improvement in a single clinical parameter but not in others, it was not considered as partial remission. Radiological remission was defined as; the disappearance of all lesions on MR, US, or mammography. The presence of still-enhancing lesions was considered as radiological non-response.

Relapse was defined as disease recurrence after 3 months of remission. Persistent disease was considered as patients who

never achieved remission (3). If a new lesion developed (clinically or/and radiogically) in a patient who had been in remission for at least 3 months, this was evaluated as "relapse". If the patient developed a new lesion before remission was achieved, it was considered "non-response" to treatment.

Statistical Analyses

IBM SPSS 24 software for Windows (SPSS Inc., Chicago, Illinois) was used for statistical analyses. Descriptive statistics are presented as mean ± standard deviation and median (minimum-maximum) values for measured variables and frequency and percentage (%) for categorical data. Categorical variables of patients with and without relapse were compared using Pearson's chi-square test and Fisher's exact test, as appropriate. Factors related to relapse were evaluated by univariate and multivariate regression analyses. A value of $p<0.05$ was considered statistically significant.

RESULTS

Basic Characteristics and Clinical Features of Patients with IGM

A total of 108 patients were included in the study. The ratio of patients with pregnancy and with OCS use at the time of diagnosis was 3.7% (n=4) and 3.7% (n=4). The ratio of patients with less than 5 years since their last pregnancy was 35.8% (n=29). The ratio of patients with less than 5 years since the last lactation was 39.5% (n=32). The demographic data of the patients are shown in Table 1.

The most common clinical findings of patients with IGM at presentation were pain (99.1%), palpable mass (81.5%), stiffness (77.8%), erythema (76.9%), nipple discharge (50.9%), and axillary LAP (36.1%), in order of frequency. Both breasts were affected in 17.6% of the patients. The clinical findings of the patients at presentation are summarized in Table 2.

The frequency of laboratory and radiological findings and other diagnostic methods used in the diagnosis of patients with IGM are summarized in Table 3. Core biopsy was predominantly (75.9%) used in the diagnosis of patients. The ratio of patients who underwent culture was 51.8%. The most commonly used radiologic method in the diagnosis was ultrasonography, which was performed in all patients.

Treatment and Clinical Response in Patients with IGM

Table 4 summarizes the treatments administered to patients with IGM and their treatment responses. The most commonly administered drugs were, in order of frequency, CS (91.7%), MTX (74.1%), antibiotics (63%), non-steroidal anti-inflammatory drugs (41.7%), AZA (13.9%), colchicine (5.6%), and TNF inhibitors (0.9%). The most commonly used form of IS treatment was the MTX and CS combination 78 (72.2%). The ratio of patients receiving CS alone was 19 (17.6%). The ratio of patients who were operated on only and did not use IS drugs was 6.5%. The ratio of patients who received no treatment was 2.8%.

The evaluation of treatment responses revealed that 63% of the patients had partial remission and 9.3% had complete remission. There was no response to treatment in 8.3% of the patients, and relapse was observed in 15.7%.

Comparison of Patients with and without Relapse and Factors Affecting Relapse

When patients with and without relapse were compared, no difference was found between the two groups in terms of demographic data, laboratory findings, and radiological findings. Among the clinical findings, only the relapse rate was different in patients with fistulization and ulceration. 52.9% (9/17) of relapsed patients had fistulization compared with 24.1% (21/87) of non-relapsed patients (p=0.037). While 41.2% (7/17) of relapsed patients had ulceration, 47.1% (41/87) of non-relapsed patients had ulceration (p=0.034). The ratio of arthritis and EN was not different between relapsed and non-relapsed patients.

When patients with and without relapse were compared in terms of drugs used, it was found that 71.4% of patients with relapse used MTX, whereas 92.9% of patients without relapse used MTX. The relapse rate was 13.2% (10/76) in patients receiving MTX and 44.4% (4/9) in patients not receiving MTX (p=0.037). The relapse rate was 36.8% (7/19) in patients receiving only CS and 10/85 (11.8%) in patients not receiving CS (p=0.014). There was no significant difference between patients with and without relapse in terms of the other drugs used.

Factors affecting relapse were evaluated using univariate analysis. Among the clinical findings, the presence of inversion, fistulization, and ulceration were evaluated as prognostic factors; (p=0.017, p=0.021, p=0.017 respectively). Among the drugs used, MTX and CS alone use were independent risk factors; (p=0.027, p=0.011, respectively). When the factors found to be significant in univariate analysis were evaluated using multivariate analysis, CS alone use was found to be an independent risk factor. The relapse rate was higher in patients receiving CS alone.

Evaluation of Clinical Response According to the IS Drugs Used

Of the 95 patients who received CS, 8.4% (n=8) had no response, 67.4% (n=64) had partial response, 8.4% (n=8) had complete response, and 15.8% (n=15) had relapse. None of the 19 patients who received CS alone had no response, 47.4% (n=9) had partial

Table 1. Demographic characteristics of IGM patients	
Age, years, mean ± SD	36.6±6.7
Age at diagnosis, mean ± SD	34.3±6.1
Symptom duration, years, median (min-max)	1.5 (0.1-8)
Follow-up time, years, median (min-max)	2 (0.5-6)
Number of pregnancies, median (min-max)	2 (1-8)
Smoking status, n (%)	*Active smoker, 6 (5.6%) *Quit, 5 (4.6%) *Never smoked, 68 (63%) *Unknown, 27 (25%)
BMI, mean ± SD	27.2±4.1
Comorbidities, n (%)	
No	81 (75%)
Lung diseases	0 (0%)
Pulmonary hypertension	0 (0%)
Asthma	2 (1.9%)
Diabetes Mellitus	5 (4.6%)
Obesity (BMI>30)	5 (4.6%)
Hypertension	5 (4.6%)
Congestive heart failure	0 (0%)
Coronary artery disease	3 (2.8%)
Cerebrovascular event	0 (0%)
Renal failure	0 (0%)
Inflammatory bowel disease	1 (0.9%)
Psychiatric disorder	3 (2.8%)
Atopic eczema	1 (0.9%)
Liver disease	0 (0%)
Concomitant rheumatologic diseases	
Familial mediterranean fever	1 (1.2%)
Vasculitis limited to the skin	1 (1.2%)
Spondyloarthropathy	1 (0.9%)
Tuberculosis history	0 (0.0%)
History of sarcoidosis	0 (0.0%)
Oral contraceptive history, n (%)	*Never used, 61 (56.5%) *Using at the time of diagnosis, 4 (3.7%) *Used in the past, 12 (11.1%)
Intrauterine device history	*Never used, 63 (58.3%) *Using at the time of diagnosis, 11 (10.2%) *Used in the past, 3 (2.8%)
Pregnancy history	*None, 2 (1.9%) *Currently pregnant, 4 (3.7%) *Previous pregnancy, 77 (71.3%)
Time since the last pregnancy	*<5 years, 29 (26.8%) *>5 years, 21 (19.4%)
Time since the last lactation	*No lactation history, 0 (0.0%) *<5 years, 32 (29.6%) *>5 years, 17 (15.7%)

Patient percentages were calculated according to the total number of patients, IGM: Idiopathic granulomatous mastitis, SD: Standard deviation, BMI: Body mass index, min-max: Minimum-maximum, n: Number*

Table 2. Clinical characteristics of IGM patients

Clinical findings at diagnosis	n (%)
Erythema	83 (76.9%)
Nipple inversion	20 (18.5%)
Stiffness	84 (77.8%)
Palpable mass	88 (81.5%)
Pain	107 (99.1%)
Fistulization to the skin	30 (27.8%)
Ulceration	20 (18.5%)
Nipple discharge	55 (50.9%)
Axillary LAP	39 (36.1%)
Arthralgia	33 (30.6%)
Arthritis	3 (2.8%)
EN	14 (13.0%)
Arthritis + EN	5 (4.6%)
Fever	15 (13.9%)
Weight loss	8 (7.4%)
Affected breast	**n (%)** *Right only, 39 (36.1%) *Left only, 48 (44.4%) *Bilateral, 19 (17.6%)

IGM: Idiopathic granulomatous mastitis, LAP: Lymphadenopathy, EN: Erythema nodosum, n: Number*

response, 15.8% (n=3) had complete response, and 36.8% (n=7) had relapse. Clinical response was observed in 63.2% of patients who received only CS.

Of the 76 patients receiving MTX, 10.5% (n=8) had no response, 69.7% (n=53) had partial response, 6.6% (n=5) had complete response, and 13.2% (n=10) had relapse. Among patients receiving MTX, 76.3% showed clinical response. Among patients receiving AZA (n=15), 1 had no response, 11 had partial response, 1 had complete response, and 2 had relapse. Clinical response was observed in 80% of patients receiving AZA. The evaluation of clinical response according to the drugs used and the type of treatment administered is shown in Table 5.

DISCUSSION

Despite the increase in the frequency of patients diagnosed with IGM in recent years, available data on the clinical course and treatment of the disease are still limited. There is no consensus on the treatment of IGM because the number of prospective studies is limited and retrospective case series usually involve some patients. While patients with IGM were usually managed by general surgeons and gynecologists in the past, they have recently been increasingly managed by rheumatologists. In this study, we aimed to examine the follow-up and treatment of IGM

Table 3. Laboratory and radiologic findings and diagnostic methods used in patients with IGM (n=108)

Initial laboratory values	
ESR, mm/h, median (min-max)	30 (3-117)
CRP mg/L, median (min-max)	12 (2-96)
Prolactin, median (min-max)	14 (5-80)
Biopsy	*Excisional, 20 (18.5%) *Core, 82 (75.9%)
Culture	*No culture, 50 (46.3%) *Culture performed, no growth, 51 (47.2%) *Culture performed, the existence of growth, 5 (4.6%)
Radiology findings	
Breast US findings	*Mass-like areas with unclear borders, 50 (46.3%) *Phlegmonous changes, 1 (0.9%) *Increased density and fluid effusion, 83 (76.9%)
Mammography findings	*Focal asymmetry, 3 (2.8%) *Skin thickening, 2 (1.9%), *Scattered densities 11 (10.2%), *Masses and abscesses, 10 (9.3%)
Breast MRI	*Not performed, 75 (69.4%) *Performed-compatible with IGM, 30 (27.8%) *Performed-incompatible with IGM, 1 (0.9%)

IGM: Idiopathic granulomatous mastitis, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, US: Ultrasonography, MRI: Magnetic resonance imaging, min-max: Minimum-maximum, *

from the perspective of rheumatologists, and our experience in IGM follow-up and treatment is presented from the perspective of rheumatology.

Consistent with previous data, most patients in our series were young to middle-aged women, and the majority had a recent (last 5 years) history of child delivery and/or breastfeeding. Previous studies have indicated that pregnancy and breastfeeding are major factors responsible for IGM, especially in the reproductive age group, and may be risk factors for relapse (10-14). In our study, 75% of patients had a history of one or more pregnancies. Of the 81 patients with a history of pregnancy, information on the number of years before the diagnosis of IGM was available only in 50 patients, and 58% of these patients had a history of pregnancy within the last 5 years. Similar to our study, Barreto et al. (13) reported that 63% of patients had a history of pregnancy within the last 5 years. In our study, the ratio of patients with OCS use at the time of diagnosis was 14.8%, whereas it was 17%

in another study. In this study, elevated PRL levels were observed in 5 patients; however, none of the patients with elevated PRL levels had a history of pregnancy, breastfeeding, or any medication that might have increased PRL at the time of IGM diagnosis (15). In a previous study, five patients had elevated PRL levels without any underlying cause (13). In our study, pregnancy, breastfeeding, use of OCS, and elevated PRL were not found to be risk factors in terms of relapse.

The most common clinical findings in our study were pain, palpable mass, stiffness, erythema, nipple discharge, and axillary LAP. These findings are similar to other literature data. In our study, the concomitance of EN and arthritis was 4.6%. The incidence of EN was 13%, which is considerably higher than that in other cohorts. In a recent systematic review of 3060 cases, the incidence of EN was found to be 8% (15). The high incidence of EN and arthritis in our cohort may be partly explained by the fact

Table 4. Treatment and clinical response in IGM patients

Drugs used, n (%)	
NSAID	45 (41.7%)
Antibiotics	68 (63%)
Colchicine	6 (5.6%)
CS	95 (87.9%)
AZA	15 (13.9%)
MTX	80 (74.1%)
TNF inhibitors	1 (0.9%)
Initial CS dose	32 (4-80)
CS dose at the last visit	4 (0-24)
The total duration of CS, months, median (min-max)	10 (2-48)
Was CS treatment discontinued? n (%)	*No, 31 (28.7%) *Yes, 72 (66.7%)
Total IS duration, months, median (min-max)	9.5 (2-48)
AZA dose, median (min-max)	100 (100-150)
MTX dose, median (min-max)	15 (10-20)
Initial treatment approaches for patients, n (%)	*Surgery alone, 7 (6.5%) *IS treatment after failed surgery, 12 (11.1%) *Concomitant surgery + IS treatment, 4 (3.7%) *Patients receiving IS medication, 98 (90.7%) Medication use ratios of patients receiving IS treatment among all patients; *CS alone, 19 (17.6%), *MTX and CS, 78 (72.2%) *AZA and CS, 16 (14.8%) *TNF inhibitor + other IS, 1 (0.9%) *No medication, 3 (2.8%) Medication use ratios of patients receiving IS treatment; *CS alone, 19 (19.4%), *MTX and CS, 78 (79.6%), *AZA and CS, 16 (16.3%), *TNF inhibitor + other IS, 1 (1.02%)
Clinical response, n (%)	*No response, 9 (8.3%) *Partial response (at least 50% clinical and radiologic improvement at 3/6 months), 68 (63%) *Complete response (complete clinical and radiologic remission at 6 months), 10 (9.3%) * Relapse, 17 (15.7%)

IGM: Idiopathic granulomatous mastitis, NSAID: Non-steroidal anti-inflammatory drug, CS: Corticosteroid, AZA: Azathioprine, MTX: Methotrexate, TNF: Tumor necrosis factor, IS: Immunosuppressive, *, n: Number

Table 5. Clinical response according to drugs used and treatment modalities

	Non-response	Partial response	Full response	Clinical response (Partial + Full)	Relapse
CS alone (n=19) (%)	0 (0)	9 (47.3)	3 (15.8)	12 (63.2)	7 (36.8)
CS (n=95) (%)	8 (8.4)	64 (67.4)	8 (8.4)	72 (75.8)	15 (15.8)
Colchicine (n=6) (%)	0 (0)	4 (66.6)	0 (0)	4 (66.6)	2 (33.3)
MTX (n=76) (%)	8 (10.5)	53 (69.7)	5 (6.6)	58 (76.3)	10 (13.2)
AZA (n=15) (%)	1 (6.6)	11 (73.3)	1 (6.6)	12 (80)	2 (13.2)
MTX+ CS (n=74) (%)	8 (10.8)	50 (67.6)	6 (8.1)	56 (75.7)	10 (13.5)
AZA+ CS (n=16) (%)	1 (6.3)	12 (75)	1 (6.3)	13 (81.25)	2 (12.5)
Surgery alone (n=7) (%)	0 (0)	3 (42.8)	1 (14.3)	4 (57.1)	3 (42.8)
Postoperative IS (n=12) (%)	1 (8.3)	6 (50)	2 (16.6)	8 (66.6)	3 (25)
Surgery + IS at the same time (n=4) (%)	0 (0)	3 (75)	1 (25)	4 (100)	0 (0)
No treatment (n=3) (%)	1 (33.3)	2 (66.6)	0 (0)	2 (66.6)	0 (0)

CS: Corticosteroid, MTX: Methotrexate, AZA: Azathioprine, IS: Immunosuppressive, n: Number

that rheumatologists are more likely to identify these conditions. It may also suggest that IGM is a systemic inflammatory disease and that follow-up by rheumatologists may benefit the disease.

Although medical imaging provides important diagnostic information for the diagnosis of IGM, the definitive diagnosis of IGM relies on histological examination of tissue obtained from open biopsy (incision/excision) or core needle biopsy. Hovanessian Larsen et al. (16) used core needle biopsy in 46 of 48 cases of IGM in their series and reported success rates above 95%. When core biopsy fails to definitively diagnose IGM, an open biopsy is required to histologically confirm the presence of non-necrotizing granulomas. In our study, all patients underwent biopsy, and core biopsy was the most commonly used method in our cohort. Core biopsy was performed in 75.9% of the patients. The pathology results of 6 patients were not available.

In the literature, the optimal treatment for IGM is observation alone, antibiotic therapy, surgical resection, CS, and ISs (13). However, there is no standard treatment for IGM. It has been reported in many studies that patients with persistent symptoms are often prescribed different and multiple antibiotics (13,16-20). In our study, it was observed that 63% of the patients were prescribed antibiotics. Culture was performed in 55 (50.9%) of our patients, and growth was detected in 5 (0.9%). IGM is, by definition, a sterile inflammatory disease; therefore, antibiotic treatment is usually unsuccessful. It seems to be a more rational approach to administer antibiotic treatment according to microbiological culture results and to patients with growth.

Rheumatologists are often interested in granulomatous diseases and are more familiar with treatment options for ISs, which are not within the expertise of breast surgeons. To date, case series of CS, MTX, AZA, or TNF inhibitors have been reported in the treatment of IGM (7,15,18-22). Studies in the literature have shown that CS treatment may be effective in reducing mass size and improving abscess formation in patients with IGM. Some studies have indicated CS as a single drug or as first-line therapy before surgical excision because, in many publications, they allow for the reduction in the size of multiple and complicated lesions (7,15,19). Some authors recommend CS treatment only for refractory and recurrent cases.

Early data on the use of CS for IGM proposed an initial dose of 60 mg daily, but recent publications suggest that half this dose is equally effective (3,7,19). In our study, the starting dose of CS was found to be 32 mg MP or equivalent. Long-term and high-dose CS treatment may be associated with numerous side effects. In addition, studies in the literature report that a relapse rate of approximately 50% is possible when reducing the dose of CS (1). Although CSs have been used by many as first-line treatment for IGM, they are associated with significant risks when used long-term. Having additional should be is treatment options for IGM is important both in terms of preventing relapses and reducing the side effects of CS. In our study, the relapse rate in patients receiving CS alone was significantly higher than that in patients receiving CS and IS concomitantly. CS use alone is an independent risk factor for relapse.

In the literature, studies are showing the efficacy of MTX in reducing disease recurrence, suppressing inflammation, preventing complications, reducing the side effects of CS, and reducing the dose of CS in addition to achieving disease remission (3,15,22). In the study by Akbulut et al. (21) a total of 541 cases of IGM since 1972 were retrospectively analyzed and it

was shown that the addition of MTX therapy to CS therapy was effective in the management of IGM. Ringsted and Friedman (3) mentioned the rheumatologic approach in a series of 28 cases. In this study, patients treated with MTX had the highest relapse-free remission rates. In our study, the relapse rate of patients receiving MTX was 13.2% and that of patients not receiving MTX was 44.4%. Although our data show that patients treated with MTX have a higher remission rate, prospective, randomized studies comparing MTX with CS or other ISs with MTX would be very useful.

Similarly, Konan et al. (23) have shown the efficacy of AZA for treating IGM. In our study, remission was observed in 13 of 16 patients (81.3%) treated with AZA because of pregnancy or MTX-resistant disease. Among the treatments administered, the highest clinical response rates were observed in AZA plus CS treatment. The other treatment with the second highest response rate was the MTX plus CS combination. In terms of treatment modality, remission was observed in all patients who received both surgery and IS treatment simultaneously. Although a definite statement cannot be made because the number of patients who received surgery and IS treatment simultaneously was only 4, the combination of both appears to be increasing the response rates. In another study, surgery alone or in combination with CSs was found to have the lowest recurrence rates with 6.8% and 4%, respectively (24). In another study, 80% of patients treated with MTX, 42% of patients treated with CSs alone, and 66% of patients treated with CSs and surgery combined reported recurrence-free remission (3). In our study, patients who received postoperative IS treatment were found to be the second most frequent in terms of response to treatment, and the third most frequent in this respect were patients who only underwent surgery. In support of this finding, in our study, the highest relapse rate was found in patients who underwent surgery alone and who did not receive IS. The next highest relapse rate was observed in patients who received CS alone. When all the findings are evaluated together, it appears that the addition of ISs, especially KS, to the treatment is more effective in achieving emission and preventing relapses than surgery alone.

TNF inhibitors may also be effective for treating resistant cases (14). Cases treated with etanercept and adalimumab have been reported in the literature (25-28). In our study, one patient was treated with adalimumab. Because only one patient was using TNF inhibitors, it was not possible to evaluate the effect of TNF inhibitors in treatment based on this study. Further studies, including more cases, are needed to evaluate TNF inhibitors as effective agents in suppressing inflammation in IGM. In our study, colchicine was also used in 6 patients. Although it is not possible to conclude whether colchicine alone is effective, it may be one of the treatment options that might be considered in patients with EN or arthritis.

The appropriate duration of treatment in patients with IGM remains unclear. Previously, it has been noted that IS treatment should be continued until complete remission because otherwise, the relapse rate might be high. The commonly reported treatment duration is on average 12 months (29). In our study, the duration of IS treatment was found to be 10 (2-48) months.

Our study included patients who were followed up for at least 6 months. The mean follow-up period was 2 years. The follow-up period in our study was quite long, and the relapse rate was quite low compared with the data reported in the literature. The most powerful feature of this study is that it is multicenter and the number of patients is quite high compared with other data in the literature.

The main limitation of our study is its retrospective design. Except for one prospective case series, all data in the literature are retrospective case series (10). Further studies with larger samples and prospective designs are needed to confirm the efficacy of systemic IS therapies for treating IGM.

CONCLUSION

IS drugs including CS, MTX, AZA, and TNF inhibitors seem to be efficient for treating IGM. CS alone use is associated with relapse, and the use of other IS drugs such as MTX is particularly effective in reducing relapse in IGM.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from by Fırat University Non-interventional Research Ethics Committee (approval number: 9613, date: 06/07/2022).

Informed Consent: The study was designed retrospectively.

Authorship Contributions

Surgical and Medical Practices: S.E., M.S.A., L.A., M.A.B., B.K., S.S.K., Concept: S.E., M.Ş.A., O.C., Ş.K.E., M.A.B., B.K., S.S.K., Design: S.E., M.S.A., M.Ş.A., S.Z., O.C., F.A., O.Z., Ö.K., E.İ., S.Y., L.A., Ş.K.E., H.B., M.A.B., Y.S., A.K., H.A., B.K., S.S.K., Data Collection or Processing: S.E., M.S.A., M.Ş.A., S.Z., O.C., F.A., O.Z., Ö.K., E.İ., S.Y., L.A., Ş.K.E., Y.S.,H.B., M.A.B., A.K., H.A., B.K., S.S.K., Analysis or Interpretation: S.E., M.Ş.A., F.A., Ö.K., Ş.K.E., H.B., M.A.B., Y.S., A.K., B.K., S.S.K., Literature Search: S.E., S.Z., O.C., O.Z., S.Y., H.B., M.A.B., Y.S., A.K., B.K., S.S.K., Writing: S.E., M.S.A., M.Ş.A., E.İ., M.A.B., Y.S., H.A., B.K., S.S.K.

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ORIGINAL ARTICLE

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INTRALESIONAL STEROID THERAPY IN PATIENTS WITH IDIOPATHIC GRANULOMATOUS MASTITIS

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Abstract

Aim: Idiopathic granulomatous mastitis (IGM) is a rare chronic inflammatory breast disease. Histopathology is characterized by non-caseating granulomas. Although oral contraceptive use, pregnancy, breastfeeding history, high prolactin levels, smoking, and chemical irritation have been blamed for its etiology, it has not been fully elucidated. We studied the responses obtained using intralesional (IL) steroid application in addition to conventional treatments in patients with IGM referred to the rheumatology and radiology departments of Fırat University Research Hospital.

Material and Methods: Seventy-six female patients diagnosed with IGM who were followed between January 2021 and May 2023 were included in the study. The pathologies of the patients, whose average age was 36.5±6.8 years, were compatible with IGM. In terms of differential diagnoses, other conditions that could cause granulomatous mastitis were excluded. The data obtained were analyzed with appropriate statistical methods using statistical package for social sciences (SPSS) for Windows 25.

Results: Remission was achieved in 55.3% of patients (42 patients). While remission was observed in 61.6% of the patients who received IL steroids, remission was achieved in only 23.1% of the patients who did not receive IL steroids, and this rate was found to be statistically significant (p=0.010). There was no statistically significant difference between the treatments received by patients who achieved remission and those received by patients whose treatment continued (p>0.05).

Conclusion: In our study, the treatments received by patients who were and were not administered IL steroids were similar, but a significant difference was observed in patients who were administered IL steroids in terms of achieving remission. This suggested that IL steroid administration would have a positive contribution to the treatment response.

Keywords: Idiopathic granulomatous mastitis, intralesional injection, steroid treatment

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a benign chronic inflammatory breast condition, first described in 1972 by Kessler and Wooloch (1). IGM most often presents in women of childbearing age within a few years of pregnancy. It is most common in women of Asian, Hispanic, Middle Eastern, or African origin (2,3). Rarely, IGM has also been reported in nulliparous women and men (4,5).

It mimics breast cancer and abscesses. However, its etiology is still unknown. The pathogenesis of IGM remains unclear,

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although evidence suggests that it is likely autoimmune in nature. Specific causes of infection with some *Corynebacterium* species, oral contraceptive pills, trauma, foreign body reactions, hyperprolactinemia, and diabetes mellitus should also be excluded (5). Environmental and genetic factors may also play an important role in the underlying etiology of the disease (6). Histopathologically, IGM is characterized by non-caseating granulomas around the lobules and ducts in the breast (5).

It usually causes symptoms such as a mass in the breast, pain, skin redness, abscess, fistula, nipple retraction, and discharge (7).

In diagnosis, it is first necessary to perform breast imaging with ultrasound, mammography, or magnetic resonance imaging. The main diagnosis is made histopathologically by core needle biopsy (8).

IGM treatment and management are not fully standardized yet. Treatment of IGM involved antibiotics, corticosteroids, immunosuppressants, methotrexate, colchicine, other anti-inflammatory agents, and surgical treatment modalities. Corticosteroids were first used by DeHertogh et al. (9) in 1980. Although steroid treatment is primarily used, methotrexate and azathioprine are also used as steroid dose reducers (10). Healing and cosmetic problems create disadvantages in surgical treatment methods. In recent studies, fluid aspiration and intralesional (IL) steroid injection approaches have been used as treatment methods (11,12). The use of local treatment has also been deemed valuable in terms of reducing the side effects of systemic treatment.

In our study, we studied the responses obtained from IL steroid application in addition to conventional treatments in patients with IGM.

MATERIAL AND METHODS

All female patients diagnosed with IGM who were followed up in the Fırat University Research Hospital Rheumatology and Radiology Clinics between January 2021 and May 2023 were included in the study. A total of 77 newly diagnosed patients were included. This was a prospective study. The diagnosis of IGM was confirmed histopathologically in all patients. For differential diagnosis, patients were examined and screened for tuberculosis, infectious causes, sarcoidosis, antineutrophilic cytoplasmic antibody-related vasculitis, and connective tissue diseases. Patients were divided into two groups depending on the treatment method: those who received IL steroid treatment and those who did not. The status of achieving remission and the treatments they received were compared between the two groups. The study protocol was approved by Fırat University Non-interventional Research Ethics Committee (approval number: 9613, date: 06/07/2022).

Statistical Analysis

All collected data were recorded in SPSS for Windows 25. Normal distribution analysis of variables was performed using Kolmogorov-Smirnov and Shapiro-Wilk tests. t-test for data complying with normal distribution; Mann-Whitney U test was used for non-parametric data that did not comply with normal distribution. For data complying with normal distribution, the results are mean ± standard deviation; for data that does not comply with normal distribution, the results are given as median and minimum-maximum. The chi-square test was used for categorical variables. Pearson's correlation test for parametric data for the existence of relationships between numerical values. For non-parametric data, Spearman's correlation test was used. Values with a p-value of 0.05 will be considered statistically significant. In the correlation analysis, r>0.3 and p-values below 0.05 were considered significant.

RESULTS

A total of 77 patients were included in the study. One of the 77 patients was excluded from the study because she discontinued treatment voluntarily during follow-up. All patients had given birth. The demographic and laboratory characteristics of the patients, whose average age was 36.5±6.8 years, are shown in Table 1. Remarkably, the average body mass index of the patients was 27.06±3.5 kg/m^2, which was above normal.

In our study, 42.1% of the patients received antibiotic treatment before or after diagnosis, and the most frequently used treatments were oral steroids (88.2%) and methotrexate (85.5%) (Table 2).

Remission was achieved in 55.3% of the patients (42 patients). While remission was observed in 61.6% of the patients who received IL steroids, remission was achieved in only 23.1% of the patients who did not receive IL steroids, and this rate was found to be statistically significant (p=0.010). There was no statistically significant difference between the treatments received by patients who achieved remission and those received by patients whose treatment continued (p>0.05) (Table 3). There was no statistically significant difference between the patients who received and those who did not receive IL steroid injection in terms of the treatment they received (p>0.05). The number of IL steroid injections (p=0.024) and total steroid dose (p=0.054) were found to be lower in patients with complete response (drug free remission).

A positive correlation was found between baseline C-reactive protein (CRP) levels and the number of IL injections (r=0.380, p=0.002) and total IL steroid dose (r=0.439, p=0.001). There was no difference in treatment response between those who had ≥3 births and those who had 2 births. However, it caught

Table 1. Demographical and laboratory characteristics

	All patients (n=76)	IL GC injections		p*
		Yes (n=63)	No (n=13)	
Mean age (years)	36.53±6.8	35.89±7.1	39.62±4.4	0.020
Mean BMI (kg/m²)	27.06±3.5	26.96±3.7	27.67±1.8	0.353
Mean pregnancy counts (n)	2.92±1.6	2.9±1.7	3.0±1.1	0.476
≥3 pregnancies (%)	51.6	50	60	0.562
Breastfeeding in the last 5 years (%)	88.7x	88.5	90	0.888
Smoking (active and history) (%)	8	7.7	10	0.593
ESR (mm/h)	39.95±22.6	39.7±22.9	41.1±21.7	0.706
CRP (mg/L)	18.48±27.5	18.6±28.5	17.9±22.9	0.971
WBC (10^3/µL)	8.87±2.4	8.96±8.9	8.4±1.6	0.591
HGB (g/dL)	12.61±1.4	12.7±1.3	12.1±1.3	0.069
PLT (10^3/µL)	388.9±387.9	396.4±423.1	352.7±118.7	0.777
ALB (g/dL)	4.5±0.3	4.5±0.3	4.4±0.3	0.072
GLOB (g/dL)	2.96±0.9	2.9±1.0	3.1±0.6	0.109

*p values for comparing IL GC injected and not injected patient, IL GC: Intralesional glucocorticoid, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: White blood count, HGB: Hemoglobin, PLT: Platelet, ALB: Albumin, GLOB: Globulin, n: Number

our attention that as the number of pregnancies increased, the number of injections also increased.

DISCUSSION

The clinical management of IGM patients is challenging. While some patients may present with a solitary mass that regresses spontaneously, others may experience marked erythema, fluid collection formation, and recurrent fistulization from the onset of the disease (13).

IGM is an orphan disease whose diagnosis and etiology have not been elucidated, and it has recently become a field of interest in rheumatology because of its response to immunosuppressive treatments. If it is not treated considering the risk of recurrence, it may very rarely go into remission without treatment. However, the use of immunosuppressive treatments such as steroids, methotrexate, and azathioprine is often required (3). In recent years, there has been an increasing interest in immunosuppressive treatments and IL steroid administration to reduce their side effects (14-19). It also provides advantages during breastfeeding and pregnancy. In our study, we examined the responses obtained with IL steroid application in addition to conventional immunosuppressive treatments in patients with IGM. Pregnancy and lactation are also included in the etiology of IGM. Because the number of IL injections increased as the number of pregnancies increased in our study (r=0.276, p=0.048), we thought that multiple pregnancy and/or multiple breastfeeding might be risk factors for severe disease. A correlation was observed between the CRP level measured at diagnosis and the number and dose of IL injections. This may suggest that higher doses of steroids or alternative therapy should be considered in patients with elevated CRP levels at baseline. We interpreted the fact that the number and dose of IL steroid applications were higher in patients who did not achieve remission and that the need for treatment in patients with an aggressive course increased, as expected. In our study, the treatments received by patients who were and were not administered IL steroids were similar, but a significant difference was observed in patients who were administered IL steroids in terms of achieving remission. This suggested that IL steroid administration would positively contribute to the treatment response (Figure 1). In addition, reducing the risk of systemic side effects and accelerating the

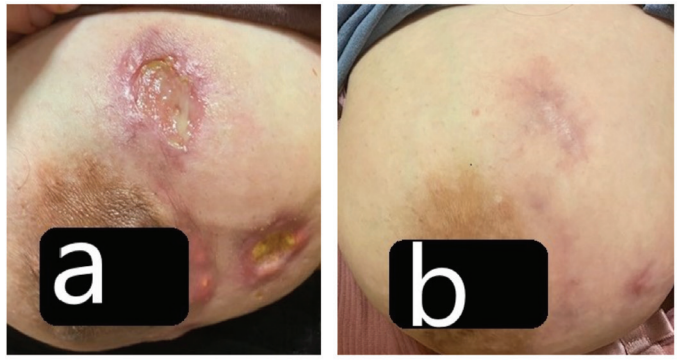

Figure 1. Glandulary lesions and wet wounds (a) healed after IL corticosteroid injections (b)
IL: Intralesional

Table 2. Clinical characteristics

	All patients (n=76)	IL GC injections		p*
		Yes (n=63)	No (n=13)	
Number of IL GC injections		2.29±1.8		
Total provincial GC dose (methylprednisolone mg)		57.41±47.3		
Localizations (%)				
-Left	63.2	60.3	20.8	0.521
-Right	26.3	28.6	15.4	
-Bilateral	10.5	11.1	7.7	
Antibioteraphy (%)	42.1	42.9	38.5	0.958
Systemic GC (%)	88.2	87.3	92.3	0.611
MTX (%)	85.5	84.1	93.2	0.445
AZA (%)	21.1	20.6	23.1	0.844
ADA (%)	2.6	3.2	0	0.515
Reached remission (%)	55.3	61.6	23.1	0.010

*p values for comparing IL GC injected and not injected patients, IL GC: Intralesional glucocorticoid, MTX: Methotrexate, AZA: Azathioprine, ADA: Adalimumab, GC: Glucocorticoid, n: Number

Table 3. Clues for remission of IGM

	Treatment discontinued* (n=42)	Treatment ongoing (n=34)	p
IL GC injection (%)	92.9	70.6	0.010
Number of IL GC injections	1.9±1.3	2.9±2.2	0.024
Total provincial GC dose (mg)	48.5±39.9	71.4±55.1	0.054
Localizations (%)			
-Left	56.3	43.8	0.947
-Right	55	45	
-Bilateral	50	50	
Antibioteraphy (%)	40.5	44.1	0.749
Systemic GC (%)	88.1	88.2	0.915
MTX (%)	88.1	82.4	0.479
AZA (%)	16.7	26.5	0.297
ADA (%)	0	5.9	0.111

*Treatment discontinued due to remission, IGM: Idiopathic granulomatous mastitis, IL GC: Intralesional glucocorticoid, GC: Glucocorticoid, MTX: Methotrexate, AZA: Azathioprine, ADA: Adalimumab, n: Number

treatment response were seen as important advantages. There are also other studies showing that local steroid application is beneficial (16,19).

Study Limitations

The limitations of this study are that the follow-up period of the patients continued for the last year and that the same dose of steroids was not administered because the progression of the patient clinics was not the same.

CONCLUSION

In conclusion, remission and discontinuation of treatment were nearly three times higher in IL steroid-injected IGM patients in our study. It can be suggested that IL steroid injection should be considered for treating IGM. However, this suggestion is a candidate to handle in randomized and placebo-controlled studies.

Ethics

Ethics Committee Approval: The study protocol was approved by Fırat University Non-interventional Research Ethics Committee (approval number: 9613, date: 06/07/2022).

Informed Consent: This was a prospective study.

Authorship Contributions

Surgical and Medical Practices: M.S.A., Concept: M.S.A., Design: M.S.A., A.K., H.A., Data Collection or Processing: M.S.A., A.K., H.A., İ.G., S.S.K., Analysis or Interpretation: M.S.A., A.K., H.A., İ.G., S.S.K., Literature Search: M.S.A., A.K., H.A., Writing: M.S.A.

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

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CASE REPORT AND LITERATURE REVIEW

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THREE CASES OF BREAST CANCER CAUSING PARANEOPLASTIC ARTHRITIS: A CASE REPORT AND LITERATURE REVIEW

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Abstract

There is an interesting and complex relationship between rheumatic diseases and malignancy. Paraneoplastic arthritis is caused by the effects of many hormones and cytokines secreted from the underlying hidden tumor tissue. There is no direct invasion or mechanical pressure of the tumor tissue. In particular, in the early rheumatological disease period, the diagnosis should be reconsidered in cases unresponsive to conventional treatment. It should be noted that there may be another underlying etiological factor in cases unresponsive to treatment. In this review, we discussed in detail three breast cancer cases that presented with early arthritis and were found to have breast cancer in the follow-up. In the literature, serological markers, pathological diagnosis, and imaging in breast cancer-associated paraneoplastic arthritis cases are not presented in detail. In our cases, serological markers, pathological diagnosis, and breast magnetic resonance imaging are presented in detail.

Keywords: Paraneoplastic arthritis, breast cancer, arthritis

INTRODUCTION

Paraneoplastic arthritis (PA) is a condition that develops because of mediators such as cytokines, hormones, or immunoglobulin released from the tumor tissue (1,2). The emerging arthritis condition and accompanying laboratory findings are similar to those of many rheumatological diseases. It is very difficult to distinguish them from early rheumatoid arthritis (RA). However, conditions such as older age of the patient, low steroid response, and negative autoantibodies may help in the differential diagnosis (3).

In the case series of PA we previously reported, after lung cancer, breast cancer is one of the most common solid tumors that cause PA (3). Here, we aimed to review the characteristics of 3 patients who presented with the clinical features of early RA and were later diagnosed with breast cancer, as well as the cases of PA caused by breast cancer in the literature.

CASE REPORT I

A 58-year-old female patient presented with pain, swelling, and limitation of motion in the hand, wrist, and metacarpophalangeal (MCP) joints. She said that her complaints had been for the last 3 weeks. There was morning stiffness lasting approximately 1 hour. The patient had no other complaints in the history. There were no complaints such as weight loss, fever, or night sweats. Physical examination revealed no features in other system examinations, except for the locomotor system examination. Her routine laboratory workup was unremarkable, aside from a raised

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erythrocyte sedimentation rate (ESR) of 46 mm/hour, C-reactive protein (CRP) of 14 mg/dL, and positive antinuclear antibody (extractable nuclear antigen panel negative). Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) autoantibody were negative. Conventional radiographs were taken, and no pathology was detected except for soft tissue swelling. She was treated for early RA and started on hydroxychloroquine (HCQ) 200 mg twice daily and prednisolone 5 mg once daily, with good clinical response. Three months after her initial arthritis, she presented to us with complaints of right breast swelling and mass, which resulted in a breast biopsy. Breast biopsy was reported as estrogen receptor-positive invasive ductal carcinoma. She was started on neoadjuvant chemotherapy, and after chemotherapy, a mastectomy was performed. After the treatments, there were no joint complaints.

CASE REPORT II

A 56-year-old female patient was admitted with complaints of pain, swelling, and limitation of movement in her shoulders, hand proximal interphalangeal (PIF), MCP, and wrists, which lasted 1 month. The patient had no other complaints in the history. There were no complaints such as weight loss, fever, or night sweats. Physical examination revealed no features in other system examinations, except for the locomotor system examination. Her routine laboratory workup was unremarkable aside from a raised ESR of 39 mm/hour and CRP of 19 mg/dL. RF, anti-CCP autoantibody, and antinuclear antibody were negative. Conventional radiographs were taken, and no pathology was detected except for soft tissue swelling. She was treated for early RA and started on HCQ 200 mg twice daily and prednisolone 10 mg once daily. Her complaints regressed within 2 weeks. There were no joint findings. She presented to us with complaints of right breast swelling and mass, which resulted in a tru-cut breast biopsy. MRI of the patient's breast is shown in Figure 1. Breast biopsy was reported as estrogen receptor-negative invasive ductal carcinoma. The patient was referred to the oncology department, and paclitaxel and carboplatin were started as adjuvant therapy by the oncology department. There was no increase in joint complaints after chemotherapy.

CASE REPORT III

A 44-year-old female patient presented with complaints of pain and swelling in the 2nd-3rd metatarsopharyngeal (MTF) joints of the right foot and left wrist for the last 1 month. There was morning stiffness lasting about 1 hour. Examination revealed swollen and tender joints involving her left wrist andleft second-third MTF joints. There were no other significant physical findings on examination. The patient had no other complaints in the history. There were no complaints such as weight loss, fever, or night sweats. Physical examination revealed no features in other system examinations, except for the locomotor system examination. Her routine laboratory workup was unremarkable aside from a raised ESR of 44 mm/hour and CRP of 14 mg/dL. RF, anti-CCP autoantibody, and ANA were negative. Conventional radiographs were taken, and no pathology was detected except for soft tissue swelling. She was treated for early RA and started on HCQ 200 mg twice daily and prednisolone 5 mg once daily. Her complaints regressed within 1 month. After 2 months, she presented with pain that started in the right breast and a palpable mass. The patient's breast MRI image is shown in Figure 2.

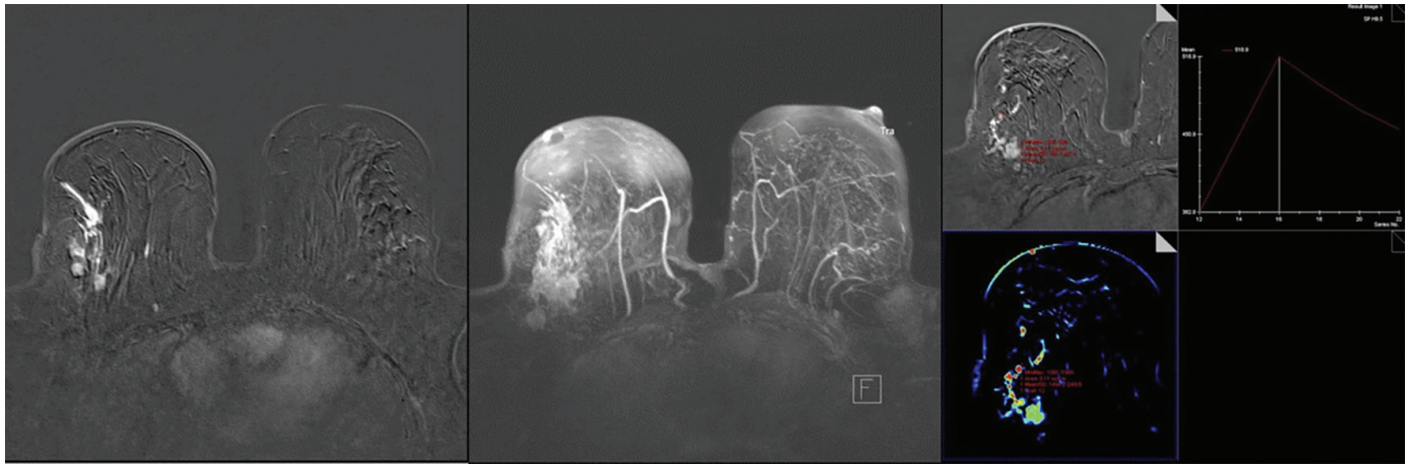

Figure 1. Left: Asymmetric regional enhancement in the right breast on subtraction images, middle: Maximal intensity projection image, right: Type 3 contrast enhancement pattern in mean curve analysis

The patient underwent breast biopsy, and the pathological diagnosis was lobular carcinoma. The breast biopsy was reported as C-erb-B2-positive invasive lobular carcinoma. A patient with bone and lymph node metastases underwent mastectomy after neoadjuvant chemotherapy. Chemotherapy treatment is currently ongoing. Joint complaints regressed after chemotherapy treatment.

DISCUSSION

PA is an important entity and a good imitator in rheumatology practice. The pathogenesis of PA is a direct effect of toxins produced by tumor cells, which trigger inflammation in the tissues where PA manifests. In addition, tumoral expression of antigens shared by the cells targeted by the autoimmune disease or to the release of intracellular antigens from apoptotic tumor cells can cross-react with synovial antigens to trigger PA (4).

In breast cancer, which has a significant rate among patients with PA, we presented 3 cases that developed an RA-like clinic 3 months before the cancer diagnosis. Two of these cases were invasive ductal cancer and one was invasive lobular cancer. In addition, metastases were present in two cases. In the largest PA series we have reported so far in the literature, the most common solid tumor after lung cancer was breast cancer. The pathological diagnosis of only 2 of them was known, and both were adenocarcinomas.

Among the 20 solid tumors reported by Morel et al. (5), only one case was breast cancer. The pathological diagnosis of this case was adenocarcinoma. The joints involved in this case were the small joints of the hand and wrist. In the series of 3 cases performed by Pines et al. (6), one female case aged 60 years had breast cancer, and the pathological diagnosis was adenocarcinoma. The patient had symmetrical polyarticular involvement and RF was positive. In the solid tumor series of 13 cases performed by Padhan et al. (7), 1 case was breast cancer and she presented with the complaint of polyarthritis. The patient's RF and anti-CCP autoantibodies were negative. The case was accompanied by palmar fasciitis. The mean time for patients to be diagnosed with breast cancer was 6 months. There was no palmar fasciitis in our patients. Especially in female patients over 50 years of age, patients with negative autoantibodies should be followed closely. It should be examined in terms of common malignancies (breast cancer) specific to that age range. In another study, in the case series of 39 solid tumor-associated PA cases by Kisacik et al. (3), 8 patients had breast cancer and 2 patients had a pathological diagnosis of adenocarcinoma. Solid tumor-associated arthritis usually has an acute onset and presents as an asymmetrical and oligoarticular joint pattern. In our breast cancer-associated arthritis cases, there was an acute onset, oligoarticular, and asymmetrical involvement pattern. The demographic characteristics of the cases reported in the literature who developed PA due to breast cancer are shown in Table 1.

In a study, when compared with cases with early RA, malignancy-related arthritis cases present with more asymmetric, oligoarticular, and large joint involvement, and it seems useful to be careful in this respect (3). In the series of 21 cases performed by Wen et al. (8), 1 female patient was diagnosed with RA, and she was diagnosed with breast cancer at the end of 12 months. In the cases we have presented, the pathological type of breast cancer has been described in detail. In the cases we presented, it was determined that they had breast cancer within 3 months. In cases where early RA is considered and steroid and non-steroidal anti-inflammatory treatment is started and no response is obtained, it may seem appropriate to conduct a malignancy screening considering that age range. In addition, in female patients diagnosed with seronegative arthritis, breast, and other organ examinations should not be ignored in the clinical examination and should be performed carefully. The clinician should be careful in this regard.

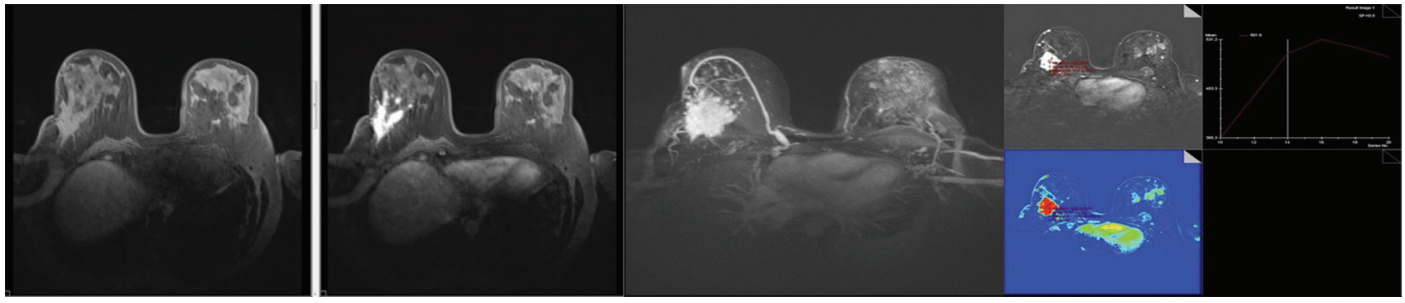

Figure 2. Left: Comparison of pre-contrast and early arterial phase T1 fat-suppressed images, middle: MIP image, right: Type 3 contrast enhancement pattern in mean curve analysis

MIP: Maximal intensity projection

Table 1. Demographic characteristics of the cases in the literature

Author(s) referance	Patients number	Age (years)	Joint pattern	Serological markers (RF, anti-CCP)	Pathological diagnosis
Morel et al. (5)	1	ND	Symmetric polyarthritis Wrists, hands	RF; negative CCP; ND	Galactophoric Adenocarcinoma
Pines et al. (6)	1	60	Symmetric polyarthritis	RF; positive CCP; ND	Adenocarcinoma
Padhan et al. (7)	1	66	Polyarthritis (MCJ, wrists, PIJ)	RF and CCP; negative	ND
Kisacik et al. (3)	8	43-66	Asymmetrical, oligoarticular	ND	2 patients adenocarcinoma 6 unknown
This study	3	58, 56, 44	Asymmetrical, oligoarticular	RF and CCP; negative	Ductal carcinoma Lobular carcinoma

RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide, ND: Not determined, MCJ: Metacarpophalangeal joint, PIJ: Proximal interphalangeal joint

PA can be caused by both solid and hematological malignancies. In our series, 60% of solid tumors, 40% of hematological malignancies, and 43.5% of solid tumors consisted of lung cancer (3). In another study, 76% of cases were solid tumors and 24% were hematological malignancies (5). Lung cancer cases constituted 50% of solid tumors (5). Lymphoma and leukemia among hematological malignancies are prominent diagnoses.

In cases of PA, malignancy is usually diagnosed after arthritis. In our previous series, the mean time between symptoms and malignancy was 5 months (3). In another series, this rate was found to be 4.4 months (5). In the cases presented here, the diagnosis of malignancy was made within an average of 3.3 months.

CONCLUSION

PA must be considered in cases of early arthritis. It is important that breast cancer has an important place in paraneoplastic cases, that patients should be questioned in their anamnesis, especially in seronegative cases, and that imaging methods should be used in cases of clinical suspicion. Breast cancer is the most common PA after lung cancer. Because the treatment response and clinical course of the pathological subgroups are different, it can provide more information in the subsequent follow-ups of patients who develop arthritis. Consequently, studies with larger case series related to pathological subgroup classification are needed in breast cancer-associated PA series.

Ethics

Informed Consent: Informed consent forms were obtained from the patients.

Authorship Contributions

Surgical and Medical Practices: F.A., N.Y.S., E.K., Concept: F.A., N.Y.S., E.K., Design: F.A., N.Y.S., E.K., Data Collection or Processing: F.A., N.Y.S., E.K., Analysis or Interpretation: F.A., N.Y.S., E.K., Literature Search: F.A., N.Y.S., E.K., Writing: F.A., N.Y.S., E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT AND LITERATURE REVIEW

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SUCCESSFUL INFLIXIMAB TREATMENT IN COGAN SYNDROME WITH CARDIAC COMPLICATIONS

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Abstract

Cogan's syndrome (CS) is a rare chronic autoimmune vasculitis that can have significant systemic consequences and progress with progressive and inflammatory eye (interstitial keratitis, scleritis, episcleritis, uveitis) and audiovestibular (sensorineural hearing loss, vertigo, tinnitus) involvement. Vasculitis is observed in approximately 15% of patients with CS and may present as aortitis, large-vessel vasculitis (Takayasu-like), moderate arteritis, or other vasculitic syndromes. In this case report, we present the development of severe aortic and mitral valve insufficiency in a patient diagnosed with CS who was admitted to the hospital with episcleritis and sensorineural hearing loss.

Keywords: Cogan's syndrome, episcleritis, infliximab, large-vessel vasculitis

INTRODUCTION

Cogan's syndrome (CS) is a rare chronic autoimmune vasculitis that can have significant systemic consequences and progress with progressive and inflammatory eye (interstitial keratitis, scleritis, episcleritis, uveitis) and audiovestibular (sensorineural hearing loss, vertigo, tinnitus) involvement (1). Vasculitis is observed in approximately 15% of patients with CS and may present as aortitis, large-vessel vasculitis (Takayasu-like), moderate arteritis, or other vasculitic syndromes.

In this case report, we present the development of severe aortic and mitral valve insufficiency in a patient diagnosed with CS who was admitted to the hospital with episcleritis and sensorineural hearing loss. Written and verbal consent was obtained from the patient and his relatives.

CASE REPORT

A 44-year-old female patient was admitted to our clinic with progressive bilateral sensorineural hearing loss and episcleritis for approximately two years. The patient had increased dyspnea, exertional dyspnea, and high acute-phase responses in recent years. In the patient's examination. Blood pressure was 140/90 mmHg, hear beat was 110 beats/min, and breath rate was 18 beats/min. Physical examination revealed no features other than a decrease in breath sounds in the right lung base. Cardiological examination of the patient revealed findings consistent with severe aortic and mitral valve insufficiency. CS was considered in the foreground in the patient. The patient's treatment was started with methylprednisolone at a dose of 0.5 mg/kg/day and methotrexate at a dose of 15 mg/week. Heart valve replacement was then performed via cardiovascular surgery because of severe valve insufficiency. Histopathological findings consistent with CS were also observed in the pathological examination of the aortic root (Figure 1 and 2). Because of the lack of adequate clinical and laboratory responses in the patient, whose cardiac function improved significantly during follow-up, azathioprine at a dose of 3 mg/kg/day was added to the treatment. Severe stenosis

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was found in the left renal artery during the evaluation of the patient who developed intermittent hypertensive attacks and continued acute phase elevation during follow-up. Infliximab (5 mg/kg/4 weeks) was added to the treatment regimen. Currently, the patient is still under treatment with infliximab to prevent disease relapse.

Tumor necrosis factor-alpha (TNFα) is a cytokine released during infection and inflammation. It is mainly produced by activated macrophages. However, other cell types have also been shown to produce TNFα at various stages of inflammation (2). Other cells known to produce TNFα include lymphocytes and even fibroblast and endothelial cells. In recent years, anti-TNFα drugs have been evaluated for systemic vasculitis and different results have been obtained. Disease Modifying Anti Rheumatic Drug (DMARD) treatments used with varying success rates include cyclophosphamide, methotrexate, cyclosporine, mycophenolate mofetil, and azathioprine (3,4). As biological DMARD treatments, infliximab therapy has an important potential therapeutic area when used in combination with corticosteroids. When the literature is reviewed, there are CS patients with severe systemic involvement treated with infliximab. Our patient had corticosteroid and methotrexate treatments until aortic insufficiency and cardiac surgery. Following aortic pathological evaluation, azathioprine and then infliximab were added to the patient's treatment. The patient's infliximab treatment was given every four weeks for a total of six months.

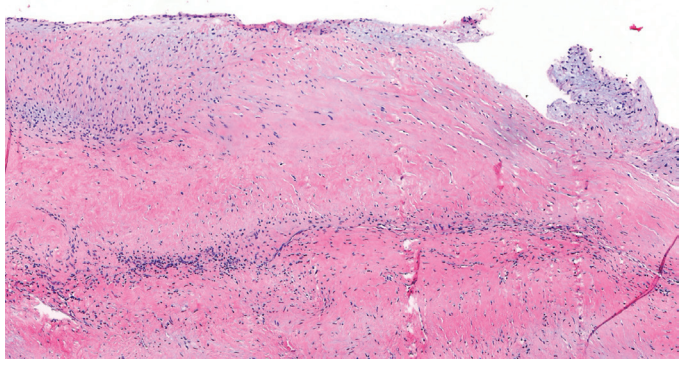

Figure 1. Mononuclear inflammatory cell infiltration, neovascularization, and myxoid degeneration

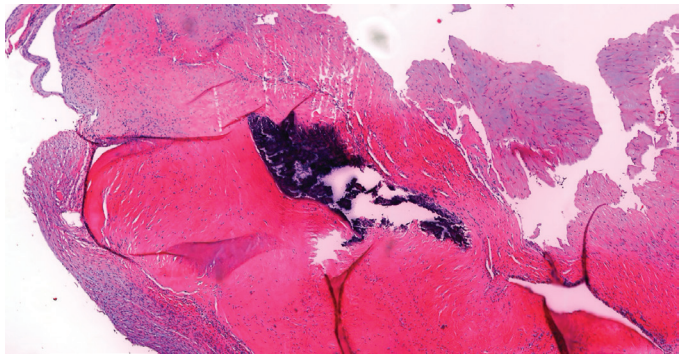

Figure 2. Hyalinization and calcification of the vascular intima media

In previous studies, aortic valve replacement was required in almost half of the patients diagnosed with CS. Permanent vascular damage can be prevented by early diagnosis of the disease and use of other immunosuppressive agents, in addition to high-dose systemic glucocorticoid therapy to be started urgently (5). Severe aortic insufficiency develops approximately 3 years after diagnosis (6). In the present case, the development of valve insufficiency requiring aortic and mitral valve replacement in the first two years after hearing loss, early diagnosis, and effectiveness of TNF inhibitor therapy in appropriate cases are emphasized (7,8).

Ethics

Informed Consent: Written and verbal consent was obtained from the patient and his relatives.

Authorship Contributions

Concept: S.G., M.Ç.G., D.G., Design: S.G., M.Ç.G., D.G., Data Collection or Processing: S.G., D.G., F.Ö., Analysis or Interpretation: M.Ç.G., D.G., F.Ö., Literature Search: D.G., Writing: S.G., F.Ö.

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

Financial Disclosure: The authors declared that this study received no financial support.

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IMAGE ARTICLE

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PARADOXICAL SARCOIDOSIS CASE

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Keywords: Paradoxical, sarcoidosis, certolizumab

INTRODUCTION

A 56-year-old female patient was being followed up with ankylosing spondylitis, and as her pain increased, certolizumab treatment was initiated by her physician. After receiving 5 doses of certolizumab, the patient presented with weight loss 8 kg in 1 month, fatigue, loss of appetite, and widespread joint pain. Cervical ultrasonography (USG) was performed since lymphademegaly was detected in the neck during the physical examination. On USG, 17x13 mm lymphademegaly was detected at the bilateral cervical level 3. In the analysis, it was found to be C-reactive protein: 36 mg/dL, erythrocyte sedimentation rate: 8 mm/hour and angiotensin converting enzyme 43 mcg/L. Bilateral hilar lymphadenomegaly was detected on thorax and abdominal computed tomography (CT) (Figure 1). Because of the biopsy taken under the guidance of Ebus, non-casing granuloma was detected. Because lymphademegaly was not detected in the patient's thorax CT scan take 8 months ago, the patient was diagnosed with paradoxical sarcoidosis. Certolizumab was discontinued, and the patient was followed up. Such reactions tend to improve or resolve with the discontinuation of the agent (1).

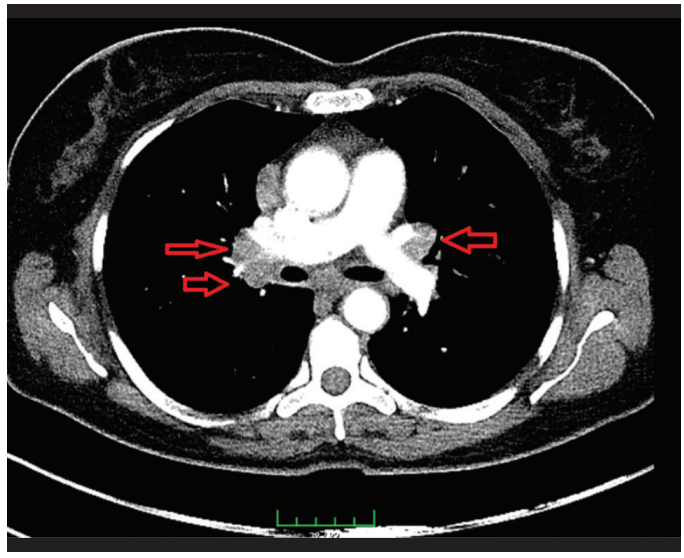

Figure 1. Bilateral hilar lymphademegaly

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Ethics

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Authorship Contributions

Surgical and Medical Practices: P.D.Y., B.E., S.P., Concept: S.P., Design: S.P., Data Collection or Processing: P.D.Y., Analysis or Interpretation: B.E., Literature Search: B.E., Writing: B.E.

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

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