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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

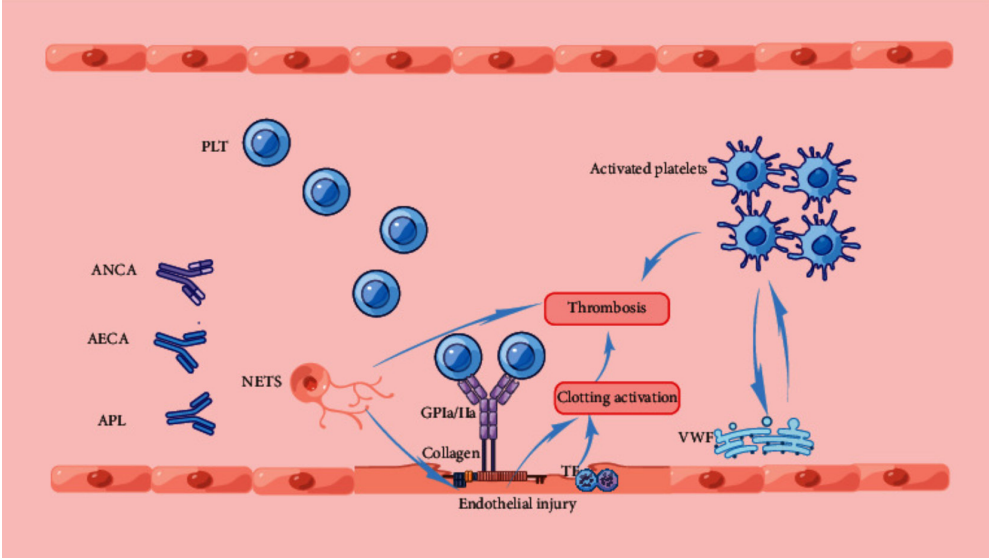

Figure 1. When endothelial cells are destroyed by autoantibodies (ANCA, AECA, aPL) and neutrophil extracellular traps, collagen and TF are exposed in the circulating blood, activating the coagulation cascade. Circulating platelets directly adhere to collagen via glycoprotein Ia/IIa surface receptors. 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.

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