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Thromboembolic disease in vasculitis

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Abstract

Purpose of review—To give an overview of recent clinical findings of thromboembolic disease in vasculitis and provide insight into possible explanations of the association between thrombosis and inflammation.

Recent findings—A high incidence of venous thrombotic events has recently been described in four distinct cohorts of patients with antineutrophil cytoplasmic antibodies-associated vasculitis (AAV), especially during periods of active disease. No factors other than the vasculitis itself have been identified that explain this high occurrence of thrombosis. Several studies have shown an increased rate of thrombosis in Behçet's disease, with a different clinical presentation than that observed in AAV. Recent laboratory findings provide exciting insights into a bidirectional feedback loop between coagulation and inflammation that may be applicable to vasculitis.

Summary—Thrombosis is an important clinical manifestation of some types of vasculitis. Better understanding of the association of thrombosis with inflammation in vasculitis might lead to development of clinically useful biomarkers and new approaches to therapy. Additionally, study of the specific factors involved in thrombosis in systemic vasculitis could help explain the role of inflammation in more common settings of venous thrombotic events.

Keywords

antineutrophil cytoplasmic antibodies; Behcet's disease; microscopic polyangiitis; thrombosis; vasculitis; Wegener's granulomatosis

Introduction

Thromboembolic disease is an increasingly recognized feature of several forms of systemic vasculitis. Venous thrombotic events (VTEs) have been well recognized manifestations of Behçet's disease for decades; however, it is only in the last few years that a markedly increased incidence of VTEs has been demonstrated to occur among patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV). These findings have clinical importance given the substantial morbidity and mortality associated with thromboembolic disease. Additionally, given the complex interactions in vasculitis of inflammation, structural vessel damage, and endothelial biology, thrombotic disease in vasculitis provides an intriguing biological model that may provide insight into the relationship between inflammation and thrombosis. Further understanding the biology of thrombosis in vasculitis could lead to the development of useful disease biomarkers, progress in understanding the pathophysiology of vasculitis, and even lead to new therapeutic targets. This article will review findings from recent clinical studies on thrombosis in vasculitis, summarize current understanding of the biology related to these

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clinical events, and briefly outline possible causal mechanisms for the observed association between vasculitis and thrombosis.

Thrombosis in antineutrophil cytoplasmic antibodies-associated vasculitis

Venous thrombosis was first reported as a possible manifestation in AAV in 2003 [1] and there is now evidence from four distinct cohorts of patients from North America and Europe that AAV is associated with an increased incidence of venous thrombosis (Table 1) [2–3, 4•] compared with the rates of VTE in the general population [5] or among individuals with chronic inflammatory diseases [2].

In 2005, Merkel *et al.* [2] reported an increased incidence of VTEs in AAV among 180 people with Wegener's granulomatosis enrolled in the Wegener's Granulomatosis Etanercept Trial (WGET) in the United States [6]. All subjects were enrolled during a period of active disease and were assigned to either etanercept or placebo in addition to treatment with glucocorticoids and either cyclophosphamide or methotrexate. Subjects were evaluated every three months, which included determination of disease activity as measured by the Birmingham Vasculitis Activity Score for WG (BVAS/WG) [6] and full interim medical history. Information on VTEs prior to the study onset was obtained, and there was continuous surveillance for VTEs during the trial [7]. All VTEs were clinically apparent and confirmed with diagnostic studies. Thirteen individuals had had VTEs prior to enrollment in the trial. Among the 167 individuals without a history of VTE, 16 experienced events during 228 person-years of observation, an incidence of 7.0 VTEs per 100 person-years. The VTEs were either deep venous thrombosis (DVT) of lower extremities or pulmonary embolism. Most VTEs occurred during or closely following periods of active disease. No difference was found in use of acetylsalicylic acid (ASA) or hospitalization length among those who suffered from VTE versus those who did not.

In 2006, Weidner *et al.* [3] retrospectively reviewed all patients who were treated for AAV at a single nephrology clinic (University of Erlangen-Nürnberg, Germany) during a 16-year period. This patient population is different from the WGET cohort as it included patients with microscopic polyangiitis and renal-limited vasculitis; moreover, all patients had kidney involvement. Thirteen of 105 patients had VTEs during the 367.5 person-years of observation, yielding an incidence of 4.3 events per 100 person-years. Twelve of the 13 events occurred during periods of active vasculitis. No patients with VTEs in this cohort were found to have protein C, protein S, or antithrombin deficiencies, antiphospholipid antibodies, the factor V Leiden mutation, or the nephrotic syndrome.

In a report from the Netherlands in 2008, Stassen *et al.* [4•] looked at VTE in a cohort of 198 patients with AAV, including Wegener's granulomatosisG, microscopic polyangiitis, and renal-limited vasculitis. During a median follow-up period of 6.1 years, 25 VTEs occurred in 25 patients, an incidence of 1.8 events per 100 person years. Similar to what was found in the two above-outlined studies, a much higher incidence of VTE (6.7 per 100 person years) was observed during periods of active disease. VTEs were more common among the subset of patients with microscopic polyangiitis and renal-limited vasculitis than among patients with Wegener's granulomaotsis (24 vs. 7.0%, $P < 0.01$).

A recent study from France [8] (so far only published as an abstract) also addressed thrombosis in AAV (Churg Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis). These investigators found that 7.6% of 845 patients with AAV had VTEs during a mean follow up of 58 months. Most of the VTEs occurred in close temporal proximity to the time of diagnosis of vasculitis.

The importance of established hypercoagulable risk factors in the development of VTE in AAV remains to be fully determined. The prevalences of antiphospholipid antibodies and common genetic mutations associated with hypercoagulability were recently determined among individuals in the WGET study [9•]. Although there was a slightly increased prevalence of antiphospholipid antibodies among persons with Wegener's granulomatosis compared with the general population (confirming prior reports), there was no association found between the presence of anticardiolipin antibodies and VTE. Additionally, the same study reported that the prevalences of mutations in factor V Leiden, prothrombin G20210A, and methylentetrahydrofolate reductase were not different among patients with Wegener's granulomatosis and VTE compared with rates in the general population [9•].

In summary, recent studies from four different cohorts of patients with AAV strongly suggest an increased occurrence of VTE associated with these types of vasculitis and that this increase in thrombosis is tightly associated with vasculitis disease activity.

Thrombosis in Behçet's disease

It is well accepted that thrombosis is a common feature of Behçet's disease. However, there is considerable uncertainty as to the exact prevalence of thrombotic manifestations in this disease with estimates ranging from 10–30% of patients [10–15,16,17] (Table 2). VTEs appear to be much more common among males [11,13,14,16], a finding in contrast with studies on VTE in AAV, where no striking gender differences were seen comparing those who had a history of VTE to those who did not [3,7•]. Estimates may differ due to different methods of event ascertainment; also, some studies include superficial thrombophlebitis as a type of VTE, whereas others do not.

The clinical presentation of thrombosis in Behçet's disease is different from what is observed in AAV and other hypercoagulable states. Superficial subcutaneous thrombophlebitis and DVTs are the most common thrombotic events in Behçet's disease. Thromboses at unusual sites such as cerebral sinuses or hepatic veins are often described, as are intracardiac thrombi [10,14,18–20]. Despite the increased prevalence of DVT in Behçet's disease, pulmonary embolism appears to be rare. In a study of 137 patients from Turkey, two had pulmonary embolism [14] and in a report of 170 Japanese patients with Behçet's disease who underwent postmortem examinations, pulmonary thrombi were found in only one case [21]. Similarly, in a large series of 5095 patients with Behçet's disease from Iran, with a median observation period of 3 years, only six patients had pulmonary embolism [17]. In a systematic review focusing on pulmonary involvement in Behçet's disease it was found that when thrombi are located within the pulmonary vasculature, pulmonary vasculitis or an aneurysm is almost always present [22].

In Behçet's disease there appears to be a spatial relationship between thrombosis and inflammation. Superficial thrombophlebitis is characterized by clinical features of inflammation surrounding the thrombus. In a study of 13 patients with Behçet's disease and pulmonary artery aneurysms, all individuals either had thrombi in the affected vessels at initial evaluation or subsequently developed such thrombi [23]. Intracardiac thrombi in Behçet's disease are associated with heavy inflammatory infiltrates both in the thrombus itself and sometimes also in the underlying myocardium [19]. A recent report assessed the usefulness of anticoagulation in addition to immunosuppressive agents for thrombosis in Behçet's disease. In this small retrospective study, no decrease in recurrent VTEs was observed among those treated with anticoagulation compared with those who received immunosuppressive therapy alone [24•].

Several studies have examined the prevalence of thrombophillic factors among patients with Behçet's disease [25–31]. A meta-analysis reported no difference in the prevalence of factor

V Leiden, prothrombin mutation (G20210A), or methylenetetrahydrofolate reductase mutation among patients with Behçet's disease versus controls. However, considering only patients with Behçet's disease, there was a statistically significant association between prothrombin mutation (G20210A) and thrombotic events. In a subanalysis restricted to studies from Turkey, an association between factor V Leiden and thrombosis also was observed [32].

In summary, VTEs are common in Behçet's disease and occur in association with underlying vasculitis. Further insight to the role of inflammation in thrombus formation may help to define further the optimal treatment of VTE in Behçet's disease.

Thrombosis in other vasculitides

Information on thrombosis in other vasculitides is based mainly on case reports and small case series, making it difficult to determine if there are true associations between other forms of vasculitis and thrombosis.

In a small study from the UK, a significantly increased prevalence of VTEs was found among 28 people with giant cell arteritis (GCA) or polymyalgia rheumatica (PMR) compared with healthy controls: 8/28 (29%) patients with GCA/PMR vs. 1/28 (4%) controls [33]. Among patients with GCA, anticardiolipin antibodies and increased levels of lipoprotein were associated with VTE [33]. In another study of 34 patients with GCA from Italy, 8 ischemic cerebral or cardiac events occurred and 12 patients had optic neuropathy. No VTEs were reported. Seventeen of the 34 patients had anticardiolipin antibodies, but no association with ischemic events was found [34].

Large artery stenosis is a well known complication of GCA [35], but to what extent these occlusive events are mediated by thrombosis is unclear. Microthrombosis could also play role in anterior ischemic optic neuropathy, which is the main cause for blindness in GCA. Aspirin has been shown to decrease the rate of ischemic events in GCA [36,37], potentially through its antiplatelet properties. Larger studies on the occurrence of thrombotic events in GCA are needed.

Takayasu's arteritis (TAK) is characterized by stenoses and occlusion of large arteries, and less commonly by aneurysms. As in GCA, it remains unclear to what extent occlusion of large arteries is preceded by a thrombotic event in TAK. One study found the presence of thrombus in a large artery in seven of 24 patients with TAK who underwent imaging with CT scans [38] but additional confirmatory research is needed. Case reports have also described thrombotic events in TAK where suction thrombectomy and urokinase have restored flow through large-vital arteries [39,40].

In a recent study from France of patients with several types of vasculitis (so far only published as an abstract), those with polyarteritis nodosa (PAN) had fewer VTEs than did patients with AAV [8]. Several arterial thrombotic events have been described in PAN in the setting of positive antiphospholipid antibodies [41–43]. Thrombotic thrombocytopenia purpura has also been described in PAN [44].

In Kawasaki's disease, thrombosis is a well known sequela of structural changes in coronary arteries [45]. The association between markers of platelet activation and coronary artery lesions [46,47] and the utility of aspirin in Kawasaki's disease supports the possible importance of thrombosis in this disease.

Few VTEs have also been reported in Henoch Schönlein Purpura (HSP). Venous sinus thrombosis has been described in an adolescent who had just recovered from HSP; this VTE

occurred in the setting of a positive test for the lupus anticoagulant [48]. Bilateral lower extremity DVTs was recently reported in an adult with HSP and the prothrombin 20210A mutation [49]. Acute arterial thrombosis has been reported with HSP in the setting of positive antiphospholipid antibodies [50].

Interplay of vascular endothelium, thrombosis, and inflammation

Results from studies of patients with thrombotic events without underlying inflammatory disease, and of people with inflammatory diseases but no clinical thrombotic events, both suggest a link between inflammation and thrombosis. In people without an underlying inflammatory disease, VTE is followed by rises in inflammatory markers [51]. Furthermore, after a first VTE, elevation of inflammatory markers is associated with increased risk of a future event [52]. In patients with inflammatory diseases measures of platelet activation, coagulation, and fibrinolysis have been found to correlate with disease activity even in the absence of clinically detectable thrombotic events [53,54].

In AAV, fibrinoid necrosis is a prominent feature on histologic examination. The term `fibrinoid' refers to material that looks like fibrin under light microscopy. Although the exact chemical composition of the lesion is not known, immunohistochemical analysis has confirmed the presence of fibrin in the lesion [55], linking this end product of the coagulation cascade to the scene of inflammation and structural vessel damage in AAV.

It is generally agreed that an initiating event in activation of the coagulation cascade *in vivo* is expression of active tissue factor (TF), which sets off repeated iterations of activation of individual coagulation factors that ultimately lead to build-up of fibrin and formation of a thrombus [56•]. Active TF comes in contact with other major components of the coagulation cascade through two main pathways. First, disruption of the endothelial layer exposes active TF on the underlying connective tissue. In vasculitis, this is a conceptually attractive mechanism for thrombosis in Behçet's disease and vasculitis affecting large and medium sized arteries, where thrombosis is seen in spatial association with vessel destruction and inflammation [19,23,38]. In AAV, there is necrosis of endothelial cells, which become detached from their underlying basement membrane. This injury could set off activation of the coagulation cascade.

A second mechanism by which active TF interacts with the coagulation system involves several inflammatory cytokines that can induce TF expression on endothelial cells and circulating monocytes [57]. In AAV, endothelial cells become detached from their underlying basement membrane, and the quantity of circulating endothelial cells in peripheral blood has been found to correlate with vasculitis disease activity [58]. It is, therefore, possible that circulating endothelial cells expressing TF play a key role in clinical thrombosis in AAV occurring at sites distant from areas of active vasculitis. It is also possible that circulating cytokines induce TF expression on endothelial cells and monocytes in the setting of intact endothelium. Other potential mechanisms of association between AAV and thrombosis have been proposed; including that widespread endothelial dysfunction occurs in vasculitis and results in a decreased production of thrombomodulin and other anticoagulant factors [7•].

Activated platelets, a major constituent of thrombi, could also play role in thrombosis in vasculitis. Upon activation, platelets release multiple cytokines including CD40 ligand (CD40L) and vascular endothelial growth factor (VEGF), which further stimulate coagulation by induction of TF expression on both monocytes and endothelial cells [59,60]. Platelet-derived CD40L also induces an inflammatory response at the endothelial level that subsequently upregulates cell adhesion molecules and secretion of chemoattractants for leukocytes (including the chemokines MCP-1 and IL-8) [59]. One study found that VEGF

levels were elevated in patients with AAV and were associated with severe disease [61]. Most of the proposed explanations for the association between thrombosis and vasculitis focus on thrombosis resulting from antecedent inflammation. However, it is possible that through activated platelets the thrombotic process is one of the driving forces behind inflammation in vasculitis. Thus, the importance of thrombosis in AAV might reach beyond clinically detectable thrombi to microthrombosis having a direct relationship with inflammation in vasculitis.

Conclusion

Local thrombosis is a well documented consequence of structural abnormalities affecting vessels in people with several types of vasculitis. In large and medium vessel vasculitis, thrombosis may contribute to stenosis and occlusion. Additionally, in AAV and Behçet's disease, there is strong evidence for an increased risk of VTE. In AAV there is an association between thrombosis and periods of increased disease activity, whereas in Behçet's disease there appears to be spatial relationship between inflammatory responses in the thrombus itself and the underlying vessel wall. Many questions remain about how thrombosis and vasculitis are linked, and the roles of both disease specific and traditional thrombotic risk factors remain to be fully defined.

Treating physicians should have a low threshold for evaluating patients with vasculitis for thrombosis, especially in AAV and Behçet's disease, and particularly during periods of active disease. Currently, it is not recommended to screen for thrombosis among asymptomatic individuals, and the role, if any, of prophylactic treatment with antiplatelet agents and anticoagulants remains to be defined. There are no data to inform physicians on the appropriate duration of anticoagulant treatment for VTE in vasculitis.

Continued exploration of the clinical spectrum of thrombosis in vasculitis and the links between thrombosis and inflammation should yield important insights into the pathophysiology of vasculitis and may also lead to new therapeutic targets for vasculitis.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• • of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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Table 1

Clinical studies on thrombosis in antineutrophil cytoplasmic antibodies-associated vasculitis

Study	Patient population	Number of patients	Thrombotic events	Calculated incidence of VTE
Merkel *et al.* 2005 [2].	Patients with WG enrolled in a multicenter clinical trial	180	16 VTEs: 9 DVT 2 PE 5 DVT and PE	7.0/100 person-years.
Weidner *et al.* 2006 [3]	Patients with WG and MPA receiving care from a single nephrology clinic	105	13 VTEs 7 DVT 1 PE 5 DVT and PE	4.3/100 person-years
Stassen *et al.* 2008[4•]	Patients with WG, MPA, RLV	198	25 VTEs (in 23 patients) 17 DVT 3 PE 5 DVT and PE	1.8/100 person-years; 6.7/100 person years during period of active disease

DVT, deep vein thrombosis; MPA, microscopic polyangiits; PE, pulmonary embolism; RLV, renal-limited vasculitis; VTE, venous thrombotic event; WG, Wegener's granulomaotsis.

Table 2

Selected studies of thrombosis in Behçet's disease

Study	Patient population	Number of patients	Thrombotic events.
Koç *et al.* 1992 [14]	Patients at a single clinic in Ankara, Turkey (1986–1990)	137	SVT 19 (13.9%); DVT 22 (16.1%)
Gürler *et al.* 1997 [13]	Patients seen at single clinic in Ankara, Turkey (1976 to 1997).	2147	SVT 229 (10.6%); DVT 197 (9.1%)
Ames *et al.* 2001 [11]	Patients seen at a single clinic in London, United Kingdom	73	DVT 18 (24.7%)
Shahram *et al.* 2004 [17]	Patients seen at single hospital in Teheran, Iran (1975–2005)	5059	SVT 2.4%[a]; DVT 6%[a]
Sarica Kucukoglu *et al.* 2006 [16]	Patients seen at a single clinic in Ankara, Turkey (1980–2004)	2319	SVT 177 (7.6%); DVT 99 (4.3%)
Düzgün *et al.* 2006 [12]	Patients from a hospital in Ankara, Turkey	180	SVT 48 (26.7%); DVT 61 (33.9%)

DVT, deep venous thrombosis; SVT, superficial venous thrombophlebitis.

[a] only percentages provided.