Haemorrhage and thrombosis: tackling two sides of a single vasculitic disease

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Venous thrombotic events (VTE) are well recognized as being associated with systemic inflammation, infection and malignancies. Their early diagnosis and timely treatment are important in preventing disease morbidity and improving outcomes. Numerous autoimmune diseases have been linked with VTE, for example, there is a 2-fold increased risk of venous thrombosis in rheumatoid arthritis, coeliac disease and inflammatory bowel disease compared with the general population, which is further increased during disease flares [1]. In anti-neutrophil cytoplasm antibody (ANCA)-associated small vessel vasculitis (AAV), VTE have been reported from small cohort series and from larger randomized clinical trials, with rates of up to 18 times that found in the general population [2–4]. Increased risk of VTE occurs mostly in the context of acute AAV disease (where it is 5-fold commoner than during remission) [4], and may precede or follow AAV presentation; however, even patients in remission remain pro-thrombotic. Both deep-vein thrombosis and pulmonary emboli are common, although the former appear to predominate in many series. An incidence of between 1.8 and 7 cases per 100 patient-years has been reported from cohort studies and clinical trials, with predominance in patients with PR3-ANCA in some series, but not others [2–4]. Classic risk factors are not always present in those patients with VTE and when present do not differ in incidence between those AAV patients with or without VTE, suggesting that the other factors, such as inflammatory disease itself predisposes to VTE [4]. What specifically drives the propensity for thrombotic events in systemic vasculitides? Virchow’s triad, described over 150 years ago, defines contributing factors to thrombogenesis, which may also be applied to systemic vasculitis; (i) abnormal blood constituents, (ii) abnormal blood flow and (iii) abnormal blood vessel walls. Circulating inflammatory factors have been shown to be important in provoking VTE with C-reactive protein (CRP), IL-6, tumour necrosis factor and factor VIII, all known to be elevated in acute AAV, stimulating endothelial production of procoagulant factors such as tissue factor, von Willebrand factor, prothrombin fragments 1 and 2, D-dimer and plasminogen activator inhibitor type 1 (PAI-1), while also activating factor X in the coagulation cascade [5–8]. Abnormal blood flow may result from hyperviscosity and platelet aggregation in the context of systemic inflammation with elevated levels of fibrinogen [8], or loss of anti-thrombogenic factors in association with nephrotic range proteinuric renal injury [9]. Finally, the activated vascular endothelium, found in AAV, plays a critical role in orchestrating several contributing abnormalities promoting thrombosis. Activation of primed polymorphonuclear cells by ANCA results in endothelial cytotoxicity and generates procoagulant apoptotic bodies and loss of anti-thrombogenic capacity. Moreover, recent reports of anti-plasminogen and anti-tissue plasminogen activator antibodies, in a proportion of patients with AAV, suggest that these antibodies may directly interfere with the coagulation pathway and promote VTE [10, 11].

As a result of these significant clinical associations of AAV and VTE, some practitioners advocate the use of prophylactic anticoagulant therapy for acute or relapsing patients during their disease presentation. Difficulty arises when patients have a bleeding tendency, as may be found in those with significant renal impairment or in patients with associated pulmonary haemorrhage (PH), a defining feature of AAV which occurs in up to a quarter of patients [12]. In those uncommon cases, where there may be coincident VTE and PH, a significant management dilemma arises. The true extent of this problem has not been fully investigated to date, and neither has the issue of how to manage such complex patients with dual thrombotic and haemorrhagic complications been addressed.

In this issue, De Souza et al. highlight their experience of dealing with AAV patients presenting with this combination of venous thrombosis and concurrent PH. The authors show that in their cohort of 35 patients with severe PH secondary to systemic vasculitis, 20% had concurrent VTE with 57% of cases diagnosed with AAV, 29% with anti-glomerular basement membrane disease and 14% (one patient) with anti-synthetase syndrome [13]. Importantly, although some ‘classic’ risk factors were present in the vasculitic patients (obesity, smoking,
pregnancy, previous history of VTE and family history of VTE), all the patients presented with VTE at the time of acute vasculitis. Simple thrombophilia testing (for levels of protein C and S, and antithrombin III) as well as screening for anti-cardiolipin antibodies, in just over half of their subjects, proved negative. VTE was diagnosed by a combination of CT angiography in six patients and duplex sonography in five. PH was identified by a combination of a drop in haemoglobin, respiratory failure, haemoptysis, bronchoscopy and new alveolar shadows on radiography. The authors managed six of these patients with anti-coagulation, mostly in the form of low-molecular-weight heparin, with insertion of vena caval filters in half of these. This approach was successful in five, without worsening of PH, but provoked new-onset PH in the sixth subject 2 weeks after anti-coagulation was initiated. One patient received a vena caval filter but no systemic anti-coagulation. Three of these six anti-coagulated patients also underwent plasmapheresis. Importantly, no patients died and only the patient who was not anti-coagulated developed a further pulmonary embolus following treatment. The basis for individualizing therapy in this cohort is not clear, why one patient was not anti-coagulated and why some, but not all, of the subjects had vena caval filters inserted is not discussed and would clearly be helpful to understand how these experienced clinicians came to these decisions. Moreover, it would be desirable to understand the trigger for performing CT angiograms in this cohort of patients who already had respiratory compromise and a diagnosis of PH. Perhaps, the combination of VTE and PH is more common than we imagine, as not all patients with alveolar haemorrhage routinely undergo assessment for pulmonary embolism or deep-vein thrombosis. Interestingly, up to 10% of critically ill surgical patients in the intensive care unit have pulmonary emboli diagnosed, but these are thought to contribute to death in only 1.3% of subjects following post-mortem examination [14].

Management of VTE in patients with PH secondary to systemic vasculitis adds significant complications to an already potentially life-threatening multi-system disorder, which frequently requires joint management with Intensive Care Physicians. Both development of lung haemorrhage and VTE require prompt treatment, as mortality rates can be up to 50% despite plasmapheresis and immunosuppression [12, 15]. The clinical decision regarding the timing of anti-coagulation is therefore important as clearly both immunosuppression and anti-coagulation are vital steps in achieving favourable outcomes. Plasma exchange is indicated in the presence of PH, and is generally performed with fresh frozen plasma (FFP), to prevent further loss of coagulation factors that could exacerbate a bleeding tendency. However, FFP could propagate thrombus formation in susceptible patients. According to De Sousa et al. the overall risk: benefit in these patients with combined PH and VTE is to combine immunosuppression, treating the underlying inflammatory disorder, with anticoagulation and vena cava filters. It is important to remember that this can provoke worsening or new-onset PH in a minority of patients. Perhaps, this report should prompt us to look more carefully, in a prospective manner, for this combination of features associated with systemic vasculitis that may provide better understanding and stratification of whom to treat with anticoagulation and when.

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(See related article by De Sousa et al. Venous thromboembolism with concurrent pulmonary haemorrhage in systemic vasculitis. Nephrol Dial Transplant 2012; 27: 4357–4361.)

References


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