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REVIEW

Narrative Review of Hypercoagulability in Small-Vessel Vasculitis

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Pauci-immune necrotizing and crescentic glomerulonephritis (GN) is the most common etiology of rapidly progressive GN. Clinical presentation in those afflicted is usually related to rapid loss of kidney function. We report the case of a 70-year-old woman who came to medical attention for signs and symptoms related to lower-extremity deep vein thrombosis (DVT). At presentation, the patient had biochemical abnormalities consistent with active GN, which quickly progressed to rapid loss in kidney function requiring renal replacement therapy. Kidney biopsy revealed small-vessel vasculitis with glomerular crescents. Serologic studies were negative for antineutrophil cytoplasmic antibody antibodies and other causes of acute GN. Plasmapheresis, immunosuppressive, and anticoagulant therapies were prescribed. Absence of other apparent end-organ involvement with vasculitis pointed toward renal-limited small-vessel vasculitis, yet presence of *unprovoked* DVT argues for systemic vascular inflammation. This case illustrates that venous thrombosis can be the presenting manifestation in patients with vasculitis and silent, severe end-organ involvement. The epidemiology and pathophysiology of venous thromboembolism in small-vessel vasculitis are discussed in this report.

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Pauci-immune necrotizing and crescentic GN accounts for 60% to 80% of all cases of rapidly progressive GN.[1] The histopathology is characterized by small-vessel fibrinoid necrosis, crescent formation affecting variable proportions of glomerular capillaries, little or no glomerular hypercellularity, and little or no deposition of immune complexes in the glomerular capillaries or interstitial arteriolar vessel walls.[1,2] This pathology is most often attributed to a systemic, small-vessel, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), as defined by the presence of circulating antineutrophil cytoplasmic antibodies (i.e., antimyeloperoxidase [anti-MPO] or anti-proteinase 3 [anti-PR3] antibodies).[2] Although subcategorizations predominate (i.e., microscopic polyangiits, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis), patients often present with mixed features. Pauci-immune, ANCA-negative crescentic GN is a related entity, and the literature concerning clinical manifestations, prognosis, and comparative effectiveness of various treatment options is limited in this disorder.[1]

Small-vessel vasculitides commonly present with nonspecific symptoms of fatigue, weight loss, arthralgias, skin rash, changes in urine appearance or urine output, or—less commonly— hemoptysis suggestive of pulmonary-renal syndrome.[3,4] Despite the well-documented link between AAV and increased incident venous thromboembolism (VTE), VTE is not a common presenting symptom in small-vessel vasculitis.[5–7] Factors associated with incident VTE in AAV include the presence of PR3-positive ANCA, urinary red blood cell casts, pulmonary hemorrhage, and cardiac involvement.[8] Across all cases of VTE, the overall percentage of unprovoked VTE attributable to vasculitis has not been well described. Epidemiologic studies have not discussed renal-limited vasculitis as an independent etiology of VTE,[9] even in studies of autoimmune disorders.[10,11] Moreover, the association between vasculitis and VTE has not been described in ANCA-negative vasculitis, likely because pauci-immune,

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Table 1. Laboratory data

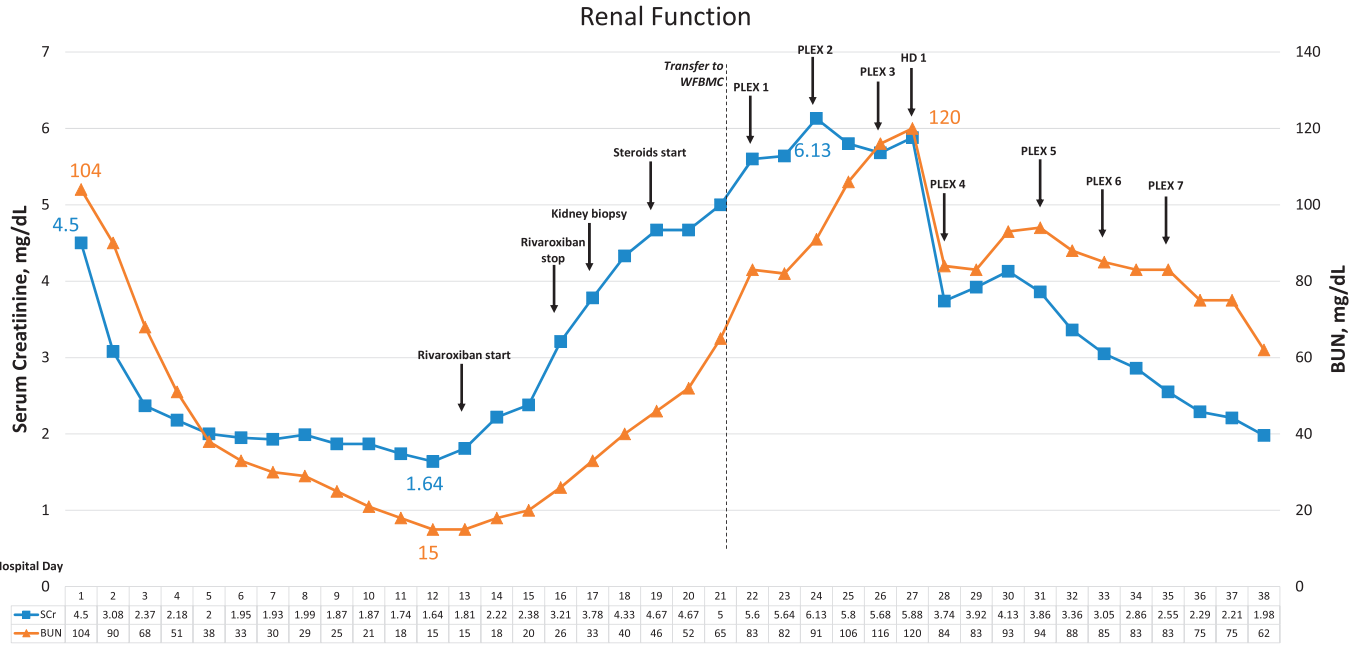
Variable	38 d before admission (baseline)	6 d before admission	Day of admission, other hospital	Reference range, other hospital	Day of admission, this hospital[a]	Reference range, this hospital
Serum						
Hemoglobin (g/dl)	14.0	13.4	12.1	12.0–15.0	8.8	12.0–16.0
Hematocrit (%)	41.4	40.2	35.8	36.0–46.0	26.8	37.0–47.0
White cell count (per mm^3)	7800	15,500	16,700	4500–10,500	20,200	4800–10,800
Differential (%)						
Neutrophils	41	69	76		84	
Lymphocytes	25	15	6		8	
Monocytes	21	13	15		8	
Eosinophils	13	2	3		0	
Basophils	1	1	1		0	
Platelet count (per mm^3)	241,000	218,000	343,000	150,000–400,000	394,000	160,000–360,000
Sodium (mmol/l)	141	134	129	135–146	131	135–146
Potassium (mmol/l)	4.7	4.2	4.5	3.5–5.3	3.6	3.5–5.3
Urea nitrogen (mg/dl)	18	16	104	8–24	83	8–24
Creatinine (mg/dl)	1.19	1.06	4.50	0.50–1.10	5.60	0.50–1.50
Estimated glomerular filtration rate (ml/min per 1.73 m^2)	46	53	9	≥60	7	≥60
Alanine aminotransferase (U/l)	22	15	24	5–50	22	5–50
Aspartate aminotransferase (U/l)	30	17	34	5–40	24	5–40
Alkaline phosphatase (IU/l)	67	73	130	25–125		
Protein (g/dl)						
Total	7.0	7.0	7.5	6.0–8.3	5.8	6.0–8.3
Albumin	4.1	4.0	3.4	3.5–5.0	2.5	3.5–5.0
Prothrombin time (sec)			13.7	11.6–15.2		8.9–12.1
International normalized ratio			1.04	0.00–1.49		<5.00
Partial thromboplastin time (sec)			32.5	24.0–37.0		≤30
Urine						
Color		Amber	Amber	Yellow		
Clarity		Cloudy	Cloudy	Clear		
Specific gravity		1.016	1.015	1.005–1.030		
pH		5.0	5.0	5.0–8.0		
Protein (mg/dl)		30	30	Negative		
White cells per high-power field		12	32	0–3		
Red cells per high-power field		>182	>182	0–3		
Protein-to-creatinine ratio (random, mg/g)			2920.63	0–200		

[a]Twenty-one days after admission to other hospital.
To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
Reference values are affected by many variables, including the patient population and the laboratory methods used.

ANCA-negative GN is poorly understood and generally understudied. In addition, a major limitation in the current literature regarding VTE in renal vasculitis is the lack of a clear pathophysiologic mechanism to explain the association. In this report we discuss a case of rapidly progressive, pauci-immune, ANCA-negative crescentic GN following presentation for an unprovoked DVT. We further discuss hypercoagulability in vasculitis, including the prevalence, possible mechanisms underlying its pathophysiology, and treatment challenges.

Case Presentation

A previously healthy 70-year-old woman presented to an outside hospital emergency department with complaints of left lower-extremity edema and pain. Initial Doppler ultrasound of the lower extremities was negative for DVT. Urinalysis showed hematuria and bacteriuria; therefore, the patient was discharged with cephalexin. Six days later, she presented again to the emergency department with worsening left lower extremity edema and was admitted to the hospital. A repeat venous Doppler ultrasound revealed extensive DVT involving the left common femoral vein, profunda femoris vein, superficial femoral vein (proximal and mid), with additional impaired compression but laminar flow seen in the left popliteal vein, posterior tibial vein, and peroneal vein. At the time of admission, a complete blood count showed a hemoglobin count of 12.1 g/dl; metabolic panel demonstrated serum creatinine (SCr) 4.5 mg/dl (baseline of 0.9 to 1.0 mg/dl), and blood urea nitrogen (BUN) 104 mg/dl (Table 1). Blood work obtained 1 month before the initial presentation showed SCr 1.19 mg/dl and BUN 18 mg/dl.



Hospital Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
SCr	4.5	3.08	2.37	2.18	2	1.95	1.93	1.99	1.87	1.87	1.74	1.64	1.81	2.22	2.38	3.21	3.78	4.33	4.67	4.67	5	5.6	5.64	6.13	5.8	5.68	5.88	3.74	3.92	4.13	3.86	3.36	3.05	2.86	2.55	2.29	2.21	1.98
BUN	104	90	68	51	38	33	30	29	25	21	18	15	15	18	20	26	33	40	46	52	65	83	82	91	106	116	120	84	83	93	94	88	85	83	83	75	75	62

Figure 1. Serum creatinine (mg/dL) and blood urea nitrogen (mg/dL) by hospital day. Abbreviations: SCr, serum creatinine; BUN, blood urea nitrogen; PLEX, plasma exchange; HD, hemodialysis; WFBMC, Wake Forest Baptist Medical Center.

Systemic anticoagulation with heparin infusion for management of acute DVT was initiated. Renal function initially improved with administration of i.v. fluids and discontinuation of benazepril (Figure 1). Spot urine studies demonstrated sodium 56 mmol/liter, osmolality 448 mOsms/kg, protein/creatinine ratio of 2920 mg/g creatinine, and >182 red blood cells. Gross hematuria, present after placement of a urinary catheter, resolved early in the hospitalization and the patient had normal urine output. Within 48 hours of transitioning to rivaroxaban for long-term anticoagulation, SCr increased to 3.21 mg/dl, and international normalized ratio (INR) peaked at 4.51; therefore, rivaroxaban was discontinued, and i.v. heparin was restarted (Figure 1). Laboratory studies demonstrated persistent leukocytosis, although the patient remained afebrile, and the clinical examination, with additional workup, was negative for an infectious etiology. Computed tomography (CT) of the chest, abdomen, and pelvis with i.v. contrast was performed, redemonstrating evidence of DVT, bilateral pleural effusions, and no evidence of occult malignancy. Renal biopsy was performed on the 17th day of hospitalization, and the patient was transferred to a tertiary academic medical center on the 22nd hospital day for further management of acute renal failure.

Renal Biopsy Findings

An ultrasound-guided kidney biopsy was performed at the outside hospital on Day 17 of hospitalization (23 days after the initial presentation, 5 days before transfer to the tertiary medical center). Evaluation by light microscopy revealed that 27 of 52 glomeruli were involved with focal necrosis and/or crescent formation (Figure 2a and b); the unaffected portions of the glomeruli appeared normal, with no endocapillary or mesangial hypercellularity. Numerous tubular cross sections showed red cell casts (Figure 2c and d). There was mild edema with a mild lymphoplasmacytic interstitial infiltrate (Figure 2b and c). There was only mild interstitial fibrosis supporting the clinical findings of acute rather than chronic renal failure. The arteries showed mild arterial intimal expansion, and arterioles displayed mild hyalinosis; no arteritis was identified. Immunofluorescence staining on frozen tissue was negative for IgG, IgA, and complement C1q deposition in the glomerular, tubular, or interstitial compartment and showed mild-to-moderate IgM and complement C3 deposition within the glomerular mesangium (Figure 2f). Electron microscopy was not performed. Altogether, these findings showed evidence of a pauci-immune necrotizing and crescentic GN.

On the patient's arrival at the tertiary care center, the patient's chief complaint was worsening edema in the left lower extremity. Review of systems was negative for fever, cough, hemoptysis, fatigue, weight loss, night sweats, arthralgias, diarrhea, emesis, oral ulcerations, and rash. Past medical history included hypothyroidism; essential hypertension; pure hypercholesterolemia; and mild, intermittent asthma. She had never been treated with hormone-replacement therapy, and there was no history of pregnancy miscarriage.

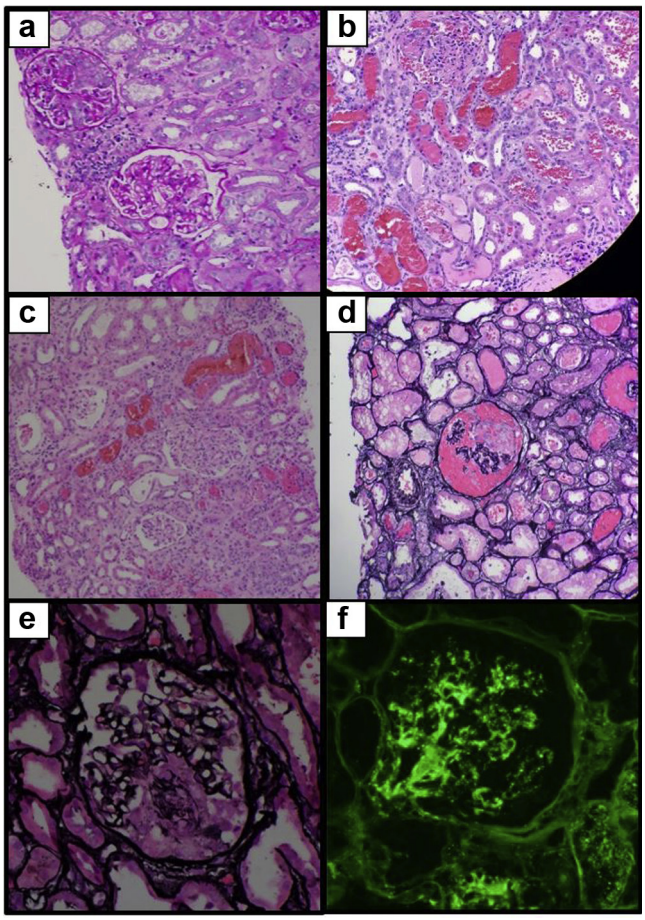


Figure 2. (**a**) Periodic acid-Schiff staining at demonstrates glomerulus with a cellular crescent (upper left) adjacent to a normal appearing glomerulus. (**b**) and (**c**) Hematoxylin and eosin staining show cellular crescents, red blood cell casts, and mild tubulointerstitial edema and lymphoplasmacytic infiltrate. (**d**) Methenamine periodic acid-Schiff staining demonstrates cellular crescents and pooling of red blood cells in the Bowman's space and renal tubules. Panel (**e**) Methenamine periodic acid-Schiff staining shows focal necrosis with destruction of the glomerular basement membrane. Panel (**f**) Direct immunofluorescence microscopy shows mild C3 deposition (1+) in the glomerular mesangium.

Table 2. Laboratory data for workup of renal failure

Serum	Value	Reference range
Antinuclear antibody	1:320, speckled	<1:80
Antiglomerular basement membrane antibody (U)	<0.20	<1.0
Anti-MPO antibody (U)	<0.20	<0.40
Anti-PR3 antibody (U)	<0.20	<0.40
Antidouble stranded DNA antibody (Crithidia)	13.5	<30
Anti-DNase B antibody (U/ml)	<76	0–300
Antistreptolysin O antibody (IU/ml)	<20	0–530
Lupus anticoagulant	Not detected	Not detected
Cryoglobulin (% ppt)	Negative	Negative
Creatinine kinase (IU/l)	49	30–223
Free κ/λ ratio	1.30	0.26–1.65
Complement C3 (mg/dl)	177	87–200
Complement C4 (mg/dl)	40	19–52
C-reactive protein (mg/l)	322.8	<3.0
Erythrocyte sedimentation rate (mm/h)	89	0–30
Serum protein electrophoresis	No M-spike seen	
Hepatitis panel		
Hepatitis B surface antibody	Nonreactive	Nonreactive
Hepatitis B core antibody	Nonreactive	Nonreactive
Hepatitis C antibody	Nonreactive	Nonreactive
Hepatitis A IgG and IgM antibodies	Nonreactive	Nonreactive
Hepatitis B surface antigen	Nonreactive	Nonreactive
Disseminated intravascular coagulation panel		
International normalized ratio	2.25	<5.00
Partial-thromboplastin time (sec)	108.9	≤30.0
D-dimer (ng/ml FEU)	1670	190–500
Fibrinogen (mg/dl)	80	180–363
Hypercoagulability workup		
Factor V Leiden mutation	Not present	Not present
Factor II mutation	Not present	Not present
Anticardiolipin IgA antibody	<9.4	<15.0
Anticardiolipin IgG antibody	<9.4	<15.0
Anticardiolipin IgM antibody	<9.4	<15.0
Beta-2-glycoprotein IgG antibody (U/ml)	<9.4	<15.0
Beta-2-glycoprotein IgM antibody (U/ml)	<9.4	<15.0

Reference values are affected by many variables, including the patient population and the laboratory methods used.

There was no family history of autoimmune disease, coagulation disorders, DVT, or malignancy. She did not smoke tobacco, drink alcohol, or use illicit drugs.

On physical examination, the patient appeared tired. Her temperature was 97.6 °F, pulse 88 beats per minute, blood pressure 147/81, respiratory rate 18, and oxygen saturation 94% while she was breathing ambient air. Weight was 87.8 kg, approximately 13 kg above baseline. The lungs had bibasilar coarse crackles. The left lower extremity demonstrated 3+ pitting edema to the thigh, whereas the right lower extremity demonstrated 2+ pitting edema to the mid-shin. There were no dermatologic findings, and the remainder of the examination was normal.

Laboratory tests obtained for workup of acute renal failure are summarized in Table 2. SCr level peaked at 6.13 mg/dl on the 24th day of admission (30 days from initial presentation). Renal and urinary ultrasound with Doppler studies was negative for renal vein thrombosis, obstruction, and anatomic abnormalities.

Treatment and Outcome

Considering the diagnosis of small-vessel vasculitis with severe renal involvement, immunosuppressive therapy and plasma exchange were initiated. The patient was treated with pulse-dose i.v. methylprednisolone 500 mg/d for 3 consecutive days, followed by oral prednisone 60 mg daily, along with oral cyclophosphamide 1 mg/kg per day (75 mg daily). In light of severe renal dysfunction, 7 plasma-exchange treatments were prescribed over 14 days. Midway through the plasma-exchange treatment course, the patient underwent 1 session of hemodialysis. After 4 plasma-exchange treatments with albumin, the patient

received alternating albumin and fresh frozen plasma replacement because of bleeding from her vascular access and labile heparin partial thromboplastin times (PTTs). In this case, the decision to initiate cyclophosphamide therapy was based on guidelines for pauci-immune crescentic GN[12] and previous case reports of ANCA-negative patients,[2,13] as most clinical trials include patients with detectable ANCA serology at diagnosis.[14–16]

The patient was discharged on hospital day 39, with SCr level of 1.86 mg/dl. Medications on discharge consisted of a tapering scale of prednisone to discontinuation over 24 weeks, oral cyclophosphamide for 4 to 6 months, with plans to continue maintenance immunosuppression with azathioprine 1.5 mg/kg per day for 24 months. Warfarin was selected for long-term anticoagulation. Three months after discharge, the patient had persistent lymphedema secondary to her DVT. Laboratory analysis showed SCr 1.40 mg/dl and BUN 22 mg/dl; urinalysis demonstrated hematuria (16 to 22 red blood cells), proteinuria (≥300 mg/dl), 31 to 40 white blood cells, and spot urine protein/creatinine ratio of 1151 mg/g creatinine (decreased from a peak of 2920 mg/g).

Discussion

This patient's initial contact with medical care was motivated by lower extremity discomfort secondary to DVT. Subsequent workup led to the diagnosis of small-vessel vasculitis with negative ANCA serology and severe renal involvement. Clinical management of this patient raised key issues and gaps in the current understanding of ANCA-negative small-vessel vasculitis, which are discussed in the following section.

Antineutrophil Cytoplasmic Antibody Negativity

Some have advocated for the inclusion of ANCA-negative, pauci-immune crescentic GN in the spectrum of AAV,[17] as it is possible that ANCA-negative vasculitis may simply represent a failure of current assay detection techniques.[18,19] However, there is emerging evidence of a distinct pathophysiology. Several mechanisms for ANCA-negative, crescentic GN have been proposed linking non-ANCA antibodies to increased neutrophil activation in the glomerulus.[1,20] Although the exact identity of these activating factors is unclear, several known inducers of neutrophil induction (e.g., autoantibodies to human lysosomal-associated membrane protein-2 and antiendothelial cell antibodies) have been implicated.[21–23] Higher levels of neutrophil degranulation are seen in ANCA-negative, pauci-immune patients with GN compared with ANCA-positive patients,[21] and an increased neutrophil presence in Bowman's capsule results in more severe glomerular lesions.[22] A competing hypothesis pointing to a defect in the alternative pathway of complement—leading to destructive accumulation of activated complement molecules in the glomerulus—has recently been proposed, although with less clinical correlation.[24] Finally, macrophage cells that disrupt Bowman's space in ANCA-associated GN may also play a role in ANCA-negative disease.[25] In summary, the extent to which the pathology in ANCA-negative disease differs from ANCA-positive, crescentic GN remains under investigation, and molecular studies point toward mechanisms with overlapping neutrophil, complement, and macrophage dysregulation.

Superimposed Anticoagulant-Related Nephropathy

Given the temporal relationship between this patient's worsening renal function, increasing INR, the predominance of red blood cells and red blood cell casts in the renal tubules on renal biopsy, and the administration of rivaroxaban, anticoagulant-related nephropathy was considered as a possible etiologic component of her deteriorating kidney function. Anticoagulant-related nephropathy was first described by Brodksy *et al.* (2009) in relation to administration of warfarin and has subsequently been redemonstrated with novel oral anticoagulants.[26–28] It is more common in patients with underlying chronic kidney disease, and renal function can recover after discontinuation of the offending agent.[29,30] In our case, the patient had no history of chronic kidney disease but had recently developed crescentic GN. Her renal function continued to decline after discontinuation of rivaroxaban, likely due to the ongoing small-vessel vasculitis. Although we attribute the findings of red cell casts to anticoagulation, it is unfortunately not possible to pinpoint the underlying etiology on histolopathology and therefore introduces the question of whether they may have been due to the vasculitis. The existing literature on red cell casts in AAV is focused primarily on urine sediment rather than renal histology,[8,31] which limits our ability to address this question.

Hypercoagulability and the Prevalence of Venous Thromboembolism in Small-Vessel Vasculitis

Given the lack of available literature on pauci-immune, ANCA-negative crescentic GN, we focus our discussion primarily on evidence in AAV. Complications of hypercoagulability, such as DVT or pulmonary embolus, have been noted as extrarenal complications of AAV[32] and are common in active disease.[5,33,34] For example, Stassen *et al.* (2008) describe VTE incidence of 6.7 per 100 patient-years among patients with active AAV and 1.8 per 100 patient-years in patients with AAV in remission, which was significantly higher than the incidence of VTE in the general population of 0.3 per 100 patient-years.[33] Importantly, there was no

statistical difference in the distribution of classic VTE risk factors between patients with AAV who did and did not develop VTE in the follow-up period, and most patients had at least 1 traditional risk factor.[33] Reports of incidence and prevalence of VTE in AAV offer large variations. In a 20-year population-based cohort, the hazard ratio for DVT in AAV was 6.25 (95% confidence interval, 1.16–33.60).[7] Among AAV patients with no underlying coagulopathy or risk factors, VTE incidence was found to be 4.3 per 100 person-years by Weidner *et al*. (2006),[32] versus 1.47 per 100 person-years described by Kang *et al*. (2018).[35] Unfortunately, however, the concomitant presence of traditional VTE risk factors or hypercoagulable conditions is not always specified.[8] For example, 1 patient in the Eisenberger *et al*. (2005) cohort had a pulmonary embolism approximately 3 weeks before development of microscopic polyangiitis, although it is not clear if there was a provoking factor.[36] One of the earliest analyses of VTE in AAV by Merkel and colleagues (2005) described an incidence rate of 7 per 100 patient-years, although classic VTE risk factors were not specifically noted.[37] Nonetheless, the majority of available evidence suggests increased risk of VTE in AAV, regardless of the subcategorization of disease (granulomatosis with polyangiitis, microscopic polyangiitis, etc.) or severity of disease.

Most commonly, the reported embolic events in AAV are not the presenting feature of the disease but rather occur in the months after diagnosis.[35,37] Similar to our case, exceptions to typical presentations have been previously reported. One report describes a patient presenting with intermittent fevers, night sweats, and abdominal pain who was found to have bilateral renal vein thrombosis and bilateral pulmonary emboli on admission.[38] Serologic workup was positive for anti-myeloperoxidase antibodies (MPO), lupus anticoagulant, and anticardiolipin antibodies.[38] Given the positive hypercoagulability workup, the unique contribution of AAV to the embolic events cannot be quantified in this case. This is consistent with the reported 8% prevalence of anticardiolipin antibody and lupus anticoagulant in primary systemic vasculitis.[39]

In contrast to classic AAV, hypercoagulability has not been described as a common feature of ANCA-negative, pauci-immune GN, nor has it been described as the presenting complaint in occult disease. Our patient had no known prothrombotic risk factors such as smoking, recent surgery, hormone-replacement therapy, trauma, malignancy, or immobilization, and she was up to date on her age-appropriate cancer screening. Serologic testing did not reveal an underlying hypercoagulable state, apart from nephrotic range proteinuria and associated hypoalbuminemia. Decreased serum albumin is positively associated with risk of VTE in nephrotic syndrome.[40,41] The mechanism is presumed multifactorial, including compensatory hepatic hyperproduction of procoagulants (fibrinogen, factors V and VIII),[42] decreased synthesis of natural anticoagulants (free protein S, antithrombin III),[42] and impaired fibrinolysis, as albumin is a required cofactor for binding plasminogen to fibrin.[43] The triad of hypoalbuminemia, hypercholesterolemia, and elevated fibrinogen in nephrotic syndrome further contribute to increased platelet aggregation[42,43] and abnormal clot architecture.[44] Although there was likely an element of concomitant anticoagulant-related nephropathy in this case, the improvement in kidney function in response to plasmapheresis therapy strongly suggested an underlying inflammatory process driven by circulating immune factors. Therefore, we conclude that the event of VTE in this case was likely related to the underlying systemic inflammatory process that led to renal decline, as otherwise hypothesized in ANCA-positive small-vessel vasculitis. Despite absence of other clinically apparent end-organ involvement with small-vessel vasculitis, the presence of DVT without other known prothrombotic factors argues for a systemic inflammatory and autoimmune condition rather than renal-limited small-vessel vasculitis.

Pathophysiology of Hypercoagulability in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Thromboembolic disease has also been increasingly recognized as a common complication in other vasculitides. The hierarchy of VTE risk among various autoimmune and vasculitis disorders has been described by several investigators.[5,45–47] With the exception of Behçet disease, in which venous thrombosis is the most common vascular manifestations,[34,46] the incidence of VTE in AAV appears to be higher than in other autoimmune, inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, or polyarteritis nodosa, suggesting a novel pathway.[5,37,48] Several mechanisms have been proposed to underlie the pathophysiology of VTE in systemic inflammatory conditions of vasculitis and autoimmune disease. Figure 3 summarizes putative pathways linking inflammation and disordered immune system with development of VTE and the clinical data are summarized in Table 3.[40,49–62] The proposed mechanisms, not mutually exclusive, perturb the elements of Virchow's triad classically used to explain the pathophysiology of VTE: blood flow, endogenous constituents of anti- and prothrombosis, and the vessel wall.[63,64] Central to the model for the development of

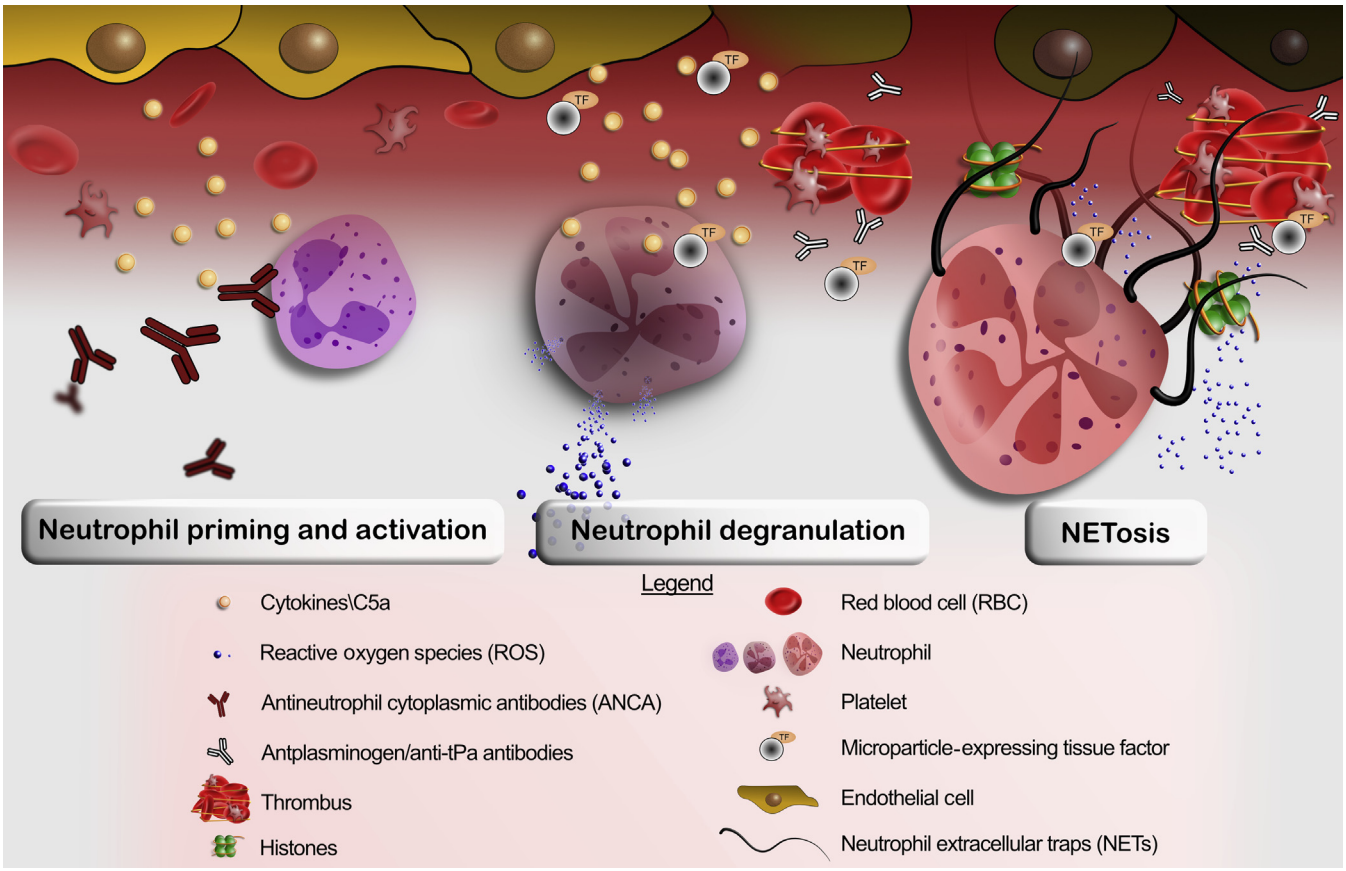


Figure 3. Schematic representation of select potential mechanisms that promote thrombosis in vasculitis and autoimmune disease. Primed, activated neutrophils interact with endothelial cells, with consequent endothelial damage, production of reactive oxygen species, and release of proinflammatory cytokines and chemokines. Dysfunctional endothelial cells, activated from the oxidative stress, express adhesion receptors with further recruitment of leukocytes and platelets; and expose subendothelial tissue factor, which initiates the extrinsic coagulation pathway. Interactions between activated endothelial cells and platelets with neutrophils result in the formation of intact and fragmented neutrophil extracellular trap (NET) networks in vascular beds. The externalized histones within NETs promote the propagation of intravascular blood coagulation, von Willebrand factor binding, and platelet adhesion and activation, which amplifies thrombosis. Antiplasminogen and antitissue plasminogen activator antibodies inhibit the process of fibrinolysis, thereby supporting the propagation of blood coagulation, rather than triggering its initiation. Overall, the neutrophils, endothelial cells, NETs and circulating antibodies likely operate in concert to initiate, enhance and propagate blood clot formation.

VTE in vasculitis and autoimmune diseases is endothelial cell injury, which triggers a cascade of molecular factors that interconnect the immune and coagulation systems as summarized here.

- **Neutrophils are primed by proinflammatory factors, activated, and interact with endothelial cells.** Proposed priming factors include granulocyte-mediated colony stimulating factor (GM-CSF),[53] complement 5a (C5a),[53,65] and tissue factor (TF).[53] Tissue necrosis factor alpha (TNFα) was initially favored to be a key mediator;[56] however, *ex vivo* experiments using TNFα inhibitors did not result in decreased neutrophil priming.[53,55] In comparison, inhibiting C5a did prevent neutrophil priming and the downstream effects.[53] In AAV, primed neutrophils are thought to be primarily activated by serum ANCAs,[56,66] although additional neutrophil activators may also be involved.[21,57,67] The activated neutrophils interact with the endothelial cells with consequent oxidative stress, increased expression of adhesion molecules, and further recruitment of leukocytes and platelets.[55,68] Disruption of the vascular endothelium creates a microenvironment that promotes thrombosis and increases vascular wall permeability. Thrombogenic TF is released from the activated endothelial cells and exposed subendothelial matrix.[69]
- **Primed, activated TF-positive[54] neutrophils degranulate and release reactive oxygen species, TF-positive microparticles (MPs),[52,53,55] and TF-positive neutrophil extracellular trap (NET) molecules,[66] which activate the coagulation cascade.**[53,60] A detailed review of NET formation can be found in Laridan *et al.* (2019).[70] Briefly, upon activation, the neutrophils release chromatin and other nuclear, cytoplasmic, and granular proteins in the extracellular space that encompass the NET

Table 3. Summary of existing literature pertaining to the pathophysiology of AAV and VTE

Reference	Study description	*Ex vivo* or serologic findings	Conclusions
Berden *et al.* (2010)[49]	Assessment of prevalence and function of anti-plasminogen antibodies in two populations of patients with AAV (UK n = 74; Dutch n = 38)	Antiplasminogen antibodies present in 25% of both AAV cohorts (vs. 2% in controls). In the UK cohort, 24% of the antiplasminogen antibodies delayed fibrinolysis (vs. none of the controls), with a mean delay of 5.2 minutes (SD 2.8).	Antiplasminogen antibodies and anti-tPA antibodies are more prevalent in AAV and can delay fibrinolysis. These antibodies were also associated with higher percentages of fibrinoid necrosis and cellular crescents, as well as worse renal function.
Hao *et al.* (2013)[50]	Detection of antiplasminogen antibodies during active disease and remission in patients with AAV (n = 104)	Antiplasminogen antibodies were detected in 18.3% of patients with AAV (vs. none of controls). Presence of antiplasminogen antibodies correlated with higher levels of ESR, creatinine, and CRP. Antibody positive patients had higher BVAS.	Presence of circulating anti-plasminogen antibodies is associated with both active systemic and renal disease in patients with AAV.
Hilhorst *et al.* (2013)[51]	Assessment of the risk of hypercoagulability in patients with AAV in remission and no recent VTE (n = 31)	Endogenous thrombin potential was elevated in patients compared with matched controls (137% vs. 90%). Factor VIII was also elevated (159% vs. 137%), as was tissue factor pathway inhibitor (122% vs. 101%).	Patients with AAV in remission demonstrate elevated coagulability, which may be due to persistent endothelial dysfunction and may partially explain the elevated risk of VTE.
Hong *et al.* (2012)[52]	Investigation of the role of ANCAs and neutrophil microparticles in children with AAV (n = 9)	ANCAs stimulate the release of neutrophil microparticles from primed neutrophils. The microparticles increase production and release of ROS, IL-6, IL-8, and thrombin. Patients with AAV had higher levels of circulating microparticles than inactive disease (642 x 10^3/ml vs. 237 x 10^3/ml) or controls.	The interaction of ANCAs with primed neutrophils generates a proinflammatory and prothrombotic environment through the release of neutrophil microparticles and their downstream effects.
Huang *et al.* (2015)[53]	Investigation of the role of C5a priming in the pathway between ANCA stimulation and the generation of microparticles and NETs in patients with AAV (n = 11)	Neutrophils primed with C5a released more TF-positive microparticles and NETs after ANCA activation than those primed with a positive control. The TF-positive NETs can generate thrombin and TAT complexes.	C5a mediates the activation of the coagulation system in AAV via neutrophil activation.
Kambas *et al.* (2012)[54]	Investigation of the inclusion of TF in NETosis and its role in hypercoagulability in patients with sepsis (n = 8)	Neutrophils release TF to NETs via autophagy. This TF stimulates generation of thrombin and subsequent PAR-1 signaling to activate the coagulation cascade.	Neutrophil derived TF co-localized in NETs may explain the prothrombotic state in sepsis.
Kambas *et al.* (2014)[55]	Investigation of TF expression and neutrophil dynamics in patients with AAV (n =17)	Renal biopsies demonstrate TF-positive NETs. Elevated circulating DNA and TF expressing neutrophil microparticles are correlated with disease activity.	Hypercoagulability in AAV may be due to the thrombotic potential of circulating neutrophil microparticles expressing TF and/or the downstream activation of the coagulation cascade.
Kessenbrock *et al.* (2009)[56]	Assessment of the role of NETs in small-vessel vasculitis (n =12)	ANCAs activate neutrophil nuclei to induce NETosis. Both PR3 and MPO colocalize within the NET. Renal biopsies of small-vessel vasculitis also demonstrate proximity of NET components and IFNα to neutrophil infiltrates in pathologic glomeruli. Serum IFNα and circulating MPO-DNA are elevated in patients with active disease and absent in controls.	NETosis is present in small-vessel vasculitis and is stimulated by ANCAs. NET formation was not observed in healthy controls or controls with multiple sclerosis, suggesting the specific auto-antigenicity of ANCAs in small-vessel vasculitis.
Kraaij *et al.* (2018)[57]	Investigation of NET formation in patients with MPO- and PR3-positive AAV (n = 99)	Increased NET formation is present in both MPO- and PR3-positive patients compared with controls. However, it does not correlate to serum ANCA levels. NETosis is higher in active disease/relapse than remission, infection, or healthy controls.	NETosis is independent of ANCA (either MPO or PR3) but related to disease activity in patients with AAV.
Ma *et al.* (2014)[58]	Analysis of coagulation profiles in a prospective cohort of patients with AAV (n = 399)	4% of patients with active disease developed VTE (vs. none in remission). Compared with those in remission, patients with active AAV had higher levels of serum D-dimer (0.8 mg/L [0.4, 1.5] vs. 0.28 mg/L [0.2, 0.55]), fibrin-degradation products (5.6 mg/L [5.0, 10.0] vs. 1.9 mg/L [1.2, 2.8]), and platelets (269 ± 127 x 10^9 /L vs. 227 ± 80 x 10^9 /L)	Hypercoagulability in active disease states of AAV may be due to abnormal fibrinolysis.
Mendoza *et al.* (2019)[40]	Prospective cohort analysis of incident VTE, microparticle tissue factor activity (MPTFa), and anti-plasminogen antibodies in patients with AAV in remission (n = 41)	29.3% of patients developed VTE during the study period. Patients who developed VTE have higher mean peak MPTFa than controls (14.0 [4.3-36.6] vs. 0 [0-3.5]). MPTFa is associated with VTE during active disease and remission. Antiplasminogen antibody is associated with VTE during remission (HR 1.17 [1.03-1.33]). VTE risk is increased 4-times for each 1 g/dl decrease in serum albumin (HR 4.4 [1.5-12.0]).	Patients with AAV in remission are at higher risk of VTE, possibly due to elevated MPTFa and increased antiplasminogen antibodies. Additionally, serum albumin may be a useful biomarker for assessing VTE risk.
Nakazawa *et al.* (2012)[59]	Case report of fatal, concomitant DVT and pulmonary hemorrhage in a patient with MPA (n = 1)	NETs are present within the thrombus and the glomerular crescents. The NETs within the thrombus are characterized by increased histone-citrullination compared with thrombi from control patients.	NETosis may be contributing to both hypercoagulability and glomerular damage in patients with MPO and other forms of small-vessel vasculitis.

(Continued on next page)

Table 3. (Continued) Summary of existing literature pertaining to the pathophysiology of AAV and VTE

Reference	Study description	*Ex vivo* or serologic findings	Conclusions
Salmela *et al.* (2015)[60]	Prospective cohort analysis of coagulation factors in patients with AAV (n = 21)	9.5% of patients developed VTE during the study period. Incidence rate was 9.0 per 100 person years. Both active disease and remission are associated with higher levels of Factor VIII, von Willebrand factor antigen, and von Willebrand factor ristocetin cofactor activity. Anti-thrombin activity is normal during active disease but elevated during periods of remission. In patients with active disease, D-dimer and prothrombin fragments are 5.0 and 2.6 times higher, respectively, than controls and are associated with lower eGFR.	Hypercoagulability in AAV is associated with elevated Factor VIII activity, thrombin formation, and fibrin turnover both in active disease and remission.
Shida *et al.* (2018)[61]	Case report of drug-induced MPO-ANCA with subsequent analysis of the pathogenesis of NETs during spontaneous reactivation of disease (n = 1)	Anti-NET antibody was present in the patient's serum at time of relapse, with simultaneous increase in NET induction activity, not seen during remission.	Anti-NET antibodies may induce NETosis to reactivate AAV, which may amplify the ANCA-NET cycle of disease activity.
Van Montfoort *et al.* (2013)[62]	Case-control analysis of circulating nucelosomes and systemic neutrophil activation in patients with DVT (n = 195)	Elevated levels of circulating nucleosomes and activated neutrophils are present in patients with DVT (vs. controls). Higher level of nucleosomes is associated with higher odds of DVT (aOR 3.0 [1.7, 5.0]).	The dose-dependent relationship between circulating nucleosomes, activated neutrophils, and DVT may partially explain the prothrombotic state in systemic inflammatory conditions. Circulating nucleosomes may be a useful biomarker for NETosis and risk of VTE.

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; aOR, adjusted odds ratio; BVAS, Birmingham vasculitis activity score; CRP, C-reactive protein; CSS, Churg-Strauss syndrome; DNA, deoxyribonucleic acid; DVT, deep vein thrombosis; eGRF, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HR, hazard ratio; IFNa, interferon alpha; IL, interleukin; IgAN, IgA nephropathy; IVC, inferior vena cava; MPA, microscopic polyangiitis; MPTFa, microparticle tissue factor activity; NET, neutrophil extracellular trap; PAN, polyarteritis nodosa; PE, pulmonary embolism; Ref, manuscript reference; ROS, reactive oxygen species; TAT, thrombin-antithrombin; TF, tissue factor; tPA, tissue plasminogen activator; UK, United Kingdom; VTE, venous thromboembolism; WG, Wegner's granulomatosis.

molecular network. Both MPs and NETs precipitate the development of clots via expression of TF[55] and are capable of promoting thrombin formation.[53] The exposed nucleosomes that compose NETs[70,71] allow for platelet, red blood cell, and plasma protein adherence, as well as clot stabilization through thrombin-dependent fibrin formation.[62,71] NETs additionally cause direct endothelial damage, which is independently prothrombotic.[65,68] Patients with AAV demonstrate increased coagulation cascade activity via elevated fibrin turnover,[60] thrombin,[60] D-dimer,[58,60] thrombin antithrombin complexes,[53] and fibrin degradation products.[58] NETs also stimulate increased ANCA production via dendritic cell activation of autoreactive T helper and B cells, which feeds back into neutrophil activation.[61,72]

- **Inhibition of fibrinolysis.** Plasminogen has been described as an autoantigen in PR3-positive small-vessel vasculitis, and its interaction with autoantibodies directed toward complementary PR3, a protein encoded by the antisense RNA of the PR3 gene, is able to block conversion to plasmin.[73] Antiplasminogen antibodies have been detected in up to 26% of patients with MPO-positive and PR3-positive vasculitis, whereas only present in 2% of the control population. Antitissue plasminogen activator (tPA) antibodies were also detected in nearly 20% of patients with AAV and more commonly in patients with coexisting antiplasminogen antibodies. Functional *in vitro* studies showed that antiplasminogen and anti-tPA antibodies retarded fibrinolysis.[49] In some studies, circulating antiplasminogen antibodies were associated with systemic and renal disease activity of AAV.[49,50] Although antiplasminogen antibodies are not alone sufficient to cause a thrombotic event, they may contribute to the prothrombotic environment critical to clot formation and propagation.[73]

The clinical significance of NETs was evaluated by Nakazawa and colleagues (2012), who described a case of MPO-positive vasculitis with diffuse alveolar hemorrhage in which thrombosis of the left common iliac vein was incidentally discovered on imaging.[59] Autopsy allowed for identification of NETs within the thrombus itself [59] and within the glomerular crescents.[56,59] Furthermore, there was an increased burden of histone-citrullination in the thrombus compared with thrombi from patients with non-AAV VTE,[59] which is consistent with the description of NETs as a scaffold and stimulus from thrombus formation.[71] *Ex vivo* studies indicate that NET scaffolding can be dismantled with heparin therapy.[71] These findings are supported by studies demonstrating decreased serum NETs and attenuated NET activity following remission of disease.[55,57,68] Active regulation of NETs could be a promising strategy to treat small-vessel vasculitis as well as thrombosis complicating the disease process.

Challenges in the Treatment of Hypercoagulability in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

A major challenge in the treatment of small-vessel vasculitis is the potential for exacerbation of hemorrhagic complications (i.e., diffuse alveolar hemorrhage) with treatment of acute VTE secondary to

hypercoagulability. This must be considered in the decision to initiate plasma exchange, as it removes essential clotting factors that regulate the coagulation cascade. Plasma exchange is recommended as an adjunct therapy for patients with severe renal disease or pulmonary hemorrhage, although there is no consensus on the definition of *severe* renal disease.[74–76] Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest 7 treatments of plasma exchange over a period of 14 days, with 60 ml/kg replaced with 5% albumin.[12,17] If pulmonary hemorrhage is present, then plasma is preferred for replacement fluid.[76] In clinical practice, the choice of replacement fluid in plasma exchange is variable and often depends on the clinical context.[77] The theoretical risk of treating small-vessel vasculitis with plasma replacement fluid in a patient with both high risk bleeding and VTE rests on the possibility of extending the existing clot or precipitating a new thrombus following infusion of prothrombotic factors.[78,79] The French Vasculitis Study Group noted 10 instances of venous thrombosis following plasma exchange (using unspecified replacement fluid); clinical implications of DVT in the context of plasmapheresis therapy were not discussed.[80]

The hypothesized benefit of plasma exchange in AAV relies on the removal of pathogenic ANCAs, as ANCAs are typically IgG antibodies readily eliminated during the exchange.[81] In ANCA-negative small-vessel vasculitis, the beneficial effects of plasma exchange have been postulated to be derived from removal of cytokines, complement, and other proinflammatory molecules, as well as human lysosomal-associated membrane protein-2 antibody or other antibodies that are hypothesized to contribute to the disease process.[23,75] It has also been suggested that some cases of ANCA-negative GN are misclassified because of poor detection of MPO in standard clinical assays and would therefore benefit from plasma exchange for removal of ANCAs.[82] Although plasma exchange may benefit patients with less severe renal disease at presentation, it is an invasive and expensive therapy, with insufficient evidence to be more broadly employed.[77] Furthermore, although patients receiving plasma exchange demonstrate initial improvement in renal function, studies have not shown consistent long-term effects on outcomes of dialysis-dependent renal failure or mortality.[75,77,81,83,84] The highly anticipated Plasma Exchange and Glucocorticoids for Treatment of ANCA-Associated Vasculitis (PEXIVAS) trial publication may help clarify the use of plasma exchange in treating AAV, yet its utility in ANCA-negative small-vessel vasculitis will continue to remain poorly defined.[85]

Renal biopsy is often needed to diagnose the underlying etiology of acute renal failure and is common for patients with AAV. However, biopsy carries significant risks for those who are coagulopathic owing to the chance of retroperitoneal bleeding, as exemplified by this case.[86] Standard practice is to hold anticoagulation before biopsy to minimize bleeding; thus, for patients needing ongoing anticoagulation, transition to heparin infusion is preferred in the peribiopsy period to minimize time off anticoagulation.[86,87] In patients taking warfarin or a factor Xa inhibitor, it is recommended to withhold these agents for at least 72 hours before biopsy, whereas a heparin infusion may be continued until several hours before biopsy.[88] Anticoagulation may be resumed as soon as 12 hours postbiopsy, although a period of 48 to 72 hours is preferred, depending on the risk of thrombosis.[88] An alternative to percutaneous renal biopsy is transjugular renal biopsy, which was first developed for simultaneous hepatic and renal biopsies in patients with multiorgan dysfunction.[89] Although this approach can be considered, transjugular renal biopsies carry the additional risk of contrast-induced nephropathy and higher rates of capsular perforation.[86] The high complication rates with a transjugular approach in patients with underlying coagulopathy is similar overall to percutaneous renal biopsy in this patient population.[89]

Another challenge in this case was the superimposed anticoagulant-related nephropathy. Continuation of anticoagulation was, nevertheless, mandatory in this patient. It is interesting to note that continuation of systemic anticoagulation was eventually possible, without further deterioration of renal function. We suspect that the initiation of treatment for vasculitis mitigated the glomerular pathologic changes, which, in turn, reduced the risk of further progression of anticoagulant-related nephropathy. Even though treatment with vitamin K antagonist warfarin was ultimately elected over direct oral anticoagulant therapy for treatment of acute DVT, there is insufficient literature to suggest differential risk profile for glomerular hematuria between the various pharmacologic options of systemic anticoagulation.[30,90] The existing observational data comparing non-vitamin K oral anticoagulants (such as rivaroxaban, dabigatran, and apixaban) and warfarin have substantial methodologic limitations.[91,92] Avoiding anticoagulation entirely is possible; using alternatives, such as vena cava filters, may be considered. However, these devices are not routinely used in the absence of an acute proximal DVT with a major contraindication to anticoagulation (i.e., massive bleeding, impending surgery), given the substantial costs, risks (i.e., infection, migration, filter thrombosis), need for a second retrieval procedure, and lack of strong evidence suggesting benefit in either VTE rate

or mortality.[93–95] Further prospective evidence is needed to guide treatment of hypercoagulability in patients with known anticoagulant-related nephropathy.

Importantly, the state of hypercoagulability may persist even after clinical remission of AAV and ANCA-negative small-vessel vasculitis.[33,35,40] The pathophysiology of sustained hypercoagulability is thought to be due to ongoing endothelial dysfunction secondary to persistently elevated endogenous thrombin potential and factor VIII,[51,60] as well as antiplasminogen antibodies and microparticle tissue factor activity.[40] This may suggest a benefit of ongoing anticoagulation following disease quiescence.[33,40] However, just as there is no consensus on the overall immunosuppressive therapy duration for AAV,[17,96] there is insufficient evidence to dictate the duration of anticoagulation therapy for thromboembolic events in patients with small-vessel vasculitis.[5]

Conclusions

This case describes an unusual presentation of biopsy proven pauci-immune, ANCA-negative crescentic GN. Further delay in the diagnosis of small-vessel vasculitis would have taken place if not for her VTE, which suggests occult small-vessel vasculitis may exist despite profound histopathologic activity. To our knowledge, there are no other examples of VTE as the presenting complaint of pauci-immune, ANCA-negative crescentic GN in the literature. In this case, the hematologic manifestation of vasculitis translated into development of lower extremity DVT, which rendered the disease non-renal limited and of questionable *small-vessel* designation. The patient's clinical course highlights the tension in treating concomitant high-risk bleeding and hypercoagulability in renal vasculitis as well as the need for further research to clarify the subtleties in the pathophysiology and treatment of ANCA-negative small-vessel vasculitis.

DISCLOSURE

All the authors declared no competing interests.

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