

CASE REPORT

Deep vein thrombosis: An unusual way of revealing microscopic polyangiitis. Deep vein thrombosis in microscopic polyangiitis

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Abstract

Unexplained deep vein thrombosis may justify screening for antineutrophil cytoplasmic antibody-associated vasculitis as it can be an unusual presentation of this disease.

KEYWORDS

nephrology,

1 | INTRODUCTION

Microscopic polyangiitis (MPA) is an antineutrophil cytoplasmic antibody-associated vasculitis (AAV). It is characterized by necrotizing inflammation of the small vessel. Renal impairment and alveolar hemorrhage are the most frequent manifestations. Venous system involvement has received much attention in recent years. The relationship between AAV and thromboembolic (TE) complication has been well documented.¹ However, deep vein thrombosis is rarely the first clinical manifestation. According to literature findings, <5% of AAV have TE complication at presentation.² Only one case of AAV with bilateral vein thrombosis (VT) has been reported.³ We report the second case of MPA presenting with renal vein thrombosis.

2 | CASE PRESENTATION

A 33-year-old woman was presented without any past medical history. She had no prior history of deep VT. She consulted for abdominal pain and vomiting. Upper gastrointestinal endoscopy was normal. In view of the persistence of abdominal pain, an abdominal computed tomography was performed and revealed left renal VT.

The patient was therefore hospitalized for anticoagulation treatment and further investigation. Subcutaneous low molecular weight heparin was delivered. Physical examination was normal. The patient appeared euolemic, with a blood pressure of 120/75 mm Hg. There was no synovitis, nor cutaneous rash. Her urinalysis revealed hematuria (2+) and proteinuria (2+). She had no nephrotic syndrome, and proteinuria was

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2.7 g/day. A thrombophilia workup has been performed. It included antiphospholipid antibody (lupus anticoagulant, anticardiolipin antibodies), antithrombin III, protein C, protein S, factor V Leiden mutation, and homocysteinemia. They were all negative. Laboratory findings are mentioned in Table 1.

In view of the abnormalities of her urinalysis, she underwent renal biopsy.

Thirty-four glomeruli were analyzed by light microscopy, and 26 glomeruli were involved with necrotizing glomerulonephritis with cellular crescent formation. None of the glomeruli were sclerotic (crescentic class II of Berden's classification for AAV).

No endocapillary nor mesangial hypercellularity was noted. Tubulointerstitial cross sections were normal. There was mild arterial intimal expansion, and arterioles showed mild hyalinosis; no arteritis was identified (Figure 1).

Immunofluorescence staining was negative for IgA, IgG, IgM, and C1q. Electron microscopy was not performed.

The presence of circulating antineutrophil cytoplasmic antibodies against myeloperoxidase (MPO-ANCA), in the plasma, was confirmed using enzyme-linked immunoassays (ELISA). The diagnosis of PAM was retained.

Associated alveolar hemorrhage was suspected as the patient had an unexplained anemia despite the absence of

hemoptysis. Bronchoscopy with bronchoalveolar lavage was performed (BAL). The BAL fluid showed elevated numbers of hemosiderin-laden macrophages. Thoracic computed tomography was performed and confirmed the diagnosis of alveolar hemorrhage.

Pulses of methylprednisolone 1 g daily for 3 days were prescribed followed by oral Prednisone 1 mg/kg/day for 4 weeks. Doses of prednisone were then tapered down over 4 months. Monthly intravenous Cyclophosphamide at the dose of 0.75 g/m² during 6 months was also prescribed. The patient received seven plasmapheresis sessions with 60 mL/kg of replacement fluid containing albumin and fresh frozen plasma. Due to concerns of alveolar hemorrhage, anticoagulation was discontinued to prevent further exacerbation of bleeding.

During 6 months of follow-up, the patient was asymptomatic and she had normal serum creatinine level.

The patient has given his written informed consent to publish his case including publication of images.

3 | DISCUSSION

This observation illustrates the already known link between AAV and thromboembolic complications. There is a risk of acute venous thrombosis during AAV significantly higher than the general population ($\pm 1/1000$) or among patients with chronic inflammatory disease.²

The prevalence of VT complications in AAV varies widely in the literature [Table 2]. Nevertheless, the epidemiological data in this field are still limited.

They have been initially described in pediatric patients⁴ and then confirmed in a large randomized study conducted by WGET Research Group.⁵ Alvis et al showed that patients with AAV have a risk of VTE three times higher than healthy subject.¹

Chronic inflammation and other hypercoagulable states such as antiphospholipid syndrome are known to play an important role in the predisposition toward TE complications.^{6,7}

Systemic vasculitis such as Behçet's disease, Takayasu, and AAV is a group of chronic inflammatory disorders, and they are associated with increased risk of VTE.⁸

The pathophysiology of TE manifestation is well recognized in Behçet's disease and Takayasu but it remains unclear in AAV since vascular involvement of medium or large veins is rarely observed.^{7,9}

Numerous additional specific factors during AAV that may lead to the development of venous thrombosis were identified.

ANCA-activated neutrophil induce oxidative stress which causes endothelial dysfunction and then generate thromboses.¹⁰ Hilhorst et al compared patients with AAV in remission with sex- and age-matched healthy subject, and they found that patients with AAV have an increased endogenous

TABLE 1 Laboratory findings

Variable	Result
Serum hemoglobin (g/dL)	10
VGM (μ^3)	90
White cell count	6770
Neutrophils	4010
lymphocytes	2360
Platelet count	370 000
Sodium (mmol/L)	138
Potassium (mmol/L)	4.5
Urea nitrogen (mg/dL)	9
Creatinine (mg/dL)	0.9
Protein (g/dL) Total	66
Albumin	40
Thrombophilia screen	
Antiphospholipid antibody	
Lupus anticoagulant	Negative
Anticardiolipin antibodies	Negative
Antithrombin III	Normal
Protein C	Normal
Protein S	Normal
Factor V Leiden mutation	Negative
Homocysteinemia	Normal
Urine	
Protein (g/day)	2.7

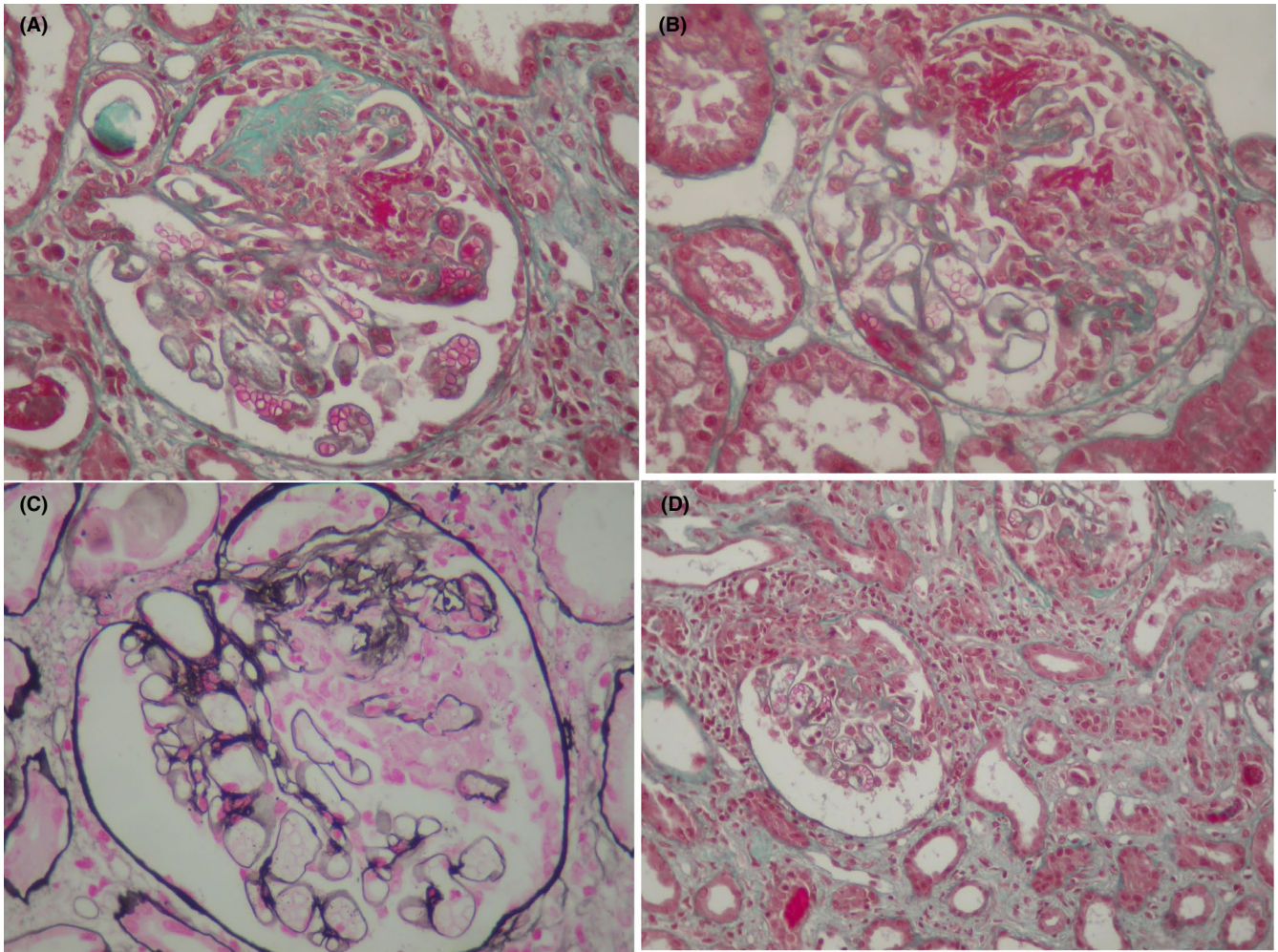


FIGURE 1 A, Light microscopy reveals glomeruli with segmental fibrinoid necrosis and focally fibrocellular crescent formation (Masson trichrome stain, 20 \times). B, Light microscopy reveals glomeruli with segmental fibrinoid necrosis and focally cellular crescent formation (Masson trichrome stain, 20 \times). C, Rupture of the glomerular basement membrane (arrow) with Reticulin stain (40 \times). D, Interstitial fibrosis and mononuclear inflammation within the interstitium (Masson trichrome stain, 10 \times)

thrombin potential and factor VII compared to healthy subjects.¹¹

Recently, Emmi et al¹² have described new mechanisms of neutrophil activation involved in thromboembolic complications during AAV. Indeed, neutrophils primed by ANCA degranulate and release extracellular nucleic acids capable of trapping bacterial agents. These extracellular neutrophil traps (NETs) are involved in thrombotic events. NETs, in turn, contain MPO and PR3 and therefore act as self-antigens.¹³ NETs are also able to induce thrombosis by inhibiting the tissue factor inhibitor and by activating platelets.¹⁴ Neutrophils are able to release high levels of NET expressing tissue factor during active AAVs.¹⁵

Recent studies have found a link between platelet microparticles (MPs) and activated neutrophils during AAV.¹⁵ These MPs contain inflammatory mediators and are involved in the activation and destruction of endothelial cells.¹⁶⁻¹⁸

Christina Wlodek and Michael Gregory Robson reported the first case of AAV presenting with renal vein thrombosis

in 2012.³ The patient had a Lupus anticoagulant and anticardiolipin antibodies which is not the case of our patient.

Regarding treatment of VT in AAV, both timely immunosuppressive agents and anticoagulants are important to achieve favorable outcomes. Strategies including unfractionated heparin, low molecular weight heparin, and aspirin have been reported when facing VT in active AAV patients. Low molecular weight heparin and unfractionated heparin with a vitamin K antagonist have the same efficiency with no differences in bleeding risk. The short-term use of anticoagulations is usually about 6 months. Long-term use is often indicated for patients with recurrent or severe VT.¹⁹

The therapeutic choice for patients with AAV complicated with alveolar hemorrhage and VT is often a difficult decision.

The benefits of anticoagulation treatment need to be balanced carefully against the potential risk of bleeding. The use of anticoagulation therapy may increase the risk of alveolar hemorrhage.

TABLE 2 Data from articles specifically focusing on vein thrombosis in patients with antineutrophil cytoplasmic antibody-associated vasculitis

Author	Faurschou et al ^{5,21}	Kang et al ^{6,22}	Isaacs et al ^{7,23}	Stassen et al ^{8,24}	Weidner et al ^{9,25}	Henry et al ^{10,26}
Number of included patients	180	204	162	198	105	133
Etiologic diagnosis	GPA	GPA (111) MPA (38) EGPA(14) RLV(27)	GPA (105) MPA (56)	GPA (143) MPA (34) RLV(21)	GPA MPA RLV	GPA (45) MPA (88)
Number of patients With VT	9	14	22	23	12	23
Characteristics of patients with VT						
Median Age (year)	Not mentioned	50	54.2 ± 19.7	60	58.2	69.7 ± 10.1
Gender (M/F)	Not mentioned	7/7	8/14	13/10	9/4	11/12
Organs involved						
Kidney	Not mentioned	11	5	16	12	23
MSK		4	Not mentioned	-		-
ENT		7	Not mentioned	-		8
Lung		8	12	10		8
Eye		3	Not mentioned	-		-
Skin		2	Not mentioned	-		4
Nervous system		0	Not mentioned	-		2

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; GBM, glomerular basement membrane; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MSK, musculoskeletal; PR3, proteinase 3; RLV, renal-limited vasculitis; VT, venous thrombosis.

In our case, we decided to discontinue low molecular weight heparin due to the active alveolar hemorrhage, and no further exacerbations of VT were found.

We also used plasmapheresis in order to remove ANCA and other circulatory factors such as inflammatory cytokines, complement, and coagulation factors from the systemic circulation. Hence, plasmapheresis is a logistical and important therapeutic intervention for both alveolar hemorrhage and VT.²⁰

Regarding immunosuppressive therapy, a combination of corticosteroids and cyclophosphamide is the standard strategy of care for AAV when attempting to induce remission. High-dose prednisolone at 1 mg/kg/day should be used for at least 1 month, and methylprednisolone pulse therapy may also be used if a rapid effect is needed. In our case, we used cyclophosphamide. However, due its side effects such as gonadal suppression and infertility, mycophenolate mofetil can be used to induce remission.²⁰

Our observation is unique: Renal vein thrombosis revealed MPA. The patient had proteinuria without nephrotic syndrome that could explain the thrombosis. She had normal serum creatinine level despite severe renal lesions. It emphasizes the key role of the renal biopsy in the diagnosis of AAV especially when clinical findings are atypical. The presence of renal vein thrombosis may explain hematuria and proteinuria but

should never delay the kidney biopsy in some cases. More, two complications of AAV occur simultaneously: VT and alveolar hemorrhage making the therapeutic decision difficult.

4 | CONCLUSION

Venous thromboembolism is probably underestimated during AAV. The occurrence of renal vein thrombosis is exceptional. This complication may be the only manifestation of the disease. To consider the diagnosis of AAV over the occurrence of renal vein thrombosis seems unusual but can save the patient's life. We take advantage of this article to remind that there are no current recommendations for prophylaxis, screening, or treatment of VT during AAV.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

MJ and HG: wrote the first draft of the article. HG, MK, and TBA: critically reviewed and edited drafts. RA and RG: were the pathologists.

ETHICAL APPROVAL


The patient has given his written informed consent to publish his case including publication of images.

DATA AVAILABILITY STATEMENT

Patient data are available.

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