Complement-mediated thrombotic microangiopathy in ANCA-associated vasculitis: an underrecognised but treatable overlap

Dear Editor,

Thrombotic microangiopathy (TMA) is an uncommon but clinically severe condition characterised by microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury. With the exception of thrombotic thrombocytopenic purpura (TTP), the diagnosis of TMA remains challenging due to the lack of rapid and specific diagnostic tests. TMA may occur in association with infections, medications, malignancy, pregnancy, transplantation, and autoimmune diseases (1). In this context, complement-mediated TMA, formerly termed atypical haemolytic uremic syndrome, represents a rare yet potentially devastating complication that may be underrecognised in patients with ANCA-associated vasculitis (AAV).

We read with great interest the recent literature highlighting the expanding role of complement dysregulation in systemic autoimmune diseases and would like to contribute two illustrative cases of AAV complicated by complement-mediated TMA, both of which showed marked clinical improvement following terminal complement inhibition with eculizumab.

Both patients presented with biopsy-proven pauci-immune crescentic glomerulonephritis associated with PR3-ANCA and MPO-ANCA positivity, respectively, and demonstrated multisystem involvement at presentation. The first case exhibited ENT, ocular, pulmonary, and renal manifestations, while the second case presented with cutaneous, renal, and hematologic involvement. The key clinical features, laboratory findings, and treatment courses of both cases are summarised in Table I. During the disease course, each developed persistent thrombocytopenia and microangiopathic haemolytic anaemia with schistocytes on peripheral blood smear, unresponsive to conventional immunosuppressive therapy and plasma exchange. Importantly, ADAMTS13 activity was preserved in both cases, effectively excluding thrombotic thrombocytopenic purpura. These findings raised strong suspicion for complement-mediated TMA. Despite standard immunosuppressive therapies, including corticosteroids, plasmapheresis, rituximab and cyclophosphamide, both cases showed insufficient or partial responses prior to the initiation of eculizumab. Initiation of eculizumab resulted in rapid haematologic recovery and stabilisation or improvement of renal function. In one case, dialysis could be discontinued, while the other achieved sustained renal stability under combined immunosuppressive and complement-inhibitory therapy. Notably, recurrence of TMA features coincided with vasculitis relapse, suggesting a dynamic interaction between ANCA-driven inflammation and complement-mediated endothelial injury.

Table I. Clinical characteristics, laboratory findings, and treatment course of the two cases.

Feature	Case 1	Case 2
Age/Sex	50/Male	68/Female
ANCA type	PR3-ANCA (+)	MPO-ANCA (+)
Initial presentation	Fever, arthralgia, epistaxis, episcleritis, pulmonary nodular infiltrates, renal involvement	Lower extremity skin rash, severe acute kidney injury, microangiopathic haemolysis
Haematologic findings	MAHA, thrombocytopenia, schistocytes	MAHA, thrombocytopenia
ADAMTS13 activity	Normal	Normal
Initial therapy	Steroids → plasmapheresis → rituximab (insufficient response)	Steroids → plasmapheresis → rituximab (partial response)
Relapse therapy	Steroids → plasmapheresis → cyclophosphamide (discontinued due to thrombocytopenia) → rituximab	Steroids → plasmapheresis → cyclophosphamide (no renal response)
Eculizumab	Initiated after persistent TMA → haematologic and renal recovery → dialysis discontinued	Initiated after persistent TMA → haematologic stabilisation
Renal outcome	Recovery of renal function, dialysis discontinued	Chronic kidney disease, dialysis-dependent
Maintenance therapy	Rituximab + eculizumab	Azathioprine + eculizumab

Emerging evidence supports a mechanistic link between neutrophil extracellular traps (NETs), endothelial damage, and activation of the alternative complement pathway in ANCA-associated vasculitis (AAV) (2-4). NETs may serve as a scaffold for complement components, facilitating local complement amplification and promoting microvascular thrombosis (3,4). Complement-mediated thrombotic microangiopathy (TMA) has been increasingly reported in association with autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome, and more rarely in AAV (1, 5, 6). However, its true prevalence in AAV is likely underestimated because of overlapping clinical features and the absence of pathognomonic histological findings (1, 5).

A recent systematic review identified only a limited number of reported AAV cases complicated by systemic TMA, with a predominance of MPO-ANCA positivity and inconsistent histological confirmation (5). Our cases are concordant with these observations and further emphasise that the absence of classic TMA lesions on kidney biopsy does not exclude a systemic complement-mediated process, particularly when hematologic manifestations predominate.

These observations have important clinical implications. In patients with AAV presenting with unexplained thrombocytopenia, microangiopathic haemolytic anaemia, or poor renal recovery despite adequate immunosuppressive therapy, complement-mediated TMA should be actively considered (1, 5, 6). Early diagnostic evaluation, including peripheral blood smear examination and ADAMTS13 activity testing, is essential to exclude thrombotic thrombocytopenic purpura and to guide appropriate management, as timely initiation of complement inhibition may prevent irreversible organ damage (1, 7).

Although genetic testing for complement regulatory abnormalities was not performed in our cases, the clinical phenotype and sustained hematologic and renal response to eculizumab strongly support complement dysregulation as a key pathogenic driver (4, 6, 7). Whether complement-mediated TMA represents a secondary consequence of systemic inflammation or a parallel pathogenic pathway unmasked during vasculitis flares remains to be clarified.

In conclusion, complement-mediated TMA should be recognised as a rare but potentially treatable overlap syndrome in AAV. Increased clinical awareness and early therapeutic intervention may significantly improve renal and haematologic outcomes in selected patients.

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