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CASES WITH A MESSAGE

Thrombotic microangiopathy in a patient with eosinophilic granulomatosis with polyangiitis: case-based review

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Abstract

The correct diagnosis, classification and therapeutic management of thrombotic microangiopathies (TMA) continue to be a challenge for the clinician. We report a rare case of eosinophilic granulomatosis with polyangiitis (EGPA) as a trigger for complement-mediated TMA in a 57-year-old man who was successfully treated with corticoids, cyclophosphamide and therapeutic plasma exchange. Additionally, we review few other cases reported in the literature and the pathophysiological pathway of association between TMA and EGPA. We found that the mutual relationships between the inflammation triggered by vasculitis, the exacerbated complement activation, together with hypereosinophilia and endothelial damage seem to be the key in explaining the connection between both entities. We suggest that an understanding of the multi-causal nature of TMAs is crucial for the correct diagnosis and treatment of these patients.

Keywords Thrombotic microangiopathy · Eosinophilic granulomatosis with polyangiitis · Complement-mediated diseases · Atypical haemolytic uremic syndrome · ANCA-associated vasculitis

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) affecting the small and medium-sized arteries. It is characterised by asthma often accompanied by pulmonary infiltrates, ear-nose-throat manifestations, peripheral blood and tissue eosinophilia, and occasionally followed by a multisystemic vasculitic phase involving skin, joints, heart, kidneys and nervous or gastrointestinal systems [1].

Thrombotic microangiopathies (TMA) are a heterogeneous group of life-threatening disorders characterised by microangiopathic haemolytic anaemia and thrombocytopenia (MAHAT), and ischemic organ injury, with kidney and brain impairment predominantly. The pathological feature is vascular damage that is manifested by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall [2]. Despite difficulties in the classification, TMAs can be divided into primary and secondary. In their primary form, there is evidence supporting a defined abnormality with known pathophysiology as the probable cause: thrombotic thrombocytopenic purpura (TTP) (acquired and hereditary), complement-mediated TMA (CM-TMA) formerly called atypical haemolytic uremic syndrome (aHUS), Shiga toxin–mediated haemolytic uremic syndrome, drug-induced TMA and rare hereditary metabolism and coagulation-mediated TMA. However, it also occurs secondarily as a complication of a number of systemic conditions including disseminated intravascular coagulation, cancer, malignant hypertension (HTN), infections, hematopoietic stem cell or organ transplantation, autoimmune diseases and pregnancy-associated syndromes (severe preeclampsia/HELLP syndrome) [2–5].

We described an extremely rare case of EGPA presenting with TMA and a review of the literature was done.

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Case report

A 57-year-old man was diagnosed with severe persistent bronchial asthma and sinusopathy and was treated with low-dose prednisone, bronchodilators and montelukast. 18 months later, the patient was admitted for malaise, fever, symmetrical arthritis of the wrists and the proximal and distal interphalangeal joints, generalised stiffness and myalgias, paraesthesia in fourth and fifth fingers of the left hand and a worsening of his usual dyspnoea, commencing the week before. 1 day prior admission, the patient presented a palpable purpura in the legs and no HTN, dyslipidaemia, diabetes or other diseases or addictions were reported. The physical examination was as follows: body temperature 37.8 °C, blood pressure 130/80 mmHg, pulse rate 100/min, respiratory rate 22/min and blood oxygen saturation by pulse oximetry 96% (FiO_2 28%). Auscultation revealed wheezing over the entire lung field. The laboratory data are summarised in Table 1. A chest x-ray showed pulmonary infiltrates in both lung fields, which were confirmed in a chest-computed tomography with ground-glass opacities especially in the lower lobes. Based on these clinical findings, EGPA was suspected and we initiated intravenous methylprednisolone (40 mg/day) treatment after which the fever and musculoskeletal symptoms disappeared concomitantly with an improvement of the rash, dyspnoea and pulmonary infiltrates.

On the 5th day, the patient presented laboratory findings suggestive of MAHAT (anaemia and thrombocytopenia with haemolysis findings, schistocytes, undetectable haptoglobin and a negative direct antiglobulin test), proteinuria and worsened renal function (Table 1). ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was 73% (normal range 6–100%) and the ADAMTS13 inhibitor was absent. All the microbiological tests for detecting an infectious trigger were negative. On the basis of these findings, a diagnosis of TMA was made and the patient was treated with pulsed methylprednisolone (500 mg/day for 3 consecutive days), a single pulse of cyclophosphamide (1 g) and plasmapheresis on 4 consecutive days. Soon after the treatment, the eosinophilia and the schistocytes disappeared, haemolytic anaemia and proteinuria improved, and renal function normalised (Table 1). ANCA test results were positive for antibodies directed against myeloperoxidase (anti-MPO) with a perinuclear staining pattern. A skin biopsy

Table 1 Evolution of laboratory findings

	6 Months before admission	On admission	5th Day of admission	After plasmapheresis	3 Months after discharge	1 Year after discharge	1.5 Years after discharge
Leukocytes, cells/mm^3 (3500–10,500)	10,250	18,830	28,450	10,960	5870	5680	6320
Eosinophils, cells/mm^3 (20–550)	1125	8850	18,120	680	150	70	70
Haemoglobin, mg/dL (11–17)	15.4	14.9	8.2	10.6	13.9	15.1	14.7
Reticulocytes, % (0.5–2)	–	–	2.3	7.2	–	–	1.3
Platelets, cells/mm^3 (120,000–450,000)	229,000	273,000	59,000	432,000	232,000	223,000	195,000
Creatinine, mg/dL (0.67–1.2)	0.89	0.46	1.4	1.1	0.96	1.1	1.04
C3 complement, mg/dL (90–180)	–	–	148	–	72.8	–	77.8
C4 complement, mg/dL (10–40)	–	–	37	–	17.2	–	15.9
Proteinuria, g/24 h (< 0.05)	(−)	(−)	2.4	0.3	(−)	(−)	(−)
Haematuria	(+++)	(+++)	(+++)	(+++)	(+)	(−)	(+)
LDH, U/dL (< 248)	164	345	739	184	195	147	151
Total bilirubin, mg/dL (0.3–1.2)	0.8	1.1	2.5	0.94	0.53	0.53	0.9
Schistocytes	–	–	8%	< 1%	< 1%	–	< 1%
CRP, mg/L (0.02–5)	0.4	95	66	3.0	0.6	0.6	0.3
ESR, mm/h (1–10)	5	81	–	28	5	5	5
Haptoglobin, mg/dL (30–200)	–	–	Undetectable	–	64	–	124
D-Dimer, mg/L (< 0.5)	–	–	3.9	–	0.28	–	–
Anti-MPO, AI (0.2–0.9)	–	126.8	–	–	5.7	(−)	(−)
ANA, ENA, direct Coombs test	–	(−)	–	–	(−)	–	(−)
ADAMTS13 activity, % (> 6)	–	–	73%	–	–	–	–

LDH lactate dehydrogenase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *Anti-MPO* anti-myeloperoxidase antibodies, *ANA* antinuclear antibodies, *ENA* anti-extractable nuclear antigens antibodies

specimen obtained 3 days before the TMA showed vasculitis with an eosinophilic perivascular inflammatory infiltration without granulomas. With regard to the electromyoneurographic study, we observed signs of moderate sensory-motor axonal neuropathy.

Considering all these results, a diagnosis of EGPA was made which fulfilled all the six criteria (asthma, eosinophilia, polyneuropathy, pulmonary infiltrates, sinusopathy and extravascular eosinophils) of the American College of Rheumatology [6]. The patient was discharged with prednisone 30 mg/day and a tapering dose protocol. A renal biopsy was carried out 1 month after the clinical onset with the following findings (12 glomeruli): interstitial inflammation with eosinophils, some thickened arterioles with fibrinoid occlusion and no proliferative changes or glomerular thrombi. The immunofluorescence studies showed sparse IgA deposits, C3 and C4d in some arterioles and in the glomerular basement membrane of some glomeruli.

Next-generation DNA sequencing obtained from peripheral blood showed no pathological variants of the 14 genes associated with CM-TMA (*CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, C3, CFI, CD46* (*MCP*), *CFB, THBD, DGKE, CFP* and *ADAMTS13*). However, the patient was carrying a risk haplotype, CFH (H3) in heterozygosis, for CM-TMA. Additionally, a heterozygous variant of uncertain significance was identified in exon 4 of *CFHR5* (c.432A>T), which causes the substitution of an amino acid from lysine to asparagine in position 144 (p.Lys144Asn).

1 year and half after discharge the patient remained asymptomatic, anti-MPO declined until they become negative, renal function and proteinuria were normal and there were no analytical data suggestive of TMA (Table 1).

Methods

We have performed a comprehensive literature search for case reports with patients presenting TMA and EGPA using the following keywords (MeSH; English languages): [Churg–Strauss vasculitis (or syndrome)] or [eosinophilic granulomatosis with polyangiitis] or [ANCA-associated vasculitis] and [(acute) thrombotic microangiopathy] or [(typical or atypical or secondary) haemolytic uremic syndrome] or [thrombotic thrombocytopenic purpura]. MEDLINE/Pubmed and Scopus databases were used for this search and were last accessed on 11th November 2018 [7].

Results and discussion

In addition to ours, we only found three case reports of patients with a potential TMA and EGPA simultaneous diagnosis [8, 9]. A short description of the four cases can be found in the Table 2.

Fukui et al. reported a case of EGPA simultaneously associated with TMA and with systemic lupus erythematosus (SLE). Given that SLE is a recognised trigger of TMA [5, 8, 10] it is difficult to establish to what extent either one of them (EGPA or SLE) contributed to the development of the microangiopathy. The kidney biopsy and the genetic study of the complement are not reported in the case report of this patient. Recently, Cao et al. have reported two more cases. The first consisted of a 50-year-old man with poorly controlled HTN despite receiving two antihypertensive drugs, ANCA-negative EGPA and an atypical HUS with confirmed genetic mutations in the complement system (Table 2). In this case, two factors beside EGPA could have contributed to the development of the TMA: the malignant HTN [11] and some confirmed genetic mutations of the complement system. Finally, Cao et al. also report the case of a 57-year-old woman with EGPA. After her daughter developed an atypical HUS, genetic mutations of the complement system were confirmed in both women (Table 2). However, the patient had no symptoms or laboratory findings suggestive of TMA at the time of publication of the article and therefore should not be considered affected by atypical HUS despite being a carrier of the genetic mutation.

We report a rare case of EGPA as a trigger for confirmed TMA. Although the nomenclature is confusing we performed the diagnosis of CM-TMA based on the following data: presence of MAHAT and acute kidney injury with compatible renal biopsy, the exclusion of TTP diagnosis on the basis of normal ADAMTS-13 activity, low complement levels during follow-up and a risk haplotype for CM-TMA.

The mechanism or mechanisms by which EGPA may trigger the development of TMA are not fully understood; however, here we suggest that vasculitis, eosinophil-mediated cytotoxicity and the complement system could be important factors explaining the co-occurrence of both conditions.

The link between TMA and connective tissue diseases (CTD) is known. In a large Japanese registry of 919 patients with TMA, 221 (24%) presented CTD and allied pathologies, mainly SLE and systemic sclerosis. However, only 2% of these patients (19 of 919) had vasculitis: polyarteritis nodosa (7 patients), ANCA-related glomerulonephritis (GN; 7 patients), granulomatosis with polyangiitis (2 patients) and others (3 patients) [12]. In another study, out of 220 consecutive patients with AAV (not including those with EGPA) and biopsy-proven GN, 30 (14%) had biopsy evidence of TMA [13], all of which suggests greater subclinical incidence of the disease. Although the pathophysiological association between TMA and vasculitis is not clear, endothelial injury is the basic pathophysiological mechanism of both entities [14, 15]. Compared to other AAVs, the rarity of the association between EGPA and TMA may be due in part to the fact that the EGPA is the least frequent AAV and the one with the least renal involvement; however, other immunological,

Table 2 Description of case reports

	Case 1 (Ref. [8])	Case 2 (Ref. [9])	Case 3 (Ref. [9])	Our case
Age (years)/sex	71/M	50/M	52/F	57/M
Type of TMA	TMA (no TTP)	Atypical HUS	No symptoms	CM-TMA (atypical HUS)
Main findings	Asthma, sinusitis, dyspnoea, pleural effusion, pulmonary infiltrates	Asthma, sinusitis, weakness, malaise, dyspnoea, retinal haemorrhage, CNS deficits due to hematoma	Asthma, weight loss, skin lesions, peripheral neurological deficits	Asthma, sinusitis, malaise, fever, dyspnoea, arthritis, skin lesions, peripheral neurological deficits pulmonary infiltrates
Renal function	↑ Creatinine, proteinuria, microscopic haematuria	↑ Creatinine, proteinuria, microscopic haematuria	Normal	↑ Creatinine, proteinuria, microscopic haematuria
Haemolytic anaemia[a]	Present	Present	Absent	Present
Thrombocytopenia	Present	Present	Absent	Present
Eosinophilia	Present	Present	Present	Present
Autoimmunity studies	Anti-MPO (+), anti-dsDNA (+)	Negative for: ANA, ANCA, anti-GBM, cryoglobulinemia and Coombs test	Anti-MPO (+), ANA (+)	Anti-MPO (+), Coombs test (−)
Hypocomplementemia	Present (C3 and C4)	Present (C3)	Not reported	Absence in the acute phase, present (C3) during the follow-up
ADAMST13 activity	49.8%	Normal	Not reported	73%
Renal biopsy	Not done	Diffuse interstitial eosinophilic infiltration and TMA features	Not done	Interstitial eosinophilic infiltration and TMA features
Skin biopsy	Fragmentation of the lamina elastica interna; deposition of C3 in the vessel wall	Not done	Dermatitis with eosinophilic infiltration	Vasculitis with eosinophilic infiltration without granulomas
Complement genes mutation study	Not done	CFH risk polymorphism (c.1231T>To) (heterozygosis)	CFH risk haplotype (homozygous) MCP (c.286+2T>G) CFI (c.1534+5G>T)	CFH risk haplotype (heterozygosis) CFHR5 (c.432A>T)
Concomitant or underlying disorders	Systemic lupus erythematosus	Malignant hypertension	Daughter with atypical HUS	None

Ref. reference, *M* male, *F* female, *TMA* thrombotic microangiopathy, *TTP* thrombotic thrombocytopenic purpura, *HUS* haemolytic uremic syndrome, *CNS* central nervous system, *MPO* myeloperoxidase, *dsDNA* double-stranded deoxyribonucleic acid, *ANA* antinuclear antibodies, *ANCA* anti-neutrophil cytoplasmic antibodies, *anti-GBM* antiglomerular basement membrane, *CFH* complement factor H, *THBD* thrombomodulin, *CFI* complement factor I, *MCP* membrane cofactor protein

[a]Defined as ↓ haemoglobin, ↓ haptoglobin, ↑ lactate dehydrogenase, ↑ total bilirubin and presence of schistocytosis

environmental or genetic factors could also explain low rates of EGPA–TMA diagnosis.

On the other hand, eosinophil-mediated cytotoxicity towards endothelial cells and its pro-thrombotic effect is well known. Eosinophils contain large amounts of several highly cationic proteins that are released in the microenvironment and in the bloodstream upon activation [16]. The cytotoxic and pro-coagulant properties of eosinophils are essential in the end-organ dysfunction of eosinophil-associated disorders including asthma, hypereosinophilic syndrome, EGPA and parasitic diseases [17–19]. There are some cases in the literature where TMA and eosinophil-associated disorders coexist (4 patients with hypereosinophilic syndrome and 1 patient with eosinophilic pneumonia [20–22]) In this regard, eosinophil infiltrates and deposition of major basic protein (a cationic protein) was observed in kidney biopsies of two patients with hypereosinophilic syndrome who developed acute renal failure and TMA [20]. In our series, all patients with EGPA and TMA had hypereosinophilia and the two patients who underwent kidney biopsies presented interstitial eosinophilic infiltration, suggesting the importance of eosinophils in the pathophysiology of TMA in these cases. However, since most patients with EGPA and other eosinophil-associated disorders have a large amount of eosinophils and only a very small number of them develop TMA, other mechanisms or genetic factors must necessarily be involved.

The uncontrolled activation of the alternative pathway of the complement is the pathophysiological basis of endothelial damage in CM-TMA [23, 24]. However, although hypocomplementemia may indicate excessive activation of the alternative pathway, a low C3 level is present in less than half of atypical HUS patients [25, 26]. One possible explanation is that an ongoing acute phase reaction may drive the synthesis of complement factors, which would mask the increased consumption of such factors. Accordingly, in our patient, C3 and C4 levels were normal in the acute phase but C3 levels were low during the follow-up. Although AAVs have been considered pauci-immune pathologies and hypocomplementemia is uncommon, the activation of the alternative pathway of the complement seems to be essential in the pathogenesis of AAV [27–29]. Furthermore, Manenti et al. suggest that there is a relationship between low C3 levels and the likelihood of finding histologic features of TMA in kidney biopsies in AAV patients [30]. Thus, the activation of the complement seems to be the triggering event of TMA in AAV patients.

Several mutations (loss-of-function mutation in a regulatory gene or a gain-of-function mutation in an effector gene) and risk haplotypes have been described in the alternative complement pathway proteins associated with CM-TMA [5, 25, 31–34]. Nevertheless, as it happens in our case, there are no disease-causing mutations in the genes of complement components or in their regulators in approximately 50% of clinically suspected atypical HUS cases [25, 26], indicating that new pathological variants, unscreened genetic mutations or non-complement-mediated mechanisms may play an important role in the development of microangiopathy. It should be noted that our patient carries the CFH-H3 haplotype (which corresponds to the CFHtgtgt risk haplotype for CM-TMA) in heterozygosis. Although this haplotype has been involved in the penetrance of the disease rather than in its development, it is strongly associated with CM-TMA [35–37]. In the series of Manenti et al., 5 out of 6 patients with glomerulopathy and atypical HUS were homo- or heterozygous carriers of this risk haplotype, in some cases even without a disease-causing mutation [38]. In addition, a heterozygous variant in exon 4 of CFHR5 (c.432A>T) was identified in our patient. This modification was described in other patients with CM-TMA; however, it was considered to be a non-disease-causing alteration [39, 40]. Nevertheless, this variant is exceptional in control populations and more studies are necessary to assess the association of this alteration and CM-TMA.

In regard to the therapeutic management of TMA, it still remains the topic of much debate. The use of therapeutic plasma exchange in CM-TMA and other non-TTP TMA is controversial due to the absence of well-designed randomized trials [41, 42]. In spite of this, the aggressive treatment of the underlying trigger seems reasonable [3]. Therefore, the use of high-dose corticosteroids and other immunosuppressive drugs to decrease the systemic and vascular inflammation and eosinophilia are highly recommended in TMA associated with EGPA. As regards the complement system, it is of critical importance to gain a full understanding of the intervening role of the complement in these cases. Indeed, the complement inhibitor eculizumab (a humanized monoclonal antibody functioning as a terminal complement inhibitor and an approved treatment for CM-TMA [42–44]) could have an added benefit in TMA associated with AAV via the inhibition of the alternative complement pathway triggered by vasculitis as in case 2.

In conclusion, it is reasonable to suggest that when a predisposing genetic background exists, EGPA could act as a trigger for the development of TMA through the interrelationship between the activation of the complement system and the associated endothelial damage. Despite its rarity, this complication should be taken into consideration in the differential diagnosis and management of patients with systemic vasculitis, and particularly in those with EGPA. Further studies and clinical reports are needed to determine the precise pathophysiological mechanisms involved in these life-threatening conditions and to improve the therapeutic approach.

Author contributions All the authors have contributed to patient management and clinical procedures, have drafted and revised the manuscript and have approved the final version.

Compliance with ethical standards

Conflict of interest JB, NNN and JMS declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patient to publish this case report.

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