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Exceptional Case

Renal thrombotic microangiopathy and FIP1L1/PDGFRα-associated myeloproliferative variant of hypereosinophilic syndrome

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Abstract
We report a case of renal thrombotic microangiopathy (TMA) in a myeloproliferative variant of hypereosinophilic syndrome (HES) in a 24-year-old man which resolved with imatinib therapy. This is one of a few cases in the literature to date describing TMA in HES, suggesting that the pathogenesis of thrombosis is at least in part related to damage from activated eosinophils.

Keywords: hypereosinophilic syndrome; imatinib; thrombotic microangiopathy

Background

Thrombotic microangiopathy (TMA) is a rare but serious medical disease characterized by endothelial injury, thrombus formation and resultant microangiopathic haemolytic anaemia (Coomb's-negative anaemia with schistocytes in the peripheral smear), thrombocytopoenia and organ dysfunction. Various agents, including bacterial toxins, viruses and endothelial shear stress [1], can induce TMA. Hypereosinophilic syndrome (HES) is characterized by marked (>1500×10^6/L) and prolonged (>6 months) eosinophilia with end organ involvement in the absence of known eosinophil-associated diseases [1]. HES most commonly involves the heart, lungs, nervous system and skin. Kidney disease is thought to be rare in HES [2]. In previously reported HES cases, only two cases of renal TMA have been described [3]. We report another case of renal TMA related to the myeloproliferative variant of HES.

Case report

A 24-year-old Caucasian man presented with headaches. Over a period of 1 week, he developed fatigue, malaise and headache without fever, rashes or gastrointestinal complaints. His past medical history was marked by two highway accidents without head trauma. On admission, his blood pressure was 175/100 mmHg. Physical examination was unremarkable, with normal cardiovascular, pulmonary and neurological examinations. Laboratory test results were serum creatinine level, 1.81 mg/dL (160 µmol/l) (MDRD creatinine clearance 50 mL/min/1.73 m^2); glomerular proteinuria 4 g/24 h and urinalysis showed >100 red blood cells/high-power field and aseptic leukocyturia. There was also stigma of mechanical haemolysis (haemoglobin 10.7 g/dL, haptoglobin <0.05 g/L, lactate dehydrogenase levels 1135 IU/L, positive schistocytes with a low platelet level of 130 000/mm^3). Leukocyte count was 23 510/L with 78% eosinophils. Other causes of hypereosinophilia were excluded. Serology for ascaris, toxocara, trichinella and strongyloides was negative; stool ova and parasites were absent. The serum IgE level was normal (<28 U/L). Immunological tests were negative [Coomb's test (direct and indirect), antineutrophil antibody, antineutrophil cytoplasmic antibody, antiphospholipid antibodies; anti-double-stranded DNA; antiextractable nuclear antigen; glomerular basement antibodies]. Complements C3, C4 and CH50 were normal. HIV and hepatitis (B and C) serologies remained negative. Blood and urine cultures were negative. Chest X-ray films were normal. Echocardiograms, including a transoesophageal echocardiogram, did not reveal abnormalities. Magnetic resonance imaging of the heart showed a circumferential thickening of the left ventricular myocardium, right ventricular posterior wall, papillary muscles and left atrial wall.

Transjugular kidney biopsy contained 24 glomeruli; none were sclerosed. Two glomeruli showed proliferative arteriopathy in small arterioles associated with thrombosis (Figure 1a). Five additional glomeruli had capillary thrombosis for a total of 28% thrombosed glomeruli. Six glomeruli showed global mesangiolysis and/or thrombosis of afferent arterioles. It associates mucoïd endarteritis lesions with interstitial fibrosis (40%) and tubular atrophy related to previous TMA flares. The interstitium showed mild fibrosis and mild chronic inflammation with

eosinophil infiltration (Figure 1b). Focally, eosinophils filled tubular lumens forming tight white cell casts. Routine immunofluorescence was negative for IgG, IgA, IgM, C3, C4, C1q, albumin and λ and κ chain deposits. Fibrinogen deposits were focally positive within thrombosed arterioles. Electron microscopy was not performed. These findings were consistent with TMA.

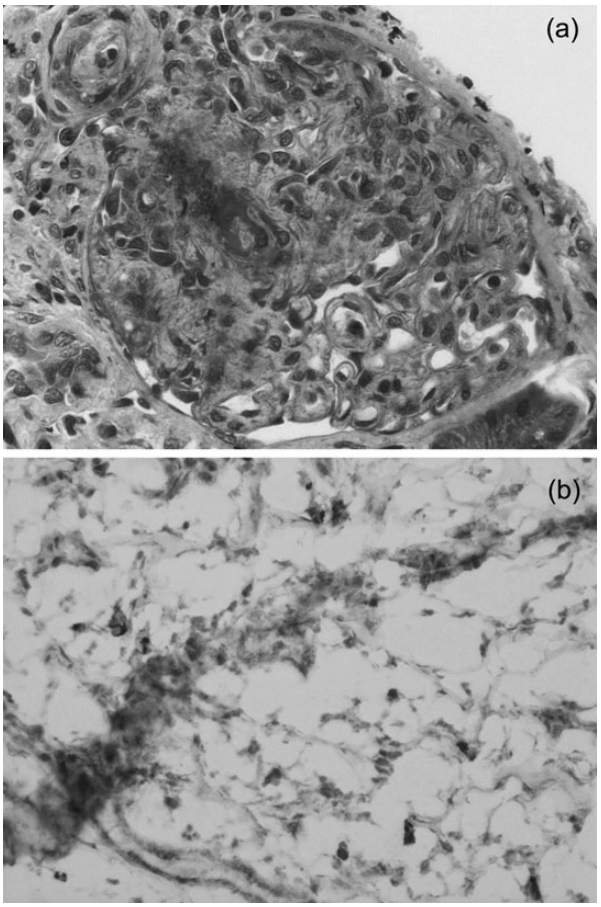

Fig. 1. (**a**) Occlusion of one capillary by a thrombus. The mesangial matrix is expanded. Some glomerular capillary walls are thickened by expansion of the subendothelial zone (Masson's trichrome). (**b**) Eosinophilic granulocytes (frozen section; Giemsa's stain).

Immunofluorescence with antibody antieosinophil granule major basic protein-1 (MBP1) was not performed. No constitutional abnormalities or heterozygous missense mutations were found in Factors H, I or MCP, the three major regulatory proteins of the complement alternative pathway. Plasma A disintegrin-like and metalloprotease with thrombospondin type 1 motif, 13 (ADAMTS13) activity remained detectable at a level >50%. Acquired or constitutive anti-ADAMTS13 antibodies were undetectable.

A bone marrow biopsy revealed an increased number of eosinophils and eosinophil precursors (37% of cells) and myelocytes and precursors (19%), and transcripts were positive for Fip1-like 1/platelet-derived growth factor receptor alpha (*FIP1-L1/PDGFR*α) and negative for *BCR-Abl* and *FGFR1* (fibroblast growth factor receptor 1).

Imatinib 100 mg b.i.d was added on top of daily antihypertensive treatment including irbesartan/hydrocholothiazid 300/12.5 mg, aliskiren 300 mg, amlodipine 10 mg; urapidil 120 mg and rilmenidine 1 mg. A year later, his condition remains stable with a white cell count of 7900/L, normal (2%) peripheral blood eosinophils and a serum creatinine level of 1.8 mg/dL (158.4 µmol/L) with negative proteinuria. Repeat magnetic resonance imaging of the heart showed apical subendocardial perfusion defect with delayed contrast enhancement compatible with endomyocardial fibrosis and apical subepicardial nodular contrast enhancement.

Discussion

This is the first case of renal TMA related to FIP1L1/PDGFRA-associated myeloproliferative variant HES.

Since 1975, three criteria have been used to define HES: blood eosinophilia >1500/µL for >6 months; lack of evidence of parasitic, allergic or other known causes of eosinophilia and presumptive signs of organ involvement [4]. Our case fulfilled the diagnostic criteria of HES with the exception of duration. However, the relative importance of

Table 1. Renal TMA associated with HES

Characteristics	Patient 1	Patient 2	Our patient
Age, years	15	26	24
Sex	Boy	Man	Man
Race	African American	White	White
Haematological findings			
Haemoglobin, 13.8–17.2 g/dL	9.8	13.3	10.7
Platelets, 140–440 × 10^3/ per mL	76 × 10^3	101 × 10^3	130 × 10^3
Schistocytes	Not available	Positive	Positive
LDH, 300–750 IU/L	15,190	Not available	1135
Eosinophils cells/mL	11.139	4.998	18.340
Bone marrow biopsy, eosinophil infiltration	80%	44%	37%
Transcript positivity	Not available	Not available	FIP1L1/PDGFRα
Kidney disorders			
Blood pressure, mmHg	Not available	Not available	170/100
Serum creatinine mg/dL (µmol/L)	10.9 (959)	2.2 (194)	1.81 (160)
Creatinine clearance, mL/mn:1.73 m^2		57.2	50
Proteinuria, g/24 h	+++	3.44	4
Urinalysis, cells/high-power field	50 red blood cell	Not available	100 blood cells
Kidney biopsy	Mesangiolysis Arterial thrombosis Eosinophilic infiltrate	Arteriole thrombosis Glomerular capillary thrombosis Eosinophil infiltrate	Arteriole thrombosis Glomerular capillary thrombosis Eosinophil
Treatment	prednisone, rituximab	Prednisone; imatinib.	Imatinib
Follow-up	At 6 months:	At 12 months:	At 12 months
Serum creatinine mg/dL (µmol/L)	5.2 (458)	1.8 (159)	1.70 (150)
Eosinophils cells/L	Not available	595	300

HES duration is controversial. Simon *et al.* [5] emphasized the importance of effective therapies to halt progression of organ damage that can occur with HES, rather than waiting if the criterion of duration has not been met. Our patient initially presented with renal and cardiac involvement associated with eosinophilia and haemolytic anaemia.

Renal involvement in HES is rare including eosinophilic interstitial nephritis [6, 7], immunotactoid glomerulonephritis (GN) [8], crescentic GN [9], membranous glomerulopathy [10, 11] and renal infarction [12]. Two cases of TMA associated with HES have been reported [3]; in this case it was not stated whether or not mutation FIP1L1/PDGFRA existed (Table 1). Patients were successfully treated with corticosteroids alone (first patient) or associated with imatinib (second patient). Our patient's symptoms and hypereosinophilia resolved under imatinib alone. It is assumed that MBP1 and eosinophil peroxidase injured the endothelium and may have promoted thrombosis by altering the clotting system via platelet activation [13] and thrombomodulin anticoagulant effect impairment [14].

Cardiac involvement is the most severe complication of this clinical situation [15] and is present in 40% of cases [16]. The overall mortality rate is ∼75% in untreated patients 3 years after diagnosis [17]. Deposition of eosinophil granule proteins also occurs in cardiac tissues in the virtual absence of eosinophil infiltration.

Our case demonstrates that renal TMA can be a significant manifestation of HES and resolves with the administration of imatinib, suggesting that eosinophil-mediated damage to the renal vessel endothelium may be one of the mechanisms of thrombus formation. Recognition of this occurrence may aid in the diagnosis and treatment of patients with eosinophilia. Further studies may provide further insights into the pathogenesis of renal TMA related to HES.

Conflict of interest statement. None declared.

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