Exceptional Case

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

Anne Lyse Langlois1, Nathalie Shehwaro1, Claire Rondet2, Youssef Benbrik1, Karim Maloum3, Victor Gueutin1, Philippe Rouvier4 and Hassane Izzedine1

1Department of Nephrology, Pitie Salpetriere Hospital, Paris, France, 2Department of Internal Medicine, School of Medicine, Department of General Practice, Saint Antoine Hospital, UPMC University Paris 06, Paris, France, 3Department of Haematology, Pitie Salpetriere Hospital, Paris, France and 4Department of Pathology, Pitie Salpetriere Hospital, Paris, France

Correspondence and offprint requests to: Hassan Izzedine; E-mail: hassan.izzedine@psl.aphp.fr

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), thrombocytopenia 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 × 10⁶/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 m²); 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/mm³). 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 mucoid 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.

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/PDGFRα) 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

| Characteristics                     | Patient 1  | Patient 2  | Our patient |
|-------------------------------------|------------|------------|-------------|
| Age, years                          | 15 (Boy)   | 26 (Man)   | 24 (Man)    |
| Sex                                 | African American | White     | White       |
| Haematological findings             |            |            |             |
| Haemoglobin, 13.8–17.2 g/dL         | 9.8        | 13.3       | 10.7        |
| Platelets, 140–440 × 10³ per mL     | 76 × 10³   | 101 × 10³  | 130 × 10³   |
| Schistocytes                        | Not available | Positive   | 1135        |
| LDH, 300–750 IU/L                   | 15,190     | Not available | 18,340  |
| Eosinophils cells/mL                | 11,139     | 4,998      | 37%         |
| 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/min:1.73 m² | 57.2     | 3.44       | 50          |
| Proteinuria, g/24 h                  | +++        | Not available | 4           |
| Urinalysis, cells/high-power field  | 50 red blood cell | Not available | 100 blood cells |
| Kidney biopsy                       | Mesangiolysis | Arteriole thrombosis | Arteriole thrombosis |
|                                    | Arterial thrombosis | Glomerular capillary thrombosis | Glomerular capillary thrombosis |
|                                    | Eosinophilic infiltrate | Eosinophil | Eosinophil |
|                                    | Prednison; rituximab | Prednison; imatnib | Prednison; imatnib |
| Treatment                           | At 6 months: | At 12 months: | At 12 months: |
| Follow-up                           |            |            |             |
| Serum creatinine mg/dL (μmol/L)     | 5.2 (458)  | 3.8 (159)  | 1.70 (150)  |
| Eosinophils cells/L                 | Not available | Not available | 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/PDGFRα 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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