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CASE REPORT

A case report and literature review of IgA nephropathy presenting as nephrotic syndrome in polycythemia vera

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Abstract

A 66-year-old non-smoker presented with a 2-week history of new-onset pedal oedema and gross haematuria. On evaluation, he was found to be hypertensive and oedematous with a haemoglobin of 19.1 g/dl, platelet count of 546,000/mm^3, and creatinine of 2.6 mg/dl. Urine examination revealed abundant RBCs with 3+ albumin on three separate occasions. His 24-h urine protein level was 3830 mg/day, with a serum cholesterol level of 303 mg/dl. Secondary erythrocytosis and thrombocytosis tests were negative. Bone marrow examination revealed hypercellularity, erythroid hyperplasia, tight clusters of large megakaryocytes, and megakaryocytic hyperplasia suggestive of polycythemia vera. PCR analysis revealed a JAK2V617 F (exon 14) mutation. In view of nephrotic syndrome, azotemia, and microscopic haematuria, a renal biopsy was performed, which revealed features of IgA nephropathy with advanced interstitial fibrosis and tubular atrophy. He was started on angiotensin receptor blockers with hydroxy urea as a part of treatment. This case report highlights the association of glomerular disease with polycythaemia vera and the need of prompt renal biopsy for diagnosis and management.

Keywords IgA nephropathy · Polycythemia vera · Nephrotic syndrome · Glomerular disease

Introduction

Polycythemia vera is a haematological condition characterized by elevated haemoglobin level of 16.5 g/dl in men and 16 g/dl in women, JAK2 mutation, characteristic bone marrow morphology, and subnormal erythropoietin levels [1]. IgA nephropathy is the most common primary glomerular disease in adults, with variable clinical presentations ranging from asymptomatic microscopic haematuria to rapidly progressive glomerulonephritis [2]. Polycythemia vera-associated kidney disease includes focal segmental glomerulosclerosis mesangioproliferative glomerulonephritis, minimal change disease and IgA nephropathy [3, 4]. We report an uncommon case of IgA nephropathy masquerading as a nephrotic syndrome in the clinical context of polycythaemia vera.

Case description

A 66-year-old male, who was a non-smoker without any comorbidities, presented with history of pedal oedema for 2 weeks. He had one episode of gross haematuria for

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which he sought medical attention. He was found to have a blood pressure of 170/100 mm Hg on presentation, and clinical examination revealed mild splenomegaly and normal palatine tonsils. Laboratory investigations revealed a haemoglobin (Hb) of 19.1 g/dl, white blood cell count of 8700, and platelet count of 546,000/mm3. His creatinine was 2.6 mg/dl with normal electrolytes. The serum albumin was 2.6 g/dl with normal liver enzymes. The patient had elevated cholesterol (303 mg/dl) and triglyceride (386 mg/dl) levels. His urine examination revealed plenty of RBCs/hpf with 3+ albumin on three separate occasions and 24-h urine protein level of 3830 mg/day. His complement levels were normal and urine culture was sterile. Ultrasonography revealed mild splenic enlargement, with normal-sized kidneys and increased cortical echogenicity. All causes of secondary polycythemia and thrombocytosis were reliably ruled out by clinical history and laboratory and radiological investigations. In view of the polycythemia, a bone marrow biopsy was performed, which revealed erythroid hyperplasia, megakaryocytic hyperplasia, and a prominent tight cluster of large megakaryocytes with dysmegakaryopoiesis, consistent with polycythemia vera. Serum erythropoietin level was 2.2 mIU/ml which was subnormal. Cytogenetic analysis of peripheral blood and bone marrow revealed a JAK2V617F (exon 14) mutation. Renal biopsy was performed in view of nephrotic syndrome, microscopic haematuria, and azotaemia, which revealed 21 glomeruli, of which 17 were sclerotic globally. Viable glomeruli showed mesangial hypercellularity with segmental sclerosis of the glomerular tuft (Fig. 1).There was advanced interstitial fibrosis and tubular atrophy(IFTA) in the biopsied sample around 50%.There was arteriolar hyalinosis and the arteries showed fibrous intimal proliferation with severe luminal narrowing. Immunofluorescence revealed IgA(3+) (Fig. 2) and C3(2+) positivity in the mesangium, leading to a diagnosis of IgA nephropathy(M0E0S1T2C0–MEST-C score). He was started on telmisartan at the maximum tolerated dose along with hydroxyurea 500 mg twice daily as part of the treatment strategy. On follow-up after 2 months, he has a stable creatinine 2.5 mg/dl, haemoglobin 16.2 g/dl, 24-h urine protein of 1740 mg/day and urine showed 2+ albumin with 3–4 RBCs/hpf.

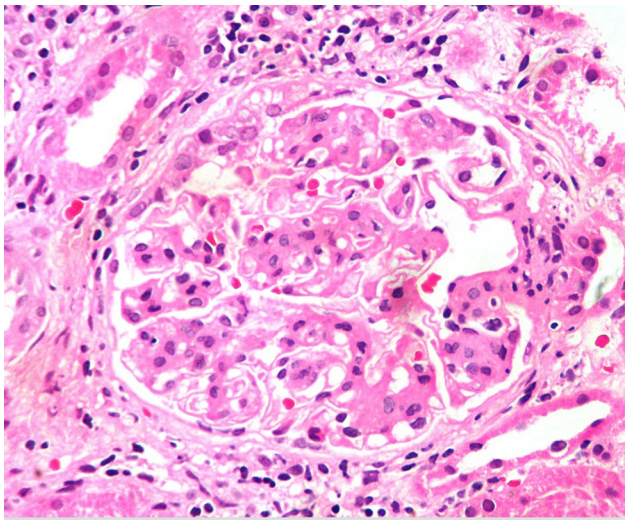

Fig. 1 Haematoxylin and eosin stain showing mesangial hypercellularity and mesangial matrix expansion of the glomerular tuft (magnification: 600 DPI;400×)

Discussion

Polycythemia vera is a heterogeneous haematological disorder with clonal expansion of hematopoietic progenitor cells and a predominant male predisposition [5]. The mean age of diagnosis is around 60 years with an estimated incidence of 2.3–2.8 per 100,000 persons/years{5]. It is characterized by thrombotic and haemorrhagic risks that are influenced by smoking, the extent of leucocytosis and thrombocytosis, and generic cardiovascular risk factors [1, 5]. The WHO 2016 laid down the diagnostic criteria for polycythemia vera which is inclusive of 3 major criteria and one minor criterion [1]. The major criteria include Hb > 16.5 g/dl in men or 16 g/dl, trilineage growth including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic megakaryocytes on bone marrow biopsy and a JAK2V617 F (exon 14) or equivalent exon 12 mutation [5]. The minor criteria include subnormal erythropoietin levels [1]. All three major criteria or two major criteria with one minor criterion clinch the diagnosis of polycythemia vera [1, 5].

IgA nephropathy is a primary glomerular disease caused by defective galactosylation of polymeric IgA [2]. IgA nephropathy presenting as nephrotic syndrome is uncommon, with an estimated global incidence of around 5–10%

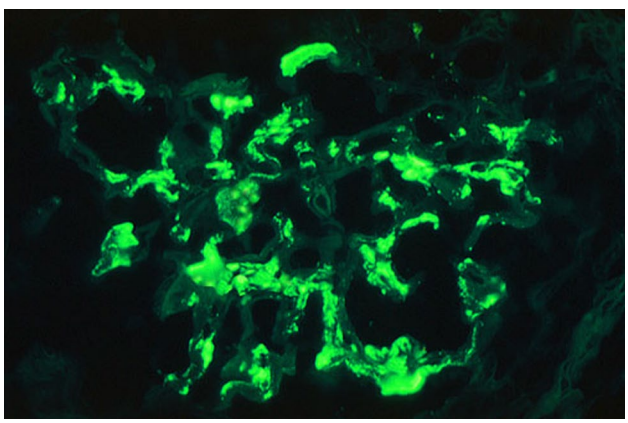

Fig. 2 Immunofluoroscence showing diffuse granular IgA(3+) along the mesangium (magnification: 600 DPI;400×)

[6]. This clinical phenotype is characterised by minimal change type of podocyte foot process effacement with favourable response to corticosteroids which portends a better prognosis [6]. A higher degree of proteinuria(> 3 g/day), advanced interstitial fibrosis and tubular atrophy, global glomerulosclerosis, and crescents are poor prognostic indicators in IgA nephropathy [2, 6]. Sustained proteinuria (> 3 g/day) compared to less than 1 g/day was considered the single most important predictor of faster decline of eGFR in IgA nephropathy [7].

Renal lesions associated with polycythemia include Focal segmental glomerulosclerosis, IgA nephropathy, mesangioproliferative glomerulonephritis, membranoproliferative glomerulonephritis and minimal change disease [4, 8]. The pathogenesis of renal lesions include hyper viscosity, intrarenal hypertension, vascular thrombi, glomerular capillary occlusion, tissue ischemia and abnormal activation of megakaryocytes which finally culminate in glomerular sclerosis [1, 8]. Medical literature reports around 9 cases of polycythaemia vera with IgA nephropathy out of which 6 presented with nephrotic syndrome similar to our case [8]. Mesangioproliferative lesions have a favourable prognosis while crescentic and sclerotic glomerulonephritis progress to chronic kidney disease [8, 9]. Increased expression of platelet-derived growth factor [PDGF} in polycythaemia vera is postulated to increase production of IgA by palatine tonsils, promote IgA immune complex formation, reduce clearance and enable mesangial cell proliferation thereby contributing to the pathogenesis of IgA nephropathy [8, 9]. Advanced vascular changes in the form of severe arteriosclerosis and fibrous intimal proliferation in the interlobular arteries in IgA nephropathy have a direct impact on the degree of proteinuria and renal impairment [10] which was evident in our case.

The treatment strategies are aimed at polycythemia vera and IgA nephropathy in a holistic manner, which include phlebotomy, hydroxyurea, low-dose aspirin (for increased thrombotic risk), hypouricemic agents, and anti-proteinuric measures using angiotensin-converting enzyme inhibitors and steroids (in specific clinical conditions) [1, 8, 9, 11]. Tonsillectomy is indicated in IgA nephropathy with tonsillar infection associated with mild to moderate renal damage, but has no clinical benefit in patients with advanced renal disease, as in our case [12].

Our case report is unique in that our patient presented with nephrotic syndrome, gross haematuria and moderate renal insufficiency, but had advanced histological changes of IgA nephropathy. We found the utility of steroids futile in the clinical context of severe IFTA in renal biopsy. Our patient had macroscopic haematuria despite having a mild proliferative pattern (M0E0S1T2C0), which indicates the role of increased expression of chemokine receptor CX3CR1 on peripheral blood mononuclear cells, leading to glomerular capillary wall damage and permeability in viable glomeruli, thereby leading to macroscopic haematuria [13]. He was treated with maximum tolerated doses of telmisartan and hydroxyurea. This case report highlights the importance of prompt diagnosis of varied glomerular diseases in polycythaemia vera using renal biopsy and the need for appropriate prognostication of IgA nephropathy associated with such myeloproliferative disorders.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This case report was drafted after written informed consent of the patient in conformity with CARE clinical case reporting guidelines and Declaration of Helsinki. The authors are accountable for all aspects of the work (including full data access, integrity of the data, and accuracy of the data analysis) to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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