Crescentic Glomerulonephritis Associated with Polycythaemia Vera: A Rare Occurrence

Abstract

Glomerular diseases are one of the most challenging entities in terms of diagnosis and management, especially when associated with systemic illnesses such as malignant disorders. Herein, a case of crescentic glomerulonephritis (CrGN) associated with polycythaemia vera (PV) in a 50-year-old female is described. She presented with bilateral pedal oedema, splenomegaly, renal dysfunction and severe proteinuria. On evaluation, we found PV and CrGN. Renal involvement in PV is rare and generally considered as a manifestation of hypervolemia or high-viscosity-induced renal hyper-perfusion and hyper-filtration. This is a unique case of immunologically-mediated renal disease in PV.

Keywords: *Crescentic glomerulonephritis, polycythaemia vera Acute kidney injury, Nephrotic syndrome*

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Introduction

Glomerular crescents are dramatic lesions, more often than not associated with severe and devastating clinical presentation in the form of rapidly progressive glomerulonephritis (RPGN). Most crescentic glomerulonephritis (CrGN) occurs in association with systemic autoimmune diseases. Occasionally, it may be diagnosed with systemic diseases like malignant neoplasms. One such condition is polycythaemia vera (PV). PV is a panhyperplastic, malignant stem cell disorder in which phenotypically normal red cells, granulocytes and platelet accumulate in the absence of a recognizable physiological stimulus. Thromboembolic events are among the most important cause of morbidity and mortality.[1] A variety of renal disease has been described in the literature.[2] Herein, we report a rare case of pauci-immune CrGN in a patient of PV.

Case Presentation

A 50-year-old female was referred to our hospital for renal dysfunction. She reported having anorexia, early fatigability, bleeding gums (3–4 episodes), lower limb swelling and abdominal fullness for the past 4 months. Her symptoms had worsened over 15 days before the presentation with progression to anasarca. She denies any history suggestive of oliguria, hematuria, dysuria, flank pain, increase the frequency of urination, fever, nausea, vomiting, dyspnea, rash, headache, or neurologic symptoms. She had used over-the-counter medications (pantoprazole and multivitamins) intermittently for the same. She had consulted her primary care physician for the above complaints and was referred to because of renal dysfunction.

Her past medical history revealed bilateral knee joint arthritis for the past 10–15 years, for which she used non-steroidal anti-inflammatory drugs (NSAIDS) intermittently. She denied any form of addiction nor any adverse reactions to medications. Her family history was unremarkable for malignancy, autoimmune or renal diseases.

On physical examination, she was conscious and coherent with a heart rate of 86 beats/min, blood pressure of 156/86 mmHg, respiration at 18 breaths/min, temperature 37.2°C and oxygen saturation 99% in ambient air. She weighed 56 kg, height 152 cm and body-mass index of 24.3 kg/m^2. There was a moderate degree bilateral lower limb pitting oedema. Abdominal examination revealed massive splenomegaly crossing the midline. Voided urine was high-coloured without clots. The rest of the examination was unremarkable.

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Her initial lab values are shown in Table 1. Her peripheral smear revealed normocytic normochromic closely packed RBCs, few polychromatophils, neutrophilic leukocytosis and thrombocytosis with giant platelets. 2-D echocardiography revealed normal systolic function (Left ventricular ejection fraction, LVEF-63%) and grade 1 diastolic dysfunction. No evidence of any vegetation. Abdominal ultrasonography confirmed the splenic enlargement (19 cm in its longitudinal axis) with normal echo texture and showed bilaterally hyperechogenic kidneys of normal size, shape and parenchymal thickness. She was scheduled for bone marrow and renal biopsy.

Her Bone marrow biopsy [Figure 1a] revealed irregularly thickened and thinned bony trabeculae, extensive marrow fibrosis with entrapped myeloid precursor and megakaryocytes. Megakaryocytes exhibited para trabecular clustering with pleomorphism. Reticulin stain showed grade III condensations. These features were indicative of PV with secondary myelofibrosis which was confirmed by positive JAK2 V617F mutation.

Examination of renal biopsy [Figure 1b and c] revealed 8 glomeruli. All glomeruli showed circumferential cellular crescents. Interstitium had sparse lymphocytic and neutrophil infiltrates. Vessels were unremarkable. Immunofluorescence was negative for IgG, IgM, IgA, C3C, C1q, K and L. Electron microscopy revealed thickened glomerular basement membrane with a mean thickness of 431.4 nm. Significant effacement of foot processes of visceral epithelial cells was noted (about 50–60%) along with scattered subendothelial, intramembranous and mesangial electron-dense deposits. A few tubuloreticular inclusions were identified in the glomerular endothelial cell cytoplasm. Neutrophils were seen in few capillary lumina.

She underwent 3 sessions of phlebotomies to reduce hematocrit to <50%. She was initiated on a pulse dose of methylprednisolone (IV 500 mg/day for 3 days) and intravenous cyclophosphamide (500 mg). The patient's clinical condition and renal parameters deteriorated, on day 7 of hospitalization, the patient had worsening of dyspnea and developed haemoptysis necessitating intensive care. She was mechanically ventilated and received CRRT and plasmapheresis. Despite all measures, she succumbed to her illness.

Discussion

Renal involvement in PV is infrequent, often late and rarely recognised. Clinically, it presents nephrotic range proteinuria and/or renal insufficiency. The histopathological pattern of involvement is mostly glomerular. The

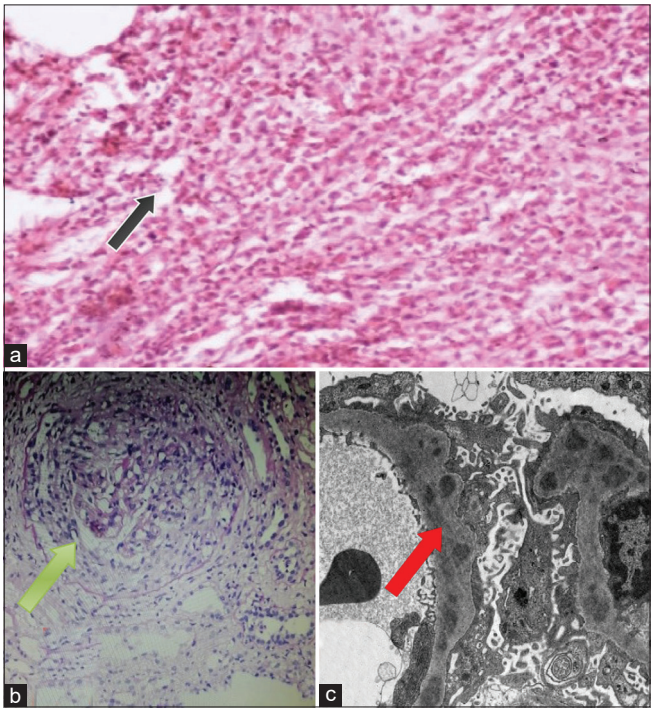

Figure 1: (a) Hypercellularity and increased number of myeloid precursor; (b) showing circumferential cellular crescent (green arrow); (c) EM-showing significant visceral foot process effacement and multi-compartmental deposits (red arrow)

Table 1: Laboratory values at the time of hospitalisation

Variable	Value	Variable	Value	Variable	Value
Haemoglobin (grams/dL)	16.0	Calcium (mg/dL)	8.9	C3 (mg/dL)	53
Packed cell (volume %)	52.0	Uric acid (mg/dL)	11.1	C4 (mg/dL)	19
Total leukocyte (count cells/mm^3)	27400	Serum phosphorous (mg/dL)	5.4	ANA	Neg
Platelets (lakh/mm^3)	5.2	SGOT/SGPT (U/L)	17/10	ANCA	Neg
ESR (mm/h)	2	Total protein (g/dL)	6.7	AntidsDNA	Neg
Reticulocyte count	2.50	Serum albumin (g/dL)	2.9	AntiGBM abs	Neg
BUN (mg/dL)	34	LDH (U/L)	631	HsCRP (mg/L)	30.20
Serum creatinine (mg/dL)	2.4	Urine microscopy	3+	Procalcitonin	0.50
		Protein	25-30/hpf		
		Red cells	15-20/hpf		
		Pus cells			
Serum sodium (mmol/L)	141	24-h urine protein (g)	8.04	PT (s)	13.60
				INR	1.20
Serum potassium (mmol/L)	4.2	Urine Culture	No growth	HBV/HCV/HIV	Neg

various pattern described in the literature includes IgA nephropathy, focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), CrGN and thrombotic microangiopathy.[2]

The possible pathogenesis of PV associated-renal disease may be as follows.

1) An increase in blood volume and viscosity causes passive expansion of the capillaries and intimal injury, ultimately leading to tissue ischaemia and renal injury
2) PV is often associated with hypertension and hyperuricemia, which affect renal microcirculation
3) The medications used for PV treatment can cause renal impairment e.g., interferon, hydroxyurea[3,4]
4) Abnormal activation of megakaryocytes leading to glomerulosclerosis[5]
5) Various cytokines and growth factors PDGF, TGF-β has also been implicated in the pathogenesis.[6]

Plomely *et al*., in 1983, described six patients with PV and proteinuria, all were hypertensive; 3 had thrombotic episodes, 2 had impaired renal function and 3 patients had a diffuse mesangial proliferative glomerulonephritis.[7] Sharma *et al*., in 1995, reported a case of FSGS with PV in a 40-year-old female patient who presented with hypertension and proteinuria.[8] Similarly, Kasuno *et al*., in 1997, described 2 cases of crescentic IgA nephropathy in association with PV, showing simultaneous improvement of both diseases during treatment.[9] Oymak *et al*., in 2000, reported a case of PV presenting with rapidly progressive glomerulonephritis and pyoderma gangrenosum.[10] In a literature review done by Hong Chen in 2015 *et al*.,[2] 23 cases of PV associated with renal disease were analysed of which 21 had undergone renal biopsy. The histological pattern in these cases included 8 cases of IgAN, 10 cases of FSGS (Focal segmental Glomerular sclerosis), 2 cases of MPGN (Membranoproliferative Glomerulonephritis) and 1 case of rapidly progressive glomerulonephritis (RPGN). The average age at the time of the biopsy was 53.43 years, with slight male preponderance (1.63:1). All patients had hypertension at presentation, 14 cases had nephrotic range proteinuria and 12 cases had moderate to severe renal insufficiency. Out of 23 cases, 5 cases progressed to end-stage renal disease (ESRD) and required routine dialysis. To our knowledge, this is the first case presenting with pauci-immune CrGN in association with PV.

In the present case, the diagnosis of PV was straight forward in the background of polycythaemia, leucocytosis, thrombocytosis, massive splenomegaly and typical findings in Bone marrow biopsy which was further supported by positive JAK2V617F mutation. Renal biopsy was consistent with the diagnosis of pauci-immune CrGN. Electron Microscopy showed evidence of thickened glomerular basement membrane (GBM), ED (electron-dense) deposits in multiple compartments and diffuses visceral foot process effacement. It is important to consider the following questions: 1) Is Glomerular involvement a complication of PV or comorbidity? 2) Does PV increase susceptibility for crescentic transformation? 3) Possibility of dual glomerular pathology? 4) The dilemma in the management, whether to manage as a case of PV or as CrGN? It is known that PV is characterised by abnormal and high leucocytosis and thrombocytosis, which is said to play a crucial role in the pathogenesis of CrGN, so is there any link between the two? Seronegative ANCA vasculitis is a well-known entity, whether this was a case of ANCA vasculitis where polycythaemia acted as a trigger to unmask robust autoimmune response. In the absence of significant tubulointerstitial and vascular changes, hypertension was a less likely pathogenic mechanism for renal dysfunction. Crescent formation and renal haemodynamic changes secondary to polycythaemia look like a more plausible mechanism for renal dysfunction. Electron microscopic findings of GBM thickening, diffuse visceral foot process effacement and multicompartmental ED deposits raises the possibility of other underlying glomerular pathology, which might be able to explain the presence of nephrotic range proteinuria as well.

Conclusion

This case was a rare association of pauci-immune CrGN and PV. Although a variety of pathological lesion has been described in the literature, CrGN should always be considered in the differential diagnosis of patients with PV presenting with acute kidney injury. At present, whether renal involvement in PV is a complication or comorbidity remains unclear. More experimental and clinical evidence is required to establish a causal relationship and appropriate treatment strategies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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