

## Case Report

# A rare clinical syndrome of refractory secondary hypertension, renal artery stenosis and erythrocytosis

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### Abstract

Clinical syndrome of refractory secondary hypertension, renal artery stenosis and secondary erythrocytosis could occur in the same patient. We report a rare case of refractory secondary hypertension, renal artery stenosis and primary erythrocytosis as an expression of polycythaemia rubra vera (PV) and suggest that erythrocytosis in a hypertensive renovascular occlusive disease may be primary due to underlying PV. This clinical syndrome should be excluded in such patients with refractory hypertension.

**Keywords:** erythrocytosis; hypertension; polycythaemia; stenosis

### Background

Secondary erythrocytosis is well-known to be associated with renal artery stenosis but the prevalence of this association in patients is unknown. Impairment of kidney function is followed by decreased erythropoietin secretion and anaemia. In 1962, Penington [1] postulated that factors which impaired renal perfusion should lead to increased erythropoietin secretion and secondary erythrocytosis. The first report in 1965 [2] and subsequent papers [3] have suggested a similar pattern of erythrocytosis and hypertension secondary to increased erythropoietin and renin secretion in response to renal ischaemia. Each of these patients had shown to have secondary polycythaemia. We report an unusual case of renal artery stenosis occurring in a patient with polycythaemia rubra vera (PV).

### The case

A 40-year-old non-diabetic, non-smoking female was referred to us for evaluation and management for severe refractory hypertension which she had been experiencing for the previous 5 months. She was diagnosed to have hypertension during a routine evaluation, 5 years back. Initially, her blood pressure (BP) was well controlled with two antihypertensive drugs—amlodipine and atenolol. However, her BP became difficult to control in the last 5 months, requiring

an increment in dose of antihypertensive drugs and the addition of three extra classes of drugs including clonidine, prazosin and thiazide. Despite all these efforts, her BP was still high. There was no history of treatment with drugs like angiotensin-converting inhibitors and angiotensin II receptor blockers.

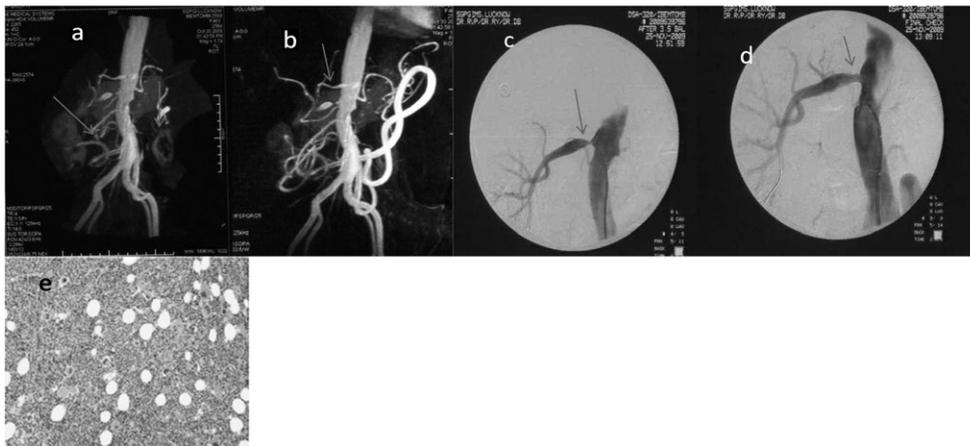
Her pulse was palpable in all limbs without brachio-brachial and radio-femoral delay. Her BP was 180/110 mmHg without significant difference in BP between all limbs and without postural fall. She was plethoric and had congested conjunctiva. On systemic examination, she had splenomegaly and right renal abdominal bruit above umbilicus.

Her haematocrit, haemoglobin, leucocyte count and platelets count were high (Table 1). She had elevated creatinine [estimated glomerular filtration rate (eGFR) 37 mL/min/1.73m<sup>2</sup>], high uric acid level and +2 proteinuria (Table 1). Fundus examination showed Grade 4 hypertensive retinopathy. Ultrasound and Doppler examination showed bilateral normal size kidneys, absent flow to left kidney and stenosis of main right renal artery at origin and splenomegaly. Magnetic resonance angiogram (MRA) of abdominal vessels was suggestive of multiple arterial stenosis including stenosis of bilateral renal artery (Figure 1a and b). Serum erythropoietin level was 32 mU/mL (normal 4–24), measured by commercially available ELISA kit. Workup to rule out

**Table 1.** Showing details of investigations done<sup>a</sup>

Haemoglobin	16.4 gm/dL
Haematocrit	56
WBC count	45 000/mm <sup>3</sup>
Platelets count	540 000/mm <sup>3</sup>
Serum creatinine	2.1 mg/dL
eGFR	37 mL/min/1.73m <sup>2</sup>
Serum Na	136 mmol/L
Serum K+	4.2 mmol/L
Serum uric acid	10.3 mg/dL
Lipid profile	With in normal limit
EPO level	32 mU/mL (normal 4–24)
Urine routine and microscopy	+2 protein

<sup>a</sup>eGFR, estimated glomerular filtration rate; WBC, White blood cell; EPO, Erythropoietin.



**Fig. 1.** (a) MRA of abdominal aorta and its branches showing stenosis of bilateral renal artery and celiac artery. (b) MRA of abdominal aorta and its branches showing stenosis of bilateral renal artery and celiac artery. (c) DSA of renal artery stenosis at origin (d) post angioplasty and stenting. (e) Bone marrow histology in polycythaemia vera patients-hematoxylin and eosin-stained bone marrow biopsy revealed increased cellularity with predominantly erythroid hyperplasia.

hypercoagulable states was unremarkable. Bone marrow examination was done, in view of increased cell count of trilineage series and was suggestive of chronic myeloproliferative disorder like PV or chronic myeloid leukaemia (CML) (Figure 1e). Cytogenetic analysis like JAK-2 mutation and bcr-c-abl fusion was done to further differentiate between CML and PV. As JAK-2 mutation was present, confirming the diagnosis of PV.

Diagnosis of PV with multiple arterial stenoses including bilateral renal artery stenosis due to atherothrombosis associated with refractory renovascular hypertension (in malignant phase) was made.

Her BP became controlled with the increment in dosage of antihypertensive medications and addition of oral hydralazine. Meanwhile, hydroxyurea was started to control total cell counts. Digital subtraction arteriography (DSA) was done along with balloon angioplasty and right renal artery stenting by intervention radiologist. (Figure 1b and c). After stenting, BP started to decline gradually >72 h and became well controlled with only two antihypertensive drugs. Her renal functions (creatinine 1.1 mg/dL, eGFR 58.47 mL/min/1.73m<sup>2</sup>) became normal after 1 week of intervention. Antiplatelet drug aspirin was added. Her haemoglobin, leucocyte count and platelets count came down to normal within 4 weeks of starting chemotherapy.

## Discussion

Our case is a rare presentation of PV. A diagnosis of PV was made in this patient on the findings of splenomegaly, an elevated cell count of trilineage series, with compatible changes in the bone marrow and normal oxygen saturation. Patients with this disease are often hypertensive although the reason for this is unclear. It is not related to blood viscosity [4] and does not appear to resolve after venesection [5]. However, in our patient, hypertension was refractory and was found to be secondary to an ischaemic kidney. Significant renal artery stenosis along with stenosis of mesenteric artery was confirmed by the demonstration of

marked narrowing of these arteries on MRA and later DSA. Occlusive vascular disease is possibly due to atherothrombosis and may occur in conjunction with PV and related chronic myeloproliferative disorder. Thrombosis may involve virtually any site of the venous, arterial and/or microcirculatory districts but cerebral, cardiac and mesenteric arteries seem to be particularly involved but the degree of occlusion leading to ischaemic renal injury is rare [6]. Given the complex interaction between blood cells and the vessel wall, it is possible that atherogenesis may also be accelerated in these patients. Hyperviscosity, endothelial damage due to leucocyte activation with subsequent thrombus formation, hyperhomocysteinaemia and hyper expression of activating genes such as *JAK2* and *STAT5* are all features characteristic of PV and other chronic myeloproliferative disorders that may contribute, along with other risk factors, to the development and progression of atherothrombosis [7]. In PV, platelet abnormalities have been identified to cause reduced haemostatic effectiveness, on the one hand, and increased platelet activation *in vivo*, on the other [6]. An increased biosynthesis of thromboxane A<sub>2</sub> has been reported, suppressible by low-dose aspirin and thus suggestive of a platelet origin. [6]. A recent randomized trial in patients with PV demonstrated the safety and efficacy of low-dose aspirin in preventing both venous and arterial thromboses over a period of 3 years [8].

The unusual finding of an elevated erythropoietin level in our patient implies that the renal ischaemia was significant and may even have led to an exacerbation of polycythaemia. Increased erythropoietin concentration should not deter the diagnosis of polycythaemia vera in a patient, with RAS and erythrocytosis, when splenomegaly, high thrombocyte and leucocyte count are present.

Cytotoxic treatment with hydroxyurea in PV may be beneficial in both through its antiproliferative effect on haematopoiesis and on the atherosclerotic plaques, atherogenesis being described as a proliferative disease of the vessel wall [9].

So, in a patient who presents with refractory hypertension, renal artery stenosis and erythrocytosis together, we should consider two possible causes of this clinical

syndrome: (i) renal artery stenosis with secondary refractory hypertension giving rise to secondary erythrocytosis. (ii) PV causing primary erythrocytosis, renal artery stenosis with secondary hypertension possibly due to an atherothrombotic mechanism.

*Conflict of interest statement.* None declared.

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