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Case Report

Blue kidney in a pale patient—a case for a causal association between renal haemosiderosis in paroxysmal nocturnal haemoglobinuria and chronic kidney disease

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Abstract

A 50-year-old man presented with pancytopenia and chronic renal impairment. He had evidence of intravascular haemolysis. The direct antiglobulin (Coomb's) test was negative. Paroxysmal nocturnal haemoglobinuria (PNH) was diagnosed by the Ham acid haemolysis test. There were no other clinical risk factors that could be implicated in chronic kidney disease (CKD). A renal biopsy revealed extensive haemosiderosis affecting proximal tubular cells and associated interstitial fibrosis as well as tubular atrophy. No glomerular or vascular lesions were seen. These findings strengthen the case for a causal relationship between renal haemosiderosis in PNH and CKD.

Keywords: chronic kidney disease; haemolysis; haemosiderosis; kidney; paroxysmal nocturnal haemoglobinuria (PNH)

Background

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired stem cell disorder characterized by the clonal expansion of abnormal haematopoietic cells carrying a mutation in the phosphatidylinositol glycan class A (PIG-A), X-linked gene. PNH clones fail to generate glycosylphosphatidylinositol (GPI) or to express a series of GPI-linked membrane proteins including complement-regulatory proteins, resulting in complement-mediated intravascular haemolysis.

The majority of cases of PNH with renal involvement reported in the literature had acute kidney injury that occurred in the setting of massive haemoglobinuria during an acute haemolytic episode. The literature on chronic kidney disease (CKD) in patients with PNH is scanty, and uncertainties have existed regarding the link between renal haemosiderosis due to chronic low-grade haemolysis in PNH and chronic renal damage.

Case report

A 50-year-old normotensive and non-diabetic man of Asian origin was admitted for investigation of anaemia and progressive renal impairment. Anaemia and renal dysfunction had been noticed 6 years ago (haemoglobin 7.6 g/dL, serum creatinine 137 μmol/L and creatinine clearance 52 mL/min) during consultation at another hospital after which the patient was lost to follow-up. There were no urinary symptoms or previous history of nephrolithiasis, urinary tract infections, flank pain or dark coloured urine. He denied taking any regular medication including non-steroidal anti-inflammatory agents.

On examination, he looked extremely pale. Blood pressure was 110/60. There was no lymphadenopathy, organomegaly or signs of cardiac decompensation. The laboratory findings are summarized in Table 1.

He had severe normochromic anaemia, anisopoikilocytosis, granulocytopenia and thrombocytopenia. Subsequent work-up confirmed intravascular haemolysis as evidenced by increased serum LDH, reduced haptoglobin and haemosiderinuria. The direct antiglobulin (Coomb's) test was negative implying that haemolysis was of non-immune origin. A bone-marrow biopsy was carried out that showed marked erythroid hyperplasia, dyserythropoietic features and reduced iron stores. No malignant cells were seen. Diagnosis of PNH was made by the Ham test indicating complement-mediated red blood cell lysis. Flow cytometric studies were not performed.

Serum biochemistry revealed moderately severe renal impairment with a creatinine clearance of 28 mL/min/1.73 m^2. This was associated with a low-grade proteinuria of 0.68 g/day. Urine was negative for the Bence-Jones protein, and serum electrophoresis did not show any monoclonal band. ANA was negative, and there was no hypocomplementaemia. Ultrasonography showed unobstructed, normal-sized echogenic kidneys with decreased corticomedullary differentiation. A renal biopsy was performed. The predominant finding was that of widespread

Table 1. Laboratory studies

Lab studies	Patient	Normal range
Haemoglobin (g/dL)	5.9	13–17
Red blood cells ($\times 10^6/\mu$L)	1.9	4.5–5.5
Reticulocyte (%)	4.05	< 1
MCV (fL)	91	80–96
White cell count ($\times 10^3/\mu$L)	2.7	4–11
Platelets ($\times 10^3/\mu$L)	170	140–440
Ferritin (μg/L)	38	24–336
Serum iron (μmol/L)	13	8–28.6
Iron saturation (%)	28.9	15–45
TIBC (μmol/L)	45	45–80
Haptoglobin (mg/dL)	< 5.8	27–139
Glucose (mmol/L)	4.6	3.3–5.5
Creatinine (μmol/L)	258	62–124
Total bilirubin (μmol/L)	27	3.5–24
Alkaline phosphatase (U/L)	100	40–129
ALT (U/L)	25	0–40
AST (U/L)	69	0–37
Lactic dehydrogenase (U/L)	1777	240–480

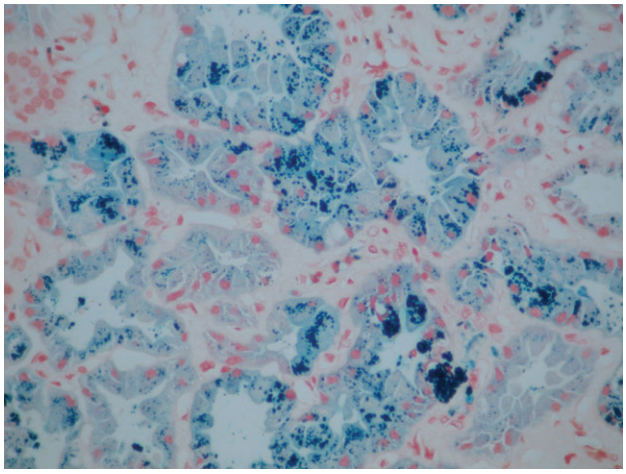

Fig. 1. Perls' Prussian blue staining (400 $\times$) showing haemosiderin deposits in proximal tubular cells—"blue kidney".

haemosiderosis involving the proximal tubular cells (Figure 1) that gave a blue tinge to the specimen on application of Perls' Prussian blue stain. This was associated with interstitial fibrosis and tubular atrophy affecting ~30% of the core. Glomeruli and blood vessels were normal and immunofluorescence was negative.

Discussion

Intravascular haemolysis of a magnitude sufficient to fully saturate the binding capacity of haptoglobin leads free haemoglobin to pass through the glomerulus. The filtered haemoglobin is partially reabsorbed by proximal tubular epithelium. Renal handling of haemoglobin is quite similar to that of glucose; once the capacity of renal tubular cells is exceeded during a major haemolytic episode, haemoglobin appears in urine. In the tubular cells, haemoglobin iron is rapidly extracted and stored as ferritin and haemosiderin. Some iron is re-used for the synthesis of haemoglobin, but its mobilization for this purpose is slow. When iron laden tubular cells slough into urine, both ferritin and haemosiderin may be detected in urine. The capability of the kidney to shed and replace its iron-laden tubular cells may reduce but not always protect it against injury by siderosis.

Can PNH lead to CKD? If yes, then is CKD a direct consequence of renal haemosiderosis? Is there a true causal link between renal iron overload in PNH and CKD? Answers to these questions are not clear and have stirred a lot of controversy in the past.

Early reports refuted any association between PNH and CKD [1,2]. Leonardi *et al*. reported 'no significant functional impairment of renal function' even where renal haemosiderosis was of many years' standing. However, laboratory data pertaining to the assessment of renal function were limited in these studies; in some cases, serum creatinine/creatinine clearance was not mentioned. Contrary to these reports, Clark *et al*. noted that many of their patients with PNH did indeed have subnormal creatinine clearances or had evidence of chronic tubular dysfunction in the chronic steady state [3]. Following this, a few other cases of CKD were described in patients with longstanding PNH [4–6].

Our case is unique in several aspects: (1) the patient had no previous admissions with haemolytic crisis/AKI, but had well-documented evidence of CKD over a few years. (2) There were no other risk factors that could be implicated in CKD, i.e. no hypertension, diabetes mellitus, connective tissue disease, exposure to nephrotoxins, recurrent urinary tract infections or urinary tract obstruction. Difficulty in establishing with certainty a causal relationship between renal haemosiderosis in PNH and CKD had previously arisen from the fact that several patients had other comorbid conditions that could have contributed to renal dysfunction. (3) Renal histology did not reveal any alternative cause for renal dysfunction; the only findings were those of haemosiderosis, interstitial fibrosis and tubular atrophy. This is in contrast to the histology findings in the cases described by Kumpers *et al*. and Clark *et al*. who turned out to have features of hypertensive arterionephrosclerosis [7] and microthrombotic infarctions [3], respectively. Zachee *et al*. described a case of PNH with CKD and renal haemosiderosis [5]. The patient had hypertension that was not under optimal control on two anti-hypertensive agents suggesting a possible pathogenic role of hypertension in renal damage. It would have been interesting to know if there were any hypertensive arteriolar changes on renal biopsy. (4) Renal haemosiderosis was purely 'haemolytic' in origin with no 'transfusional' component as the patient had never received any blood transfusions. The patient described by Zachee *et al*. had received multiple blood transfusions for severe anaemia raising the possibility that transfused iron load could have contributed to renal haemosiderosis [5].

Renal impairment associated with mesangial expansion, hypercellularity, glomerulosclerosis, interstitial fibrosis and tubular atrophy has been reported in animal models of experimental haemosiderosis [8] as well as in patients with beta thalassaemia [9]. The prevailing hypothesis for chronic iron overload-induced nephrotoxicity is that of an oxidant injury to cellular membrane phospholipids by reactive oxygen species (ROS). Zhou *et al*. demonstrated that renal iron overload in experimental haemosiderosis was

associated with an increase in both plasma and renal tissue malondialdehyde—a lipid peroxidation product, and an increase in expression of renal endothelial and inducible nitric oxide synthase (eNOS and iNOS) [8]. Iron chelation with deferoxamine in patients receiving red blood cell transfusions as supportive therapy for chronic anaemias such as beta thalassaemia, sickle cell disease and myelodysplastic syndromes attenuates organ dysfunction, strongly suggesting a pathogentic role of iron-induced ROS generation [10,11].

Conclusion

Renal tubular iron deposition resulting from chronic haemolysis is an important aetiologic factor for CKD. On the basis of clinical and histopathological findings of our case, we feel that renal haemosiderosis can, *per se*, lead to CKD in patients with PNH. Future prospective studies involving a large number of patients with PNH can help establish this causal association.

Conflict of interest statement. None declared.

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