CASE REPORT

The bronze kidney: membranous glomerulonephritis associated with iron overload

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SUMMARY

A 55-year-old man with a history of diabetes mellitus, hypertension and hypercholesterolaemia developed increasing peripheral oedema over the course of several months. He was found to have nephrotic range proteinuria (15.7 g/24 h). His renal ultrasound scan was normal and the autoimmune screen was negative. His renal biopsy demonstrated evidence of membranous glomerulonephritis and increased iron deposition. At this juncture, a serum ferritin was checked which showed an initial value 933 µg/L with transferrin saturation at 96.6%. A subsequent liver biopsy also showed evidence of iron overload but without fibrotic changes. Genetic studies including C282Y HFE, ferroportin and DMT1 studies were also negative. He was subsequently treated with interval venesection which was associated with significant symptomatic and biochemical evidence of improvement in oedema and proteinuria.

12 mmol/L and his glycated haemoglobin was only 5.1%. His blood renal (urea 5.7 mmol/L, creatinine 102 µmol/L), liver (international normalised ratio 1.0) and bone profile were normal with the exception of a serum albumin of 19 g/L. His 24 h urinary protein excretion was 15.7 g. The renal ultrasound scan, antinuclear factor, antineutrophil cytoplasmic antibody screen, serum protein electrophoresis and rheumatoid factor were all normal. His subsequent renal biopsy showed features consistent with established membranous glomerulonephritis (MG) as well as the striking presence of haemosiderin granules within tubular epithelial cells (figure 1). The kidney biopsy showed no other features which would be consistent diabetic nephropathy.

Investigations for haemolysis (reticulocytes, bilirubin and lactic dehydrogenase) were negative; however, serum ferritin and transferrin saturations were found to be grossly abnormal at 933 µg/L (12–300 µg/L) and 96.6% (20–50%), respectively. His haemoglobin and haematocrit were 15.3 and 0.39 L/L, respectively. A liver biopsy was performed which also demonstrated excess iron deposition primarily within hepatocytes and around the portal triads; however, there was no evidence of progressive hepatic fibrosis or cirrhosis. He did not have biochemical evidence of hypogonadism (testosterone 26 nmol/L, luteinizing hormone 10.9 U/L, follicle-stimulating hormone 8.5 U/L).

Genetic studies were performed including C282Y, ferroportin and DMT1 assays but these were all negative. There was no history of recurrent blood transfusions or excessive iron ingestion. Analysis of the blood did not suggest defective haematopoiesis, and there was no evidence of chronic liver disease to suggest alternative causes of iron overload.

DIFFERENTIAL DIAGNOSIS

There are a considerable number of potential causes for nephrotic syndrome which are usually classified initially on the histological and immunohistochemical features of the renal biopsy. These classical pathological patterns are then associated with other clinical diseases. The pathological pattern in this case was MG associated with marked haemosiderin deposition.

MG is often primary; however, there are a number of secondary associations including: systemic lupus erythematosus, drugs (penicillamine, bucillamine, gold salts, antitumour necrosis factor therapy, tiopronin, non-steroidal anti-inflammatory drugs), hepatitis B, hepatitis C, malignancy,

BACKGROUND

This case, to the best of our knowledge, is the first time a patient with haemochromatosis has presented with nephrotic syndrome. This disease is known to be associated with multisystem pathology, and its predilection for causing diabetes, cardiomyopathy and liver cirrhosis is well known; however, renal deposition of iron appears to be a phenomenon that has not been previously reported in the literature.

CASE PRESENTATION

A 55-year-old man who had worked as an agronomist developed bilateral lower limb oedema. He also presented with some difficulty with reduced libido and erectile dysfunction. His medical history included diabetes, hypertension and hypercholesterolaemia. He had a 20 pack year smoking history and did not drink alcohol to excess. He reported that his mother died at age 49 from 'uraemia' and hypertension. There was no other family history of diabetes, kidney or liver disease. He did have some exposure to organophosphate compounds.

On examination, he had male pattern baldness, bruising and signs of skin fragility, slight swelling of the second and third metacarpophalangeal joints as well as 3 cm hepatomegaly. His heart rate was 60 bpm with an initial blood pressure of 150/80. His initial urine dipstick showed proteinuria and haematuria.

INVESTIGATIONS

The patient was found to be hypertensive with ambulatory blood pressure monitoring showing mean values of 159/103. His total cholesterol was

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Figure 1 Histopathology of kidney biopsy. (A) Silver stain of a representative glomerulus, showing spike formation and holes in the glomerular basement membranes (see insert lower right corner), characteristic for membranous glomerulonephritis (original magnification $\times 400$). (B) Immunohistochemistry for IgG showing granular membranous staining, consistent with membranous glomerulonephritis (original magnification $\times 400$). (C) Electron microscopy showing a glomerular capillary loop with numerous subendothelial immune deposits (see arrows), surrounded by newly formed basement membrane material, consistent with membranous glomerulonephritis stage III (original magnification $\times 6000$). (D) H&E stain showing subtle granular iron pigment in tubular epithelial cells (see arrows; original magnification $\times 400$). (E) Pearls iron stain highlights abundant iron deposition in tubular epithelial cells (original magnification $\times 400$).

haematopoietic cell transplant, graft versus host disease, diabetes mellitus and sarcoidosis.¹

The association between the improvement in proteinuria and serum albumin levels and the start and maintenance of regular venesection suggests that the reduction of iron overload may be associated with remission in the MG. A progressive improvement in proteinuria over a period of year is also seen in cases of MG secondary to exposure to gold. The alternative possibility is that the renal pathology spontaneously remitted over a similar time course which would certainly be plausible if the MG was primary or associated with diabetes mellitus with improved glycaemic control.²

TREATMENT

His hypertension was controlled with lisinopril 5 mg daily. Atorvastatin 40 mg daily effectively reduced the cholesterol levels to 4.5 mmol/L. Education and diet modification were adequate to maintain good diabetic control initially. Once haemochromatosis was firmly established as the diagnosis biweekly 450 mL venesections were started.

Following 3 months of venesection, the transferrin saturations fell to 25.7%, the ferritin levels fell to 478 ng/mL with a fall in urinary protein excretion to 5.5 g/24 h. Over the subsequent months, the interval of venesection was gradually reduced. He now requires venesection approximately once per year. His urinary protein excretion rate is approximately 1.5 g/24 h.

OUTCOME AND FOLLOW-UP

Over a period of around a decade, his diabetic control deteriorated, so metformin, gliclazide and then insulin were sequentially

introduced. Unfortunately, he also suffered a left frontoparietal infarct which left him with some mild right-sided weakness. The patient's brother accepted an offer to screen for evidence of iron overload; none was found.

DISCUSSION

It is also possible that the finding of MG is either entirely coincidental and a primary presentation unassociated with other pathology or that it is associated with diabetes mellitus. A literature search of the MEDLINE and EMBASE databases using the search terms 'diabetes mellitus' and 'membranous glomerulonephritis' found two articles confirming an association in two case series.^{3 4} In one case series of 80 Iraqi men with diabetes mellitus, 20 were found to have MG.³

The author has not been able to find any cases of nephrotic syndrome or MG being associated with iron overload of any aetiology through an interrogation of the MEDLINE and EMBASE databases. There also appear to be no published reports on the findings at renal biopsy of patients with iron overload syndrome on either database.

This case highlights the fact that iron overload syndromes may have a more varied genetic, pathological and clinical pattern of distribution than classically taught. It highlights the potential need to screen for iron overload in cases of MG without an obvious clinical association or in association with diabetes mellitus and to monitor for evidence of nephrotic syndrome or renal injury in patients with iron overload syndromes.

Learning points

- ▶ Iron overload can cause multisystem pathology and has known associations with diabetes, cardiomyopathy and hepatic fibrosis and cirrhosis.
- ▶ The specific association with nephrotic syndrome, specifically membranous glomerulonephritis, has not been noted in clinical literature previously.
- ▶ If evidence of iron deposition is found on renal biopsy in the absence of evidence of haemolytic processes, the diagnosis of haemochromatosis should be considered.

Contributors AJ oversaw the investigation and diagnosis and provided direction in the wording and style of the document. JRB was responsible for the investigation

and management of the patient's nephrotic syndrome. VB provided interpreted images of the patient's renal biopsy.

Competing interests None.

Patient consent Obtained.

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