

Exceptional Case

## AA Amyloidosis in a patient with glycogen storage disorder and progressive chronic kidney disease

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### Abstract

Type 1 glycogen storage diseases (GSD) are inherited metabolic diseases caused by defects in the activity of the glucose-6-phosphate transporter. We present the case of a 40-year-old male with glycogen storage disease type 1b (GSD1b) who was referred to our nephrology service for evaluation of his chronic kidney disease and found to have AA amyloid deposition on renal biopsy. Amyloid is a described complication of GSD1b. As the treatment of GSD has improved, patients are surviving longer and are now presenting more frequently to adult services. It is important that clinicians are aware of the possible renal complications of GSD1b.

**Keywords:** amyloidosis; chronic kidney disease; glycogen storage disorder; proteinuria

### Background

Type 1 glycogen storage diseases (GSD) are a group of inherited metabolic disorders with an incidence of 1/100 000 live births [1] resulting from defects in the hydrolysis and transport of glucose-6-phosphate. This results in diverse metabolic effects including glycogen accumulation in the liver, kidneys and intestine, hypoglycaemia, hyperuricaemia and lactic acidosis. Twenty percent of cases are due to defects in the glucose-6-phosphate transporter and are classified as glycogen storage disorder type 1b (GSD1b). Intermittent neutropaenia and neutrophil dysfunction is a well-described feature of GSD1b [2].

Management of patients with GSD is mostly in the form of dietary supplementation with cornstarch to prevent hypoglycaemia. In addition, physicians are responsible for evaluating and treating other complications of the disease. A granulocyte colony-stimulating factor (G-CSF) may be used for patients with severe neutropaenia, hyperuricaemia can be managed with xanthine oxidase inhibitors and patients should undergo regular surveillance for liver adenomas and adenocarcinoma. Liver transplantation improves metabolic control. Other considerations include anaemia, growth failure, osteoporosis and regular screening of renal function.

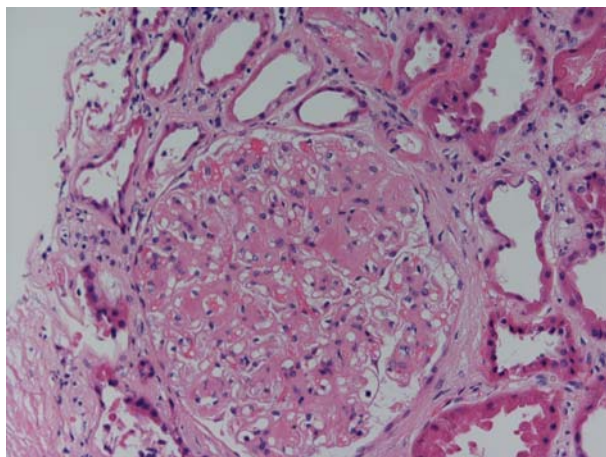
### Case report

A 40-year-old man was referred to the nephrology service for evaluation of his renal dysfunction. He had a history of GSD1b which had been diagnosed at age 2. He

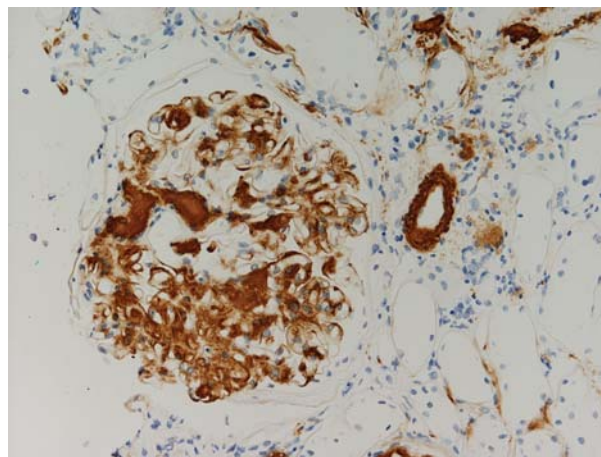
had since suffered from hyperuricaemia and occasional episodes of gout for which he intermittently self-medicated with non-steroidal anti-inflammatory drugs. He also had multiple liver adenomas. He was of Afro-Caribbean ethnicity and was born in the UK. He denied any other significant childhood infections or illnesses. He had been managed by specialist paediatric and adult metabolic teams with a modified diet. He was intolerant to ramipril, and took irbesartan 150 mg once daily for hypertension.

At initial assessment, the blood pressure was 110/80 mmHg. Blood tests showed the following results: serum urea nitrogen 53 mg/dL (19 mmol/L) and creatinine 1.80 mg/dL (160 µmol/L). Urinalysis showed 3+ protein. The urine protein/creatinine ratio was 3884 mg/g (439 mg/mmol). An ultrasound showed that the length of right kidney was 8.9 cm and the left kidney was 8.7 cm, and that the collecting systems were non-dilated. Cortical reflectivity was grossly abnormal with loss of normal corticomedullary differentiation and diffuse increased reflectivity. Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, C3, C4, serum electrophoresis, immunoglobulins and serum-free light chains were negative. He was found to be human immunodeficiency virus, hepatitis B and C virus negative. A renal biopsy was arranged on a number of occasions but he did not attend the appointments. Over the following years, he attended the general nephrology clinic intermittently, but consistently declined to attend for a renal biopsy.

Two years after his first appointment in the nephrology clinic, he was admitted to the hospital as an emergency case with abdominal pain, nausea and vomiting. His renal function had declined with the following results: urea 72 mg/dL (26 mmol/L), creatinine 3.2 mg/dL (285



**Fig. 1.** Haematoxylin and eosin stain, ×200 magnification. Involvement of the renal parenchyma by amyloid with deposition in the mesangial matrix, glomerular capillary wall and the wall of the adjacent arterioles.



**Fig. 2.** Immunostaining for AA amyloid, ×200 Magnification.

μmol/L), MDRD eGFR 26 mL/min. A repeat ultrasound of the renal tract showed unobstructed kidneys. Urinalysis was positive for blood and protein and his urinary protein/creatinine ratio was raised at 7539 mg/g (852 mg/mmol). In view of the active urinary sediment, immunological investigations were repeated but remained unremarkable. His serum albumin was 3.5 g/dL. An urgent computed tomography of the abdomen was performed without intravenous contrast and this showed multiple hypodense liver lesions, consistent with the known adenomas. The liver was not compressing the stomach. Upper gastrointestinal endoscopy was macroscopically normal with the exception of a small polyp in the first part of the duodenum. He was initially managed with intravenous glucose infusion and anti-emetics; this was discontinued after 5 days. His renal function failed to improve with hydration, and he agreed to proceed with a percutaneous ultrasound-guided renal biopsy.

Light microscopy of the biopsy specimen showed extensive involvement of the renal parenchyma by amyloid with deposition in the mesangial matrix, glomerular capillary wall and the wall of the adjacent arterioles (Figure 1, haematoxylin and eosin stain). This stained with Congo red and fluoresced green under birefringent light. Of thirty, twenty-three glomeruli were sclerosed, and there was ~40–50% interstitial fibrosis. Immunostaining was positive for serum amyloid A confirming secondary amyloidosis (Figure 2).

He was referred to the National Amyloid Centre for further investigation. An echocardiogram did not show any evidence of cardiac amyloid. Serum amyloid A was 56 mg/L (<10 mg/L). A serum amyloid P scan showed moderate amyloid load with abnormal liver, spleen and kidneys.

## Discussion

Renal disease is a common complication of GSD1. In the largest series [3] of 20 patients aged 13–47 years, 70% had persistent proteinuria. Diverse renal pathologies have been described in these patients. The predominant glomerular lesion is focal segmental glomerulosclerosis, other reported complications include nephrocalcinosis, gouty nephropathy, glycogen deposition, crescentic glomerulonephritis and a Fanconi-like syndrome [4, 5].

Current paediatric guidelines [6] suggest treatment with an ACE-inhibitor for patients with GSD1 and proteinuria or hypertension.

There are two previous reports of renal failure in patients with GSD1 caused by secondary amyloidosis in the literature. One was in a 12-year-old girl with GSD1b who developed progressive renal impairment as a feature of generalized amyloidosis [7]. The second was in a 26-year-old man with GSD1a who was found to have AA amyloid deposition in his native kidneys and subsequently underwent a combined liver and renal transplant [8]. This patient was reported to have normal renal function 1-year post transplantation, with metabolic abnormalities resolving following the liver transplant.

Possible aetiologies for the AA amyloid in our patient include the presence of multiple hepatic adenomas. Several cases of AA amyloid in association with hepatic adenomas have been reported in the literature [8–10], and this association may be explained by the production of tumour necrosis factor- $\alpha$  by the adenomas [11].

Although our patient did not report frequent previous infections, a review of his historical blood results revealed intermittent episodes of neutropaenia, without clinical sepsis. At no point did he receive treatment with the G-CSF. It is also possible that infections associated with neutropaenia resulted in a chronic inflammatory state that caused AA amyloidosis.

## Conclusion

The increased life expectancy of patients with GSD1 means that patients with this condition increasingly present to adult nephrology services. Awareness of the diverse renal pathologies in this group, including AA amyloid, is likely to result in more informed decision making in the management of these patients.

*Conflict of interest statement.* None declared.

## References

1. Melis D, Fulceri R, Parenti G et al. Genotype/phenotype correlation in glycogen storage disease type 1b: a multicentre

- study and review of the literature. *Eur J Pediatr* 2005; 164: 501–508
2. Chou J, Jun H, Mansfield B. Neutropenia in type 1b glycogen storage disease. *Curr Opin Hematol.* 2010; 17: 36–42
  3. Chen Y, Coleman R, Scheinman J et al. Renal disease in Type 1 glycogen storage disease. *N Eng J Med* 1988; 318: 7–11
  4. Reitsma-Bierens W. Renal complications in glycogen storage disease type 1. *Eur J Pediatr* 1993; 152: s60–s62
  5. Chen Y. Type I Glycogen storage disease: kidney involvement pathogenesis and treatment. *Pediatr Nephrol* 1991; 5: 71–76
  6. Visser G, Rake J, Labrune P et al. Guidelines for management of glycogen storage disease type 1- European study of Glycogen storage disease type 1. (ESGSD1). *Eur J Pediatr* 2002; 161: S112–S119
  7. Kikuchi M, Haginoya K, Miyabasyashi S et al. Secondary amyloidosis in glycogen storage disease type 1b. *Eur J Pediatr* 1990; 149: 344–345
  8. Poe R, Snover D. Adenomas in glycogen storage disease type 1. Two cases with unusual histologic features. *Am J Surg Pathol* 1988; 12: 477–483
  9. Cosme A, Horcajada JP, Vidaur F et al. Systemic AA amyloidosis induced by oral contraceptive-associated hepatocellular adenoma: a 13-year follow up. *Liver* 1995; 15: 164–167
  10. Bestard Matamoros O, Poveda Monje R, Ibernón Vilaró M et al. Systemic AA amyloidosis induced by benign neoplasms. *Nefrologia* 2008; 28: 93–98
  11. Shibasaki T, Matsumoto H, Watabe K et al. A case of renal amyloidosis associated with hepatic adenoma: the pathogenetic role of tumor necrosis factor-alpha. *Nephron* 1997; 75: 350–353

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