OMCR

Oxford Medical Case Reports, 2020;6,165–168

doi: 10.1093/omcr/omz148
Case Report

CASE REPORT

Educational case: a patient with proteinuria

Christopher N. Kassam[1], Vivian W.M. Yiu[1,2], Meryl H. Griffiths[3] and William G. Petchey[1,2,*]

[1]Department of Renal Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK, [2]Department of Nephrology, West Suffolk NHS Foundation Trust, Bury St Edmunds, UK, [3]Department of Pathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

*Correspondence address. Department of Nephrology, West Suffolk NHS Foundation Trust, Bury St Edmunds IP33 2QZ, UK. Tel: 01284 713148; Email: william.petchey@wsh.nhs.uk

Abstract

This is an educational case suitable for all readers, but aimed particularly at trainees preparing for MRCP. Using the example of a patient presenting to clinic with proteinuria, aspects of differential diagnosis, pathology and management are explored.

INTRODUCTION

A 37-year-old male Caucasian administrator presented to general nephrology clinic after his GP noted 3+ proteinuria on urinalysis.

CASE REPORT

His symptoms included tiredness and frothy urine for 6 months. He had not experienced any haematuria, lower urinary tract symptoms, flank pain, ankle swelling, breathlessness or recent weight change. He had a past medical history of obstructive sleep apnoea and was not diabetic. He took no regular medications and had no known allergies. He had a family history of cardiovascular disease on his father's side and lung cancer on his mother's side. There was no family history of renal disease. He had never smoked. A recent HbA1c performed by his GP was 41 mmol/mol (5.9%).

On examination, the patient's BMI was 38 kg/m^2, and his blood pressure was 133/76 mmHg. There was no detectable peri-orbital or pedal oedema. His JVP was not raised. His chest was clear on auscultation and his kidneys were not palpable. There was no rash. Urinalysis confirmed 3+ proteinuria and no haematuria.

Question 1: What is the most likely cause of proteinuria in this patient?

A. Diabetic nephropathy
B. **Membranous nephropathy**
C. Granulomatosis with polyangiitis
D. Lupus nephritis (class V)
E. Alport syndrome

Explanation: Membranous nephropathy is an immune-mediated glomerulopathy which is the commonest primary cause of nephrotic syndrome in Caucasian adults [1]. Diabetic nephropathy is a common cause of proteinuria, but HbA1c is not elevated and it is unusual for previously undiagnosed diabetes to present with proteinuria in the absence of other symptoms. Granulomatosis with polyangiitis is rare and tends to present with systemic malaise and multi-organ involvement; urinalysis typically shows both protein and blood. Class V lupus nephritis is a possibility in this case, but is less common than membranous nephropathy, and would often cause haematuria in addition. Alport syndrome is a genetic disorder (usually X-linked) caused by defects in type IV collagen synthesis; it is unlikely in the absence of a family history or deafness, and usually presents with progressive renal impairment rather than proteinuria. There is some evidence that primary focal

Received: September 9, 2019. **Revised:** November 28, 2019. **Editorial Decision:** December 15, 2019.

Table 1: Investigation results

	Value	Reference range
FBC		
Haemoglobin	141 g/L	135–180 g/L
Platelets	237 × 10^9/L	150–400 × 10^9/L
White cell count	7.2 × 10^9/L	4.0–11.0 × 10^9/L
U&Es		
Sodium	139 mmol/L	135–45 mmol/L
Potassium	4.2 mmol/L	3.5–5.0 mmol/L
Urea	5.1 mmol/L	2.0–7.0 mmol/L
Creatinine	76 µmol/L	55–120 µmol/L
Estimated glomerular filtration rate	>90 mL/min/1.73m^2	>90 mL/min/1.73m^2
Other blood results		
ESR	5 mm/hr	1–7 mm/hr
Albumin	37 g/L	35–55 g/L
HbA1c	41 mmol/mol	<48 mmol/mol
Total serum cholesterol	3.7 mmol/L	<5 mmol/L
Serum free light chain κ:λ ratio	0.77	0.31–1.56
Serum protein electrophoresis	No monoclonal band detected	
ANA	Not detected	
ANCA	Not detected	
Anti-phospholipase A2 receptor antibody	Not detected	
Complement C3	103 mg/dL	80–160 mg/dL
Complement C4	27 mg/dL	16–48 mg/dL
Urine results		
ACR	237 mg/mmol	<3.5 mg/mmol

segmental glomerulosclerosis may be overtaking membranous nephropathy as the leading primary cause of nephrotic syndrome, particularly in black patients; however, FSGS was not an option in this question [2].

Investigations were performed (Table 1). Additionally, screening tests for HIV, hepatitis B and hepatitis C were negative. Renal ultrasound demonstrated that both kidneys were of normal size, with no cysts or masses (bipolar length LEFT 11.3 cm, RIGHT 11.7 cm).

Question 2: What urinary albumin:creatinine ratio (ACR) indicates nephrotic-range proteinuria?

A. > 3.5 mg/mmol
B. > 30 mg/mmol
C. > 150 mg/mmol
D. > **250 mg/mmol**
E. > 300 mg/mmol

Explanation: 24-hour urinary protein excretion is no longer routinely measured due to impracticality and inaccuracies in timing urine collection; it has largely been replaced by the spot measurement of albumin:creatinine or protein:creatinine ratio (PCR). An ACR of > 250 mg/mmol corresponds to a 24-hour urinary protein excretion of > 3.5 g, the threshold for nephrotic-range proteinuria. If urinary PCR is used, the threshold is 300 mg/mmol. An ACR of < 2.5 mg/mmol (males) or < 3.5 mg/mmol (females) is considered normal, while an ACR of 2.5–30 mg/mmol (males) or 3.5–30 mg/mmol (females) indicates microalbuminuria. Note that microalbuminuria is not usually detected by urine dipsticks.

A renal biopsy was performed to establish the underlying cause of the patient's proteinuria. A biopsy of his left kidney was successfully taken. Representative sections are shown in Fig. 1.

Congo red staining was negative. Immunofluorescence showed some staining for IgM and complement C3 in sclerotic glomerular lesions, but was otherwise unremarkable.

Question 3: What is the most likely underlying diagnosis?

A. Amyloidosis
B. Diabetic nephropathy
C. Membranous nephropathy
D. **Obesity-related glomerulopathy**
E. Primary focal segmental glomerulosclerosis

Explanation: Obesity-related glomerulopathy (ORG) typically presents with sub-nephrotic proteinuria in patients with BMIs > 30 kg/m^2. Nephrotic syndrome is not usually seen, even when the proteinuria reaches nephrotic range [3, 4]. In case series, the prevalence of renal impairment at diagnosis has ranged from 33 to 44%, with 10–33% of patients eventually progressing to end-stage kidney disease [5–7]. However, in early stages of the disease, creatinine may be normal or low due to glomerular hyperfiltration. Pathologically, renal biopsy histology demonstrates glomerulomegaly and focal segmental glomerulosclerosis (predominantly perihilar in distribution), with non-specific immunofluorescence findings. In this case, the biopsy findings are not typical of either amyloidosis or membranous nephropathy. In addition, negative Congo red staining and myeloma screen make amyloidosis unlikely, while anti-phospholipase A2 receptor antibody is positive in 70% of patients with primary membranous nephropathy [1]. While the histological appearance of ORG has some similarities to that of diabetic nephropathy (so-called 'diabetoid' changes), this patient's HbA1c indicates normal glycaemic control. Primary FSGS remains a possibility; however, patients commonly present with nephrotic syndrome, glomerulomegaly is not usually seen and a perihilar distribution of sclerotic lesions is typically

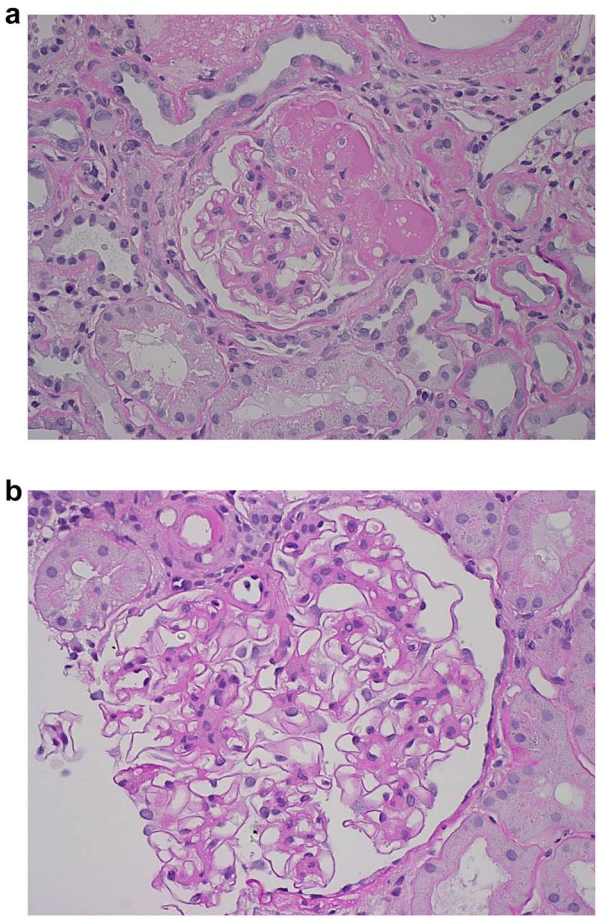

Figure 1: Representative sections from the biopsy of the patient's left kidney, H&E stain.

associated with secondary (adaptive) causes of FSGS such as ORG. It is essential to distinguish between primary and secondary FSGS so as to avoid treating obese patients with high-dose corticosteroids for prolonged periods. Electron microscopy may further assist in making this distinction: typically in primary FSGS podocyte foot processes are diffusely effaced from early in the disease course, whereas in secondary FSGS, foot process effacement is segmental and develops more slowly [8].

Question 4: How would you manage this patient initially?

A. Bariatric surgery
B. **Ramipril**
C. Spironolactone
D. Structured weight-loss programme
E. Watchful waiting

Explanation: There is no definitive evidence available as yet on the management of ORG. However, Renin-Angiotensin-Aldosterone blockade with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) is the most evidence-based intervention for reducing proteinuria and preventing progression to end-stage renal disease [3]. Indeed, NICE recommends that all patients with ACR >70 mg/mmoL due to any cause should be offered an ACE inhibitor or ARB [9]. There is also some evidence that weight-loss interventions (particularly bariatric surgery) may induce rapid improvements in glomerular hyperfiltration and proteinuria, both in patients with ORG and more broadly in obese patients with CKD [3]. However, the literature on weight-loss interventions suffers from flaws in study design and limited follow-up, and provides little evidence regarding long-term progression to end-stage renal disease.

The patient was started on ramipril 5 mg OD and advised to return for 6-monthly review in nephrology clinic. After 12 years, his BMI had increased to 41 kg/m^2, his serum creatinine had progressively risen to 622 µmol/L and his eGFR had fallen to 8 mL/min/1.73 m^2. He was referred to the low-clearance clinic to discuss renal replacement therapy (RRT).

Question 5: What is the most appropriate management option for this patient?

A. Automated peritoneal dialysis
B. Conservative management
C. Continuous ambulatory peritoneal dialysis
D. Intermittent haemodialysis
E. **Kidney transplant**

Explanation: While all patients should be offered the option of conservative management, this will not usually be the first choice in a young patient. Transplantation offers a clear survival benefit over any modality of dialysis irrespective of BMI, and current NICE guidelines suggest that patients should not be excluded from transplantation on the basis of BMI alone [10, 11]. Kidney transplant is, therefore, the most appropriate option. However, BMI $>$ 35 is associated with an increased risk of adverse outcomes including surgical complications and graft loss, and in practice, in the context of donor scarcity, many centres exclude very obese patients from transplantation or require weight loss prior to transplant listing [12]. Clinicians will, therefore, often find themselves offering other RRT modalities for obese patients, either long-term or as a bridge to transplant. There is no high-quality evidence regarding the effect of peritoneal dialysis versus haemodialysis on mortality or quality of life in adults, and the patient should be offered the choice of haemodialysis and peritoneal dialysis modalities depending on local service availability [13]. However, from a technical perspective, insertion of a peritoneal dialysis catheter would be difficult for a patient with BMI 41 kg/m^2, potentially requiring a pre-sternal catheter, which is not available at all centres.

DISCUSSION

The pathogenesis of ORG is complex and incompletely understood. Obesity is known to be associated with increased circulating levels of angiotensin II, due in part to angiotensinogen synthesis in adipose tissue [14]. Increased angiotensin II results in efferent arteriole constriction and afferent arteriole dilatation (both directly and via tubuloglomerular feedback), leading to glomerular hyperfiltration. Increased glomerular pressure is thought to lead first to glomerulomegaly and eventually to podocyte detachment and FSGS lesions. There is also evidence that insulin resistance and alterations in circulating adipokine concentrations may directly contribute to podocyte loss [3].

The prevalence of obesity (defined as BMI $>$ 30) among adults in England has risen from 15% in 1993 to 26% in 2016; similar rates are found in other parts of the UK [15]. All physicians will undoubtedly be required to manage ever-increasing numbers of obese patients. The obesity epidemic has important implications for renal medicine. Obesity is a major risk factor for both malignant and non-malignant renal disease: the relative risk for end-stage renal failure in obesity is 4.07, while 26% of non-malignant renal disease in industrialised countries is attributable to being overweight [16]. While much of this excess risk is due to the

complications of obesity such as diabetes and hypertension, a sub-population of obese patients develop proteinuria in the absence of other risk factors. Studies on these patients have defined ORG as an independent pathological entity. Indeed, in the absence of routine renal biopsy, some evidence suggests that up to 10% of cases of presumed diabetic nephropathy may in fact be wholly or partly due to ORG [17].

As obesity rates continue to rise globally, the incidence of ORG is likely to rise in tandem. Being alert to the clinical presentation of ORG may facilitate early intervention with ACE inhibitors, helping to slow progression to end-stage kidney disease in these patients.

CONFLICTS OF INTEREST STATEMENT

No conflicts of interest.

FUNDING

No funding.

ETHICAL APPROVAL

No ethical approval required.

CONSENT

No consent required.

REFERENCES

1. Couser WG. Primary membranous nephropathy. *Clin J Am Soc Nephrol* 2017;**12**:983–97.
2. Fervenza FC, Sethi S, Specks U. Idiopathic membranous nephropathy: diagnosis and treatment. *Clin J Am Soc Nephrol* 2008;**3**:905–19.
3. D'Agati VD, Chagnac A, de Vries APJ, Levi M, Porrini E, Herman-Edelstein M, *et al*. Obesity-related glomerulopathy: clinical and pathological characteristics and pathogenesis. *Nat Rev Nephrol* 2016;**12**:453–71.
4. Praga M, Morales E. The fatty kidney: obesity and renal disease. *Nephron* 2017;**136**:273–6.
5. Kambham N, Markowitz G, Valeri A, Lin J, D'Agati V. Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int* 2001;**59**:1498–509.
6. Praga M, Hernandez E, Morales E, Campos AP, Valero M, Martinez M, *et al*. Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2001;**16**:1790–8.
7. Tsuboi N, Koike K, Hirano K, Utsonomiya Y, Kawamura T, Hosoya T. Clinical features and long-term renal outcomes of Japanese patients with obesity-related glomerulopathy. *Clin Exp Nephrol* 2013;**17**:379–85.
8. De Vriese AS, Sethi S, Nath K, Glassock R, Fervenza F. Differentiating primary, secondary and genetic FSGS in adults: a clinicopathologic approach. *J Am Soc Nephrol* 2018;**29**: 759–74.
9. National Institute for Health & Care Excellence (2014). *Chronic kidney disease in adults: assessment and management* (NICE guidelines CG182). Available at: https://www.nice.org.uk/guidance/cg182/resources/ chronic-kidney-disease-in-adults-assessment-and-management-pdf-35109809343205 (19 February 2019, date last accessed).
10. National Institute for Health & Care Excellence (2018). *Renal replacement therapy and conservative management* (NICE guidelines NG107). Available at: https://www.nice.org.uk/guidance/ng107/resources/ renal-replacement-therapy-and-conservative-management-pdf-66141542991301 (10 February 2019, date last accessed).
11. Krishnan N, Higgins R, Short A, Zehnder D, Pitcher D, Hudson A, *et al*. Kidney transplantation significantly improves patient and graft survival irrespective of BMI: a cohort study. *Am J Transplant* 2015;**15**:2378–86.
12. Pham PT, Danovitch GM, Pham PC. Kidney transplantation in the obese transplant candidates: to transplant or not to transplant? *Semin Dial* 2013;**26**:568–76.
13. National Institute for Health & Care Excellence (2018). *RRT and conservative management: modalities of RRT* (NICE guidelines NG107: evidence review). Available at: https://www.nice.org.uk/guidance/ng107/evidence/b-modalities-of-rrt-pdf-6542344047 (10 February 2019, date last accessed).
14. Kalupahana NS, Moustaid-Moussa N. The renin-angiotensin system: a link between obesity, inflammation and insulin resistance. *Obes Rev* 2012;**13**:136–49.
15. Baker C. (2018). *Obesity Statistics* (house of commons briefing paper no. 3336). Available at: https://researchbriefings.files.parliament.uk/documents/SN03336/SN03336.pdf (12 February 2019, date last accessed).
16. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney Int* 2008;**73**:19–33.
17. Sharma SG, Bomback AS, Radhakrishnan J, Herlitz LC, Stokes MB, Markowitz GS, *et al*. The modern spectrum of renal biopsy findings in patients with diabetes. *Clin J Am Soc Nephrol* 2013;**8**:1718–24.