Nephrotic syndrome: delays in diagnosis and a cause of pulmonary embolism not to miss

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Introduction

Delays in diagnosis of nephrotic syndrome are common (Hull and Goldsmith, 2008) and it can be easily missed in acute hospital presentations. Although uncommon in adults, with an incidence of 3 per 100 000 per year (Hull and Goldsmith, 2008), nephrotic syndrome can be associated with significant, potentially life-threatening complications, including infection, arterial or venous thromboembolism, acute kidney injury and hyperlipidaemia (Hull and Goldsmith, 2008). It can also be associated with underlying diseases, including malignancy.

These sequalae and potential for underlying malignancy mean that timely diagnosis is vital. This article presents two cases of nephrotic syndrome where diagnosis and therefore treatment were significantly delayed.

Discussion

Nephrotic syndrome is defined by the triad of proteinuria, peripheral oedema and hypoalbuminaemia. The most common primary causes in adulthood are membranous nephropathy and focal segmental glomerulosclerosis (Kodner, 2016).

Both patients described here had hypoalbuminaemia and peripheral oedema on initial presentation. Although hypoalbuminaemia has multiple potential causes, nephrotic syndrome should be considered, especially when in combination with peripheral oedema. Urinalysis should be carried out and urine sent for protein or albumin:creatinine ratio if proteinuria is present.

Nephrotic syndrome is a pro-thrombotic condition (Mahmoodi et al, 2008). This is believed to be caused by the loss of inhibitors of coagulation in the urine, such as antithrombin III and free protein S (Kerlin et al, 2012). It should therefore be considered in any patient presenting with an apparently unprovoked embolic event. National Institute for Health and Care Excellence (2020) guidelines recommend that all patients with unprovoked deep vein thrombosis or pulmonary embolism should have baseline bloods including renal and liver function tests. Hypoalbuminaemia should trigger further investigation, as above.

Case report 1

A 52-year-old male presented in June 2019 with 2 days of breathlessness on exertion, pleuritic chest pain and light-headedness. Past medical history included a completely excised melanoma. He was taking no medication and was a non-smoker. Examination showed bilateral lower leg pitting oedema. Table 1 outlines the results of his investigations.

A computed tomography pulmonary angiogram demonstrated extensive bilateral pulmonary emboli with bi-basal consolidation. He was discharged with apixaban and oral antibiotics after 2 days.

He re-presented 1 week later with worsening breathlessness and fever. Table 1 outlines the results of his investigations. He received intravenous antibiotics and was discharged 5 days later.

The diagnosis at discharge was an unprovoked pulmonary embolism and he was advised to continue anticoagulation lifelong.

The patient was referred to outpatient nephrology from primary care in June 2020, 1 year after his initial presentation, with a raised protein creatinine ratio (430.6 g/mmol). Further investigations showed raised anti-phospholipase A2 receptor antibody levels (65 RU/ml) with primary membranous nephropathy confirmed on renal biopsy. Given the hypoalbuminaemia at initial presentation, nephrotic syndrome was the likely cause of his pulmonary embolism.

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Table 1. Investigations and results for case report 1

Results		Reference range	First presentation 13 June 2019	Second presentation 20 June 2019	September 2019	June 2020
Blood results	Creatinine (umol/litre)	59–104	114	105	–	87
	Estimated glomerular filtration rate (m/min)	60–150	63	70	–	87
	Albumin (g/litre)	35–50	28	22	–	25
	C-reactive protein (mg/litre)	0–5	51	229	–	–
	White cell count (10^9/litre)	4–10	10.1	9.9	–	–
	D-dimer (ug/ml)	0–0.5	8.0	–	–	–
	Phospholipase A2 receptor antibody (RU/ml)	<14	–	–	–	65
Chest X-ray		–	No acute findings	Small right pleural effusion and consolidation in the left lower zone	–	–
Echocardiogram		–	–	–	Left ventricular ejection fraction 60% no valvular abnormalities. Normal right ventricle	–
Urinalysis		–	–	–	–	Proteinuria
Urine protein:creatinine ratio (mg/mmol)		0–20	–	–	–	430.6

Case report 2

A 67-year-old female presented in November 2020 with 3 days of worsening peripheral oedema and breathlessness on a background of 6 months of peripheral oedema. Past medical history included obesity, hypertension and hypothyroidism, for which she was taking indapamide, levothyroxine and atorvastatin. Examination demonstrated pitting oedema to the sacrum and weeping, erythematous lower legs. Table 2 outlines the results of her investigations.

The initial diagnosis was lymphoedema with cellulitis. She was treated with intravenous meropenem and fluids. The cellulitic changes resolved and the renal function was improving. She was discharged after 9 days to have repeat bloods in primary care.

She represented in December 2020 with worsening peripheral oedema and breathlessness. On examination there was bilateral pitting oedema to the sacrum and arm oedema. Table 2 outlines the results of her investigations.

Nephrotic syndrome was now considered as the underlying diagnosis. Screening for secondary causes was negative. Anti-phospholipase A2 receptor antibody levels were raised (>1500 RU/ml), suggesting primary membranous nephropathy; this was subsequently confirmed on renal biopsy.

She received intravenous furosemide and metolazone to achieve diuresis. Prophylactic warfarin was commenced as recommended by the Kidney Disease Improving Global Outcomes Guidelines (2021) as she was considered high risk for thromboembolism. She was discharged after 21 days to continue diuresis in the community.

On review the patient had presented to primary care 6 months before the first hospital admission with peripheral oedema, hypoalbuminaemia and raised total cholesterol levels (Table 2).

Table 2. Investigations and results for case report 2

Results		Reference range	Primary care presentation May 2020	First hospital presentation November 2020	Second hospital presentation December 2020
Blood results	Creatinine (umol/litre)	59–104	80	457	195
	Estimated glomerular filtration rate (ml/min)	60–150	66	8	22
	Albumin (g/litre)	35–50	26	19	23
	C-reactive protein (mg/litre)	0–5	–	199	3
	White cell count (10^9/litre)	4–10	3.9	13.7	2.8
	Haemoglobin (g/litre)	130–180	124	89	84
	Thyroid-stimulating hormone (mIU/litre)	0.35–4.5	10.3	2.56	0.73
	Total cholesterol (mmol/litre)	0–5	9.0	–	7.5
	Phospholipase A2 receptor antibody (RU/ml)	<14	–	–	>1500
Chest X-ray		–	–	Bilateral pleural effusions	Bilateral pleural effusions
Echocardiogram		–	–	Left ventricular ejection fraction >55%, no valvular abnormalities	–
Renal ultrasound		–	–	Normal	–
Urinalysis		–	–	–	Proteinuria
Urine protein:creatinine ratio (mg/mmol)		0–20	–	–	826.3

It is also important to be aware that malignancy can be an underlying cause of nephrotic syndrome, particularly in membranous nephropathy, where the estimated prevalence of associated malignancy is 10% (Leeaphorn et al, 2014).

The delays from first presentation to diagnosis in the patients presented here were 1 year and 7 months respectively. Diagnostic delays such as this risk irreversible decline in renal function by delaying immunosuppressive therapy where appropriate. It also risks missing or delaying diagnoses of secondary causes of nephrotic syndrome, such as malignancy or systemic lupus erythematosus, and increases the risk of thromboembolic events.

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Learning points

- An underlying cause should be sought for hypoalbuminaemia.
- Hypoalbuminaemia and/or peripheral oedema should prompt urinalysis.
- If proteinuria is present, this should be quantified with urine protein or albumin:creatinine ratio.
- Consider nephrotic syndrome as a provoking factor for unexplained arterial or venous thromboembolism.

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