CASE REPORT

Nephrotic syndrome in a non-diabetic adult: A case for primary care vigilance

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SUMMARY

Nephrotic syndrome presents a diagnostic challenge in primary care due to its nonspecific symptoms, which may overlap with more common conditions such as heart failure or liver disease, and the need to exclude secondary causes. Additionally, as nephrotic syndrome is relatively uncommon in non-diabetic adults, diagnosis in this group is less straightforward. We present the case of a man who came to primary care with frothy urine, bilateral lower limb swelling and significant weight gain, without evidence of underlying heart or kidney disease. Laboratory findings suggested nephrotic syndrome, and he was referred to a nephrologist, where further evaluation, including a renal biopsy, determined the aetiology. This case provides valuable insight into real-world diagnostic challenges and management approaches in this uncommon but serious condition. It shows the importance of maintaining a high index of suspicion for nephrotic syndrome in adult patients with unexplained oedema and proteinuria by primary care doctors, and it emphasises the value of prompt specialist referral and multidisciplinary care to optimise patient outcomes.

INTRODUCTION

Nephrotic syndrome (NS) has an incidence of approximately three new cases per 100,000 adults annually.[1] Data on adult NS in Southeast Asia and Malaysia are still limited. Diagnosing NS in primary care can be particularly challenging due to the nonspecific early symptoms and the need to exclude secondary causes. Symptoms such as leg swelling and frothy urine are common in primary care and can be misinterpreted for other more common conditions like heart failure, liver disease or venous insufficiency. The key challenge is to look beyond common causes, consider NS early and order confirmatory tests promptly.

NS is characterised by proteinuria greater than 3.5g/24hr, hypoalbuminemia below 3g/dL, hyperlipidaemia and oedema. Timely diagnosis and management are essential to avoid complications.[2] The underlying causes of NS vary with age; in children under 16, minimal change disease (MCD) is the most common. However, in adults aged 15 to 65, a broader range of causes is seen. Primary glomerular diseases such as focal segmental glomerulosclerosis (FSGS), MCD, IgA nephropathy and, less frequently, membranous nephropathy (MN), are more common in adults.[2-4] Adults with NS also face additional challenges, as the disease spectrum is broader and influenced by demographic factors such as age, race and geography, encompassing both primary and secondary causes. This makes early kidney biopsy critical to accurately diagnose the condition and guide subsequent treatment, especially after excluding secondary causes.[5]

Clinical decisions made in primary care involved ordering initial investigations, managing symptoms, excluding secondary causes like infections or diabetes and referring the patient to nephrology for further evaluation and biopsy. This highlights the role of primary care doctors as the first line of detection, starting management and coordinating with specialists to ensure timely diagnosis and comprehensive care. This case report describes a 44-year-old man with symptoms suggestive of NS, demonstrating the diagnostic challenges and key clinical decisions in primary care.

CASE PRESENTATION

A 44-year-old man with underlying hyperlipidaemia (on Tab Simvastatin 40mg daily) presented to the primary health clinic with a chief complaint of progressive bilateral lower limb swelling. The swelling initially began around the ankles one month ago but gradually extended upward, becoming increasingly severe over time. Additionally, he reported persistent frothy urine for four months and an unintentional weight gain of 10 kilograms over the past seven months. His weight was 84 kg at presentation, with a BMI of 32.6kg/m². The patient expressed concern that the swelling had not resolved and was progressively worsening.

On general examination, the patient was alert and in no acute distress. Vital signs were within normal limits with a blood pressure of 122/81mmHg and a heart rate of 80 beats per minute. Physical examination revealed bilateral lower limb oedema extending up to the mid-shin. There was no facial swelling or oedema in other parts of the body. No signs of pleural effusion or ascites were observed. On cardiovascular examination, the apex beat was not displaced with no abnormal heart sounds such as S3, S4 or murmurs, which could be associated with complications of nephrotic syndrome. Respiratory examination was unremarkable. The absence of these additional signs helped further confirm the presence of NS without other systemic manifestations and may help rule out secondary causes such as heart failure, chronic liver disease or autoimmune disease.

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Table I: Investigations to exclude secondary causes of Nephrotic syndrome

Investigation	Result
Sodium	141
Potassium	4.3
Creatinine	103.6 µmol/L
Urea	3.5 mmol/L
eGFR	79 mL/min/1.73m^2
HbA1c	5.7%
HBsAG	Non-reactive
Anti HCV	Non-reactive
HIV Antigen/ Antibody	Non-reactive
TSH/Free T4	3.62 / 10.62
ANA	Positive but speckled 1:100
C3, C4	Negative

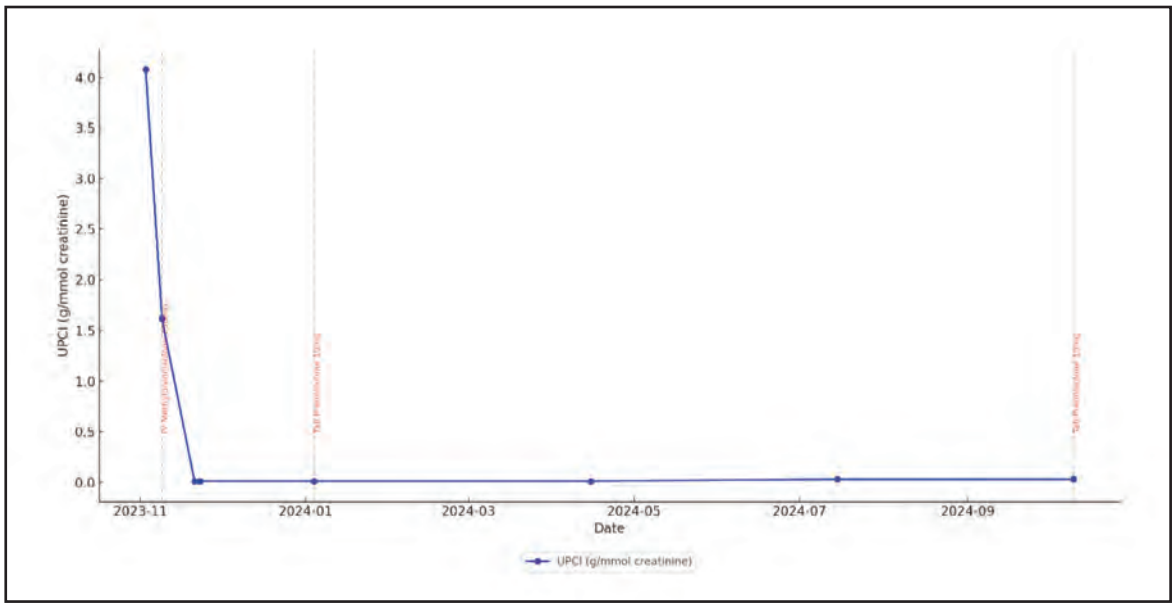

Fig. 1: Proteinuria trend with steroid treatment

Initial laboratory tests revealed proteinuria with a urine dipstick reading of 3+. The patient was also found to have an elevated urine protein-to-creatinine ratio of 4.08g/mmol, which corresponds to a 24-hour urine protein of 40g, hypoalbuminemia with an albumin level of 15g/L, and hyperlipidaemia, with total cholesterol and triglyceride levels of 16.26mmol/L and 7.79mmol/L, respectively. Liver enzymes were within normal range. These findings meet the criteria for NS. Secondary causes such as infections (hepatitis B, hepatitis C, and HIV), diabetes mellitus, thyroid dysfunction and autoimmune conditions like lupus nephritis were excluded through further laboratory testing (Table I).

The patient was initially prescribed tablet frusemide 40mg daily to reduce the oedema and scheduled for follow-up. As he was stable, outpatient management was deemed appropriate while waiting for the investigation results. He was advised to return earlier if symptoms worsened or new ones developed. However, a few days later, the patient returned earlier with worsening bilateral leg swelling now extending to the thighs and accompanied by tenderness. While thrombosis was suspected as a complication, the absence of typical symptoms of deep vein thrombosis (DVT), such as redness, warmth or pain on palpation along the veins, made DVT unlikely. This ruled out DVT as the cause and led to an urgent referral to a nephrologist and subsequent hospital admission for further evaluation.

While in the ward, a renal biopsy was performed to establish a diagnosis. The results showed mild mesangial proliferation without sclerotic changes. Immunofluorescence revealed only non-specific IgM staining, with all other markers being negative. A renal biopsy was considered necessary to identify the underlying cause of nephrotic syndrome. All key renal compartments were evaluated, but the possibility of missing FSGS due to sampling limitations was acknowledged. Although the biopsy findings were inconclusive and pointed toward MCD, the findings show the challenges in diagnosing NS, where even a renal biopsy may not fully determine the underlying cause.

The patient was initially treated with intravenous methylprednisolone and was maintained with oral prednisolone. He responded well to the treatment, showing a significant reduction in proteinuria and improving albumin levels with completely resolved oedema. Other treatments

included intravenous frusemide 80 mg once daily for 5 days, tablet simvastatin 40 mg once daily and tablet perindopril 2 mg once daily throughout the admission. The patient was discharged well from the nephrology ward after an 8-day admission, with resolution of lower limb swelling and pain. At discharge, his medications included prednisolone 30 mg once daily, frusemide 40 mg once daily, simvastatin 40 mg at night and perindopril 2 mg once daily. He was also advised to restrict fluid intake to 800 mL per day.

The patient's condition relapsed after a few months, and a repeat biopsy was recommended to confirm the findings. However, the patient declined the biopsy and preferred to continue with corticosteroid therapy, which was increased briefly during the relapse. Currently, the patient is doing well and continues regular follow-up care with both the primary care and nephrology teams (Figure 1).

DISCUSSION

NS has an annual incidence of approximately 3 per 100,000 adults.[1] In non-diabetic adults, primary glomerular diseases such as FSGS, MN and MCD are the prominent causes.[2] Secondary causes include Diabetes mellitus, infections, malignancies and autoimmune disorders, requiring comprehensive evaluation.

NS in non-diabetic adults is a complex condition with notable diagnostic and management challenges for primary care doctors. While specialist care is often needed, primary care doctors are key in early recognition, coordinating care and long-term management. This 44-year-old man case highlights these complexities, from initial suspicion to comprehensive evaluation and collaborative care.

Clinical Challenges in Diagnosis

NS often presents with generalised and subtle symptoms like peripheral oedema and frothy urine, as seen in this case. These symptoms overlap with other conditions frequently encountered in primary care, such as heart failure, liver disease or venous insufficiency. Recognising NS requires a high index of suspicion, especially in patients presenting with unexplained oedema and proteinuria. Early urinalysis and serum albumin tests help detect NS. In this case, 3+ proteinuria on dipstick, low albumin (15g/L) and high cholesterol (16.26mmol/L) were all suggestive of NS. These tests, readily available in primary care allow primary care doctors to initiate timely referrals for specialised care.[6]

While laboratory tests can suggest NS, they cannot identify the underlying cause. Renal biopsy remains the gold standard for diagnosis, as demonstrated in this case.[1,3,5] Renal biopsy is generally indicated in adults with NS as it plays a crucial role in differentiating between primary and secondary causes of NS and helps guide treatment decisions.[3,5,6] The benefits of early biopsy include better risk stratification, specific therapies and improved outcomes through early intervention. However, it is important to note that renal biopsy may not be easily accessible in all district settings in Malaysia, where limited resources and specialised personnel can delay diagnosis and treatment.[7]

Biopsy findings can be inconclusive, as FSGS may not be apparent in cases where the lesion is focal, requiring a much larger biopsy sample. When the biopsy is not definitive, the clinicians need to correlate histological results with clinical and laboratory data in order to ascertain the likely cause of the disease and its course of treatment.

Based on the biopsy findings showing mild mesangial proliferation without sclerotic changes, non-specific IgM staining on immunofluorescence and the excellent response to corticosteroid therapy, the most likely underlying cause in this patient is MCD. IgA nephropathy and membranous nephropathy was less likely due to the absence of immune complex deposits, and although FSGS can be missed on biopsy, the clinical presentation and response to treatment further support MCD as the probable diagnosis in this case.

Clinical Challenges in Management

The management of NS begins in primary care as they play an important role in managing care with symptom control and referral to nephrologist.6 In this case, diuretic therapy with frusemide was appropriately started to manage oedema. Primary care doctors should also address cardiovascular risk factors, considering the hyperlipidaemia and hypercoagulability linked to NS8. Patients with NS are also at higher risk of thromboembolic events, infections and progression to chronic kidney disease (CKD),[3,8,9] of which this patient did not suffer from these complications.

Long-term management focuses on maintaining remission, preventing relapses and managing complications. This includes using additional medications like ACE inhibitors or ARBs to reduce proteinuria, diuretics for oedema and statins to manage hyperlipidemia.[3] Monitoring kidney function and protein levels is essential, along with addressing side effects of steroids such as osteoporosis and weight gain. Regular follow-ups are important to monitor patients' condition, adjust treatment and prevent disease progression.

The cornerstone of NS treatment is immunosuppressive therapy, primarily corticosteroids.[3] In this case, the patient received methylprednisolone followed by oral prednisolone, demonstrating a standard therapeutic approach, with the patient initially responded well. However, the patient later experienced a relapse and declined a second biopsy. In this context, a prudent approach would involve reinitiating corticosteroids to achieve remission. Subsequently, introducing a steroid-sparing agent and calcineurin inhibitor like cyclosporin could be considered to maintain remission and prevent further relapses.[3]

The unpredictable course of NS requires an individualised treatment plan. Although this patient responded well to corticosteroids, some patients progress to CKD or end-stage renal disease. Primary care is essential for ongoing care, managing comorbidities, encouraging lifestyle changes and

supporting the patient's psychological health. Primary care doctors should educate patients on medication adherence, dietary changes (like low-sodium and protein-adjusted diets) and the need for regular follow-up.[1,3] These measures not only enhance clinical outcomes but also encourage patients to take an active role in their own care.

CONCLUSION

This case highlights the crucial role of primary care doctors in recognising and managing nephrotic syndrome (NS) in non-diabetic adults. It underscores the challenges posed by nonspecific symptoms and the importance of renal biopsy to establish a diagnosis. In situations where biopsy findings are inconclusive, clinicians should integrate clinical findings, laboratory data and imaging to guide treatment. Empirical treatment with close monitoring may be considered when clinical suspicion is high. Multidisciplinary collaboration is key to optimising outcomes, especially when access to specialised care is limited. This case also emphasises the need for structured referral systems between primary care and the nephrology team to ensure effective follow-up to support long-term management and reduce complications in patients with NS.

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DECLARATION

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