BMJ Case Reports

TITLE OF CASE

NELL-1 positive membranous nephropathy in association with anti-synthetase syndrome

SUMMARY

Membranous nephropathy (MN) is an important cause of nephrotic syndrome and is associated with significant adverse health outcomes including progression to end-stage kidney disease, complications relating to volume overload, and increased risk of venous thromboembolism. Primary MN is frequently linked to antibodies against the phospholipase A2 receptor (PLA2R), although a broader range of target autoantigens are emerging. We report a case of a man in his mid 60s who had been recently diagnosed with anti-synthetase syndrome presenting with nephrotic syndrome. A kidney biopsy revealed findings in keeping with MN, including positive immunohistochemical staining for the NELL-1 autoantigen. This report highlights a possible novel association between anti-synthetase syndrome and NELL-1 positive MN.

BACKGROUND

Membranous nephropathy (MN) is a rare kidney disorder with a prevalence of around 199 per million in the United Kingdom[1,2]. In MN, the glomerular basement membrane thickens and loses its integrity, permitting protein leakage from the blood into the filtrate[3,4]. The disease process is variable, with individuals presenting either with advanced kidney impairment, oedema or thrombotic events, or more indolently with unnoticed proteinuria, increased susceptibility to infections, and associated slowly deteriorating renal function[5]. Up to one third of people may progress to end-stage kidney disease by a median of five years from diagnosis[6].

There are two recognised forms of the disease: primary and secondary MN. Primary disease, accounting for 75% of cases, is due to an idiopathic immune-mediated process[3–5]. An antibody against the phospholipase A2 receptor (PLA2R) is often implicated[7], although a broader range of target autoantigens have more recently been discovered. These include neural epidermal growth factor-like 1 protein (NELL-1)[2–4], anti-thrombospondin type-1 domain-containing 7A (THSD7A), protocadherin 7 (PCDH7), neural endopeptidase, and exostosin antigens[2–4,8,9]. Less commonly, MN occurs secondary to an underlying medical condition including infection, malignancy, medications and autoimmune disease[6,10,11], making the diagnosis of MN and unearthing of possible associated morbidities important.

We present a novel case of MN with a possible link to previously undiagnosed anti-synthetase syndrome, demonstrating NELL-1 positive immunohistochemical staining on kidney biopsy.

CASE PRESENTATION

A White male in his mid 60s presented with a four-month history of progressive leg oedema, dry cough and shortness of breath. There had been no improvement in symptoms with oral diuretics

(furosemide) or inhaler therapy (budesonide/formoterol and terbutaline). He had a background of atrial fibrillation, hypertension, and interstitial lung disease (ILD) diagnosed 8 months earlier following a prolonged intensive care admission with hypoxia when he was discharged with domiciliary oxygen. He had never smoked. He reported a family history of maternal rheumatoid arthritis. On examination he was markedly salt and water overloaded with pitting oedema to his chest wall. Cardiac, respiratory and abdominal examinations were unremarkable. Blood pressure was 166/73mmHg and urinalysis showed 3+ protein, 3+ blood and was negative for nitrites and leucocytes.

INVESTIGATIONS *If relevant*

Serum creatinine was 144 micromoles/litre (eGFR 42ml/min/1.73m^2), with nephrotic range proteinuria (urine protein:creatinine ratio 1355 milligrams/millimole) and a serum albumin of 26 grams/litre. Selected other blood tests are given in **Table 1**.

Marker	Value	Reference	Units
Haemoglobin	138	130-170	grams/litre
Platelets	342	150-400	x10^9/litre
White blood cells	12.7	4-11	x10^9/litre
Albumin	**26**	35-50	grams/litre
Sodium	144	135-145	millimoles/litre
Potassium	3.8	3.5-5.3	millimoles/litre
Creatinine	**144**	60-120	micromoles/litre
eGFR	**42**	90-120	millilitres/minute/1.73m^2

Table 1 – Initial blood results on presentation. Abnormal results are bolded.

Computed tomography of his chest abdomen and pelvis revealed two structurally normal kidneys, and no suspicious masses, thickening or lymphadenopathy to suggest solid organ malignancy. Lung fields demonstrated radiographic features in keeping with his known ILD.

An immunological renal screen was positive for anti-nuclear antibodies and anti-extractable nuclear antigen antibodies. Anti-PLA2R antibodies were not detected. Anti-Ro (RO-52) and anti-PL-7 antibodies were present at high titres. C3/C4 complement levels were normal.

A subsequent kidney biopsy showed thickened glomerular capillary walls under light microscopy, in keeping with MN. Immunohistochemical staining revealed IgG4, IgG and C1q positivity, with evidence of NELL-1 glomerular deposits (**Figure 1**).

DIFFERENTIAL DIAGNOSIS *If relevant*

The differential diagnosis for nephrotic syndrome is wide, and includes diabetic nephropathy, podocytopathies (minimal change disease and focal segmental glomerulosclerosis), MN, amyloidosis (AA or AL), or mesangiocapillary glomerulonephritis. A kidney biopsy is often required to establish the underlying cause, except for people with diabetes with clearly established microvascular complications and progressive proteinuria without another obvious cause.

The kidney biopsy findings were in keeping with MN. Strong granular staining for IgG4 along the glomerular basement membrane was suggestive of primary MN, and NELL-1 positivity confirmed this as the target antigen. The concomitant anti-synthetase syndrome and C1q positivity raised suspicion of secondary MN, particularly as NELL-1 is associated with other autoimmune conditions[12]. Anti-PL-7 antibodies are found in the anti-synthetase syndrome, a condition

commonly characterised by ILD. Myositis and arthritis, although not present in this case, are also common features.

Anti-Ro positivity is associated with inflammatory myositis, particularly in association with ILD[13,14]. It is also found with Sjogren's syndrome and systemic lupus erythematosus, although there was no clinical evidence of these conditions. Systemic lupus erythematosus can cause a secondary MN, but this is less likely in the absence of 'full house' immunohistochemical staining.

TREATMENT *If relevant*

Treatment for primary MN depends on the risk of progression to end stage kidney disease. Individuals who are felt to be low-risk for progression (preserved excretory kidney function and subnephrotic proteinuria) can be managed conservatively with renin-angiotensin-aldosterone axis inhibition, blood pressure control (aiming for <130/80mmHg) and hyperlipidaemia management. Rituximab – a B-cell depleting monoclonal antibody – or calcineurin inhibition are considered for those who exhibit less than a 50% reduction in proteinuria at 6 months, or in those with an estimated GFR of <60ml/min/1.73m^2 or proteinuria equivalent >8g/day after 6 months of conservative management.

In this case, conservative management using ramipril and SGLT2 inhibition with dapagliflozin were initiated to reduce proteinuria and offer long-term nephroprotection. However, proteinuria remained static at 1600mg/ml and eGFR at 45ml/min/1.73m^2. Consequently, two doses of rituximab were administered to reduce the production of autoantibodies against the NELL-1 antigen.

OUTCOME AND FOLLOW-UP

After 12 months from presentation, his peripheral oedema has resolved and serum creatinine has stabilised at around 150 micromoles/litre (**Figure 2**). Following rituximab infusion, there has been a significant steady reduction in the protein:creatinine ratio (**Figure 3**), and normalisation of serum albumin (38 g/L, from a nadir on 23 g/L in June 2024).

DISCUSSION *Include a very brief review of similar published cases*

This case offers two areas for consideration:

- The possible association between anti-synthetase syndrome and MN
- The presence of NELL-1 positivity in MN.

The significance of NELL-1 positivity in membranous nephropathy

Recent advances have allowed the identification of several antigen targets in addition to PLA2R in primary MN[4,15,16]. Many of these antigens are also found in secondary MN (**Table 2)**. NELL-1 was first described in 2020[16], and is the second most prevalent antigen after PLA2R[12]. It is also associated with cancer in secondary MN, with up to 33% of positive cases having concomitant malignancy[17].

Antigen	Associated secondary conditions
PLA2R	Malignancy; sarcoidosis; hepatitis B; schistosomiasis [18–21]
THSD7A	Malignancy [10]
NELL-1	Malignancy; lipoic acid use; autoimmune conditions; mercury toxicity [12,17,22–24]
NDNF	Syphilis; lung malignancy [25]

PCSK 6	Non-steroidal anti-inflammatory reactions [26]
Exostosin 1 and 2	Systemic lupus erythematous; mixed connective tissue disease [15,24]
NCAM-1	Systemic lupus erythematous (lupus nephritis) [17]
PCDH7	Sjögren's syndrome; sarcoidosis [9]

Table 2 A summary of commonly isolated antigens in membranous nephropathy and associated conditions.

Autoimmune conditions are associated with a range of antigens found in MN. Whilst NELL-1 has been described in Sjögren's disease, rheumatoid arthritis, and cutaneous lupus[12,24], it has not yet been linked with anti-synthetase syndrome.

Renal manifestations of anti-synthetase syndrome

Anti-synthetase syndrome is a rare condition affecting fewer than 50,000 people in the United States; the prevalence in other countries is uncertain[27,28]. It falls within the umbrella of idiopathic inflammatory myopathies, although its clinical presentation is often multisystemic, including development of ILD, inflammatory arthritis, dermatitis, and Raynaud's phenomenon[28]. The mean age of onset is 48 years[29]. The pathogenesis involves anti-synthetase antibodies directed against aminoacyl-tRNA synthetases. These are enzymes involved with protein synthesis, fibroblast and immune regulation, and tumour suppression[28,30]. Almost all (90-100%) of those with autoantibody positivity have interstitial lung involvement,[31] with the presence of anti-Ro52 and anti-PL-7 antibodies indicating a higher likelihood of isolated ILD presentations with absent or more mild myositis symptoms than those with anti-Jo-1 antibodies[13,14,32–34].

Very few reports of renal involvement with anti-synthetase syndrome exist. MN has been described in one case, but the associated antigen was unclear[35]. A scleroderma-like renal crisis in anti-PL-7 positive anti-synthetase syndrome has also been reported[36]. All other described renal manifestations were IgA-related nephropathy[35]. Hence, our case seems to be the first described example of NELL-1 positive MN associated with anti-PL-7 and Ro-52 positive anti-synthetase syndrome.

In conclusion, understandings of the antigens associated with MN is improving year-on-year[2]. Whilst only one case has linked an anti-synthetase syndrome to MN, we are the first, to our knowledge, to describe a possible association with NELL-1 as a specific antigen marker. The link may be coincidental, but given the temporality in presentation, together with NELL-1-positivity occurring in various autoimmune conditions, a possible association is prudent to consider. Practically, NELL-1 positivity might prompt deeper investigation to exclude secondary conditions, namely malignancy and autoimmune disease. Those with anti-synthetase syndrome should at least have a urine dip or urine protein:creatinine quantification to exclude underlying glomerular disease.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- NELL-1 positivity is typically associated with primary forms of MN, or malignancy-associated secondary MN.
- We describe a possible association between anti-synthetase syndrome and MN with NELL-1 positivity.
- The pathophysiological link between anti-synthetase syndrome and NELL-1 positive MN warrants further research.
- NELL-1 positivity in MN should prompt investigation for both malignancy and inflammatory myositis.

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FIGURE/VIDEO CAPTIONS

Figure 1 – Renal biopsy tissue (a) Glomerulus stained with haematoxylin and eosin examined under light microscopy exhibiting thickened, ‘stiff’ capillary walls. (b) Immunohistochemistry showing strong granular staining along the glomerular basement membrane with IgG4, which also stains some tubular basement membranes. (c) Immunohistochemistry showing glomerular deposits positive for NELL-1. (d) Electron microscopy showing abundant electron-dense subepithelial deposits along the glomerular basement membrane with occasional intervening basement membrane spikes, and diffuse foot process effacement.

Figure 2 – Serum creatinine trend**.**

Figure 3 – Urinary protein:creatinine ratio trend.

PATIENT'S PERSPECTIVE

Connective tissue disease, ILD, and nephritis can lead to fatigue in their own right, but together the effects seem to be synergistic. It is not easy to treat, requires adaption to a daily routine and its resolution depends on the success or otherwise of treatment, which in my case is currently not known or limited. Fatigue is very illustrative of my thoughts and concerns. I literally fall asleep without warning and at odd times of the day. I have no control over these events and would rather spend time awake. I also know that my increasing drowsiness may indicate that my ILD has worsened and that it is significant to me.

Fatigue can also be caused through medication. I slept for fourteen hours the day after the rituximab infusion was administered. My wife and I often joke that our medication cupboard is like a pharmacy. Previous experience has taught me that organisation is important in dealing with treatment. I've designed a template to ensure the care and treatment administered is consistent and correct. That said, it is quite possible that the combination of medication is in fact aiding the fatigue.

Is fatigue a disability? It is certainly a handicap. I used to do activities long into the evening but that is not possible now. People often relate to visible disabilities but a person feeling fatigued is not always obvious to the observer. It is also not always clear to me how much importance the Welfare services apply to such symptoms. However, to someone who has written all their life, a lack of concentration through fatigue can be very disabling.

So, dealing with severe illness is always about life expectancy and the quality of life. It is, also, about reducing those problems which to the patient seem bigger than they might to other

individuals and society at large. Sleep is important, but I am tired of feeling fatigued and I am hoping that future events will eventually help me stay awake!

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