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VASCULAR THREADS AND NEPHRON NESTS: EXPLORING THE ASSOCIATION BETWEEN TAKAYASU ARTERITIS AND MEMBRANOUS NEPHROPATHY

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ABSTRACT

Takayasu arteritis (TA) primarily causes ischaemic nephrosclerosis but can occasionally be associated with glomerulopathy. We report a case of a female in her twenties with PLA2-negative, THSD7A-positive membranous nephropathy (MN) refractory to rituximab, who presented with neck pain and new-onset hypertension. Blood work showed elevated inflammatory markers. Imaging of the head and neck revealed focal dilation and irregularity of the vertebral arteries, consistent with TA. The patient was started on treatment with steroids, followed by mycophenolate mofetil, which led to the resolution of symptoms and nephrotic syndrome. This case highlights an uncommon sequence of events, with MN presenting before TA, underscoring the need to consider TA in differentials for patients with MN. Notably, this is the first reported case in a young female, emphasising the need for further understanding of TA-associated glomerular diseases. Additionally, the presence of THSD7A in MN, despite negative malignancy workup, is also noteworthy.

KEYWORDS

Nephrotic syndrome, proteinuria, vasculitis, Takayasu arteritis, renal biopsy

LEARNING POINTS

- Membranous nephropathy (MN) and Takayasu arteritis (TA) have distinct clinical presentations; therefore, diagnosing coexisting MN and TA is challenging, which may lead to delayed diagnoses.
- A multidisciplinary approach with tailored treatments is essential for prompt diagnosis and optimal management.
- Comprehensive follow-up studies are vital to understand the pathogenesis of this rare amalgamation, refine targeted treatment strategies and potentially improve overall prognosis.

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INTRODUCTION

Takayasu arteritis (TA) is an autoimmune disease characterised by granulomatous inflammation affecting the aorta and its branches[1]. This rare form of large-vessel vasculitis can lead to segmental stenosis, occlusion or dilation of the vessels, resulting in multiple organs being affected[2].Renal complications in TA are primarily attributed to ischaemic injury, with primary glomerular disease being uncommon[3]. Glomerulopathies associated with TA usually include membranoproliferative glomerulosclerosis, IgA nephropathy, focal segmental glomerulosclerosis and crescentic glomerulonephritis[4]. Notably, membranous nephropathy (MN) is rarely associated with TA[5]. This case report discusses the exceptionally rare occurrence of MN in the setting of undiagnosed TA.

CASE DESCRIPTION

A female patient in her twenties with mild intermittent asthma was found to have significant proteinuria during her routine annual examination. The patient was subsequently referred to nephrology for further evaluation. She reported occasional joint pains but denied any hair loss, rash, mouth ulcers, morning stiffness, joint inflammation, lower extremity swelling or any respiratory, abdominal or urinary problems. The patient denied any history of childhood diseases, intravenous drug use, pregnancy, miscarriages, blood clots, or chronic use of non-steroidal anti-inflammatory drugs or herbal medicines. Family history was unremarkable, except for lupus in her maternal aunt.

The initial workup revealed elevated creatinine at 1.15 mg/dl (baseline 0.7 mg/dl), a glomerular filtration rate of 59 ml/min and 3+ proteinuria on urinalysis, without microscopic haematuria. The patient's 24-hour urine protein was elevated at 5 g/day and her urine albumin creatinine ratio was 4,960 mg/g. The antinuclear antibody (ANA) level was 1:40 (low titre), complement C3 level was 80 mg/dl (normal 65–135) and C4 level was 22 mg/dl (normal 13–35). Further tests were unremarkable, including antineutrophil cytoplasmic antibodies, anti-dsDNA, rheumatoid factor, lupus panel, human leukocyte antigen B27, sacroiliac imaging and infectious disease screenings. The monoclonal workup – including free light-chain ratio – and serum and urine protein electrophoresis were also negative. For further evaluation a CT-guided renal biopsy was performed, which showed MN, 30% global glomerulosclerosis, but no interstitial fibrosis and tubular atrophy (IF/TA). Electron microscopy confirmed MN with multiple sub-epithelial immune deposits with partial resorption, basement membrane thickening and overlying epithelial foot process effacement. Immunofluorescence was weakly positive for IgG, C3 and kappa. The patient was also negative for thrombospondin type 1 domain-containing 7A (THSD7A), anti-phospholipase A2 receptor (anti-PLA2R) and exostosin (EXT-2).

Despite the patient being on the maximum tolerated dose of losartan, she had persistent nephrotic range proteinuria that prompted administration of rituximab. Her proteinuria

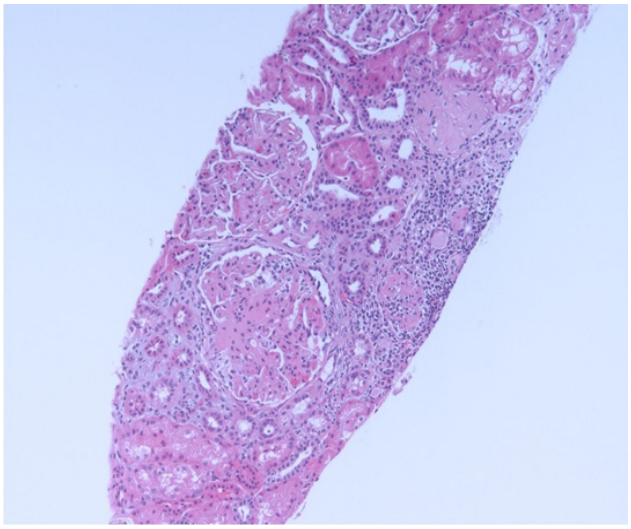

Figure 1. Renal biopsy (10×) showing sclerotic glomeruli with thickened mesangium, tubular atrophy and interstitial inflammation. This biopsy was performed after being treated with rituximab for persistent proteinuria.

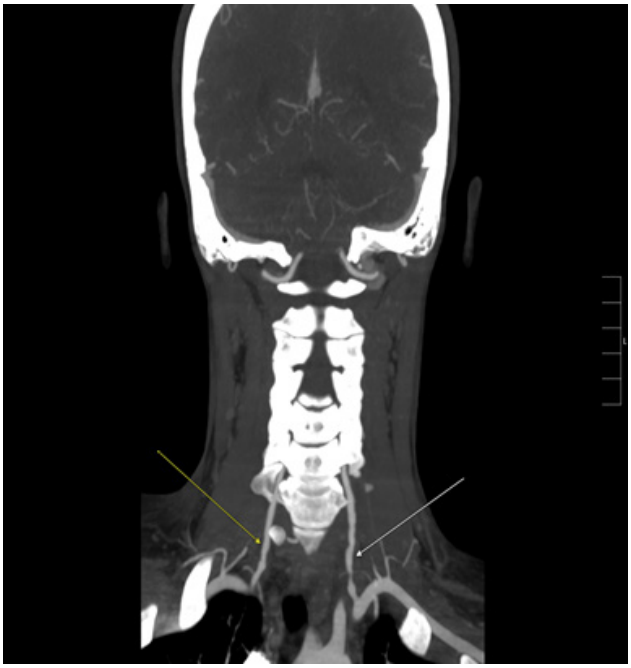

Figure 2. CT angiogram of the head and neck, showing bilateral vertebral artery stenosis (marked with arrows).

persisted, measuring 3.4 g/day in a 24-hour urine sample (less than 25% reduction from baseline). Subsequently, a repeat renal biopsy was performed, which revealed significant changes from the initial biopsy. The findings included MN, diffuse 80% global glomerulosclerosis and severe IF/TA on light microscopy *(Fig. 1)*. Granular deposits for IgG, C3 and kappa were observed via immunofluorescence, but the biopsy was negative for anti-PLA2R, Sema3, NELL-1 and EXT2. However, THSD7A was positive in the glomeruli. There was no non-sclerosed glomerulus present on electron microscopy.

Given the association of THSD7A positivity with malignancy, an extensive neoplastic workup was conducted, yielding unremarkable results. In the setting of severe IF/TA and

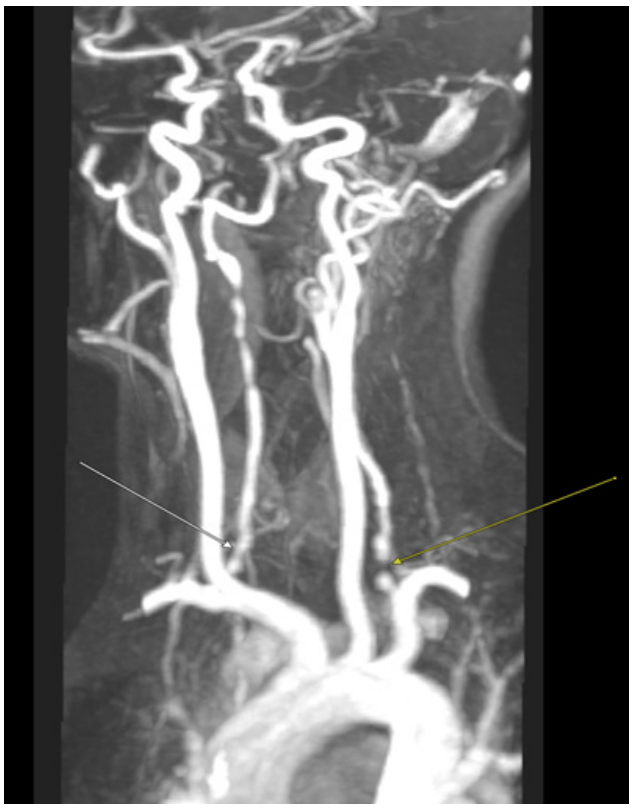

Figure 3. MRI angiogram of the head and neck demonstrating bilateral proximal vertebral multifocal stenosis (marked with arrows).

diffuse glomerulosclerosis, further immunosuppression was held and conservative management with losartan and dapagliflozin was continued with ongoing monitoring of proteinuria.

A few months later, the patient presented to the emergency department with uncontrolled hypertension and severe left-sided neck pain, accompanied by photophobia and nausea. Upon admission, she was afebrile and had a blood pressure of 190/104 mmHg, sinus tachycardia with a heart rate of 115 beats per minute and a respiratory rate of 21 breaths per minute. Physical examination revealed no visible rash. The cardiovascular, lung and abdominal examination was unremarkable. Neck auscultation revealed no vascular bruit, and the neurological exam was also unremarkable. Peripheral pulses were palpable, and there was no lower extremity oedema.

Laboratory workup showed a white blood cell count of 12,210/µl, haemoglobin 11.9 g/dl, platelets 300,000/µl, blood urea nitrogen 9 mg/dl, creatinine 0.84 mg/dl, total protein 5.9 g/dl, albumin 3 g/dl. The erythrocyte sedimentation rate was 61 mm/h, C-reactive protein 5 mg/dl (normal 0–0.25), C3 107 mg/dl, C4 32.2 mg/dl and ANA level of 1:80 (low titre). A CT angiogram of the head and neck revealed focal dilation of the right vertebral artery at the C2 transverse foramen, irregularity of both vertebral arteries beginning at the origin and surrounding soft tissue swelling. This suggested possible TA or fibromuscular dysplasia *(Fig. 2)*.

A renal ultrasound was performed, which showed no evidence of fibromuscular dysplasia or renal artery stenosis. Additionally, an MRI of the patient's brain without contrast was normal. However, an MRI angiogram of the head and neck with and without contrast showed extracranial multifocal stenosis of bilateral vertebral arteries, with severe stenosis along the left vertebral artery V1 segment. These findings were indicative of large-vessel vasculitis *(Fig. 3)*.

Extended evaluation for vasculitis, encompassing CT scans of the chest, abdomen and pelvis, yielded unremarkable results. IgG levels were low at 622 mg/dl. The patient was started on treatment with intravenous prednisone 60 mg daily during her hospital stay. She was also initially resuscitated with intravenous fluids but did not have any improvement in her kidney function. She had significant improvement in her symptoms following the initiation of steroids. Concurrently, laboratory work indicated an improvement in inflammatory marker levels *(Table 1)*.

The patient continued to remain symptom-free and was discharged home with an oral steroid taper, starting at 60 mg daily, followed by 10 mg/day dose reduction every two weeks, along with trimethoprim/sulfamethoxazole prophylaxis. She developed side effects such as acne, moon-like faeces, weight gain and tremors on high-dose steroids. Therefore, the decision was made to introduce mycophenolate mofetil as a steroid-sparing agent. Subsequent testing for erythrocyte sedimentation rate and C-reactive protein returned normal results. A repeat MR angiography conducted a month later showed the disease was stable. Notably, after six months of treatment following TA diagnosis, the patient experienced an improvement in her proteinuria, with levels decreasing from 3 g/day to 0.8 g/day *(Fig. 4)*. She remained stable with no further relapse or progression of the disease.

	Before admission	Day 0	Day 3	Discharge	Follow-up (2 months)
Creatinine (mg/dl)	1.15	0.84	1.16	0.96	1.11
ESR (mm/hr)	-	61	31	25	8
CRP (mg/l)	-	5	0.9	0.4	< 0.4
C3 (mg/dl)	80.3	107	-	-	-
C4 (mg/dl)	22	32.2	-	-	-
ANA	-	Low titre (1:80)	-	-	-
24-hour urine protein (g/day)	3	-	-	-	1.8

Table 1. Laboratory results performed during the hospitalisation and follow-up.

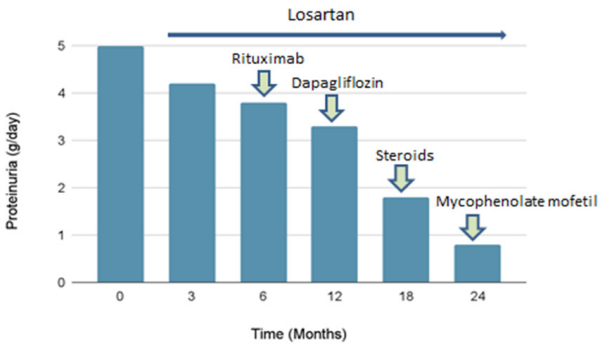

Figure 4. Trend in proteinuria over a two-year period in an adult female with MN, and new diagnosis of TA.

DISCUSSION

TA is a rare inflammatory large-vessel arteritis that predominantly affects the aorta and its branches[1,2], causing autoimmune-mediated inflammation, vascular remodelling and endothelial dysfunction[2,6]. The disease is more prevalent in the Asian population, with an incidence rate of 40 per million in Japan compared to 0.9 per million in USA[7]. TA predominantly affects females[8] and presents with varying symptoms, depending on the disease stage.

Renal involvement in TA is common and can lead to renovascular or glomerular disease[4]. The most common presentation is ischaemic nephropathy from renal artery stenosis and renovascular hypertension[1]. However, in this case both the renal ultrasound and abdominal CT scans performed were negative for renal artery stenosis and renal atrophy. Histologically, collapsed glomeruli are usually seen in the setting of renovascular hypertension and ischaemic injury[3], but they were not observed in this patient's biopsy. Therefore, renovascular involvement was unlikely in this patient.

On the other hand, glomerular involvement in TA is exceptionally rare[3,9], contrasting with the common occurrence of glomerular involvement in small-vessel vasculitis[1]. Nonetheless, there are a few reported cases of glomerulonephropathy in the context of TA. Among these, mesangioproliferative glomerulonephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, necrotising glomerulonephritis and amyloidosis are most frequently documented[3,4]. MN, a primary cause of nephrotic syndrome, is typically idiopathic (80%) or secondary (20%) to infections such as hepatitis or autoimmune diseases such as systemic lupus erythematosus, or malignancy[10]. Idiopathic MN is associated with antibodies against the phospholipase A2 receptors (PLA2R)[4]. In our case, histopathological examination revealed granular deposits for IgG, C3 and kappa via immunofluorescence, while anti-PLA2R was negative, indicating that the patient likely developed secondary MN.

We performed a thorough evaluation, including extensive clinical and laboratory investigations to investigate the possibility of an alternative aetiology. The workup was negative for any additional autoimmune or connective tissue disorders, hepatitis, malignancy, amyloidosis or IgG4-related disease. IgG4-related disease can affect the kidneys, leading to tubulointerstitial nephritis or MN[11]. Our patient's clinical presentation, histopathological findings and laboratory results showed no evidence aligning with typical features of IgG4-related disease. Specifically, the patient exhibited low IgG levels, and the biopsy showed no signs of lymphoplasmacytic infiltration, fibrosis or increased IgG4-positive plasma cells. Imaging studies also did not reveal characteristic findings such as diffuse enlargement, renal cortical hypodensities or atrophy indicative of long-standing IgG4-related disease[11].

Both TA and MN are believed to stem from autoimmune processes. TA involves immune-mediated inflammation of vessels, leading to endothelial dysfunction and vascular remodelling, possibly influenced by genetic and immune factors such as HLA class I and II, immune response regulators and proinflammatory cytokines[6]. Similarly, MN arises from autoimmune dysregulation, resulting in the formation of immune complexes and subsequent glomerular damage[10]. Several potential biological mechanisms may link TA and MN. Immune complexes formed during TA could deposit in-kidney glomeruli, causing MN. Endothelial dysfunction in TA might extend to the renal vasculature, altering glomerular permeability and causing proteinuria seen in MN[6]. Shared autoimmune mechanisms could also play a role, with abnormal immune responses targeting self-antigens, causing vascular inflammation in TA and subsequent glomerular damage. Dysregulated cytokine production in TA may contribute to glomerular injury and proteinuria in MN. Evidence suggests that immunosuppressive agents targeting TA inflammation can improve MN, indicating a shared biological pathway[4,5]. Certainly, this report aligns with the current understanding of TA and MN, suggesting a continuum of the disease processes between the two conditions. Despite these potential links, the exact mechanism remains unclear, necessitating further comprehensive studies.

Among the limited cases documenting the co-occurrence of MN and TA a notable trend emerges, particularly within the Asian population, notably Japanese individuals aged 40 and above[4,5]. Upon conducting a thorough literature review and comparing our case with other reported instances, a consistent pattern of presentation is evident. In each case, patients presented with proteinuria alongside MN, coupled with vascular manifestations such as bruits, claudication or uncontrolled hypertension in the context of TA[4,5,12,13]. This consistent pattern observed across these cases, including ours, underscores the robust association between TA and MN. Remarkably, in all cases an improvement in renal function following the initiation of treatment for TA was noted.

This case report presents a compelling narrative of the patient's journey from an initial diagnosis of MN to the subsequent discovery of TA. Despite receiving treatment solely for MN, there was no improvement in the patient's proteinuria, suggesting the presence of undiagnosed TA prior to its identification. However, upon commencement of

treatment specifically targeting TA a clear timeline emerged, showcasing improvements in both vascular inflammation and glomerular disease. This sequential response to treatment underscores the temporal relationship between the two conditions, suggesting a significant interplay.

Lastly, the patient's renal biopsy also showed positive THSD7A expression, despite the absence of malignancy. THSD7A has emerged as a significant autoantigen in MN and is associated with an increased susceptibility to malignancies, suggesting a potential role in oncogenesis. The prevalence of malignancies in THSD7A-positive MN patients ranges from 6% to 25%[14]. A recent multicentre study found that 20% of MN patients with THSD7A positivity developed malignancies after MN diagnosis[15]. Therefore, monitoring THSD7A expression in MN patients is crucial for early detection and management of associated malignancies. This is the first reported case in a young patient with TA and MN and positive THSD7A in the absence of any malignancy.

CONCLUSION

The histopathological findings, clinical consistency and biological plausibility collectively underscore the specificity of the association between TA and MN in this case. Additionally, this case highlights the intricate interplay between MN and TA, shedding light on the diagnostic challenges, therapeutic considerations and shared pathogenic mechanisms. This novel association, particularly in a young female patient, further expands the understanding of this rare entity beyond the typical age and demographic profile observed in previous cases.

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