Membranous Nephropathy Preceding Systemic Sclerosis: An Unusual Presentation of Systemic Sclerosis sine Scleroderma

Case Reports

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ABSTRACT

Background. Membranous nephropathy (MN) is generally primary, but it can also occur as a secondary form in association with infections, neoplasms or autoimmune diseases. Systemic Sclerosis (SSc), especially in its sine scleroderma forms or in its early stages, rarely manifests itself as MN.

Case report. A 60-year-old woman with onset of nephrotic syndrome and histological picture of MN, in the absence of systemic manifestations. The patient subsequently developed episodes of acute renal failure, recurrent proteinuria and clinical-serological signs suggestive of autoimmune connective tissue disease, including increasing ANA titre with anticentromere pattern and onset of Raynaud's phenomenon. The second renal biopsy showed an evolving picture with extensive interstitial fibrosis and severe arteriosclerosis, consistent with a secondary form of MN. The patient was treated with the Ponticelli regimen and subsequently with rituximab, achieving significant clinical remission. In light of the capillaroscopy and autoantibody profile, a diagnosis of very early systemic SSc (sine scleroderma) was made.

Discussion. This case highlights how MN can represent an early and atypical manifestation of SSc sine scleroderma, preceding systemic manifestations by years. The negative anti-PLA2R test, the presence of antinuclear autoantibodies and rapid histological progression pointed towards a secondary autoimmune aetiology. Repeated renal biopsy and immunological monitoring proved to be key tools for diagnosis and therapeutic management.

Conclusion. MN secondary to SSc sine scleroderma is a rare but important condition that requires attention and a multidisciplinary approach. Early classification as a secondary form allows for targeted therapy and potentially prevents progression to end-stage renal failure.

KEYWORDS: membranous nephropathy, systemic sclerosis, scleroderma

Introduction

Membranous nephropathy (MN) is considered an autoimmune glomerulonephritis. It is classified as idiopathic or primary in most cases, but it can also occur as a secondary form associated with infections, neoplasms, drugs or autoimmune diseases [1]. Systemic Sclerosis (SSc), particularly in its sine scleroderma variant or in its very early stages, is rarely associated with MN. Typical renal manifestations of scleroderma include scleroderma renal crisis (SRC), characterised by malignant hypertension, rapid reduction in glomerular filtration rate and typical vasculitic lesions such as fibrinoid necrosis of interlobular arterioles and arcuate arteries. Proliferative glomerulonephritis can occur in patients with SSc, especially in overlap forms with systemic lupus erythematosus (SLE), with histological features ranging from mesangial glomerulonephritis to diffuse proliferative forms, sometimes with immune complex deposition. In such contexts, renal biopsy plays a central role in distinguishing atypical CRS from immune-mediated glomerulonephritis potentially susceptible to immunosuppressive therapy [2]. More rarely, cases of rapidly progressive glomerulonephritis (RPGN) with crescents have been reported, in some cases associated with autoantibodies (ANCA), and forms of focal segmental glomerulosclerosis (FSGS) that may present with nephrotic syndrome [3]. An exceptional but documented entity is MN secondary to scleroderma, which typically manifests with nephrotic syndrome and an atypical course compared to primary MN. Several reviews have highlighted that, beyond scleroderma renal crisis, a spectrum of glomerular diseases may occur in systemic sclerosis, including proliferative glomerulonephritis and, rarely, membranous nephropathy [2]. In some cases described, MN was the first renal manifestation of SSc sine scleroderma or very early scleroderma, preceding the appearance of the cutaneous and systemic features of the rheumatic disease by years. The negativity of anti-PLA2R antibodies, the presence of anti-nuclear autoantibodies (ANA, in particular anti-centromere) and signs of chronic vasculopathy support a secondary aetiology in these patients [4]. Only sporadic clinical cases have been reported in the literature in which MN represents the first or only renal manifestation in patients with scleroderma or overlap connective tissue syndromes. In some cases, the diagnosis of MN preceded that of the rheumatic disease, similar to what was observed in our patient. This atypical presentation can delay clinical classification and the correct therapeutic approach [5]. The presence of antinuclear antibody tests with anti-centromere antibodies (ANA) with extractable nuclear antigen tests (ENA) and Raynaud's phenomenon may be early signs of an underlying autoimmune disease. The negativity of anti-PLA2R antibodies in these patients supports the secondary origin of nephropathy, as does the association with signs of chronic vasculopathy and severe proteinuria [6]. Systemic scleroderma (SSc) is characterised by a wide spectrum of renal complications, including scleroderma renal crisis (SRC), proliferative glomerulonephritis, overlap nephropathy with systemic lupus erythematosus (SLE) and, more rarely, nephrotic syndromes. In a Thai cohort of 26 patients with SSc who underwent renal biopsy, 19% had nephrotic syndrome, with a histological diagnosis of class V lupus nephritis. In contrast, isolated membranous nephropathy was not formally reported, while the most common presentation was rapidly progressive glomerulonephritis (RPGN) (53.9%) [7]. Proteinuria in the nephrotic range is a rare indication in SSc not associated with SLE and often requires biopsy to rule out secondary glomerular forms. The definitive diagnosis is based on the correlation between clinical, serological and histopathological data, given that the clinical presentation may not be typical: in some patients with SRC, for example, nephrotic range proteinuria and normal blood pressure have been found, which are atypical manifestations compared to the classic picture [8]. Renal biopsy is essential in cases of SSc with significant proteinuria or active urinary sediment, even in the absence of obvious signs of CRS, to identify treatable forms of glomerulonephritis, such as MN or lupus nephritis [9]. Secondary membranous nephropathy can, albeit rarely, be a renal manifestation of SSc. This association seems to emerge mainly in very early forms or in sine scleroderma variants, in which renal disease precedes the onset of the systemic and

cutaneous manifestations typical of the rheumatic disease [10]. This case adds to the scarce reports of membranous nephropathy as an early manifestation of systemic sclerosis, providing long-term follow-up with sequential biopsies and evolving serological and capillaroscopic evidence.

Case report

A 60-year-old woman with proteinuria (4 g/day) at baseline, normal renal function and arterial hypertension. The immunological profile showed positive ANA with a titre of 1:320 and an anticentromere pattern. The first renal biopsy was performed (Figure 1), showing a histological picture compatible with membranous nephropathy (stage I-II), with no glomeruli evaluable by immunofluorescence. Screening for a neoplastic aetiology was performed, with negative results. Given the low risk of progression, ACE inhibitor therapy (enalapril 20 mg every 12 hours) was initiated.

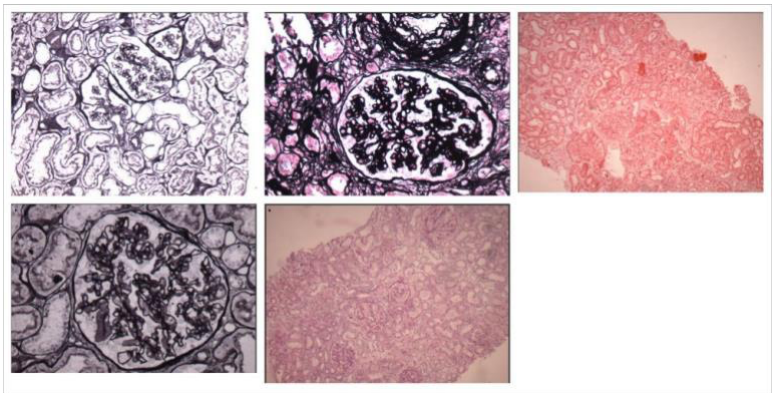

Figure 1. Diffuse thickening of the glomerular basement membrane is observed in the absence of mesangial proliferation. Overall renal architecture is preserved, with no evidence of interstitial fibrosis or tubular atrophy.

Twenty-four months later, episode of hypertensive crisis with PRES (Posterior Reversible Encephalopathy Syndrome), in particular bilateral visual acuity reduction, improved after intravenous nitroglycerin infusion. Kidney injury was found with creatinine rising to 2.3 mg/dl, proteinuria of 6 g/day, ANA positive with a titre of 1:640 with anticentromere pattern. A second renal biopsy was performed (Figure 2 and 3), confirming the picture of MN, with associated interstitial fibrosis in approximately 65% of the parenchyma, tubular atrophy (IFTA) and severe hyaline arteriosclerosis; immunofluorescence showed capillary deposits of IgG (+++), C3 (++) and IgM (+).

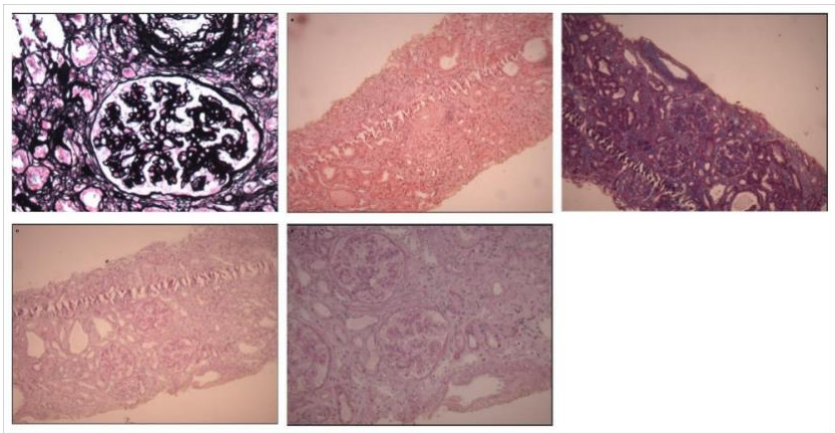

Figure 2. MN with marked progression of chronic damage, characterized by extensive interstitial fibrosis and tubular atrophy, associated with severe arteriolosclerosis.

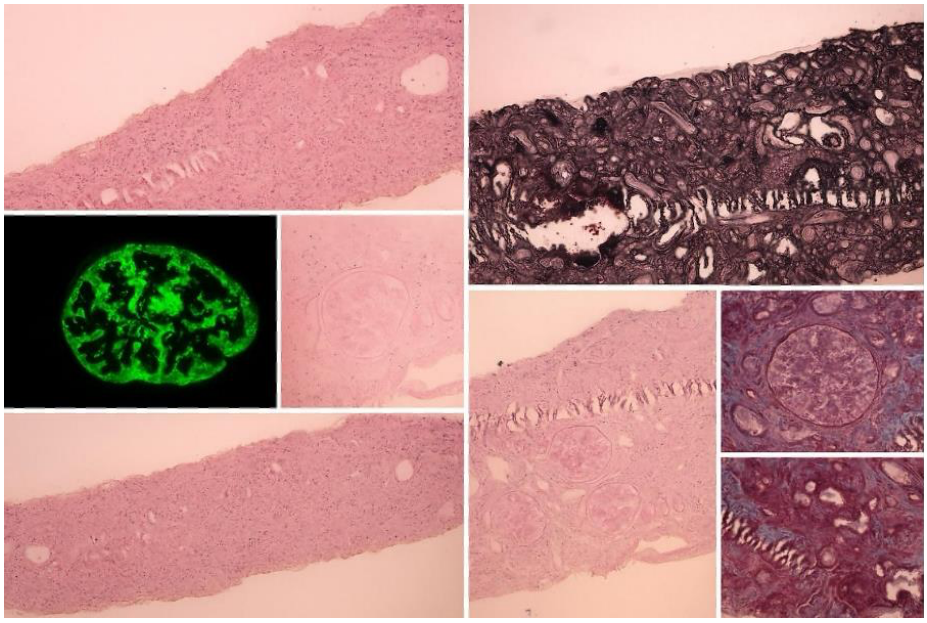

Figure 3. Evidence of advanced chronic damage with extensive interstitial fibrosis, tubular atrophy, and severe arteriolosclerosis. Immunofluorescence shows granular deposits along the glomerular capillary walls

The anti-PLA2R antibody test is negative. Immunosuppressive treatment is started for six months according to the Ponticelli regimen (cyclophosphamide and corticosteroids), achieving complete remission and improvement in renal function with creatinine 1.4 mg/dl, negativisation of proteinuria (0.5 g/day) and good control of blood pressure with enalapril 20 mg every 12 hours. After 48 months, Raynaud's phenomenon appeared in the hands with associated recurrence characterised by proteinuria 5 g/day, creatinine 1.78 mg/dL, albumin 3.7 g/dL. ANA positive with titre 1:5180 with anticentromere pattern and ENA positive with evidence of Scl-70. Rituximab 1 g was started and repeated after 14 days, with complete remission until month 72. At 80 months, the condition was in remission (proteinuria <0.1 g/day, creatinine 1.5 mg/dL). At 96 months, further relapse with the appearance of peripheral oedema, proteinuria 3 g/day, creatinine 1.9 mg/dL and albumin 2.6 g/dL. A rheumatological evaluation is performed, including periungual capillaroscopy, which reveals a typical picture compatible with early-stage scleroderma: presence of megacapillaries and vascular arborisation, without areas of avascularisation, indicative of early microvascular damage. Instrumental screening tests for organ involvement (high-resolution chest CT, spirometry, echocardiogram) are within normal limits. In light of the capillaroscopy findings and the clinical-serological profile, a diagnosis of very early SSc (sine scleroderma) is made. For insurance reasons, the use of rituximab is not authorised, and therapy with cyclophosphamide at a dosage of 2 mg/kg/day for six months is reintroduced. At 108 months of follow-up, the patient presented reduced edema and normotension, stable creatinine (1.9 mg/dl), proteinuria 7 g/day and normal albumin 3.4 g/dl. On the way to achieve partial remission (Table 1, Figure 4).

Time	Creatinine (mg/dL)	eGFR (ml/min)	Proteinuria (g/die)	Albumin (g/dL)	Therapy
zero	0.77	92	4.0	2.7	None
Month 24	2.15	26	6.0	3.8	Treatment plan Ponticelli
Month 48	1.5	40	5.0	3.6	None
Month 72	1.8	32	3.4	4.5	Rituximab
Month 80	1.5	40	0.3	4.6	Remission
Month 96	1.9	28	3.0	2.6	Cyclophosphamide
Month 108	1.95	27	7.0	3.4	Follow-up

Table 1. Clinical and biochemical follow-up over time and corresponding therapies

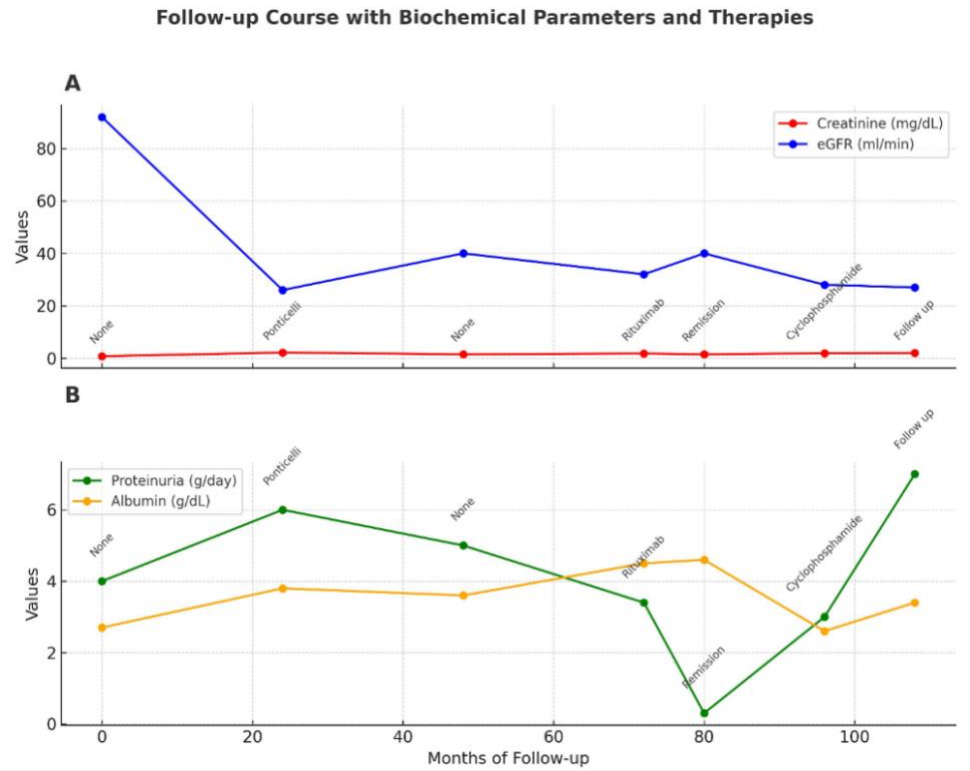

Figure 4. Follow-up course over 108 months. (A) Trends of serum creatinine and estimated glomerular filtration rate (eGFR). (B) Trends of proteinuria and serum albumin. Major therapeutic interventions (Ponticelli regimen, rituximab, cyclophosphamide) and clinical outcomes (remission, relapse, partial remission) are indicated along the curves.

Discussion

Anti-phospholipase A2 receptor antibodies of type M (anti-PLA2R) are the most specific serological biomarker for MN and, in typical clinical contexts, allow diagnosis without the need for renal biopsy. Their presence correlates strongly with disease activity and can be used to monitor therapeutic response [11]. In patients with MN, repeat renal biopsy may be crucial in cases of atypical clinical presentations, lack of response to treatment, or recurrence of nephrotic syndrome. The primary MN tends to follow a relatively indolent course, with progressive proteinuria but stable renal function; conversely, rapid deterioration of renal function, the onset of severe hypertension, or the presence of marked vascular and interstitial damage suggest a possible secondary form or overlapping glomerular disease [11].

Repeating the biopsy can provide information for reformulating the diagnosis, stratifying risk and adapting the therapeutic strategy, as illustrated in the case presented, in which the repeat examination revealed fibrotic progression with severe arteriosclerosis and immune deposits compatible with secondary MN and suspected overlapping disease. A limitation of this case is that the first renal biopsy lacked immunofluorescence analysis, which prevented the demonstration of immune complex deposition at disease onset. Nevertheless, this shortcoming was compensated by the subsequent biopsy, which provided immunopathological confirmation and, together with serological evolution, supported the diagnosis of secondary membranous nephropathy. This type of reassessment is particularly indicated when serology (e.g., anti-PLA2R negative) or the clinical picture does not align with a primary form [12].

Several studies support the importance of repeated biopsy even in cases of clinical recurrence after a phase of remission, especially when the response to immunosuppressive treatments is no longer

predictable or there is suspicion of transition to a new nosological entity (e.g., in patients with evolving systemic autoimmune diseases). Sequential histopathological monitoring therefore allows for personalised, evidence-based management of kidney disease [13]. For MN, progression to interstitial fibrosis and IFTA is generally slow and gradual, correlating proportionally with the duration and severity of proteinuria and the presence of episodes of acute renal failure. Marked interstitial and vascular involvement at onset, or accelerated progression of IFTA within a few years, are atypical features of primary MN and should raise suspicion of a secondary form or associated glomerular disease. In the case described, the second biopsy documented 65% interstitial fibrosis with severe arteriolosclerosis in a patient who had an almost normal biopsy two years earlier. This histological picture suggests an underlying chronic autoimmune vasculopathy, consistent with a subsequent diagnosis of SSc sine scleroderma. However, the interpretation of rapid histological progression as definitive evidence of secondary MN should be made with caution. Similar changes may also represent the natural course of MN under conditions of persistent nephrotic-range proteinuria and rising serum creatinine, irrespective of whether the disease is ultimately classified as primary or secondary. The negativity for anti-PLA2R and the presence of severe early hypertension reinforce the suspicion of a secondary mechanism, not immunologically mediated by classic anti-podocyte autoantibodies [14]. In primary MN, IFTA develops more slowly and generally in untreated patients or those with massive proteinuria persisting for more than 5 years. When a rapid course is observed, it is crucial to reassess the overall clinical picture and consider a re-biopsy to look for histological changes or secondary vascular complications [15]. The identification of new glomerular antigens has revolutionised the diagnostic approach to NM, especially in so-called “seronegative” cases, i.e. those with negative anti-PLA2R and anti-THSD7A antibodies. In the past, such cases were often classified as idiopathic or secondary MN based on clinical criteria, but today the existence of a variety of associated antigens is recognised, each potentially linked to a distinct clinical phenotype. Among the main antigens recently described are: NELL-1 (Neural epidermal growth factor-like 1) associated with elderly patients or those with occult solid neoplasms, but also found in non-paraneoplastic forms [16]; Exostosin 1/2 (EXT1/EXT2), detected mainly in young patients, often with systemic autoimmune diseases, particularly systemic lupus erythematosus [17]; Semaforin 3B (SEMA3B), observed in paediatric forms, but also described in adults with non-classical phenotypes [16]; Protocadherin 7 (PCDH7) and HTRA1: emerging antigens currently under study, associated with clinical-pathological patterns that are not yet well defined [18].

The discovery of new glomerular antigens has called into question the classic distinction between primary and secondary MN. In many cases, the identification of the target antigen allows for a more precise definition of the aetiology and correlates the histopathological picture with specific clinical phenotypes. This conceptual evolution suggests that the traditional classification may become obsolete and that, in the future, direct antigen typing on glomerular tissue using immunohistochemistry or mass spectrometry may guide diagnosis and therapeutic choices in a more targeted manner [19]. In the clinical case described, the double negativity for anti-PLA2R and the absence of obvious signs of secondary MN at onset initially pointed towards an idiopathic form. However, the clinical evolution and subsequent histological data (severe vasculopathy, recurrent proteinuria, onset of Raynaud’s phenomenon and ANA autoantibodies) raised the suspicion of a developing systemic autoimmune form. It is likely that, if a more advanced glomerular antigen analysis had been available, it could have identified an alternative antigen, suggesting a secondary origin from the outset.

Conclusion

The case presented is a particularly rare example of MN secondary to SSc sine scleroderma, characterised by an atypical clinical course, in which renal manifestations preceded the overt onset of systemic rheumatic disease by several years. This unusual time sequence highlights how important it is to adopt a multidisciplinary approach and maintain close follow-up in patients with apparently idiopathic MN but who have unconventional clinical or laboratory signs. Several factors pointed towards a diagnosis of secondary MN of a systemic autoimmune nature during follow-up: the persistent negativity of anti-PLA2R antibodies, a highly specific serological marker of primary MN; the early presence of severe arterial hypertension, unusual in the idiopathic form; the histological finding of marked arteriolosclerosis and extensive interstitial fibrosis in a short period of time; the progressive increase in ANA titre with anticentromere pattern, suggestive of systemic connective tissue disease; the appearance of Raynaud's phenomenon as an indicator of systemic microangiopathy; and finally, the favourable response to immunosuppressive therapy, both with the Ponticelli regimen and with rituximab, capable of inducing significant clinical remissions. This case highlights the importance of maintaining a high index of diagnostic suspicion in patients with seronegative MN, especially when atypical clinical or laboratory indicators coexist. Early classification as MN secondary to systemic autoimmune disease in its early stages or sine scleroderma allows for the timely initiation of targeted therapy and potentially prevents progression to chronic renal failure. Ultimately, repeat renal biopsy and dynamic immunological monitoring remain key tools for refining the differential diagnosis and optimising therapeutic management in complex clinical scenarios.

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