



**MEMBRANOUS NEPHROPATHY ASSOCIATED WITH SARCOIDOSIS: AN  
IDIOPATIC OR SECONDARY GLOMERULOPATHY?**

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**ABSTRACT**

Sarcoidosis is a multisystemic idiopathic inflammatory disorder characterized by non caseating granulomas of unknown cause. Renal involvement in sarcoidosis is rare. Glomerular lesions remain exceptional including essentially membranous glomerulonephritis. Membranous nephropathy (MN) is the most frequently encountered form of glomerulopathies. In fact, there is a higher than expected prevalence of MN in patients with sarcoidosis than in idiopathic glomerulopathies without sarcoidosis. As a result, sarcoidosis is listed as one of the secondary causes of MN. We report the case of a 58 year old man who was concomitantly diagnosed with MN and sarcoidosis. The question whether the glomerulopathy should be considered as idiopathic or secondary and the subsequent management are discussed.

**INTRODUCTION**

Sarcoidosis is a multisystemic idiopathic inflammatory disorder characterized by non-caseating granulomas of unknown cause.<sup>[1]</sup> Granuloma formation results from an interaction between CD4 T cells and antigen-presenting cells.<sup>[1]</sup>

Diagnosis requires a biopsy specimen and clinical exclusion of other causes of granulomatous inflammation.<sup>[2]</sup> Mediastinal and pulmonary localizations are the most common.<sup>[3]</sup> Renal involvement in sarcoidosis is rare but can be severe by progressing to irreducible and end stage of renal failure. It is most often the result of disorders of calcium metabolism.<sup>[1,2]</sup> The parenchymal involvement is frequently tubulointerstitial nephritis. Glomerular lesions remain exceptional including essentially membranous glomerulonephritis, rarely amyloidosis and exceptionally IgA nephropathy.<sup>[3,4]</sup>

Of the glomerulopathies, membranous nephropathy (MN) is the most frequently encountered. In fact, there is a higher than expected prevalence of MN in patients with sarcoidosis than in idiopathic glomerulopathies without the disease. As a result, sarcoidosis is listed as one of the secondary causes of MN. However, the mechanism by which glomerular injury occurs is unknown and the relationship is not proven. Renal sarcoidosis responds well to glucocorticoids.<sup>[1,2]</sup>

We present a 58 years old man who was concomitantly diagnosed with MN and sarcoidosis. The question whether the glomerulopathy should be considered as idiopathic or secondary and the resultant management are discussed.

**CASE REPORT**

A 58 years old man with a type 2 diabetes history for 8 years presented with full-blown nephrotic syndrome. He had a 5.7% amount of glycosylated hemoglobin A (HbA<sub>1c</sub>) associated with a normal eye examination. The patient had no constitutional symptoms, apart from an ankle edema. The rest of physical examination was unremarkable. Blood pressure was 130/70 mmHg. Laboratory data showed a normal full blood cell count, serum creatinine 61 μmol/l, blood urea nitrogen 5 μmol/l, total protein/albumin 54/18 g/l. Urine protein excretion was 16 g/24hours. Urinalysis showed proteinuria with normal urinary sediment. Urine culture was negative. Antinuclear antibody, anti-neutrophil cytoplasmic antibody, HBsAg, hepatitis C virus and human immunodeficiency virus were negative. C3 and C4 were within normal limits. Protein electrophoresis showed low level in gammaglobulin. Immunoglobulin M, IgA2 and IgG levels were 223 (40–230), 247 (70–500) and 396 (700–1600) mg/dl, respectively. Chest radiography showed no abnormalities. Ultrasound demonstrated two kidneys of normal size, shape and echogenicity. Renal biopsy was performed: On light microscopy, there were

glomeruli – all showing the same features, namely, a markedly thickened glomerular basement membrane with spike formation seen on periodic acid-Schiff and silver stains. Immunofluorescence was positive for IgG and C3 in a granular pattern along the GBM. Notably, the interstitium was normal with no inflammatory infiltrate or granulomata. Electron microscopy demonstrated subepithelial and intraepithelial dense deposits compatible with MN [fig1, fig2].

A workup for secondary MN was initiated including Esophagogastroduodenoscopy, colonoscopy, bone marrow biopsy. A CT scan of the chest, abdomen and pelvis revealed mediastinal and hilar lymphadenopathy with normal lung parenchyma.

It was decided that a tissue diagnosis of the patient's lymphadenopathy was essential for future management. Among the differential diagnoses considered were sarcoidosis, lymphoma and an infectious disease such as tuberculosis. Endobronchial ultrasound was performed, but the tissue sample obtained was insufficient. Therefore, mediastinoscopy and lymph node biopsy were performed.

Histology showed multiple epithelioid non-caseating granulomas consistent with sarcoidosis. Ziehl-Neelsen and PAS stains were negative. With an established diagnosis of sarcoidosis, complimentary laboratory data showed angiotensin- converting enzyme level of 92 U/L (normal range 12–68). Serum calcium was 8.3 mg/dl with an albumin level of 2.2 g/dl, and urine calcium 118 mg/24 hours. Prednisone 1 mg/kg daily was initiated. After 2 months no amelioration of the proteinuria was seen. It remained at nephritic levels (5.6 g/24 hours). Nevertheless, serum total protein/albumin has increased to 67/35 g/l, respectively.

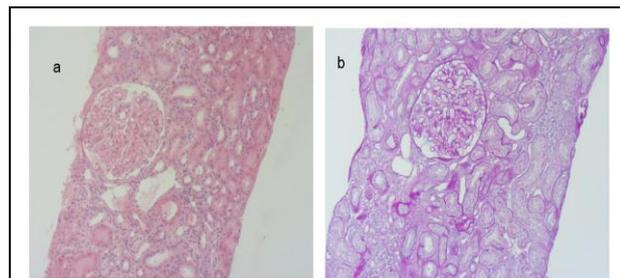


Fig1 : (a) Glomerulus in a renal biopsy specimen on hematoxylin and eosin staining, there is uniform thickening of basement membranes, which makes them appear rigid. (b) Glomerulus stained by periodic acid-Schiff showing a hint of thickening of basement membranes.

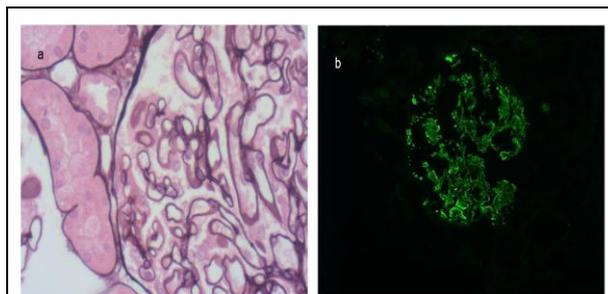


Fig2 : (a) Glomerulus stained by reticulin highlights the thickening of basement membranes, but there is a diffuse and intense granular deposit along the GBM. Mesangial areas are free of deposits.

## DISCUSSION

Renal involvement in sarcoidosis occurs in 4–22% of cases and is of diverse etiology. The most common manifestation is related to deranged calcium homeostasis due to the production of calcitriol by the granuloma epithelioid cells.<sup>[1,2]</sup> Hypercalciuria presents in up to 50% of patients with sarcoidosis, and overt hypercalcemia is found in 10–20%.<sup>[1,2]</sup> The resultant renal injury is due to nephrolithiasis and/ or nephrocalcinosis.<sup>[1,2]</sup> Other possible renal pathologies include granulomatous tubulointerstitial nephritis; obstructive uropathy due to enlarged retroperitoneal lymph nodes; vasculitis; and glomerular disease such as membranous nephropathy, focal segmental sclerosis, immunoglobulin A nephropathy and crescentic glomerulonephritis.<sup>[2]</sup>

Membranous nephropathy is the commonest cause of nephrotic syndrome in the Caucasian adult. In 85% of cases it is considered idiopathic, in the remaining 15% it is secondary.

In recent decades research was undertaken to determine the human antigen responsible for glomerulopathy. Recently, a majority of patients (70%) with idiopathic MN (iMN) were shown to harbor antibodies against the M-type phospholipase A2 receptor, indicating that PLA2R5 is a major antigen in the disease.<sup>[5]</sup> The presence of anti-PLA2R antibodies carries 70% sensitivity and 100% specificity for idiopathic MN.<sup>[5]</sup> Their prevalence in secondary MN is much lower than in iMN<sup>[6]</sup> although in this setting, it is often difficult to exclude coincidental occurrence of iMN with the underlying disorder.

MN is the most frequent glomerular disease associated with sarcoidosis although its occurrence is rare.<sup>[7]</sup> Only isolated cases of sarcoidosis-associated MN have been reported so far.<sup>[8-10]</sup>

Our patient was diagnosed concomitantly as having MN and sarcoidosis. However, the temporal association between the two does not necessarily denote a causal relationship. The question whether the glomerular disease be considered idiopathic or secondary to sarcoidosis is an important one as it affects treatment decisions.

Differentiating between idiopathic and secondary MN is sometimes difficult.

Co-localization of the immune deposits in the mesangium and/or subendothelial region, as occurs in lupus, points to a secondary MN. In addition, the IgG subclass in idiopathic MN is usually IgG4 but in secondary forms it is IgG1.<sup>[11]</sup> As stated above, the presence of anti-PLA2R antibodies is strongly indicative of idiopathic MN.

In our patient, the IgG subclass of the immune deposits was not determined and anti-PLA2R antibodies were detected. He had PLA2R antigen in immune deposits.

Renal sarcoidosis of varying clinical presentation usually responds well to steroid therapy. Improvement in kidney function is directly related to the response after 1 month of treatment.<sup>[2]</sup> Several case reports have described MN (some accompanied by tubulointerstitial nephritis) in association with sarcoidosis in which prednisone alone induced a complete remission of the nephrotic syndrome.<sup>[12]</sup> Of note is the report by Knehtl *et al.*<sup>[12]</sup> who documented such an association which responded to glucocorticoid treatment. Interestingly, in this case, PLA2R antigen was demonstrated in the immune deposits and anti-PLA2R antibodies were found in the serum. These antibodies disappeared upon remission. The authors suggested that this patient might have had idiopathic MN with coincident sarcoidosis or that it could be the first case of secondary MN with PLA2R positivity.

In recent decades research aimed to test the prevalence of PLA2R-related MN in patients with sarcoidosis and to establish a possible relationship with sarcoidosis activity. To this end, T. Stehlé *et al* searched for PLA2R antigen in sub-epithelial immune deposits, a diagnostic test which is more sensitive than serology and enables the retrospective diagnosis of PLA2R-related MN.<sup>[9,13]</sup> In conclusion, T. Stehlé *et al* show a high prevalence of PLA2R-related MN among patients with MN associated with active sarcoidosis.<sup>[14]</sup>

Therefore, detection of anti-PLA2R antibodies in serum or PLA2R antigen in biopsy should not be taken as evidence against a secondary cause, particularly sarcoidosis as is the case for our patient.

We chose to regard our patient's MN as being secondary to sarcoidosis and accordingly treated him with prednisone only. Following 2 months of steroids, amelioration of the nephrotic syndrome was seen.

## CONCLUSION

Renal involvement in sarcoidosis is uncommon but severe and can lead to chronic kidney failure. Early diagnosis and adapted treatment allows preserving renal function.

This case illustrates the difficulty in distinguishing idiopathic MN from secondary MN related to identifiable diseases.

It is tempting to postulate that sarcoidosis played a causative role in MN. The pathogenesis of possible sarcoidosis-induced glomerular disease is, as yet, unknown and the relationship has not been proven.

Because PLA2R antibodies are rarely detected in secondary MN, their occurrence in patients with active sarcoidosis suggests that the immunological setting of sarcoidosis might trigger or enhance immunization against PLA2R; although further studies are needed to understand the pathogenetic mechanisms.

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