Membranous Nephropathy Associated with Sarcoidosis: A Primary or Secondary Glomerulopathy?

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Sarcoidosis is a multisystemic idiopathic inflammatory disorder characterized by non-caseating granulomas of unknown cause [1]. Granuloma formation results from an interaction between CD4 T cells and antigen-presenting cells [1]. Diagnosis requires a biopsy specimen and clinical exclusion of other causes of granulomatous inflammation [2].

Renal involvement 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 [1,2]. Hypercalciuria presents in up to 50% of patients with sarcoidosis, and overt hypercalcemia is found in 10–20% [1,2]. The resultant renal injury is due to nephrolithiasis and/or nephrocalcinosis [1,2]. 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 [2]. Of the glomerulopathies, membranous nephropathy is the most frequently encountered. In fact, there is a higher than expected prevalence of MN in patients with sarcoidosis than in primary 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 [1,2].

We present a 38 year old man who was concomitantly diagnosed with MN and sarcoidosis. The question whether the glomerulopathy should be considered as primary or secondary and the resultant management are discussed.

PATIENT DESCRIPTION

A 38 year old previously healthy Caucasian man presented at a peripheral hospital with full-blown nephrotic syndrome. He was working as a warehouse employee in the marble and granite industry. The patient had no constitutional symptoms. Apart from ankle edema the physical examination was unremarkable. Blood pressure was 130/70 mmHg. Laboratory data showed a normal full blood cell count, serum creatinine 0.9 mg/dl, blood urea nitrogen 15 mg/dl, total protein/albumin 4.6/2.1 g/dl, total cholesterol and low density lipoprotein 237 and 140 mg/dl, respectively. Urine protein excretion was 9 g/day. Urinalysis showed proteinuria with normal urinary sediment.

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 was normal. Immunoglobulin M, IgA and IgG levels were 263 (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.

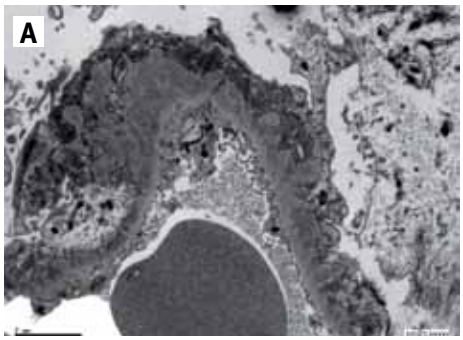
Renal biopsy was performed. On light microscopy, there were eight glomeruli – all showing the same features, namely, a markedly thickened glomerular basement membrane with spike formation seen on periodic acid-Schiff and silver stains. Immunofluorescence was positive for IgG and C3 in a granular pattern along the GBM. Notably, the interstitium was normal with no inflammatory infiltrate or granulomata. Electron microscopy demonstrated subepithelial and intraephithelial dense deposits compatible with MN stage 2-3 [Figure A]. A workup for secondary MN was initiated including a computed tomography of the chest. This revealed mediastinal and hilar lymphadenopathy with normal lung parenchyma [Figure B]. A pulmonary consultant decided not to pursue any further investigation at this stage and recommended a follow-up CT. The patient was discharged on treatment with angiotensin-converting enzyme inhibitor, statin and diuretic.

He was readmitted to our institution 2 months later in severe fluid overload. Serum albumin level had decreased to 1.7 g/dl with proteinuria 23 g/day. It was decided that a tissue diagnosis of the patient's lymphadenopathy was essential for future management. Among the differential diagnoses considered were sarcoidosis, silicosis, lymphoma and infectious disease such as tuberculosis.

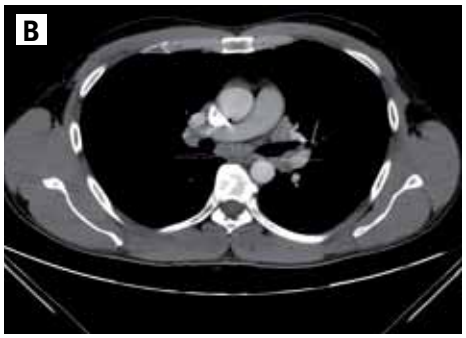
MN = membranous nephropathy

Ig =immunoglobulin

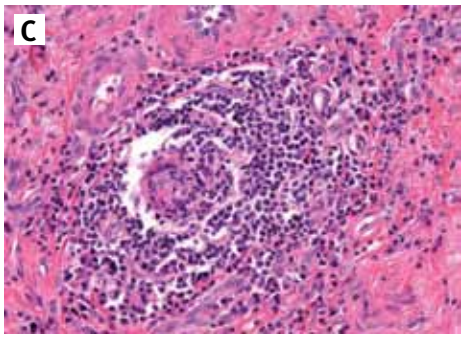
GBM = glomerular basement membrane



[A] Electron microscopy showing subepithelial and intraephithelial dense deposits compatible with MN stage 2-3



[B] CT of the chest showing mediastinal and hilar lymphadenopathy (white arrows) with normal lung parenchyma



[C] Light microscopy of mediastinal lymph node showing epithelioid non-caseating granulomas consistent with sarcoidosis

Endobronchial ultrasound was performed, but the tissue sample obtained was insufficient and mediastinoscopy and lymph node biopsy were therefore performed. Histology showed multiple epithelioid non-caseating granulomas consistent with sarcoidosis [Figure C]. Ziehl-Neelsen and PAS stains were negative. With an established diagnosis of sarcoidosis, complimentary laboratory data showed angiotensin-converting enzyme level of 73 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 60 mg daily was initiated. After 2 months no amelioration of the nephrotic syndrome was seen. Cyclophosphamide 150 mg/day was added. The patient did not respond to this combined regimen and cyclosporin A was therefore administered as second-line treatment. After 8 months on cyclosporine A no response was seen. As of today, 21 months after the renal biopsy, proteinuria remains at nephrotic levels (5.6 g/24 hours), although serum albumin has increased to 3.5 g/dl. Serum creatinine is currently 1.24 mg/dl.

COMMENT

Membranous nephropathy is the commonest cause of nephrotic syndrome in the Caucasian adult. In 85% of cases it is considered idiopathic (primary), in the remaining 15% it is secondary. Secondary causes include autoimmune disease (systemic lupus erythematosus, WHO class V), malignancy, infection (hepatitis B, hepatitis C, malaria, syphilis), drugs (penicillamine, gold salts, anti-tumor necrosis factor, non-steroidal anti-inflammatory drugs), graft vs. host disease, and sarcoidosis. MN is exemplified by the formation of subepithelial immune complexes along the GBM. Morphologically, its similarity to Heymann's experimental nephritis – a rat model produced by immunization against renal brush border antigens – prompted a search for the inciting antigen. It was finally identified as the podocyte membrane protein megalin. This protein, however, does not play a role in human MN.

In recent decades research was undertaken to determine the human antigen responsible for glomerulopathy. Alloimmune antenatal MN has been linked to antibodies against neutral endopeptidase formed in mothers deficient in the enzyme. Recently, a majority of patients (70%) with idiopathic MN were shown to harbor antibodies against the M-type phospholipase A2 receptor, indicating that PLA2R is a major antigen in the disease [3]. The presence of anti-PLA2R antibodies carries 70% sensitivity and 100% specificity for idiopathic MN [3].

Of the glomerulopathies associated with sarcoidosis, MN is the most prevalent. 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 primary or secondary to sarcoidosis is an important one as it affects treatment decisions. Differentiating between primary 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 primary MN is usually IgG4 but in secondary forms it is IgG1 [4]. As stated above, the presence of anti-PLAR2 antibodies is strongly indicative of primary MN. In our patient, the IgG subclass of the immune deposits was not determined and anti-PLA2R antibodies were not assayed.

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 [2]. 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 [5]. Of note is the report by Knehtl et al. [5], who documented such an association which responded to glucocorticoid treatment. Interestingly, in this case, PLA2R antigen was demonstrated in the immune

PAS = periodic acid-Schiff

PLA2R = phospholipase A2 receptor

deposits and anti-PLA2R antibodies were found in the serum. These antibodies disappeared upon remission. The authors suggested that this patient might have had primary MN with coincident sarcoidosis or that it could be the first case of secondary MN with PLA2R positivity.

It is generally accepted that idiopathic MN is unresponsive to steroids alone. We originally chose to regard our patient's MN as being secondary to sarcoidosis and accordingly treated him with prednisone only. Following 2 months of steroids no response was seen. This would seem to negate causality between sarcoidosis and the glomerulopathy in our case. In fact, our patient's MN is proving refractory to treatment even with the addition of cyclophosphamide and second-line treatment with cyclosporine A.

This case illustrates the difficulty in distinguishing idiopathic MN from secondary MN related to identifiable diseases. Although it is tempting to postulate that sarcoidosis played a causative role in our patient's MN, this does not appear to be the case. The pathogenesis of possible sarcoidosis-induced glomerular disease is, as yet, unknown and the relationship has not been proven.

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