Idiopathic or iatrogenic membranous glomerulonephritis? A case of spironolactone-induced membranous glomerulonephritis

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Abstract
Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults in the UK. In most cases, the aetiology remains unknown, although recent data suggested a clear mechanism of pathogenesis. In approximately a quarter of cases, however, a presumed cause is found, such as systemic lupus nephritis, malignancy, hepatitis B and various drugs. Here, we present a patient who developed MN soon after commencing spironolactone and whose condition persisted for the duration of exposure to the drug only to resolve with cessation of the drug. No cases of spironolactone-induced MN have been reported in the literature previously.

Keywords: glomerulonephritis; membranous; nephropathy; spironolactone

Case report
In August 2000, a 69-year-old Caucasian male was referred to the nephrology clinic with nephrotic syndrome. He complained of a 1-month history of ankle swelling associated with lethargy. Investigations showed proteinuria of 6.5 g/day with creatinine clearance of 113 mL/min (see Figure 1). Serum creatinine was 82 \( \mu \text{mol/L} \), albumin 26 g/L and cholesterol 6.5 mmol/L. The patient’s medications were atenolol 50 mg od, atorvastatin 10 mg nocte, fruosemide 40 mg od, lercanidipine 10 mg od, omeprazole 20 mg od, spironolactone 25 mg od, trandolapril 2 mg od and sulindac prn. He claimed not to take herbal remedies or other alternative medications, which were not prescribed by his physicians. His past medical history included a transurethral resection of the prostate with stable prostate-specific antigen levels, chronic prostatitis, resection of epididymis and chronic head and back pain. There was no family history of renal or autoimmune disease. On examination, the patient looked well with blood pressure measuring 140/78 mmHg. Other than ankle oedema extending to the lower shins, all other examinations were unremarkable. During the consultation, a renal biopsy was arranged for 2 weeks time and sulindac was substituted with paracetamol.

Renal biopsy confirmed membranous nephropathy (MN). Light microscopy demonstrated 10 glomeruli with very occasional spikes. There was no mesangial hypercellularity. The interstitium and tubules were normal. Blood vessels showed mild medial thickening and focal reduplication of the internal elastic lamina. On immunofluorescence testing, there was granular peripheral deposition of IgG, C3 and C1q. Electron microscopy showed many small subepithelial deposits.

Based on the absence of chronic renal damage and normal renal function, the patient was deemed to have relatively low risk of progression to end-stage renal failure; therefore, immunosuppression was deferred. Interim management consisted of regular observation of renal parameters and meticulous blood pressure control. Over the following 2.5 years, there was gradual progression of nephrotic syndrome and the patient experienced varying degrees of lethargy. By July 2002, proteinuria was 15.4 g/day and by December 2002, creatinine rose to 160 \( \mu \text{mol/L} \) (see Figure 1). During this period, alterations made in his medications included increase of atorvastatin, furosemide and lercanidipine as well as introduction of clopidogrel and change of atenolol for acebutolol. The patient had an episode of suspected self-resolving shingles as well as prostatitis for which he was commenced on ofloxacin and tamsulosin.

In December 2002, the patient visited an emergency department in the USA with left nipple pain, which was diagnosed as an adverse effect of spironolactone. The drug along with ofloxacin were stopped. In November 2002, prior to stopping spironolactone, his proteinuria was 10.2 g/day. By July the following year, proteinuria was 3.48 g/day. Likewise, serum albumin recovered from 30 g/L at the time of his emergency department admission to normal levels within 7 months. Full and sustained remission of proteinuria \(<0.3\) g/day has been observed since May 2005. Renal function recovered more slowly to a current baseline serum creatinine of \(~110\) \( \mu \text{mol/L} \) in the subsequent years.

Discussion
There is convincing, although circumstantial evidence to suggest spironolactone was the causative agent in this patient’s MN. The patient’s nephrotic syndrome coincides quite precisely with the period during which he was on
spironolactone, suggestive of secondary MN rather than idiopathic MN with spontaneous resolution. The disease started after his spironolactone was commenced in July 2000. There is steadily increasing proteinuria, sustained abnormally low serum albumin levels and worsening renal impairment all the while he was on the drug. His condition improved markedly immediately upon cessation of the drug. It should be said gynaecomastia remains a fortuitous side effect as without it there was no indication for stopping spironolactone.

Other causes appear very unlikely. Of the drugs implicated in MN in previous literature, the patient was taking a non-steroidal anti-inflammatory drug and an angiotensin-converting enzyme. There is no chronological synchrony of these drugs to the patient’s clinical course as sulindac was stopped soon after his first consultation and trandolapril remained unchanged. Other secondary causes were excluded as there was no history of previous autoimmune disease, infection or malignancy associated with MN [1, 2].

It is difficult to speculate the mechanism of pathogenesis in spironolactone-induced MN. Recently, the discovery of the M-type phospholipase A2 receptor as a target antigen in a majority of idiopathic MN, but not in secondary MN, has been a pivotal moment in our understanding of the disease [2]. Whether there is a common immunological cascade at work in all secondary MN that can be provoked by various causes such as infections and drugs and whether spironolactone feeds into this pathway remains to be elucidated. Regardless of the exact mechanism, it is likely that such a cascade causes either a drug-induced modulation of the antigens on podocytes or expression of newer antigens on the podocytes.

Given our still partial understanding of MN pathogenesis, it is reasonable to suppose many other agents may stimulate an immune-mediated response. As removal of the causative agent can bring about a swift resolution of MN, an exhaustive drug history is crucial: patients must be asked exactly when each medication was commenced and whether any interruptions have alleviated symptoms or improved biochemical parameters. Information about changes in diet and alternative medications should also be elicited. Prior to diagnosing membranous nephropathy as idiopathic, all efforts should be made to exclude secondary aetiology.

Conflict of interest statement. None declared.

References
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