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Case Report

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Membranous nephropathy associated with gastrointestinal stromal tumour: a case report

Adela Cimic[1], Stephen O. Pastan[2] and Vanesa Bijol[1]

[1]Department of Pathology, Emory University Hospital and [2]Department of Medicine, Renal Division, Emory University School of Medicine, Atlanta, GA, USA

Correspondence and offprint requests to: Adela Cimic; E-mail: cimicadela@yahoo.com

Abstract

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in older adults. The association of MN with neoplasia has been controversial, but several recent studies have shown increase incidence of cancer in patients with MN [1]. We report a case of a 49-year-old male with severe nephrotic syndrome and concomitant jejunal gastrointestinal stromal tumour (GIST). The combination of preoperative Imatinib mesylate chemotherapy and tumour excision was followed by complete resolution of proteinuria within 19 months, without specific treatment for MN. An association between MN and GIST has never previously been reported in the literature.

Keywords: GIST; membranous nephropathy; proteinuria

Case report

A 49-year-old male presented with severe nephrotic syndrome (proteinuria 16.8 g/day, serum albumin 1 g/dL, 3+ lower extremity oedema, severe dyslipidaemia resistant to statins), gastrointestinal bleeding and weight loss. His past medical history was notable for a coronary artery disease and myocardial infarction. Renal function tests were within normal limits, with blood urea of 13 mg/dL and serum creatinine of 0.9 mg/dL. Serum glucose (71 mg/dL), potassium (4.7 mmol/L) and sodium (140 mmol/L) were within normal limits. Tests for hepatitis B surface antigen and antibodies against hepatitis C virus and human immunodeficiency virus were negative. Tests for antinuclear antibody and anti-double stranded DNA antibody were also negative. Serum complement (C) levels were within normal range (C3: 159 mg/dL, C4: 29 mg/dL) and the serum protein electrophoresis showed no M-spike. Renal sonogram revealed normal size kidneys and an unusual mass in the left flank region. Abdominal magnetic resonance imaging showed a large (12.6 cm × 11.2 cm × 10.1 cm) heterogeneous mass of the proximal jejunum. Biopsies of both the tumour and the kidney were performed. The tumour biopsy confirmed spindle cell neoplasm, composed of uniform cells arranged in poorly formed fascicles and exhibiting scattered mitotic figures. Immunoperoxidase stains for CD34 and CD117 (c-kit) were positive in the tumour cells, while stains for smooth muscle actin, desmin and pancreatin were negative. Given the histological immunostaining properties and size of the mass, the diagnosis of gastrointestinal stromal tumour (GIST) of high malignant potential was made.

Renal biopsy was performed to investigate the cause of proteinuria. On light microscopy, the biopsy showed 71 glomeruli of normal size and cellularity. Endocapillary or extracapillary proliferative changes were not present in the glomeruli. Periodic acid-Schiff and Jones' methenamine silver-stained sections demonstrated uniform thickening of the glomerular capillary walls with 'crater' and fine 'spike'-like projections. Immunoperoxidase stain for c-kit was performed and it was negative. Immunofluorescence studies showed fine granular deposition of IgG (3+), C3 (2+) and C4 (1+) along the peripheral capillary loops. Trace deposition of IgA, IgM and C1q was also noted in the same distribution. Ultrastructural analysis revealed numerous fine granular subepithelial electron-dense deposits, separated from each other by basement membrane 'spikes' (Figure 1). Small subendothelial electron-dense deposits were also seen in several places. The mesangium revealed normal cellular elements and a mildly expanded extracellular matrix with scattered, in some places large, electron-dense deposits (Figure 1). The diagnosis of MN was made. Because of the presence of subendothelial and mesangial deposits, a secondary form of MN was suggested.

Following the biopsy results, the patient was placed on oral imatinib mesylate (400 mg/day) for 8 months, and the surgical excision of the tumour was performed when the tumour became resectable. Imatinib mesylate has been administrated continuously. The patient had never received any specific immunosuppressive therapy for MN, but his proteinuria slowly decreased to 3.0 g/day at the time of surgery, and completely resolved at 8 months after surgery (Figure 2). At that time the patient had no oedema, his serum albumin was 4.6 g/dL, serum creatinine was 1.0 mg/dL and the dyslipidaemia had resolved as well.

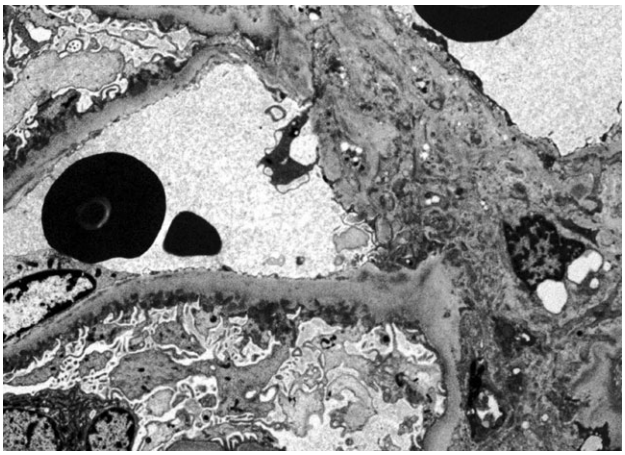

Fig. 1. Numerous subepithelial, and scattered subendothelial and mesangial electron-dense deposits (magnification ×2200).

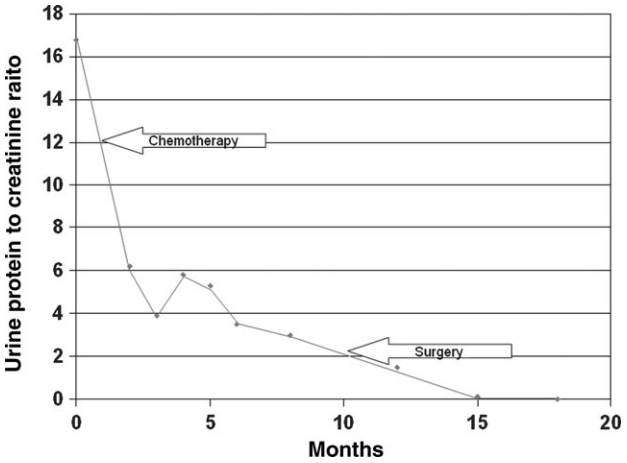

Fig. 2. Proteinuria declined and completely resolved with chemotherapy treatment and surgical removal of the tumour.

Discussion

MN frequently occurs in its primary (idiopathic) form, as a renal-limited autoimmune disease. Presumably, the process develops due to auto-antibodies directed against unique glomerular epithelial cell antigens, analogous to Heymann nephritis in the experimental animal. In a recent report, the podocyte membrane glycoprotein M-type phospholipase A2 receptor was identified as the major target of autoimmune process in idiopathic MN [2]. Subepithelial deposits form *in situ*, as antibodies bind to a membrane-based antigen and complement. A significant proportion of MN cases are, however, secondary to systemic autoimmune diseases (systemic lupus erythematosus, in particular), infections (such as hepatitis B and C, and syphilis) and drugs (d-penicillamin, hydralazine, captopril and non-steroidal anti-inflammatory drugs) [3–5]. The mechanism by which the subepithelial deposits form in secondary MN is less clear and possibly includes the deposition of circulating immune complexes in the subepithelial space, as described with hepatitis B [3].

The association of MN with cancer has been frequently reported in the literature. In the review of 240 patients with MN, 10% were found to have malignancy at the time of diagnosis; the study also showed that age, smoking and the presence of glomerular leukocytic infiltrates strongly increase the likelihood of malignancy in MN patients [1]. The mechanism by which the cancer would cause the subepithelial immune complex deposition and MN is unclear. Tumour antigens have not been demonstrated within the subepithelial deposits yet, supporting the idea of an *in situ* deposition process, as seen in the primary form of MN. The presence of subendothelial and mesangial deposits in some of these cases, however, argues against the concept of membrane-based antigen and circulating auto-antibodies, and suggests the deposition of pre-formed, circulating immune complexes. Gastric and bronchial cancers are the most frequent cancers associated with MN, but renal cell carcinoma, thymoma, prostate and breast carcinoma have been also described [6]. Some studies show that nephrotic syndrome resolves with treatment and remission of cancer [1,7].

Gastrointestinal stromal tumours are mesenchymal tumours of the gastrointestinal tract, with specific immunohistochemical c-kit reactivity and good therapeutic response to tyrosine kinase inhibitors [8]. Paraneoplastic syndromes are rarely reported in the setting of GIST; only isolated case reports of severe paraneoplastic hypoglycaemia and hypercalcaemia exist [9,10]. Nephrotic syndrome in the setting of GIST has never been reported.

The association between GIST and MN in this 49-year-old patient is unclear; however, the patient's proteinuria significantly declined with specific tumour chemotherapy, and the nephrotic syndrome and proteinuria completely resolved with the surgical removal of the tumour (Figure 2). The patient had no specific treatment for his nephrotic syndrome and no other possible cause of MN was found in his case. We conclude that MN was associated with the GIST in this patient. Complete clinical work-up in the setting of membranous glomerulopathy is warranted regardless of the patient's age. This case is a unique example of GIST-associated MN and represents the first report of nephrotic syndrome associated with GIST.

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Conflict of interest statement. None declared.

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