Spontaneous remission of immunotactoid glomerulopathy

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ABSTRACT

Immunotactoid glomerulopathy (ITG) is a rare cause of nephrotic syndrome, occurring in approximately 0.1% of native kidney biopsies. We describe a 43-year-old woman who presented with a nephrotic syndrome. Renal biopsy revealed a membranous pattern of glomerular injury. In electron microscopy the subepithelial deposits were comprised of 40 nm wide tubular structures, confirming ITG. During follow-up the patient developed a remission of proteinuria with only supportive treatment.

KEYWORDS

Immunotactoid glomerulopathy, membranous nephropathy, nephrotic syndrome, spontaneous remission

INTRODUCTION

Glomerular diseases, characterised by the presence of organised deposits, are a rare cause of nephrotic syndrome. The most common form is amyloidosis. Immunotactoid glomerulonephritis (ITG) is reported in less than 0.1% of renal biopsies. ITG can mimic membranous nephropathy in light microscopy and immunofluorescence examination. We present a patient with ITG with a membranous pattern of glomerular injury. This case illustrates that ITG may be missed in the absence of electron microscopic studies. Furthermore, remissions can occur without immunosuppressive therapy.

CASE REPORT

A 43-year-old woman was referred to the outpatient clinic with progressive tiredness, leg cramps, oedema and proteinuria. She was not using any medication. Her past medical history revealed relapsing-remitting multiple sclerosis (MS) of more than ten years’ duration. She...
had received several courses of intravenous methylprednisolone. Six years before presentation, treatment with interferon was started, resulting in a complete remission of her MS. Treatment with interferon was discontinued two years before presentation.

Physical examination was unremarkable, except for pitting oedema in the lower extremities. At the time of her initial review, her blood pressure was 130/70 mmHg. Laboratory testing showed proteinuria of 4.9 g/24 hours and hypoalbuminaemia (25 g/l). Renal function was normal (eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula was 110 ml/min/1.73 m²). Additional work-up showed normal complement levels, no antinuclear or double-stranded-DNA antibodies, no cryoglobulins, and serum and urine protein electrophoresis revealed no signs of monoclonal gammopathy. Serology for hepatitis B and C was also negative. A renal biopsy was performed, showing normal glomeruli with negative immunofluorescence and a diagnosis of minimal change disease was made. Electron microscopic examination was not performed.

In the absence of a definite diagnosis and because of the mild symptoms and normal renal function, immunosuppressive therapy was withheld. Supportive therapy was initiated consisting of a loop diuretic, an ACE inhibitor and a statin. Over the next six months her renal function remained stable, but nephrotic range proteinuria and hypoalbuminaemia persisted despite a well-regulated blood pressure <125/75 mmHg. The patient was referred for treatment advice and review of the renal biopsy. Upon light microscopic review of the initial renal biopsy, subtle abnormalities of the basal membrane were seen in some glomeruli raising the suspicion of membranous nephropathy. Unfortunately, no material was available for additional immunofluorescence and electron microscopic examination.

A new renal biopsy was performed (figure 1). Light microscopy showed ten glomeruli, two of which were globally sclerosed. Of the remainder, many glomeruli showed subtle abnormalities of the basal membrane consisting of capillary loop thickening and small areas of lucency were seen in the silver methenamine stain. No endocapillary hypercellularity was observed. There were no abnormalities of the endothelium, mesangium, Bowman’s capsule or the juxtaglomerular apparatus. Congo-red staining was negative. Immunofluorescence showed fine granular deposits of IgG, C3, kappa and lambda as seen in membranous nephropathy. However, electron microscopy revealed subepithelial immune deposits consisting of microtubules of 40 nm diameter with hollow centres arranged in parallel stacks, compatible with a diagnosis of ITG. Mesangial deposits were not observed.

The patient was diagnosed with idiopathic ITG. Therapy was directed at the findings of membranous nephropathy on light microscopy. Urinary excretion of β2-microglobulin (0.15 μg/min) and IgG (76 mg/24 hours) were both low. Therefore, supportive therapy was continued. During follow-up the serum creatinine has remained stable and proteinuria decreased. Currently, the patient has attained a remission of proteinuria (0.22 g/day) with a stable serum albumin (36 g/l; figure 2), which persists after discontinuation of all supportive medication.

DISCUSSION

ITG belongs to the class of glomerular diseases characterised by the deposition of organised often fibrillary structures. A schematic overview is given in figure 3. Silver methenamine staining can be used to distinguish between disorders replacing the normal

![Figure 1. Renal biopsy findings](image)

(A) Light microscopy showing small areas of lucency in the glomerular basement membrane (green arrows). (B) Immunofluorescence microscopy showing finely granular (almost linear) deposits of IgG along the glomerular basement membrane. (C) Electron microscopic examination (original magnification 15000x) showing highly organised subepithelial deposits made up of microtubules (hollow centre) approximately 40 nm wide (arrows).
mesangial matrix (methenamine negative) or disorders resulting in an increase of mesangial extracellular matrix (methenamine positive). Silver methenamine negative disorders with organised deposits are divided into two categories consisting of Congo red positive diseases, encompassing all types of amyloidoses, and Congo red negative disorders. Most Congo red negative organised deposits are immunoglobulin derived. The deposits cannot be recognised by light microscopy, thus a diagnosis can only be made with certainty if renal tissue is appropriately examined by electron microscopy. Moreover, the specific features of organised deposits (size, shape, arrangement; figure 3) on electron microscopy can further assist in characterisation of the various disorders. Our case emphasises the importance of electron microscopic examination of renal biopsies from patients with nephrotic proteinuria. Electron microscopy was not only necessary to detect organised deposits but also to distinguish early membranous lesions from minimal change disease. Initially a diagnosis of minimal change disease was made based on light microscopy, and negative immunofluorescence examination. However, as noted by previous studies, early membranous nephropathy does not always show capillary loop thickening by light microscopy and may lack convincing immunofluorescence findings. A study by Haas showed that electron microscopy provides useful diagnostic information in nearly half of native renal biopsies.7

ITG is a rare disease; in a large series it comprised only 0.1% of native kidney biopsies. In series of adult patients with nephrotic syndrome, ITG constituted less than 4% of the biopsies.4,10 ITG is characterised by the deposition of microtubules with a hollow core, generally measuring more than 30 nm in diameter and arranged in a parallel fashion. The deposits are usually confined to the glomerulus, specifically the mesangium and subendothelial space. Some cases also have subepithelial or intramembranous deposits.1-3 The deposits of ITG are immunoglobulin derived, and can be either polyclonal (30 to 40%) or monoclonal (60 to 70%).1 Interestingly, in a few patients with ITG and chronic lymphocytic leukaemia or related B-cell lymphoma, monoclonal deposits with a microtubular diameter <30 nm have been observed.11 Light microscopic findings associated with ITG are nonspecific and include membranoproliferative, diffuse proliferative and atypical membranous patterns.1,3

There is some debate as to whether ITG should be distinguished from fibrillary glomerulonephritis (FGN), a glomerulopathy characterised by randomly arranged, nonbranching fibrils in the mesangium and glomerular basement membrane with an average diameter of 20 nm. 1,12,13 Some regard ITG and FGN as a single disease with different ultrastructural variants, referring to both as ITG. However, several studies have shown important clinical and immunopathological differences between these two entities. Patients with ITG exhibit a higher incidence of monoclonal deposits and lymphoproliferative disorders (33 to 50% vs 0 to 7%) compared with patients with FGN.1,5,8,14

Rood, et al. Spontaneous remission of immunotactoid glomerulopathy.
ITG can occur at any age, with a peak occurrence at 60 years of age.1-8 Patients with ITG present with proteinuria, which is in the nephrotic range in more than half of the patients.1,3,8 Other findings include haematuria, hypertension and renal insufficiency. Patients with ITG have a predisposition to an underlying lymphoproliferative disease.1,9,10 A lymphoproliferative disorder should especially be considered in patients with monoclonality of the deposits on renal biopsy.1,8 ITG has also been reported in association with hepatitis C infection, HIV, leucocytoclastic vasculitis with hypocomplementaemia, lupus nephritis and cryoglobulinaemia.1 Thus, a diagnosis of ITG should lead to a search for an underlying disorder. In the present case, we were unable to identify an underlying condition. Our patient had previously been diagnosed with MS; however, there is no known association between ITG and MS.

The clinical course of patients with ITG is difficult to predict because published series have been too small, the follow-up was too short and/or they included patients with ITG secondary to underlying disorders.11,12 Nevertheless, treatment directed at the underlying disorder can lead to remission of nephrotic syndrome in patients with secondary ITG.9 In one study 83% of nephrotic patients with lymphoproliferative disease and/or paraproteinaemia attained a complete or partial remission.12 To date, there is no proven effective therapy for idiopathic ITG and the response to immunosuppressive therapy is generally poor.12 However, according to a recent study in patients with FGN, prognosis may differ according to histology, with the membranous type having the best prognosis.13 We therefore decided to treat our patient according to our protocol for idiopathic membranous nephropathy.15 For low-risk patients (normal renal function and low urinary excretion of β2-microglobulin and IgG), a wait-and-see policy is advised. During supportive therapy our patient attained a remission of proteinuria.

To our knowledge, this is the first case report describing a remission of proteinuria not induced by immunosuppressive therapy in a patient with idiopathic ITG. Admittedly, our case is somewhat different from previous reports.1,3,16 In contrast to the previously described atypical membranous nephropathy lesions associated with mesangial matrix expansion, immune deposits in our patient were typical of membranous nephropathy and mesangial deposits were completely absent. This may explain the benign course in our patient, which is similar to idiopathic membranous nephropathy.

In conclusion, we demonstrate a female patient with idiopathic ITG and a typical membranous pattern on light microscopy and immunofluorescence, who attained a spontaneous remission of proteinuria. The present case also demonstrates that a diagnosis of membranous nephropathy and/or ITG can be missed by light microscopy and immunofluorescence. Therefore, electron microscope examination is mandatory in patients with a nephrotic syndrome.

REFERENCES