

## Exceptional Case

# Nephrotic-range proteinuria on interferon- $\beta$ treatment: immune-induced glomerulonephritis or other pathway?

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### Abstract

We present a case report of a 37-year-old woman with multiple sclerosis (MS) who developed nephrotic-range proteinuria secondary to membrano proliferative glomerulonephritis (MPGN)-like disease with mesangial C3 deposition without evidence of immune-complex deposition in the context of long-term interferon- $\beta$  (IFN- $\beta$ ) therapy. The complete remission of proteinuria following cessation of IFN- $\beta$ , strongly suggests causality. To our knowledge, this is the second case report of MPGN associated with IFN- $\beta$  use. This being the case, the negative immune screen, normal inflammatory markers and the absence of immune complex deposits would imply a different pathway to that previously suggested.

**Keywords:** immune complex deposit; interferon  $\beta$ ; membrano proliferative glomerulonephritis; multiple sclerosis; nephrotic-range proteinuria

### Introduction

Interferon- $\beta$  (IFN- $\beta$ ) is a multifunctional cytokine with immune modulatory properties. It is currently the mainstay immunotherapy of relapsing-remitting multiple sclerosis (MS). IFN- $\beta$  has been linked with several types of glomerulonephritis.

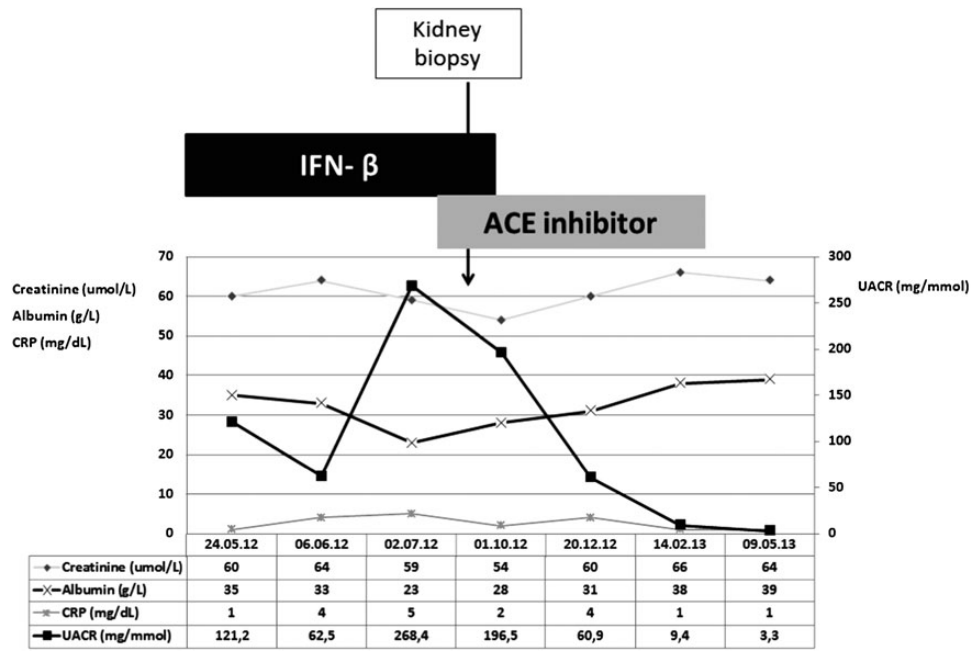
We present a case of an MS patient who developed nephrotic-range proteinuria following IFN- $\beta$  treatment over a timespan of more than 9 years. The histology was suggestive of membrano proliferative glomerulonephritis (MPGN), but the absence of immune-complex deposition suggested a non-immune IFN- $\beta$ -related disease. We also describe a literature review.

### Case report

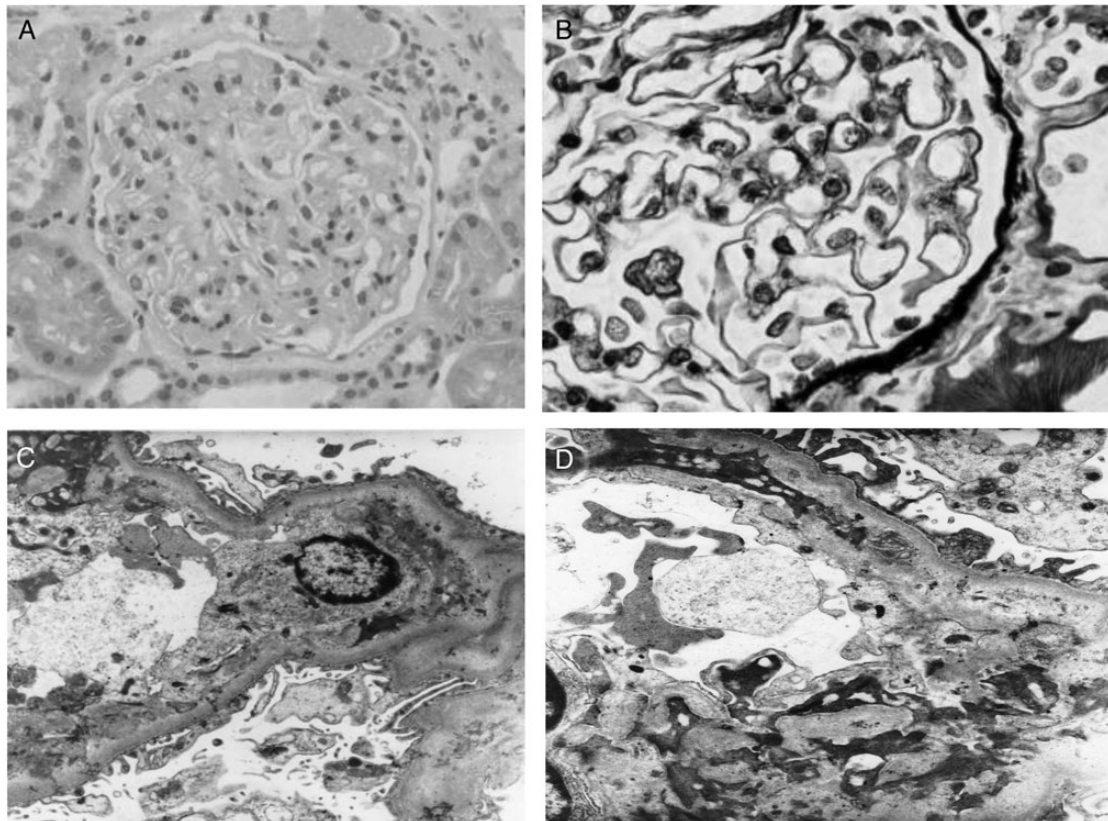
This is a case report of a 37-year-old female who was referred to our renal outpatient clinic with the incidental finding of proteinuria determined by dipstick. She had been diagnosed with MS 9 years previously. She had been on long-term IFN- $\beta$  44  $\mu$ g three times weekly for most of this time. She had a normal pregnancy 10 years previously (a year prior to her MS diagnosis). She was not on any other medication. She denied haematuria, rash, arthralgia, weight loss, nose bleeds and haemoptysis. At the time of presentation in clinic, she had a urine albumin creatinine ratio (UACR) of 268 mmol/L, equivalent to a protein leak of about 2.5 g/24 h. Her serum creatinine (Cr) was 60  $\mu$ mol/L, albumin 28 g/L, haemoglobin 11.5 g/dL, adjusted calcium 2.3 mmol/L, C-reactive protein (CRP) of 2 mg/L and normal complement levels (C3 0.98 g/L and

C4 0.19 g/L) (Figure 1). On examination, her blood pressure was 127/80 mmHg. She had normal heart sounds. Her lungs were clear and her abdomen was soft and non-tender. She had no pedal oedema. In view of the proteinuria, an angiotensin-converting enzyme (ACE) inhibitor was introduced at this point (Figure 1). Subsequently, urine culture, anti-glomerular basement membrane antibodies, myeloma screen, hepatitis B and C serology and human immunodeficiency virus were all negative. The ultrasonography showed unequal size kidneys, the right kidney measuring 10 cm and the left 12.5 cm in length.

The renal biopsy showed 11 glomeruli with a general increase in the cellularity predominantly in the mesangium (Figure 2A). There was no tuft necrosis or endocapillary proliferation. The glomerular capillary basement membrane showed foci of basement membrane irregularity and few foci of 'double contours' (Figure 2B). The tubules and interstitium appeared essentially normal. The electron micrographs confirmed focal mesangial cell interposition (Figure 2D), with new basement membrane material deposited on the internal surface. This was associated with a few small and rather 'woolly' accumulations of slightly electron-dense material, but these did not have the typical morphology of immune complex-type electron deposit (Figure 2C). Endothelial cells appeared somewhat swollen, with infrequent areas of fenestration. The epithelial cell foot processes appeared remarkably normal. There were mild mesangial cell interposition and basement membrane irregularities, with no more than a hint of glomerular hypercellularity. The immunofluorescence showed a partly particulate deposition of predominantly C3 within the mesangium with a lesser deposition of IgG, M and A. The renal biopsy report concluded that in the absence of immune-complex deposition (or linear dense



**Fig. 1.** Clinical evolution of the patient during 1 year. On the graph above, we represent the timing of biochemical parameters: serum creatinine levels, serum albumin levels, albuminuria (expressed as UACR, urine albumin creatinine ratio) and serum inflammatory markers as C-reactive protein (CRP). We also represented the treatment timeline. Our patient was on long-term IFN-β treatment since the diagnosis of multiple sclerosis (MS), 9 years prior to the clinic review. On July 2012, she developed nephrotic-range proteinuria with slight deterioration in kidney function and a drop in the serum albumin levels but normal CRP. At this point, an ACE inhibitor was introduced and the renal biopsy date was arranged. Based on the biopsy results, IFN-β was switched to Glatiramer acetate, with progressive improvement of the proteinuria even after stopping the ACE inhibitor.



**Fig. 2.** Kidney biopsy specimen. (A) Glomeruli showing a mild generalized increase in mesangial cellularity. Haematoxylin and eosin. Magnification ×100. (B) By methenamine silver stain, glomeruli showing reduplication of the glomerular basement. Magnification ×200. (C) By transmission electron microscopy, poorly defined deposits. (D) By transmission electron microscopy, photograph showing interposition of mesangial cytoplasm.

deposits), these findings justified a search for other possible causes of low-grade endothelial damage, such as the use of interferon therapy.

Unfortunately, following the renal biopsy, she bled and required embolization.

In view of the biopsy report, IFN- $\beta$  was switched to Glatiramer acetate (Copaxone<sup>®</sup>) 20 mg daily with a resultant progressive improvement of the proteinuria (Figure 1). The proteinuria remains negative at 5 months even after stopping the ACE inhibitor therapy.

## Discussion

We present the case report of a 37-year-old woman with nephrotic-range proteinuria secondary to MPGN-like glomerulonephritis without associated immune-complex deposition in the context of long-term IFN- $\beta$  therapy. The complete remission of the proteinuria after cessation of IFN- $\beta$  treatment strongly suggests an aetiological role for IFN- $\beta$  in the development of the glomerulonephritis. To our knowledge, this is the second case of MPGN associated with IFN- $\beta$  therapy but the negative immune screen, normal inflammatory markers and the absence of immune complex deposition would imply a different pathway than that previously suggested [1].

IFN- $\beta$  is one of the most effective drugs against MS. Its efficacy is thought to be related to its ability in restoring the impaired trafficking of inflammatory cells into the central nervous system and the modification of the pro-inflammatory/anti-inflammatory cytokine homeostasis. The endogenous production of type I IFNs (IFN- $\alpha$  and IFN- $\beta$ ) has a central role in the mediation of antiviral immunity and in many types of kidney diseases [2].

IFN treatment has been linked to different kinds of glomerulonephritis, including minimal change [3, 4], focal and segmental glomerulosclerosis (FSGS) [5, 6] and collapsing FSGS [7]. Glen *et al.* reported the largest cohort ( $n=11$ ) of collapsing FSGS that developed in patients during treatment with different kinds of IFN. In this patient cohort with collapsing FSGS, three patients were on IFN- $\beta$  for MS. Furthermore, no one in this group had hypocomplementaemia. They had neither signs nor symptoms of systemic lupus erythematosus (SLE). The median and mean duration of IFN therapy at the time of renal biopsy was 4.0 and 12.6 months, respectively, in this cohort.

Typically, features of MPGN on light microscopy include mesangial hypercellularity, endocapillary proliferation and capillary wall remodelling with the formation of double contours [8]. MPGN is classified into three groups electron-microscopically. Recently, it has been divided on the basis of pathophysiology, i.e. based on immune complex-mediation and complement mediation [9]. MPGN without immune-complexes or complement deposition has been described in thrombotic micro-angiopathies [10], thrombotic thrombocytopenic purpura or haemolytic-uraemic syndrome, atypical haemolytic-uraemic syndrome associated with complement abnormalities [11], the anti-phospholipid antibody syndrome, drug-induced thrombotic micro-angiopathies, nephropathy associated with bone marrow transplantation, radiation nephritis, malignant hypertension and connective-tissue disorders resulting from injury to the endothelial cells [7].

Wallbach *et al.* [1] recently published a case report of a 40-year-old woman with MS on treatment with IFN- $\beta$  who developed nephrotic syndrome. The kidney biopsy showed

tubulo reticular inclusions and positive results for all five major immunofluorescence stains (IgA, IgG, IgM, C1q and C3). The biopsy results were highly suggestive of lupus nephritis. Wallbach *et al.* on the basis of these biopsy findings, together with other reports of SLE induced by IFN [12–14], suggested that IFN- $\beta$  has the potential to induce and maintain immune complex-mediated MPGN. This is in spite of normal complement levels and absence of serological or clinical findings of SLE.

The pathway of how IFN- $\beta$  therapy triggered an MPGN-like glomerulonephritis without immune complex deposits is uncertain. Viral infections activate systemic antiviral immune responses interfering with systemic autologous IFN production and contributing to the triggering of glomerular diseases [15]. It has been reported that, IFN- $\alpha$ 4, but not IFN- $\alpha$ 5 or IFN- $\beta$ , was increasingly expressed by intrinsic renal cells during autologous nephrotoxic serum nephritis and that the amount of renal IFN- $\alpha$ 4 expression correlated with proteinuria and renal excretory function [16]. Adenovirus has been hypothesized as the trigger to make this IFN- $\alpha$ 4 over-expression functionally relevant. Although these described glomerulonephritis had immune complex deposits [17], the hypothesis of a viral infection triggering nephrotic syndrome could not explain its onset after several years of treatment (8 years in our patient, mean 12.6 months in Glen *et al.* cohort [6] and several non-specified in Wallbach *et al.* [1]).

Interestingly, the effect of IFN- $\beta$  on proteinuria remains unclear. It has been reported that IFN- $\beta$  significantly induced podocyte death and increased the permeability of podocyte monolayers and suppressed renal progenitor differentiation into mature podocytes [18]. On the contrary, there are some reports of amelioration of glomerular injury by recombinant IFN- $\beta$  treatment on animal models [19, 20]. Therefore, further larger controlled, randomized trials should clarify the effect of IFN- $\beta$  on proteinuria.

On the other hand, the absence of immune-complex deposition in our patient's renal biopsy may explain the complete remission of the proteinuria (in contrast with the partial remission in patients reported by Wallbach *et al.* [1] and Glen *et al.* [6]), and it may also suggest a better prognosis.

In summary, we report an IFN- $\beta$  related nephrotic-range proteinuria secondary to MPGN-like glomerulonephritis without immune complex deposits. It is therefore our opinion that the complete remission of proteinuria after stopping IFN- $\beta$  therapy, together with the negative immune screen, normal inflammatory markers and the absence of immune complex deposition, would justify consideration of a different pathway for the development of glomerulonephritis not previously reported.

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*Conflict of interest statement.* None declared.

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