Nephrotic-range proteinuria on interferon-β 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 membranoproliferative glomerulonephritis (MPGN)-like disease with mesangial C3 deposition without evidence of immune-complex deposition in the context of long-term interferon-β (IFN-β) therapy. The complete remission of proteinuria following cessation of IFN-β, strongly suggests causality. To our knowledge, this is the second case report of MPGN associated with IFN-β 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 β; membrano proliferative glomerulonephritis; multiple sclerosis; nephrotic-range proteinuria

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

We present a case of an MS patient who developed nephrotic-range proteinuria following IFN-β treatment over a timespan of more than 9 years. The histology was suggestive of membranoproliferative glomerulonephritis (MPGN), but the absence of immune-complex deposition suggested a non-immune IFN-β-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-β 44 µg 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 µmol/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 nontender. 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 hyper cellularity. 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.
cytopenic purpura or haemolytic complexes or complement deposition has been described in and complement mediation [9]. MPGN without immune-pathophysiology, i.e. based on immune complex-mediation and segmental glomerulosclerosis (FSGS) [5, 6] and coltours [8]. MPGN is classi
capillary wall remodelling with the formation of double con-
mesangial hyper cellularity, endocapillary proliferation and
cohort.
biopsy was 4.0 and 12.6 months, respectively, in this
toms of systemic lupus erythematosus (SLE). The median
patient cohort with collapsing FSGS, three patients were
for MS. Furthermore, no one in this group had hy-
pocomplementaemia. They had neither signs nor symp-
toms of systemic lupus erythematosus (SLE). The median
and mean duration of IFN therapy at the time of renal
4.0 and 12.6 months, respectively, in this
cohorts.
Typically, features of MPGN on light microscopy include
mesangial hyper cellularity, endocapillary proliferation and
capillary wall remodelling with the formation of double con-
tours [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 thrombo-
cytopenic purpura or haemolytic-uraemic syndrome, aty-
pical 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 hypertens-
sion 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-β 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 find-
tings, together with other reports of SLE induced by IFN
[12–14], suggested that IFN-β has the potential to induce
and maintain immune complex–mediated MPGN. This is in
spite of normal complement levels and absence of serolo-
gical or clinical findings of SLE.
The pathway of how IFN-β 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 glo-
erular diseases [15]. It has been reported that, IFN-α,4,
but not IFN-α5 or IFN-β, was increasingly expressed by
intrinsic renal cells during autologous nephrotoxic serum
nephritis and that the amount of renal IFN-α4 expression
was positively correlated with proteinuria and renal excretory function [16]. Adenovirus has been hypothesized as the trigger
to make this IFN-α4 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-specific in Wallbach et al. [1]).
Interestingly, the effect of IFN-β on proteinuria remains
unclear. It has been reported that IFN-β significantly
induced podocyte death and increased the permeability
of podocyte monolayers and suppressed renal progenitor
differentiation into mature podocytes [18]. On the con-
trary, there are some reports of amelioration of glomerular
injury by recombinant IFN-β treatment on animal models
[19, 20]. Therefore, further larger controlled, randomized
trials should clarify the effect of IFN-β on proteinuria.
On the other hand, the absence of immune-complex
deposition in our patient’s renal biopsy may explain the com-
plete 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-β related nephrotic-
range proteinuria secondary to MPGN-like glomerulone-
phritis without immune complex deposits. It is therefore
our opinion that the complete remission of proteinuria
after stopping IFN-β 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.

References
1. Wallbach M, Gröne HJ, Kitze B et al. Nephrotic syndrome in a
multiple sclerosis patient receiving long-term interferon beta
therapy. Am J Kidney Dis 2013; 61: 786–789
2. Anders HJ, Lichtnekert J, Allam R. Interferon-alpha and -beta
in kidney inflammation. Kidney Int 2010; 77: 848–854
3. Nakao K, Sugiyama H, Makino E et al. Minimal change nephro-
tic syndrome developing during postoperative interferon-
beta therapy for malignant melanoma. Nephron 2002; 90: 498–500
4. Kumasaka R, Nakamura N, Shirato K et al. Nephrotic syndrome associated with interferon-beta-1b therapy for multiple sclerosis. Clin Exp Nephrol 2006; 10: 222–225
5. Dressler D, Wright JR, Houghton JB et al. Another case of focal segmental glomerulosclerosis in an acutely uraemic patient following interferon therapy. Nephrol Dial Transplant 1999; 14: 2049–2050
6. Shah M, Jenis EH, Mookerjee BK et al. Interferon-alpha-associated focal segmental glomerulosclerosis with massive proteinuria in patients with chronic myeloid leukemia following high dose chemotherapy. Cancer 1998; 83: 1938–1946
7. Markowitz GS, Nass SH, Barry Stokes M et al. Treatment with IFN-α, β, or γ is associated with collapsing focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2010; 5: 607–615
8. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis—a new look at an old entity. N Engl J Med 2012; 366: 1119–1131
9. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. Semin Nephrol 2011; 31: 341–348
10. Goldberg RJ, Nakagawa T, Johnson RJ et al. The role of endothelial cell injury in thrombotic microangiopathy. Am J Kidney Dis 2010; 56: 1168–1174
11. Noris M, Remuzzi G. Atypical hemolytic–uremic syndrome. N Engl J Med 2009; 361: 1676–1687
12. Bonaci-Nikolic B, Jeremic I, Andrejevic S et al. Anti-double stranded DNA and lupus syndrome induced by interferon-beta therapy in a patient with multiple sclerosis. Lupus 2009; 18: 78–80
13. Gota C, Calabrese L. Induction of clinical autoimmune disease by therapeutic interferon-alpha. Autoimmunity 2003; 36: 511–518
14. Sladkova V, Mares J, Lubenova B et al. Drug-induced systemic lupus erythematosus in interferon beta-1b therapy. Neuro Endocrinol Lett 2011; 32: 4–6
15. Allam R, Lichtnekert J, Moll AG et al. Viral RNA and DNA trigger common antiviral responses in mesangial cells. J Am Soc Nephrol 2009; 20: 1986–1996
16. Fairhurst AM, Xie C, Fu Y et al. Type I interferons produced by resident renal cells may promote end-organ disease in autoantibody-mediated glomerulonephritis. J Immunol 2009; 183: 6831–6838
17. Flür K, Allam R, Zecher D et al. Viral RNA induces type I interferon-dependent cytokine release and cell death in mesangial cells via melanoma-differentiation-associated gene-5: implications for viral infection-associated glomerulonephritis. Am J Pathol 2009; 175: 2014–2022
18. Migliorini A, Angelotti ML, Mulay SR et al. The antiviral cytokines IFN-α and IFN-β modulate parietal epithelial cells and promote podocyte loss: implications for IFN toxicity, viral glomerulonephritis, and glomerular regeneration. Am J Pathol 2013; 183: 431–440
19. Satchell SC, Buchatska O, Khan SB et al. Interferon-beta reduces proteinuria in experimental glomerulonephritis. J Am Soc Nephrol 2007; 18: 2875–2884
20. Schwarting A, Paul K, Tschirner S et al. Interferon-beta: a therapeutic for autoimmune lupus in MRL-Faslpr mice. J Am Soc Nephrol 2005; 16: 3264–3272

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