INTRODUCTION

IFN- γ , a first-line immunotherapy for MS, may rarely have toxic effects on the renal microvasculature resulting in thrombotic microangiopathy (TMA) [1]. We report a case of TMA in a patient treated with IFN γ -1a for 20 years.

CASE

This 57-year-old female was diagnosed with relapsing remitting multiple sclerosis in 1988. Subcutaneous IFN γ -1a 44 μ g three times a week was commenced in 1994. She had not had a relapse since 2002.

In 2014 she presented to hospital after one week of worsening breathlessness. She had acute pulmonary oedema, acute renal failure and malignant hypertension. Her haemoglobin was 69 g/L (115-165) and platelet count 86×10^9 /L (150-300). A blood film showed microangiopathic haemolysis, with anisocytosis, bite cells, teardrop cells and moderate red cell fragmentation. Creatinine had risen to 298 μ mol/L from a normal level 6 months before. There was proteinuria of 9.39g/L (0-0.20), with no active sediment. An ADAMTS13 assay was normal at 57.3% (40-139%).

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Her renal biopsy showed active chronic TMA with glomerular capillary thrombus deposition, endothelial reactivity, vessel necrosis and wall duplication with luminal thrombus (Figure 1). Fibromuscular proliferation, focal fibrinoid necrosis and luminal thrombus was also present with within arterioles. There was fibrinogen staining of necrotic vessels as well as focal segmental fibrinogen staining of glomeruli, all typical of chronic TMA [2].

The patient was diagnosed with drug-induced TMA. Other possibilities—thrombotic thrombocytopenic purpura; infective or complement-mediated haemolytic uraemic syndrome—were excluded by normal ADAMTS13 activity and complement levels, absence of diarrhoea, and the lack of immune complex staining on renal biopsy. Her IFN²-1a therapy was discontinued and she was commenced on teriflunomide. Blood pressure was controlled on four antihypertensive agents. Twelve months later her renal function had plateaued at creatinine 215 $\mu\text{mol/L}$.

Discussion

The salient observation of our clinical-pathological report is the similarity between the vascular changes seen on this renal biopsy and previously described lung histological changes in IFN²-induced pulmonary arterial hypertension (PAH) [3]. Kavanagh *et al.* showed in his mouse model a direct toxic effect of Type I IFN on the

microvasculature of multiple organ systems via the type 1 IFN receptor and upregulation of response genes [1]. A dose-dependent spectrum of renal microvascular disease was found in transgenic mice engineered by the insertion of a murine IFN α 1 cDNA to variably over-produce Type I IFN. The renal biopsy in Figure 1 shows changes common to both human PAH and Kavanagh's mouse model—thrombus deposition and fibromuscular proliferation; local reactivity of endothelial cells; and capillary wall duplication [3,4]. This suggests a shared pathophysiological mechanism for different organ-specific forms of IFN ² microvascular toxicity. It could involve activation of the vasoconstriction cascade resulting in arterial fibromuscular intimal proliferation, or of the thromboxane cascade to induce a procoagulable state [3].

TMA appears to be related to the chronicity of IFN use. Most cases follow long-tolerated administration of doses exceeding 50 μ g per week, suggesting a cumulative toxicity effect [1]. High dosage for weight is a risk factor, and our patient had a low BMI[1]. There is often a short prodrome of rising blood pressure and declining renal function [5, 6]. Early identification of this adverse effect by clinical monitoring prevents further progression, although renal damage is not fully reversible.

References

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Figures:

Figure 1:Top. Silver Masson stain X 400mag of a glomerulus showing evidence of local reactivity of endothelial cells and capillary wall duplication.
Bottom Left. Silver Masson stain X 400mag showing fibromuscular proliferation of the arteriole.
Bottom right. Haematoxylin and Eosin stain X 400 mag showing glomerulus with endothelial reactivity and local thrombus formation.

ABSTRACT

Thrombotic microangiopathy (TMA) has been described with long-term interferon-beta (IFN- β) use. We report a case of biopsy-proven TMA in a patient with multiple sclerosis who had been having IFN- β -1a injections for twenty years. She presented with acute pulmonary oedema, renal failure, malignant hypertension, microangiopathic haemolytic anaemia and thrombocytopenia. Renal biopsy showed malignant hypertensive nephropathy and microangiopathy consistent with TMA. We postulate a dose-dependent toxicity of IFN- β -1a. Renal function stabilised after the interferon was ceased. Our report highlights similarities between microvascular changes seen in IFN-induced TMA and those observed in pulmonary arterial hypertension associated with IFN therapy. This suggests a shared pathophysiological mechanism.

Interferon beta in multiple sclerosis causing thrombotic microangiopathy: a case report

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