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The Case | The young philosopher with multiple sclerosis and proteinuria

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A 31-year-old white man with relapsing-remitting multiple sclerosis was referred to the nephrology ward by the caregiver neurologist because of the presence of new-onset subnephrotic proteinuria (from 0.7–2 g/24 h). He had been diagnosed with relapsing-remitting multiple sclerosis 15 years earlier and was initially treated with corticosteroids, followed by interferon beta-1a since 2003. No relapses had occurred in the past 3 years, during which he had been in good overall health.

He is a lean, athletic, young man with a degree in philosophy who works as a consultant and travels frequently (mainly throughout Europe). He is normotensive and has no residual neurologic deficit.

The initial workup showed normal kidneys on ultrasonography, serum creatinine level, 0.83 mg/dl (Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, 112 ml/min); blood urea nitrogen, 13 mg/dl; normal urine sediment; mild hypercholesterolemia (210 mg/dl); and hypertriglyceridemia (413 mg/dl). Complement levels, immunoglobulins, and other immunologic tests (antinuclear antibody, extractable nuclear antigen, anti–double-stranded DNA, and anti-neutrophil cytoplasmic antibody) were within the normal range. HIV and hepatitis B and C antigens and antibodies tested negative. Renal biopsy was performed (Figure 1).

What is the diagnosis?

The Diagnosis | Interferon-related associated thrombotic microangiopathy

Our patient, despite showing relatively mild proteinuria and preserved kidney function, showed severe glomerular involvement with characteristic lesions of thrombotic microangiopathy (TMA), including mesangiolysis and double contours in the kidney biopsy sample. One glomerulus showed collapsing glomerulopathy. No deposits were seen on immunofluorescent studies of 3 glomeruli. The interstitial compartment was normal. The collapsing glomerulopathy was considered most likely to be a consequence of TMA (Figures 1 and 2).

The association between multiple sclerosis and kidney diseases, namely, glomerulonephritis, albeit rare, has been previously described, including membranous nephropathy and Goodpasture syndrome.1

Interferon therapy (both alfa and beta) has been associated with renal manifestations. These include collapsing glomerulopathy and TMA.2, 3, 4 and 5 In recent reports, interferon-associated TMA was associated with an aggressive disease course and progressive and often irreversible renal function impairment.4 and 5

In our patient, interferon beta was discontinued, and a rapid drop in proteinuria was observed (<0.5 g/d within 4 weeks). Two months after interferon discontinuation, however, the patient experienced a severe relapse of optic neuritis, necessitating high doses of corticosteroids followed by azathioprine maintenance therapy.

His blood pressure at last follow-up was normal, and he had a serum creatinine level of 0.9 mg/dl and proteinuria of 155 mg/d.

The pathogenesis of interferon-associated TMA is not fully understood. The antiangiogenic activity of interferon may be the trigger for microangiopathy, whereas a report on the association with an apolipoprotein L1 high-risk genotype recently suggested the possibility that interferon and the receptors that stimulate interferon production could contribute to apolipoprotein L1–associated kidney disease, including collapsing glomerulopathy, at least in the African-American population. This high-risk genotype, however, was not present in our patient; genotyping was performed by targeted sequencing of apolipoprotein L1 exon 7.

Although nephrotoxicity is rare in patients receiving long-term interferon therapy, the onset of hypertension, proteinuria, and renal insufficiency should lead to the consideration of interferon discontinuation, which may allow for remission of proteinuria without the need for further specific therapy

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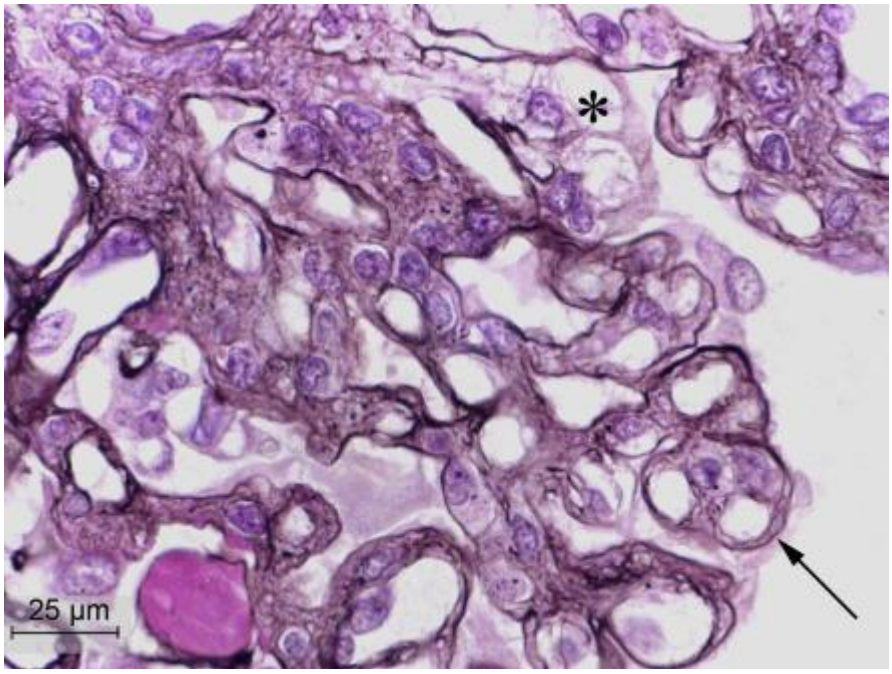

Figure 1. Acute lesions of microangiopathy with mesangiolysis (asterisk) and capillary loop doublecontours (arrow) (silver-stained section; Jones original magnification ×1000).

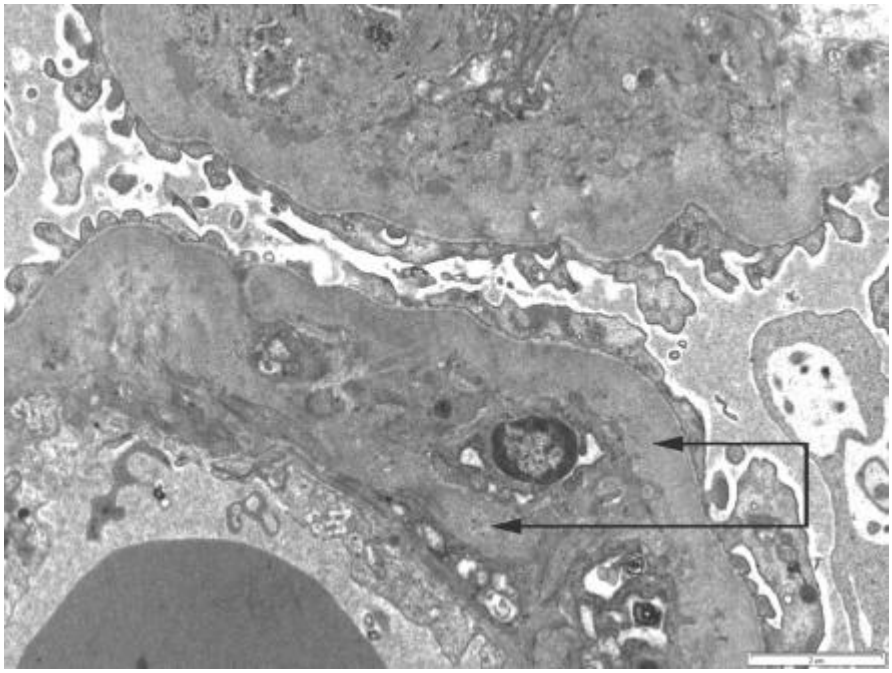
Figure 2. Ultrastructural features of thrombotic microangiopathy: double contour formation with subendothelial widening (arrows),loss of fenestrations of glomerular endothelial cells, and cellular interposition in the absence of electron dense deposits.