LETTERS

Benefit of anti-TNFα treatment for nephrotic syndrome in a patient with juvenile inflammatory bowel disease associated spondyloarthropathy complicated with amyloidosis and glomerulonephritis

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Historically, AA amyloidosis accounts for almost half of the deaths among patients with juvenile chronic arthritis, mainly due to complications of end stage renal failure.[1] Improved survival has been reported in patients whose underlying inflammatory disorder was brought to remission.[2] Tumour necrosis factor (TNFα) blocking agents have been used successfully in the treatment of inflammatory disorders complicated with AA amyloidosis.[3–5] We report the effect of TNFα in a case of AA amyloidosis secondary to juvenile spondyloarthropathy.

CASE REPORT

A 26 year old man with juvenile, inflammatory bowel disease associated spondyloarthropathy (HLA-B27+) was admitted to our hospital with proteinuria and ankle oedema.

He received combination therapy with methotrexate, sulfasalazine, methylprednisolone, and naproxen. His blood pressure was 130/80 mmHg. Table 1 shows the results of laboratory tests.

Ultrasound examination showed an increased bipolar size (130 mm) of both kidneys. A chest *x* ray examination was normal. A renal biopsy showed deposition of amorphous eosinophilic material in several glomeruli, the interstitium, and the arterial walls. The diagnosis of amyloidosis was confirmed by positive Congo red and AA stains and by electron microscopy (non-branching fibrils, approximately 10 nm width). Focal extracapillary proliferative glomerulonephritis was also present. Immunofluorescence showed mild positivity for IgA in the amyloid deposits. A rectal biopsy confirmed the diagnosis and showed no active inflammatory bowel disease.

Treatment with sulfasalazine was discontinued, the dose of methylprednisolone increased (32 mg/day), and treatment with lisinopril started. Incomplete regression of proteinuria occurred after one month (2.5 g/24 h).

Three months after diagnosis, treatment with anti-TNFα (Remicade, infliximab, Centocor, USA; 3 mg/kg; weeks 0, 2, 6, 14 and every eight weeks following) was started because of persistent arthritis. At that time the dose of methylprednisolone was 16 mg/day. With this treatment there was an

Table 1 Laboratory results at the time of admission

	Result	Normal range
Haemoglobin (g/l)	73	130–180
ESR (mm/1st h)	82	0
CRP (mg/l)	125	0.8–8
Serum albumin (g/l)	16.9	37–53
Creatinine clearance (ml/min)	68.5	75.0–125.0
C3 (g/l)	0.77	0.50–0.90
C4 (g/l)	0.10	0.10–0.40
C1q BA	Positive	
Protein G BA	Positive	
HAV	Negative	
HBV	Negative	
HCV	Negative	
ANF	Negative	
Rheumatoid factor	Negative	
Serum protein electrophoresis	No paraproteins	
Urinary protein excretion (g/24 h)	8.78	0.00–0.15
Urine sediment	Dysmorphic erythrocytes No haemoglobin casts	

ESR, erythrocyte sedimentation rate; CRP, C reactive protein; BA, binding activity; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; ANF, antinuclear factor.

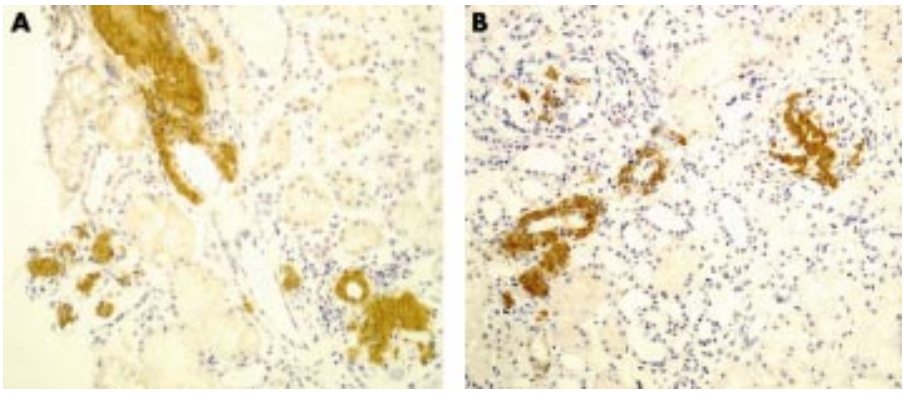

Figure 1 Renal biopsy specimen (A) at baseline and (B) after seven months of treatment. After seven months no decrease in the amount of amyloid is seen despite continuous infliximab treatment. AA stain, ×20.

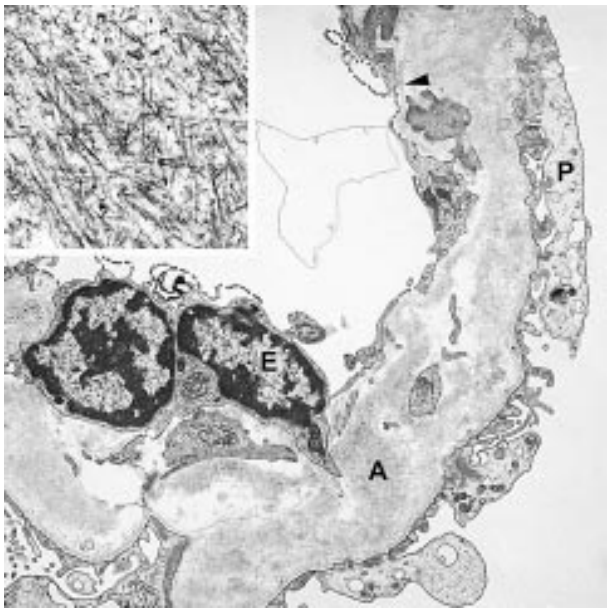

Figure 2 Amyloid depositions in glomeruli partly covered by newly formed glomerular basement membrane (×11 500). Inset: amyloid fibrils (×72 500). Arrowhead indicates newly formed basement membrane. E, endothelium; P, podocytes; A, amyloid fibrils.

immediate clinical improvement (reduction of pain and disease activity on a visual analogue scale). After six months serum haemoglobin, C reactive protein (CRP), albumin, and the erythrocyte sedimentation rate (ESR) returned to normal with further reduction of proteinuria. After nine months urine analysis was normal and protein excretion reduced to 0.24 g/24 h.

A renal biopsy was repeated after seven months of treatment. An equal amount of amyloid fibrils was present in the mesangium, the subendothelial, and subepithelial space. A newly formed basal membrane partly covered these deposits (figs 1 and 2). Immunofluorescence did not differ from the first biopsy, but there were no more signs of intra- or extracapillary proliferation.

DISCUSSION

Our patient presented with a nephrotic syndrome and dysmorphic haematuria. Renal biopsy showed amyloidosis and extracapillary proliferative glomerulonephritis. This association has been reported previously.[6] Although it remains unclear whether there is a causal relationship between these renal conditions, crescent formation is a possible explanation for the rapid decline in renal function sometimes seen in amyloidosis.

In this case IgA staining was only mildly positive in the amyloid deposits and not in the glomerular mesangium, excluding IgA nephritis, known for its association with spondyloarthropathy.[7]

A possible explanation for the improvement of the proteinuria in our patient might be the direct effect of TNFα on the pathogenesis of the nephrotic syndrome. TNFα is known to play a part in glomerular inflammation[8] and it can increase glomerular permeability for albumin.[9] Both effects can be neutralised by anti-TNFα antibodies. The systemic administration of infliximab might well have resulted in an immediate suppression of local TNFα effects in the kidney, explaining the fast improvement of the proteinuria.

Another explanation might be the profound effect of TNFα blocking agents on the production of serum amyloid A protein. A reduction in the systemic amyloid load might result in decreased amyloid deposition and structural healing mechanisms at the level of amyloidotic organs.[2] Like others we found no decrease of amyloid deposits. The new formation of glomerular basement membrane in our view is a secondary process not explaining decreased proteinuria, in contrast with reports by other authors.[10] In amyloidosis, proteinuria results from defects in the slit membrane caused by continuous deposition of amyloid fibrils in the lamina rara externa. When amyloid deposition is discontinued, the precipitated amyloid becomes "encapsulated" in the basement membrane by new formation of the latter, preventing further damage to the slit membrane.

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