Case Report

HLA-B27 Associated Spondyloarthropathy, Vasculitis, and Amyloid Enteropathy: Response to Infliximab

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ABSTRACT. In 2000 we described a patient with HLA-B27 associated spondyloarthropathy (SpA) and severe ascending aortitis requiring surgical intervention. Despite continued immunosuppressive therapy she developed narrowing of the distal part of the right subclavian artery and proximal axillary artery secondary to active vasculitis. In addition, biopsy-proven amyloid gastroenteropathy developed causing persistent diarrhea and iron deficiency anemia. Treatment with infliximab resulted in resolution of joint symptoms and rapid improvement in laboratory markers of inflammation. Diarrhea settled more gradually, such that her bowel habit had normalized 16 months after therapy commenced. (J Rheumatol 2005;32:382–5)

Key Indexing Terms:
AORTITIS HLA-B27 SPONDYLOARTHROPATHY INFLIXIMAB AMYLOIDOSIS

This is the followup of a previous report of a young woman with a number of vascular and inflammatory complications associated with a HLA-B27 associated spondyloarthropathy (SpA).

CASE REPORT

We previously reported the case of a 24-year-old woman with HLA-B27 associated SpA and severe ascending aortitis requiring surgical correction[1]. Histology of the aorta at the time of surgery showed an inflammatory cell infiltrate and destruction of the media[1]. We now describe her progress since March 1998.

Following surgical replacement of her ascending aorta she continued to experience peripheral arthralgia/arthritis and severe malaise in association with laboratory evidence of persistent inflammation. In April 1998, she represented with neck and right arm pain. Laboratory results revealed hemoglobin (Hb) 94 g/l (normal 115–150), erythrocyte sedimentation rate (ESR) 103 mm/h (1–30), and C-reactive protein (CRP) 103 mg/l (< 10). A chest computed tomography (CT) scan and echocardiography showed no evidence of aortic dissection. Ongoing vasculitis/aortitis was considered the most likely cause of her symptoms. Prednisone was increased to 60 mg daily and she commenced intravenous cyclophosphamide every 3 weeks. There was a transient improvement (Figure 1) in symptoms and laboratory indices. However, 4 months later she had again deteriorated and salazopyrin 1 g twice daily was added. Ten cycles of cyclophosphamide were completed and the prednisone gradually was reduced, but not withdrawn.

By February 1999 she had developed episodic diplopia, ataxia, nausea, and vertigo. A magnetic resonance image (MRI) of the brain revealed a small lesion in the left cerebellar hemisphere, consistent with embolic infarction of indeterminate age. Angiography of the ascending aorta and cerebral circulation was normal. Warfarin was started and she remained relatively stable until August 1999, when she presented with right hemplegia and aphasia. CT scan of the brain was normal; however, the ESR remained raised (103 mm/h) and Hb low (88 g/l). Again an active vasculitic process was thought likely, and prednisone was increased to 40 mg daily, salazopyrin was discontinued, and chlorambucil 4 mg daily was started. One month later the ESR decreased (58 mm/h). However, despite therapy she remained symptomatic, with malaise and joint pain. After 2 months chlorambucil was ceased as the prothrombin ratio became difficult to stabilize and she developed hemorrhoidal bleeding.

In March 2000 she had a flare of peripheral and axial arthritis, with inflammation in the small joints of the hands and both knees and inflammatory low back pain. A trial of minocycline produced no change in symptoms or inflammatory markers after one month and therefore was stopped.

In July 2000 she presented with persisting right arm pain and difficulty raising the arm above her head. No obvious musculoskeletal cause for her symptoms was found. MRI angiography and subsequent angiography showed a narrowing of the distal part of the right subclavian artery and proximal axillary artery (Figure 2). Angioplasty of the stenosis relieved the symptoms. Following this, mycophenolate mofetil 1 g twice daily was commenced, but was stopped after 2 months, as there was little change in her condition.

In December 2000 an episode of *Salmonella* gastroenteritis was followed by an exacerbation of peripheral and axial arthritis. She was treated with oral ciprofloxacin. Despite clearance of the infection, diarrhea persisted. In October 2001 colonoscopic biopsies revealed colitis with evidence of active inflammation and marked submucosal amyloid deposition (Figure 3).

In November 2001 a trial of infliximab 5 mg/kg was started, at Weeks 0, 2, 6, and 12, then every 8 weeks. At the time of her 6-week infusion, she reported dramatic clinical improvement in her joint symptoms and general malaise. This improvement was reflected in a reduction in CRP and elevation of Hb (Figure 1). Methotrexate (MTX) was added at Week 12 to reduce the risk of tachyphylaxis, later being substituted with azathioprine 150 mg daily because of intolerance to MTX. Prednisone was gradually reduced, but could not be completely withdrawn because of iatrogenic adrenal insufficiency. Her bowel habit normalized after 16 months of therapy. The subclavian lesion has not recurred, nor have any new vascular lesions developed since control of the inflammatory process with infliximab. She continues infliximab therapy, replacement corticosteroid, and azathioprine.

DISCUSSION

Aortitis and amyloidosis are recognized complications of

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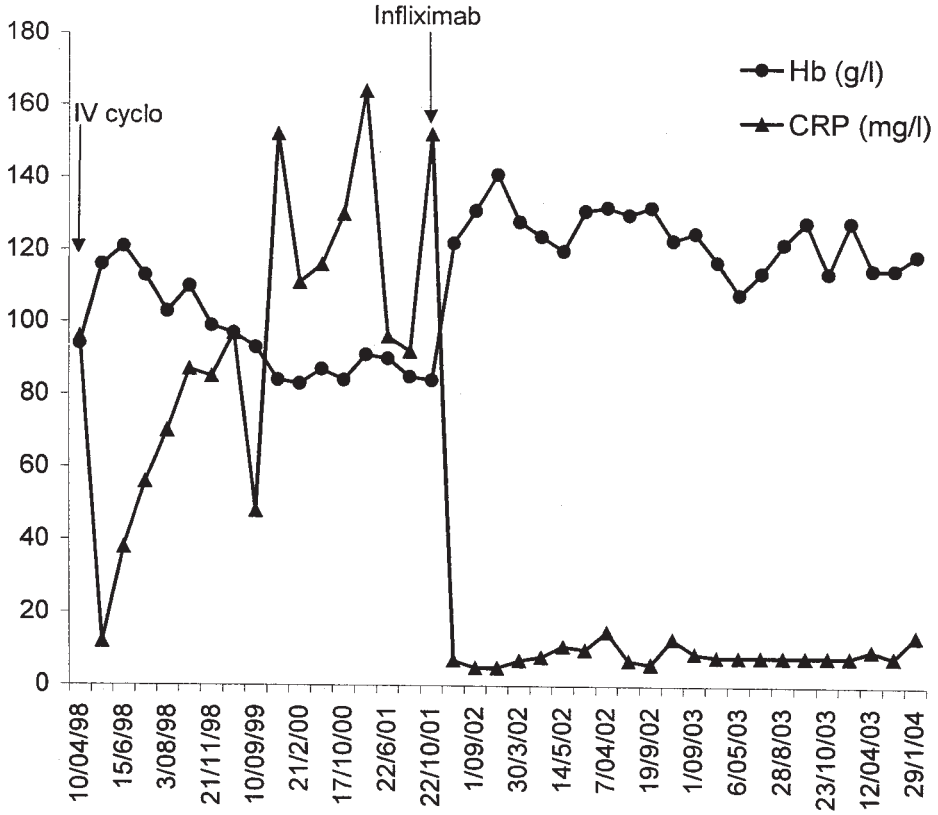

Figure 1. C-reactive protein (CRP) and hemoglobin (Hb) results over time. After intravenous cyclophosphamide was started there was a transient reduction in CRP and increase in Hb. Treatment with infliximab resulted in a rapid and sustained reduction in CRP and elevation of Hb.

ankylosing spondylitis (AS). Despite postoperative immunosuppressive therapy with various agents including prednisone, cyclophosphamide, salazopyrin, chlorambucil, mycophenolate mofetil, and azathioprine, our patient continued to show evidence of active inflammation and vasculitis and developed a subclavian stenosis and amyloid enteropathy. Treatment with infliximab resulted in rapid and sustained improvement in both clinical and serological

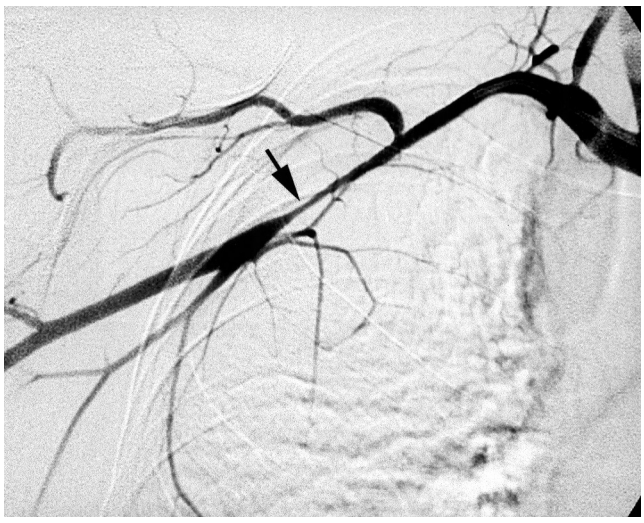

Figure 2. Angiograph (July 2000) reveals the right subclavian artery stenosis prior to angioplasty.

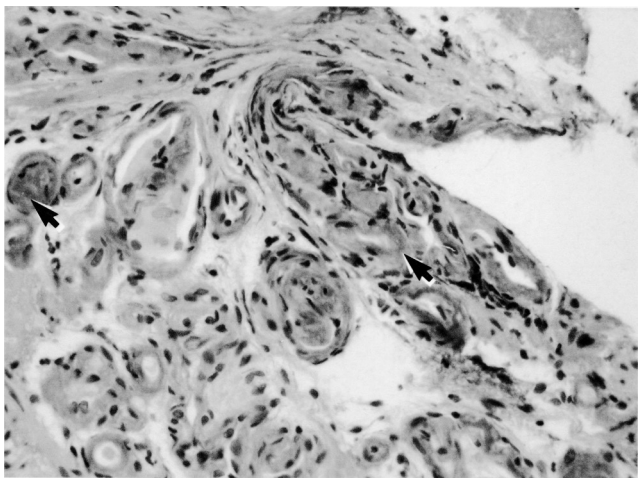

Figure 3. Congo red stain of section of bowel showing colitis with evidence of significant amyloid deposits (400× magnification). White arrows indicate amyloid deposits confirmed with birefringence.

markers of disease activity. Diarrhea was slower to settle, but did resolve completely after 16 months of therapy. A request to repeat colonoscopic large bowel biopsy was declined.

Tumor necrosis factor-α (TNF-α) has been implicated in the pathogenesis of SpA and thus its inhibition has a role in management. Serum TNF-α concentrations are increased in patients with AS compared to those with noninflammatory back pain[2]. There is abundant TNF-α mRNA in sacroiliac joint biopsies from patients with active AS[3]. Further, mice overexpressing TNF have been shown to develop bilateral erosive sacroiliitis, which can be inhibited by TNF blockade with infliximab[4].

There is now an increasing body of evidence that supports the use of TNF-α inhibitors in the management of SpA (recently reviewed[5]). As with our patient, the clinical response to infliximab has been reported to be rapid[6,7]. Interestingly, while CRP may not necessarily be a reliable marker of disease activity in AS, patients with a high CRP (as in our case) have been reported to respond better to anti-TNF-α therapy[6].

The effect of infliximab on synovial histology has been studied in patients with active knee synovitis and SpA[8,9]. There was a reduction in the synovial lining layer thickness, vascularity, and infiltration by neutrophils and macrophages. In addition, vascular cell adhesion molecule-1 expression is reduced in the synovial lining layer, and E-selectin expression is reduced in the sublining layer[9].

Our patient developed symptomatic amyloid enteropathy, presumably secondary to her prolonged uncontrolled inflammation. Interestingly, diarrhea settled 16 months after infliximab was started and has not recurred. We presume that the clinical improvement reflects histological improvement, although she has declined repeat biopsy to demonstrate this.

Secondary or reactive amyloidosis occurs in patients with chronic inflammatory diseases such as AS and rheumatoid arthritis (RA). It results from deposition of amyloid fibrils, of which the circulating precursor is serum amyloid A (SAA). TNF-α drives the inflammatory cascade, including the production of a number of hepatic proteins (CRP and SAA) that serve as serological markers of systemic inflammation. SAA contributes to the development of secondary amyloid, which is the likely source of amyloid in our patient. In patients with AS, ESR and CRP have been correlated with SAA concentrations[10].

While anti-TNF-α therapies have been shown to be highly effective in the management of both RA and AS, the effect of these agents on reversing secondary amyloidosis is not well reported. Several proinflammatory cytokines including TNF-α increase SAA concentrations, and recombinant TNF-α has been reported to enhance amyloid deposition in the Syrian hamster[11]. Concentrations of SAA < 10 mg/l have been reported to be associated with a more favorable outcome in secondary amyloidosis[12], and in patients with RA treated with the TNF-α inhibitor infliximab, SAA concentrations have been shown to be significantly reduced[13]. There may thus be a role for TNF-α blockade in the treatment of secondary amyloidosis.

A number of case reports suggest that secondary renal amyloidosis can reverse. Elkayam, *et al* reported rapid reduction of SAA and CRP and normalization of 24-hour urine protein excretion in a patient with RA and secondary renal amyloidosis in response to infliximab and MTX[14]. Drewe, *et al* reported rapid improvement in nephrotic syndrome in a patient with amyloidosis secondary to TNF receptor-associated syndrome upon treatment with etanercept[15]. In a larger series Gottenberg, *et al* examined the effects of TNF-α blockade (etanercept or infliximab) in 15 patients with renal amyloidosis secondary to inflammatory arthritis (40% AS, 33% RA)[16]. In addition to renal involvement 3 patients had diarrhea with biopsy-proven gastrointestinal amyloid deposits. The underlying inflammatory disease was controlled in 11/15 patients and proteinuria and/or renal function improved in 3/15, stabilized in 5/15, and worsened in 7/15 patients with TNF-α blockade. Interestingly, in 2 of the 3 patients with gastrointestinal amyloid, diarrhea was significantly reduced, although there was no comment on how long it took for this to occur[16].

Our case demonstrates the benefits of TNF-α blockade not only in AS, but also in amyloid enteropathy. This case adds support to the suggestion that anti-TNF-α therapies may have a role in reversing the effects of secondary amyloidosis[16]. Further controlled clinical trials are warranted.

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