Case Report

Neurological Complications of Infliximab

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ABSTRACT. The use of anti-tumor necrosis factor-α (TNF-α) therapies has led to improved outcomes in the treatment of rheumatoid arthritis (RA). However, the use of these new therapeutic agents requires careful monitoring for adverse effects. We describe 3 patients who developed neurological disease closely associated with the use of infliximab, a monoclonal antibody that binds to and inactivates TNF-α. All had evidence of polyneuropathy, demyelinating in one and axonal in 2. One patient had a central nervous system syndrome. Physicians should be aware of these potential adverse effects when treating patients with infliximab. (First Release Mar 1 2006; J Rheumatol 2006;33:1018–20)

Key Indexing Terms:
INFLIXIMAB POLYNEUROPATHY RHEUMATOID ARTHRITIS PARESTHESIA

The development and use of biologic therapies directed against proinflammatory cytokines in the treatment of rheumatoid arthritis (RA) has resulted in significantly improved outcomes for patients. One of these therapies, infliximab, is a chimeric monoclonal antibody that binds specifically to soluble tumor necrosis factor-α (TNF-α), rendering the molecule biologically inactive. TNF-α is a peptide derived from T lymphocytes and macrophages and plays a central role in the development and maintenance of the inflammatory process that occurs in RA. It has many biologic activities including proinflammatory cytokine production, enhancement of leukocyte adhesion and migration, and stimulation of the release of tissue-destroying matrix metalloproteinases[1]. Macrophages that express TNF-α are also the effector cells for both axonal injury and active demyelination[2,3]. In patients with RA, the use of infliximab has been associated with significant improvement in symptoms and in quality of life measures. These agents have also been shown to prevent radiographic evidence of joint damage[4,5]. A number of adverse effects of infliximab have been reported, including hypersensitivity reactions, infection, lymphoproliferative disease, lupus-like syndromes, demyelinating disease, and anterior toxic optic neuropathy[6,7]. Thalidomide, an agent that acts in related ways to infliximab, accelerates TNF-α mRNA degradation and has been associated with peripheral neuropathy[8].

We describe 3 patients with neurological disease strictly related to the use of infliximab for the treatment of RA. Polyneuropathy was a common feature.

CASE REPORTS

Case 1. The first patient was a 50-year-old woman with longstanding seropositive RA who developed diplopia, left hand weakness and numbness, and right foot drop 2 weeks following her fifth dose of infliximab (3 mg/kg body weight; total exposure 1000 mg). She had no previous neurological problems. Her visual symptoms resolved spontaneously within 3–4 weeks, but her sensory and motor symptoms continued to progress. A neurological examination found marked weakness of the left triceps, wrist and finger extensors, intrinsic hand muscles, right tibialis anterior and posterior, and the extensor hallucis longus. The left triceps and right patellar reflex were absent. Sensation was intact. A cranial and spinal magnetic resonance image (MRI) within 2 weeks of presentation showed a small area of nonspecific T2 hyperintensity in the left parietal subcortical white matter and in the cervical spinal cord at the level of C2–C3. Laboratory investigations including a complete blood count, electrolytes, liver enzymes, serum B12, and folate were unremarkable. She was treated with monthly infusions of intravenous gammaglobulin (IVIG), with some improvement in her strength. However, 6 months after presentation, she continued to have distal limb weakness and loss of ankle reflexes, and had developed tremor and mild distal sensory abnormalities in the feet. At this time, electrophysiological studies identified features of a demyelinating polyneuropathy with conduction block, conduction slowing and temporal dispersion in several motor territories, normal sensory conduction, and remodeled enlarged motor units. Sural nerve biopsy showed a disproportionate number of thinly myelinated fibers, mild axon loss, a single onion bulb, and a single focus of perivascular mononuclear cells, but no active axonal degeneration, amyloid, or inflammation otherwise (Figure 1). Right quadriceps femoris biopsy showed mild nonspecific changes.

At 35 months after the onset of neurological symptoms, with ongoing monthly IVIG, she has made substantial clinical gains with recovered motor

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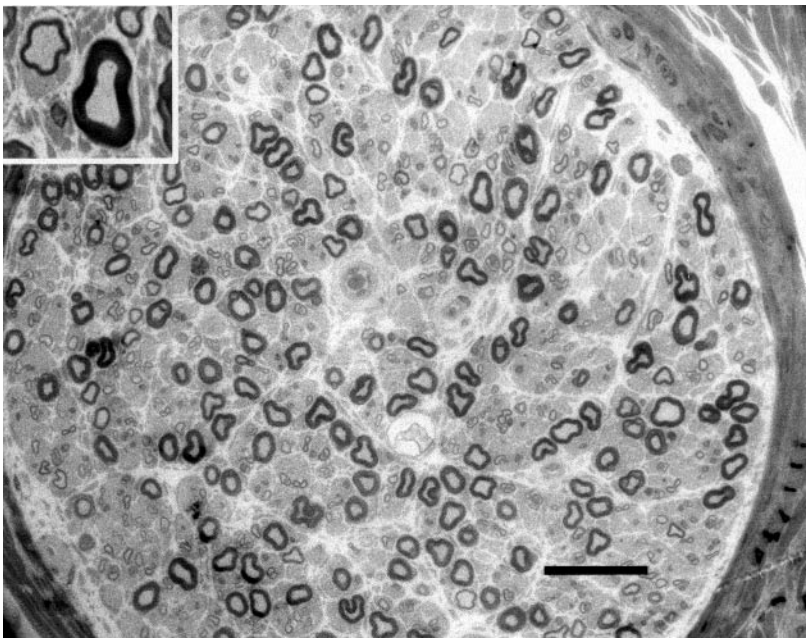

Figure 1. Transverse semithin toluidine blue-stained section of sural nerve from Patient 1. There is diffuse mild loss of large myelinated axons and an excess of thinly myelinated axons. Inset shows a thinly myelinated axon next to a normal axon [bar = 50 μm (20 μm for inset)].

power and reappearance of deep tendon reflexes. Followup brain MRI was unchanged and electrophysiological studies indicated that conduction block had largely disappeared.

Case 2. The second patient was an 85-year-old woman with an 8-year history of seropositive RA. After she had failed standard second-line therapy she was treated with infliximab, 3 mg/kg body weight. Her joint symptoms improved but she developed progressive and striking glove and stocking numbness and ataxia 2 weeks after her third dose of infliximab (total exposure 540 mg). There was a history of mild sensory loss in her soles. Neurological examination identified distal weakness of intrinsic hand muscles, areflexia, and panmodal sensory loss distal to the knees and palms, with prominent loss of position sensibility in the toes. She could not tandem walk. Laboratory investigations were normal, except for a longstanding normocytic anemia and an elevated erythrocyte sedimentation rate. Electrophysiological studies identified mild declines in motor conduction velocities, loss of sensory nerve action potentials, and distal lower limb denervation. She was treated with intravenous corticosteroids. Nine months after discontinuation of infliximab, there was improved sensation and mild electrophysiological improvement, but she remained ataxic.

Case 3. The third patient was a 68-year-old woman with seropositive RA treated with a combination of infliximab (3 mg/kg body weight; total exposure 1400 mg), leflunomide, and prednisone for 18 months. She had a good response to treatment but developed bilateral paresthesiae, then pain of her hands and feet that emerged and progressed following infliximab infusions. Neurologic examination at the time symptoms began and 4 months after discontinuing infliximab identified loss of sensation in the hands and feet, particularly involving cold sensation, pinprick and light touch with relative preservation of vibration, and position sensibility indicating development of a small-fiber sensory neuropathy. The remainder of the examination, including motor testing and deep tendon reflexes, was normal. Electrophysiologic studies were largely normal, beyond evidence of right carpal tunnel syndrome, consistent with a small-fiber sensory neuropathy. Investigations for a malignant or metabolic etiology were negative. She improved symptomatically with time and the addition of gabapentin.

DISCUSSION

We describe 3 patients with seropositive RA who developed neurological symptoms related to therapy with infliximab. All had polyneuropathy with varying degrees of motor and sensory involvement, and very prominent motor axon demyelination in one patient. While one patient (Patient 2) had very mild chronic sensory symptoms before taking infliximab, she developed a more florid and severe neuropathy with the agent. Although she improved, she had ongoing impaired balance.

RA can be associated with noncompressive neuropathies, most commonly mononeuritis multiplex or sensorimotor polyneuropathy. These are primarily found in the 2–5% of patients with RA who have vasculitis[9,10]. Approximately 40% of patients with rheumatoid vasculitis develop a noncompressive neuropathy[9]. Possible explanations for the neurological conditions in our patients include an adverse effect of infliximab, a manifestation of underlying RA, or an unrelated disease process such as chronic inflammatory demyelinating polyradiculoneuropathy or multiple sclerosis (MS) in Patient 1. Each patient had features not typically related to RA and no patient had evidence of rheumatoid vasculitis. There was improvement, but incomplete recovery in all 3 patients concurrent with discontinuation of infliximab.

Anti-TNF-α agents, such as infliximab, may be associated with central demyelination. We noted clinical and some imaging evidence of central nervous system involvement in Patient 1. No definite central demyelination (although we cannot exclude a transient event), central pontine myelinolysis, or progressive multifocal leukoencephalopathy, however, was documented. A study of 168 patients with MS revealed that

those treated with the TNF-α inhibitor lenercept had more exacerbations than those receiving placebo[11]. Treatment of 2 MS patients with infusions of humanized mouse monoclonal anti-TNF antibody increased the number of gadolinium-enhancing lesions after each treatment in both patients[12]. Apparent central demyelination was reported in a series of patients with RA treated with anti-TNF-α agents (17 with etanercept and 2 with infliximab)[13]. Thirteen of these 19 patients reported paresthesiae, but electrophysiologic results to examine peripheral nerves were not included. In all of these patients there was partial or complete resolution with discontinuation of treatment. Recently, Richez, *et al* described 2 patients who developed demyelinating neuropathies after receiving etanercept or infliximab[14]. The mechanism by which anti-TNF-α agents improve some inflammatory conditions, such as Crohn's and RA, but not others, such as MS, remains speculative[15]. An interesting possibility is that constitutive TNF-α provides ongoing signaling support to peripheral neurons and its sequestration with infliximab or mRNA degradation with thalidomide interrupts such support to cause neuropathy.

Our patients highlight an association between infliximab and peripheral neuropathy and emphasize the need to monitor for signs and symptoms of neurologic disease in patients being treated with infliximab. One must use caution in considering infliximab in patients with preexisting polyneuropathy or demyelinating disease.

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