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Infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis

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Summary
Central nervous system involvement is a severe manifestation of sarcoidosis that often requires aggressive immunosuppressive therapy. The most efficacious approach for refractory disease is unknown.

We reviewed the cases of four subjects who demonstrated active progression of neurosarcoidosis while under treatment with cyclophosphamide, and who were subsequently treated with infliximab.

All four subjects demonstrated rapid and substantial reversal of their clinical course. Radiologic findings were concordant with the clinical responses. There were no notable toxicities.

Treatment with infliximab may be more effective than cyclophosphamide for refractory central nervous system sarcoidosis. A larger, prospective study is warranted.

Central nervous system (CNS) sarcoidosis, which occurs in up to 5% of individuals with sarcoidosis, confers substantial morbidity and may portend a poor prognosis.[1,2] Treatment of severe CNS sarcoidosis typically requires aggressive immunosuppression. Corticosteroids are the mainstay of treatment, but there are patients whose disease continues to progress despite therapy with corticosteroids and immunosuppressants.

Tumor necrosis factor α (TNF-α), a key mediator of sarcoidosis, has been tied to clinical course of the disease and is a prerequisite for granuloma formation.[3,4] Infliximab is a chimeric monoclonal antibody that blocks TNF-α bioactivity. *In vitro* data suggest that it can also lyse TNF-α producing cells, alter cytokine release and induce apoptosis.[5,6] There have been several observational reports of beneficial response to infliximab for refractory systemic sarcoidosis,[7,8] including CNS sarcoidosis.[9] However, the relative effectiveness of infliximab compared to conventional cytotoxic therapy has not been studied.

Abbreviations: Azathioprine, AZA; Central nervous system, CNS; Corticosteroids, CS; Magnetic resonance imaging, MRI; Methotrexate, MTX; Tumor necrosis factor α, TNF-α.

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We recently observed dramatic responses to infliximab in four individuals with severe neurosarcoidosis that was refractory to treatment with steroids and cyclophosphamide. These examples afford an opportunity to indirectly assess the role of infliximab in severe neurosarcoidosis.

Patient 1

A 50-year-old Caucasian male presented with stiffness of the neck and shoulder girdle muscles, and left arm weakness. Magnetic resonance imaging (MRI) revealed a large enhancing lesion abutting the cervical spinal cord and multiple smaller lesions along the lower cervical spinal cord (Fig. 1). The dominant mass-like lesion was resected via a suboccipital craniotomy, along with C1—3 and C6—7 laminectomies. Intraoperative findings included intradural and extradural masses with extension into the cerebellar fossa. Pathologic exam revealed multiple necrotizing and non-necrotizing granulomas associated with chronic inflammation. Special stains and cultures for acid-fast bacilli and fungi were negative. The diagnosis of sarcoidosis was substantiated when chest imaging revealed subcarinal lymphadenopathy, leading to a confirmatory transbronchial needle aspirate diagnosis.

After four weeks of treatment with prednisone at 60 mg/day, no improvement was noted either symptomatically or on MRI. Intravenous cyclophosphamide was added at this

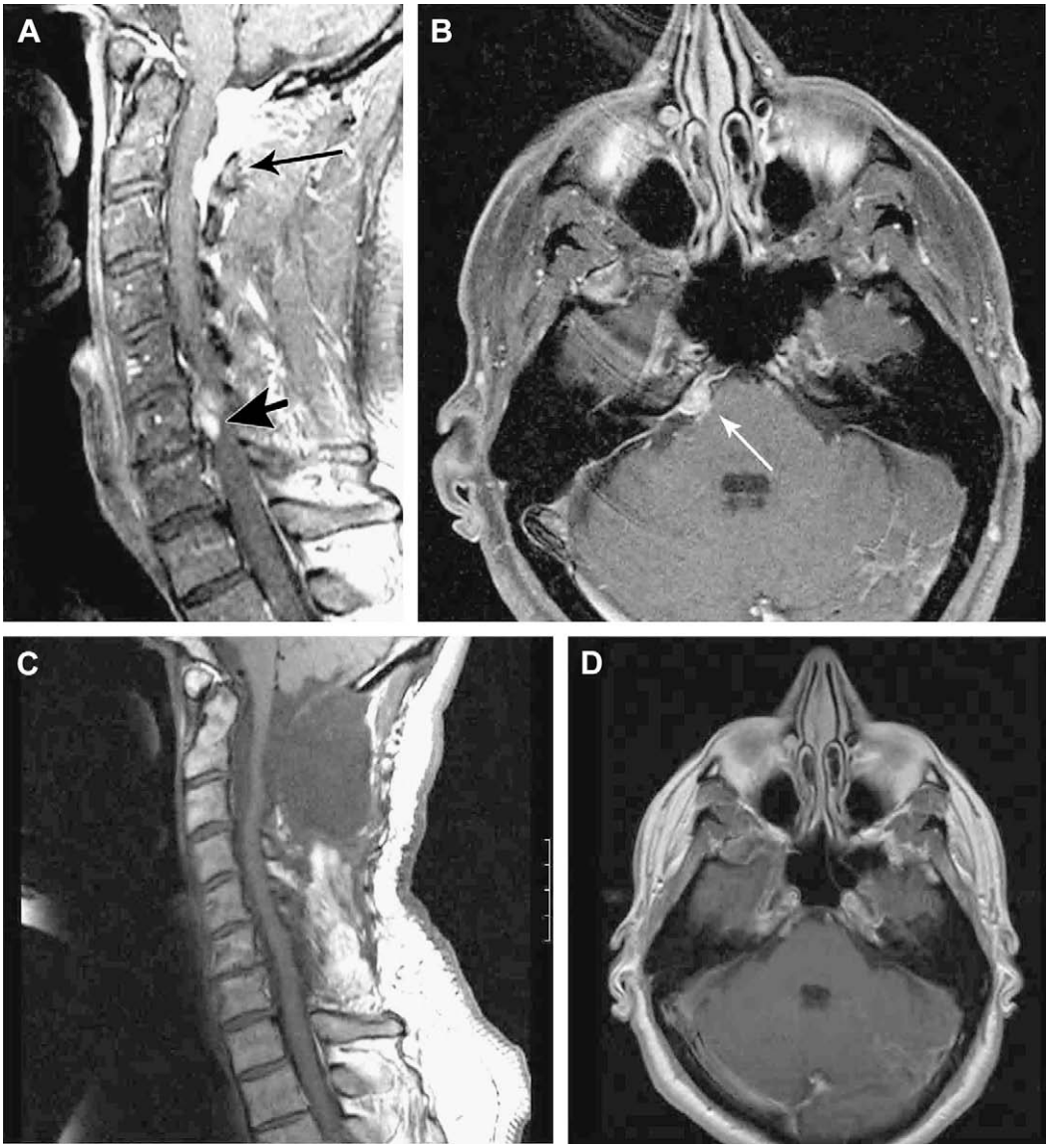

Figure 1 MRI findings for patient #1. Gadolinium-enhanced T1-weighted sagittal view (1A) demonstrated a large enhancing mass encroaching on the upper cervical spinal cord (arrow), with extension through the foramen magnum. There were also enhancing lesions in the lower cervical cord (arrowhead). Intraoperative findings revealed infiltration into the spinal cord and the nerve roots. Fig. 1B shows a transverse T1-weighted post-contrast image that revealed an enhancing lesion in the right cerebellopontine angle (arrow), with mild impingement on the pons and the right seventh and eighth cranial nerve root entry zone. Panels C and D demonstrate the MRI findings after treatment with infliximab.