

Chronic Inflammatory Demyelinating Polyneuropathy Following Anti-TNF- α Therapy With Infliximab for Crohn's Disease

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Abstract

We present a 29-year-old male with Crohn's disease who developed chronic inflammatory demyelinating polyneuropathy (CIDP) related to infliximab therapy. He developed lower extremity weakness and dysesthesia 3 weeks after a fourth infliximab dose. Laboratory examination revealed an elevated cerebrospinal fluid protein without pleocytosis. The patient initially responded to plasmapheresis therapy with marked symptomatic improvement, but relapsed and was refractory to subsequent treatments with plasmapheresis, intravenous immunoglobulin, and glucocorticoids. While a causal relationship between infliximab and CIDP cannot be proven, clinicians should monitor Crohn's disease patients who are receiving TNF- α antagonists for neurologic symptoms suggestive of demyelinating disease.

Introduction

Infliximab, a chimeric monoclonal antibody to tumor necrosis factor alpha (TNF- α), is used as an immunosuppressive agent for the treatment of moderate-to-severe Crohn's disease.¹ TNF- α antagonists such as infliximab have been associated with adverse effects, including local reactions, infections, congestive heart failure, malignancies, and demyelination of the central and peripheral nervous systems.^{2,3} Peripheral neuropathies are also uncommon manifestations of Crohn's disease.⁴ The pathophysiology of these complications has not been well elucidated—some may be immune-mediated, whereas others may arise from complications secondary to a micronutrient deficiency, a prothrombotic state, or be medication-induced.

Case Report

A 29-year-old African American man with a 3-year history of biopsy-proven terminal ileal Crohn's disease presented with bilateral lower extremity weakness approximately 3 weeks after an infliximab infusion. He was previously treated with corticosteroids and 6-mercaptopurine for Crohn's disease without improvement. Infliximab had been initiated due to persistent lower right quadrant abdominal pain and frequent bowel movements. He had received 3 infusions of 5 mg/kg on weeks 0, 2, and 6 with symptomatic improvement, followed by a dose increase to 10 mg/kg on week 12. Three weeks after this last dose, he developed lower extremity weakness and dysesthesias characterized by a tingling sensation distally in his feet. Past history included hypertension, weight loss due to Crohn's disease, and previous alcohol use. He had no personal or family history of neurologic problems or disease.

Neurologic examination revealed an alert and oriented man with normal speech and language, left fatigable horizontal nystagmus, and normal tone in all extremities. Pinprick sensation was decreased in a stocking dis-

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tribution up to both knees and in the glossary region up to the middle of both forearms. The patient was unable to walk on his heels, had mild difficulty with toe walking, and had a waddling gait that was slightly wide based.

Laboratory examination revealed an elevated cerebrospinal fluid (CSF) protein without pleocytosis and an elevated sedimentation rate. Except for low hemoglobin and hematocrit, the remaining blood work was normal. Tests for antinuclear antibody, HIV antibody, hepatitis B surface antigens, and hepatitis C antibodies were negative. Brain magnetic resonance imaging (MRI) with gadolinium contrast showed diffuse increased signal intensity throughout the periventricular white matter without associated enhancement suggestive of demyelinating process. MRI of the spinal cord was negative, and echocardiogram was unremarkable.

He was kept on corticosteroids and 6-mercaptopurine for Crohn's; infliximab was discontinued as a possible cause of the acute inflammatory demyelinating polyneuropathy. He received 2 separate treatments of intravenous immunoglobulin (IVIG). His lower extremity weakness did not improve, and he became dependent on a walker. He continued to experience dysesthesias in both upper and lower extremities. IVIG treatments were discontinued due to lack of efficacy and the patient then received 3 sessions of plasmapheresis. Within 48 hours after the third session, the patient's weakness and sensory symptoms were significantly improved and he no longer required a walker.

Approximately 3 months after undergoing plasmapheresis, the patient presented with recurrence of sensory symptoms. The symptoms included motor weakness in his distal lower extremities. He could not dorsiflex his feet when walking, but rather had to flex at the hips and knees. At this point, his diagnosis was changed from acute to chronic inflammatory demyelinating polyneuropathy (CIDP). The patient received 5 additional rounds of plasmapheresis. His bilateral upper and lower extremity weakness remained largely unchanged. Numbness, tingling, and burning in his hands and feet continued. He was started on gabapentin; the dose was titrated up to 400 mg 3 times daily with no improvement in sensory symptoms.

The patient's condition continued to deteriorate throughout the following year with marked bilateral hearing loss, inability to ambulate, and bilateral proximal interphalangeal joint contractures resulting in inability to grasp objects. He also required parenteral nutrition as a result of significant malnutrition from Crohn's disease and inability to tolerate enteral nutrition.

Discussion

CIDP is an acquired peripheral neuropathy, with both T-cell and B-cell involvement.⁵ The disease involves progressive loss of immunologic tolerance to peripheral nerve components such as myelin, Schwann cell, the axon, and motor or ganglionic neurons.⁶ To date, only 6 cases of CIDP have been reported in patients with Crohn's disease.⁷⁻¹⁰ While there is a scarcity of reports describing the onset and course of CIDP in Crohn's disease patients after treatment with TNF- α antagonists, there are reports in which the use of TNF- α antagonists for rheumatoid arthritis, psoriasis, and ankylosing spondylitis have been associated with the development of CIDP.^{14,15}

The mechanism of peripheral nerve injury associated with TNF- α is poorly understood. Evidence suggests that both cellular and humoral immune system components play a role in the pathogenesis of demyelinating peripheral neuropathies. Nerve ischemia and inhibition of signaling support for axonal transport may be secondary mechanisms of axonal loss.² Administration of TNF- α antagonist is thought to decrease apoptosis of autoreactive T-cells and potentiate T-cell receptor signaling, resulting in heightened autoimmune responses.¹⁶⁻¹⁸ Other mechanisms have also been suggested including direct nerve effects at nerve terminals, which could augment the myelin-specific T-cell response and increase the triggering immune-mediated neuropathy.¹⁹

As with other anti-TNF-associated neuropathies, discontinuation of infliximab may be ineffective in resolving neuropathy.²⁰ In our case, the development and course of neuropathologic manifestations did not appear to be correlated with Crohn's disease activity, and thus was unlikely to be an extraintestinal manifestation of IBD. Infliximab may have been directly involved in the development of CIDP, or it may have had an indirect effect by unmasking a subclinical demyelinating process. It is highly probable that the development CIDP was related to infliximab, as other sources of peripheral neuropathy were ruled out. The positive temporal relationship between doubling the infliximab dose and new-onset polyneuropathy symptoms, the previous reports of CIDP following treatment with TNF- α antagonists, and the objective evidence confirming the development of CIDP after treatment with infliximab support this conclusion. While a causal relationship between infliximab and CIDP cannot be proven, clinicians should monitor Crohn's disease patients who are receiving TNF- α antagonists for neurologic signs and symptoms suggestive of demyelinating disease.

Disclosures

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