Sensory neuronopathy associated with tumor necrosis factor inhibitor therapy

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Practical Implications

Consider a sensory neuronopathy as a peripheral nervous complication of tumor necrosis factor (TNF)-inhibitor therapy.

Tumor necrosis factor inhibitors (TNF inhibitors) have improved the treatment of inflammatory arthropathies, psoriasis, and inflammatory bowel disease.¹ The spectrum of neuropathies reported in association with TNF inhibitors has not appreciably changed over the past decade.¹ Sensory neuronopathies have not been described as such a neuropathy associated with TNF inhibitors. Such neuronopathies cause considerable proprioceptive impairment due to neuronal degeneration affecting the dorsal root ganglia (DRG).² We describe neuronopathy associated with TNF inhibitors that improves with discontinuation of TNF inhibitor therapy.

Case report

A 65-year-old, right-handed woman with a history of seronegative Sjögren syndrome (SS) and psoriatic arthritis that had been intractable to nonbiological agents was started on the TNF inhibitor infliximab. The induction dose was 3 mg/kg, given IV over weeks 0, 2, and 6, and subsequently infused at 8 mg/kg every 8 weeks. She had resolution of both skin lesions and her polyarthritis within 4 doses.

However, after 1 year of infliximab therapy, she described a “wobbly” gait. Over the course of 1–2 months, there was subacute gait deterioration associated with frequent falls and the need to ambulate with canes. She subsequently experienced further falls over the remaining year, and was ultimately relegated to a wheelchair. She was subsequently referred to our center.

Her clinical evaluation and electrodiagnostic studies confirmed a sensory neuronopathy (table). She had diffuse hyporeflexia, sensory ataxia, and impaired proprioception at the fingers and all toes, and was confined to a wheelchair. Electrodiagnostic studies revealed the loss of all sensory nerve action potentials (SNAPs) in the radial, ulnar, median, and sural nerves, with normal compound motor action potentials. The table emphasizes how the neuronopathy evolved in the absence of SS disease activity, and highlights diagnostic studies that excluded other causes of a neuronopathy. Testing for rapid plasma reagin/Venereal Disease Research Laboratory and fluorescent treponemal antibodies were not performed given there was no other evidence of neurosyphilis (i.e., Argyll-Robertson pupils).

Although neuronopathies had not previously been described as a complication of TNF inhibitor therapy, we decided to discontinue infliximab after 6 additional months of therapy

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the author is available with the **full text of this article at Neurology.org/cp**.

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Table Characteristics of neuropathy in the patient receiving infliximab therapy and after discontinuation of infliximab therapy

Characteristics	During infliximab treatment	After discontinuation of infliximab
Examination and electrodiagnostic findings		
Romberg sign	Present	Absent
Proprioception	Absent at toes and fingers	Intact
Gait	1-2 steps with 2-person assistance, otherwise relegated to wheelchair	Able to ambulate with mildly wide-based gait for unlimited distances
Sensory nerve action potentials, μV		
Radial nerve	Absent	10
Median nerve	Absent	14
Sural nerve	Absent	Absent
Tibial nerve	Absent	Absent
Presence of Sjögren-associated antibodies, immunologic markers, and disease activity		
Anti-Ro/SS-A and anti-La/SS-B antibodies	Absent	Absent
Antinuclear antibodies	Absent	Absent
Antirheumatoid factor antibodies	Absent	Absent
Polyclonal gammopathy	Absent	Absent
Cryoglobulins	Absent	Absent
Hypocomplementemia	Absent	Absent
Lung,^a kidney,^b rash, arthritis, or CNS disease	Absent	Absent
Alternative causes of a sensory neuropathy		
Glucose intolerance or diabetes, by 2-h glucose tolerance test	Absent	NA ^c
Celiac disease, by antiendomysial IgA/IgG and anti-TTG IgA/IgG antibodies	Absent	NA
Monoclonal gammopathy (i.e., M-protein) by SPEP/IPEP	Absent	NA
Anti-Hu and other antisulfatide antibodies	Absent	NA
CT scan of chest/abdomen/pelvis	No evidence of occult malignancy	NA
Antisulfatide antibodies	Absent	NA
Infectious causes (including HIV and hepatitis C)	Absent	NA
Metabolic causes (including vitamin B₁₂ deficiency)	Absent	NA
Evidence of nerve root thickening on MRI of lumbosacral spine	Absent	NA
Protein concentration in the CSF, mg/dL	31	NA

Abbreviations: IgA = immunoglobulin A; IgG = immunoglobulin G; IPEP = immunoglobulin protein electrophoresis; SPEP = serum protein electrophoresis.

^aIncludes bronchiectasis and interstitial lung disease.

^bIncludes renal tubular acidosis or evidence of interstitial nephritis.

^cIndicates not applicable, as workup for alternative causes of neuropathy was not repeated after patient improved on infliximab.

(i.e., after a total of 21 infusions). She was subsequently followed by her local physicians. She initially reported no change in her symptoms. However, in the ensuing 1–2 years after discontinuation of infliximab, she gradually reported improvement in her gait, and eventually was able to ambulate unlimited distances without assist devices.

She was therefore evaluated at our center 19 months after discontinuation of infliximab. Clinical and electrodiagnostic features of improvement were striking and are illustrated in the table. She now had normal proprioception, was able to walk unlimited distances, and had complete recovery of SNAPs at the radial and median nerve (table). When followed over the next 6 months, she continued to have sustained improvement.

DISCUSSION

We describe neuropathy developing in the context of TNF inhibitor therapy and then improving with withdrawal of TNF inhibitor therapy. Our patient was not on other medications prior to or after discontinuation of infliximab, which could have led to precipitation or improvement of her neuropathy. At nadir, our patient was relegated to a wheelchair and had diffuse loss of all SNAPs. Upon withdrawal of infliximab, she was able to independently ambulate for unlimited distances and had SNAPs that were elicited and normal in some sensory nerves (table).

Although our patient also had SS, SS is an unlikely cause of this patient's neuropathy. As noted in the table, our patient's neuropathy developed in the absence of background SS disease activity. In particular, there were no immunologic markers of B-cell hyperactivity (i.e., SS-associated antibodies), and no systemic manifestations that affected other end organs (i.e., lungs, joints, kidney, skin). Furthermore, SS-associated neuropathies inevitably progress, and are not characterized by such striking clinical and electrodiagnostic improvement in the absence of immunomodulatory therapy.^{3,4} It is possible that SS may have constituted a unique "host" factor associated with subclinical DRG injury.

Mechanisms proposed to explain the association of TNF inhibitor therapy with other neuropathies may be relevant. Just as TNF inhibitor therapy can induce antineuronal antibodies, it is interesting to consider whether infliximab was able to induce anti-DRG antibodies in our neuropathy patient. Although our patient's subacute onset of gait impairment is potentially consistent with such antibody-mediated and other inflammatory mechanisms, a more direct DRG neurotoxic effect of TNF inhibitors could also cause this subacute pattern of gait decline.

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STUDY FUNDING

No targeted funding reported.

DISCLOSURES

The author is supported by an NIH P30 AR053503 grant. Full disclosure form information provided by the author is available with the **full text of this article at Neurology.org/cp**.