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Ustekinumab-Induced Inflammatory Demyelinating Polyneuropathy in a Patient with Ulcerative Colitis

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SHORT TITLE

Ustekinumab-Induced Demyelinating Polyneuropathy

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ETHICS

Full informed consent was provided by patient

AUTHOR CONTRIBUTIONS

SH prepared the initial manuscript draft and all authors critically reviewed the manuscript before submission.

CONFLICT OF INTEREST STATEMENT

SH has served as a speaker, a consultant and/or advisory board member for Pfizer, Janssen, Abbvie, and Takeda. PI has received lecture fees from Abbvie, Warner Chilcott, Ferring, Falk Pharma, Takeda, MSD, Johnson and Johnson, Shire, and Pfizer. Financial support for research: MSD, Takeda, and Pfizer. Advisory fees: Abbvie, Warner Chilcott, Takeda, MSD, Vifor Pharma, Pharmacosmos, Topivert, Genentech, Hospira, and Samsung Bioepis. MAS has served as a speaker, a consultant, and/or an advisory board member for Sandoz, Janssen, Takeda, MSD, Falk, Abbvie, Bristol Myers Squibb, Galapagos, and Samsung Bioepis.

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Ustekinumab, peripheral neuropathy, demyelination, sub-acute inflammatory demyelinating polyneuropathy, SIDP

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To the Editors,

Ustekinumab, a monoclonal antibody targeting interleukin-12/23, is the latest biologic approved for the treatment of moderate-to-severe ulcerative colitis (UC). Although anti-tumour necrosis factor (TNF) agents are associated with central and peripheral nervous system demyelination, neurological complications of ustekinumab are exceptionally rare.¹ In pooled analyses of 12 ustekinumab registrational trials with 5884 patients and 4521 patient-years follow up, there were no cases of demyelinating disorders.² We report only the third known case of ustekinumab-induced demyelination in a patient with active UC.^{3,4}

An otherwise well 48-year-old female, with a 30 year history of left-sided UC, was treated with adalimumab in 2016 following thiopurine intolerance. Three months after dose escalation for sub-therapeutic levels, she developed paraesthesia in her hands and feet and electromyography (EMG) with nerve conduction studies (NCS) revealed features consistent with a demyelinating polyneuropathy. Adalimumab was discontinued and six weeks later she made a complete neurological recovery with conservative management without recrudescence.

In July 2021, following loss of response to vedolizumab and severe colitis (Mayo 3) on endoscopic assessment, ustekinumab was commenced. Five days following the induction infusion, she again developed paraesthesia affecting all four limbs. On this occasion, muscle weakness was more pronounced, affecting fine motor hand function and her ability to ambulate and maintain balance. Symptoms progressed and specialist neurological review revealed a symmetrical, non-length-dependent weakness, reduced sensation, and

hyporeflexia. Investigations showed raised cerebrospinal fluid protein of 0.84g/L (normal 0-0.44) and marked peripheral nerve demyelination on EMG and NCS, in keeping with a diagnosis of sub-acute inflammatory demyelinating polyneuropathy (SIDP). Infection and autoimmune screens were negative, and neuroimaging of the brain and spinal cord were also unremarkable. Ustekinumab discontinuation and intravenous immunoglobulin infusions over eight weeks led to significant improvement with resolution of neurological symptoms. Repeat neurophysiology testing six months later confirmed improvement in sensorimotor responses in upper and lower limbs.

SIDP is a rare immune-mediated disorder characterised by axonal damage and peripheral nerve demyelination, resulting in muscle weakness and impaired sensory function. There is an increased risk of demyelinating diseases in patients with IBD.⁵ Proving causality is difficult as the observed association could be the unmasking of a latent demyelinating disease or the emergence of a *de novo* demyelinating process. However, the temporal association and marked clinical and objective improvement following drug withdrawal, favours a drug-induced illness. While ustekinumab has a favourable safety profile, this case demonstrates a rare neurological side effect more typically associated with anti-TNF therapy.

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Nil

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