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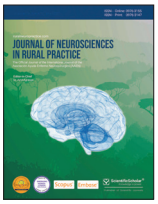

Case Report

Central nervous system demyelination associated with tofacitinib use in alopecia areata: A case report and literature review

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ABSTRACT

We describe a 23-year-old woman with alopecia areata (AA) who developed new central nervous system (CNS) demyelination while on tofacitinib therapy. After 3 months of tofacitinib 10 mg/day and topical tofacitinib, the patient had dramatic scalp hair regrowth (severity of alopecia tool score improved), but in the 4th month, she developed focal neurological symptoms. Brain magnetic resonance imaging showed multiple new T2-hyperintense lesions in the right pontine tegmentum, showing mild diffusion restriction and subtle contrast enhancement and patchy non-enhancing T2/FLAIR hyperintensities in the juxtacortical region of the right parietal lobe, deep white matter region of the right occipital and left frontoparietal lobes, and in the callosal septal interface. These features represent demyelination and cerebrospinal fluid (CSF) studies showed very high protein with negative CSF myelin oligodendrocyte glycoprotein/neuromyelitis optica antibodies and absence of oligoclonal bands. Tofacitinib was discontinued and the patient received high-dose corticosteroids. We review the literature on Janus kinase inhibitor-associated demyelination, including prior case reports, hypothesized mechanisms, risk factors, and regulatory guidance. Current evidence indicates a temporal association between tofacitinib exposure and CNS demyelination, although causality remains uncertain. The demyelinating episodes appear reversible upon drug withdrawal with immunotherapy. This case underscores the need for vigilance for neurological symptoms in patients on tofacitinib and further research into its neuroimmunologic effects.

Keywords: Alopecia areata, Central nervous system demyelination, Drug-induced demyelination, Janus kinase inhibitor, Multiple sclerosis, Tofacitinib

INTRODUCTION

Alopecia areata (AA) is a common autoimmune disease characterized by patchy hair loss. Standard therapies include corticosteroids, immunosuppressants (e.g., methotrexate, cyclosporine), and topical agents, but many cases are refractory. The oral Janus kinase (JAK) inhibitor tofacitinib (a JAK1/3 inhibitor) has shown promise in severe AA, with significant hair regrowth observed in the majority of treated patients.[1] In a retrospective series of 65 AA patients, 58% achieved >50% improvement in scalp hair (severity of alopecia tool [SALT]) score on tofacitinib, and the drug was generally well tolerated.[2] Although not Food and Drug Administration (FDA) approved for AA (tofacitinib's approved indications are rheumatoid arthritis (RA), psoriatic arthritis, ulcerative colitis, etc.), its use in dermatology is growing.

JAK inhibitors modulate immune signaling by blocking phosphorylation of signal transduction and activation of transcription (STAT) transcription factors downstream of multiple cytokine receptors. While effective, serious adverse events have emerged. In 2021, the FDA mandated black-box warnings for tofacitinib and related JAK inhibitors due to increased risks of serious infections, malignancy, thromboembolism, cardiovascular events, and mortality observed in large post-market trials.[3] Neurological complications have also been reported. There is growing recognition that targeted immunotherapies can trigger central nervous system (CNS) demyelination (an "iatrogenic MS-like" syndrome).[4] Case reports have now described new-onset CNS demyelination temporally related to tofacitinib use.[5] We present the first detailed account of tofacitinib-associated CNS demyelination in an AA patient and review the literature on reported cases, possible pathophysiology, risk factors, diagnostic workup, and outcomes after discontinuation of the drug.

CASE REPORT

A 23-year-old woman with a 6-month history of patchy AA and madarosis presented with new neurological symptoms [Figures 1 and 2]. Her AA had been severe and

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treatment-refractory, with little response to prior courses of systemic steroids, intralesional steroids, cyclosporine, and phototherapy. She was started on tofacitinib 5 mg (Tab. Betrecep, Pfizer Inc.,) twice daily and topical tofacitinib ointment (2% Jakauto Ointment, Eris Oaknet Health Care) for local application. After 3 months of therapy, the patient experienced significant hair regrowth (her SALT score improved from severe alopecia to near-complete scalp coverage).

During the 4th month of tofacitinib therapy, the patient developed double vision, gait difficulty, and loss of taste sensation. She also reported numbness in the left upper and lower limbs. Owing to these neurological symptoms, her activities of daily living were significantly restricted, resulting in a poor quality of life. Concerned about these developments, the patient discontinued tofacitinib and underwent neurological evaluation. Neurological examination revealed bilateral (B/L) upbeat nystagmus and adduction restriction in the right eye with abduction nystagmus in the left eye, suggestive of right-side internuclear ophthalmoplegia. Magnetic resonance imaging (MRI) of the brain showed T2-hyperintense lesions in the right pontine tegmentum, showing mild diffusion restriction and subtle contrast enhancement and patchy non-enhancing T2/fluid attenuated inversion recovery sequence (FLAIR) hyperintensities in the juxtacortical region of the right parietal lobe, deep white matter region of the right occipital and left frontoparietal lobes, and in the callosal septal interface [Figure 3]. These features were suggestive of demyelination. Spinal cord imaging and visually evoked potentials (VEP) were normal. Cerebrospinal fluid (CSF) analysis revealed acellular, normal glucose (83 mg/dL), with very high protein (164 mg/dL). CSF gene Xpert tuberculosis was negative, CSF myelin oligodendrocyte glycoprotein/neuromyelitis optica antibodies were negative, and there were no oligoclonal bands; CSF immunoglobulin G index was negative (0.08).

A broad serum workup [complete blood count (CBC), metabolic panel, thyroid function, antinuclear antibody (ANA), rheumatoid factor, anti-cyclic citrullinated peptide (CCP), vitamin B12 and vitamin D levels, and extractable nuclear antigen (ENA) profile] was unremarkable except for mild vitamin D deficiency, which was treated. The neurology team concluded the presentation met McDonald's criteria for multiple sclerosis [new CNS lesions with clinical symptoms, even in the absence of CSF oligoclonal bands (OCB)]. The sudden onset after the 4th month of tofacitinib suggested a drug-related effect.

Treatment

Tofacitinib, both topical and oral, was permanently discontinued. The patient was treated with high-dose intravenous methylprednisolone (1 g daily for 5 days) for acute demyelinating lesions. Her neurological symptoms began to improve following treatment, and she was discharged on a tapering course of oral corticosteroids. At 6-week follow-up, the paresthesias and numbness had completely resolved, with continued improvement in gait. Diplopia has completely resolved, and the patient reported a satisfactory quality of life. She remains under close follow-up, with a repeat MRI of the brain planned at 3 months. The patient provided informed consent for publication of her case.

Review of literature

Reported cases

Drug-induced demyelination is a recognized phenomenon with certain immunotherapies. In particular, anti-tumor necrosis factor-alpha (TNF-α) agents (e.g., etanercept and infliximab) have long been linked to new-onset or exacerbated multiple scleosis (MS).[6] For JAK inhibitors, two notable cases have been reported. Massoud *et al.* described the first case of CNS demyelination on tofacitinib in 2020: A seropositive RA patient developed multifocal demyelinating lesions (clinically and radiographically consistent with MS) after 6 years of tofacitinib therapy.[4] Those lesions were reversible upon drug discontinuation (MRI lesions resolved and no new events occurred).[4] More recently, Erçoban and Kaya reported an AA patient who developed MS-like CNS lesions after 7 months of tofacitinib for alopecia.[5] Both cases required high-dose steroids and stopping tofacitinib, and in both cases, lesions stabilized with no further progression on follow-up.[4,5] No other cases of tofacitinib-associated CNS demyelination in AA have been published to date. Other JAK inhibitors (e.g., ruxolitinib) have rarely been implicated in severe infections like john cunningham (JC) virus PML,[6] but demyelination specifically is chiefly noted for tofacitinib in these reports.

Temporal association and outcomes

In all reported cases, the timing suggests a possible causal link: New neurological signs arose months after starting tofacitinib, a latency similar to other iatrogenic demyelinating syndromes.[5] Importantly, cessation of tofacitinib and immunotherapy led to rapid clinical improvement and no further relapses, which implies a reversible drug effect rather than unmasking of aggressive MS.[4,5] Residual radiographic lesions may persist (as in our case and Massoud's), but no new lesions have been observed on serial imaging months later. These outcomes contrast with classic MS, where demyelinating activity typically continues without disease-modifying therapy. Thus, the temporal pattern and positive response to discontinuation and steroids suggest an iatrogenic process.

Pathophysiology

The mechanisms of JAK inhibitor-associated demyelination are not fully understood. Animal studies provide clues: Yoshida *et al*. found that low-dose tofacitinib paradoxically accelerated experimental autoimmune encephalomyelitis (EAE) by favoring differentiation of interleukin (IL)-17-producing T helper 17 (Th17) cells.[7] Specifically, low concentrations of tofacitinib suppressed IL-2 signaling and Th1/Th2 differentiation, effectively skewing T cells toward a Th17 phenotype.[7] Th17 cells are highly pro-inflammatory in the CNS and key drivers of demyelination in EAE and MS. Thus, tofacitinib may inadvertently enhance IL-17-mediated autoimmunity in predisposed individuals.

Massoud *et al.* proposed a similar concept: in their patient, tofacitinib might have activated "T17" cells, increasing IL-17 production and tipping the immune balance toward demyelination.[4] They also noted potential crosstalk between the JAK/STAT and TNF pathways,[4] suggesting tofacitinib could alter cytokine networks in complex ways. For example, TNF inhibition itself can paradoxically induce demyelination in susceptible persons;[5] whether JAK blockade affects TNF or other signals in the CNS are under study. *In vitro*, tofacitinib inhibits STAT1 and STAT5 more potently than STAT3, which may suppress regulatory signals (like IFN-γ/IL-4/IL-2 pathways) more than Th17-promoting IL-6/IL-23-STAT3 signals.[7] This imbalance could de-repress Th17/IL-17.

In summary, current hypotheses center on immune dysregulation: Tofacitinib may paradoxically promote pro-demyelinating Th17/IL-17 responses in some patients.[4,7] Individual factors such as genetics or latent autoimmunity likely modulate this risk. More research is needed to clarify how JAK inhibitors might unmask or incite CNS autoimmunity.

Risk factors

Little is known about predisposing factors for JAK inhibitor-related demyelination. Both reported patients (RA and AA) had autoimmune disease, which may indicate inherent immune dysregulation. Seropositive RA is associated with broad autoimmunity, and AA is driven by autoimmune attack on hair follicles. It is conceivable that subclinical predisposition (e.g., latent CNS autoimmunity) combined with tofacitinib triggers pathology. Notably, neither patient had prior CNS symptoms or imaging. No demographic or laboratory predictors have been defined. By analogy, TNF inhibitors list MS or demyelinating disorders as contraindications, even though epidemiologic links are weak.[4] For tofacitinib, clinicians should be cautious in patients with any personal or family history of demyelinating disease. Close neurological monitoring is reasonable, especially if new symptoms appear.

Diagnostic workup

In any patient receiving a JAK inhibitor who develops neurological symptoms, prompt neuroimaging is essential. MRI findings – such as ovoid periventricular and infratentorial plaques – should be interpreted in conjunction with the clinical presentation. CSF analysis can provide additional insight: The presence of oligoclonal bands supports a diagnosis of multiple sclerosis, whereas their absence, as observed in our case, does not exclude MS but may suggest a single drug-related demyelinating episode. Infectious and metabolic etiologies must also be excluded. Although formal criteria for "drug-induced MS" do not exist, a pragmatic approach involves applying established MS diagnostic criteria (e.g., 2017 McDonald criteria) to confirm CNS demyelination, followed by consideration of drug causality if lesions and symptoms arise after initiation of the agent and no alternative explanation is evident. Neurology consultation is strongly recommended. Serial MRI after discontinuation of the suspected drug can help confirm lesion stability, as demonstrated in this case.

Regulatory considerations

Although tofacitinib is approved for rheumatoid arthritis and other indications, its use in AA remains off-label pending ongoing clinical trials. The recent black-box warning for JAK inhibitors highlights general risks but does not specifically address demyelination.[3] The FDA safety communication primarily emphasized cardiovascular and malignancy risks associated with tofacitinib in RA.[4] In dermatology, Samuel *et al*. note that this warning is based on RA trial data[8] and recommend heightened vigilance for severe adverse events. At present, there are no specific FDA or EMA guidelines regarding the use of JAK inhibitors in patients with, or at risk for, demyelinating disease. By analogy with biologic disease-modifying antirheumatic drug, pre-existing multiple sclerosis may be considered a relative contraindication to JAK therapy. Importantly, in 2023, the FDA approved the first JAK inhibitor (ritlecitinib) specifically for severe AA, reflecting regulatory recognition of the class's dermatologic utility, while maintaining the same boxed warnings.

Clinicians prescribing JAK inhibitors for AA should counsel patients regarding potential serious adverse effects, including demyelination. Baseline screening – such as tuberculosis testing and cancer risk assessment – is recommended,[3] and ongoing monitoring of neurological function is prudent. Any new sensory or motor deficit should prompt immediate evaluation. Given the limited number of reported cases, no formal "rechallenge" protocol exists; in clinical practice, the drug is generally discontinued if demyelination occurs, as in our patient.

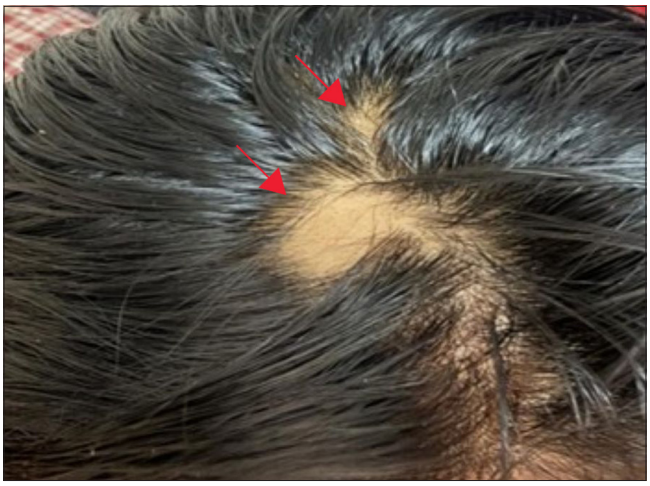

Figure 1: Patchy alopecia areata.

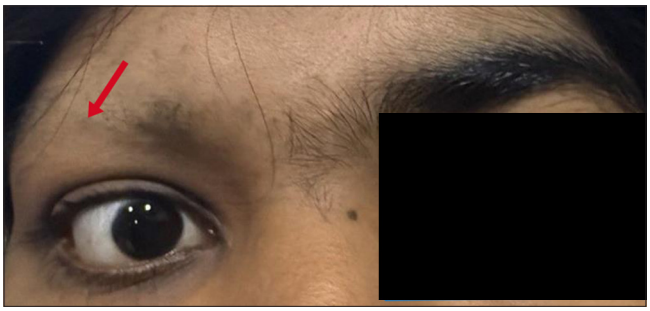

Figure 2: Madarosis of the right eye with adduction restriction in the right eye. Madarosis of the right eye is shown in red arrow.

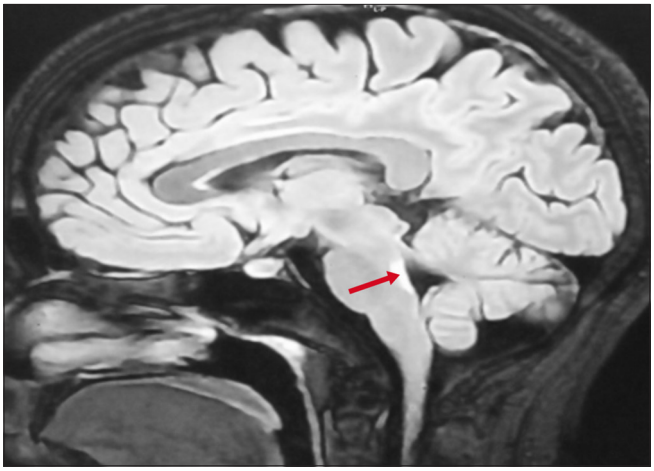

Figure 3: Magnetic resonance imaging of the brain - Sagittal T2 FLAIR image (1 mm) section showing a linear hyperintense signal in the dorsal pons close to the midline. Red arrow indicate demyelination changes.

DISCUSSION

Our case adds to the sparse but concerning reports linking tofacitinib to CNS demyelination. The strong temporal association – new CNS lesions emerging after several months of therapy – and reproducible outcomes, namely symptom resolution following drug discontinuation and corticosteroid treatment,[4,5] support a drug-related effect rather than coincidental multiple sclerosis onset. The rapidity of neurological improvement and lesion stabilization contrasts with the typical course of untreated MS, suggesting an iatrogenic phenomenon. However, definitive causality cannot be established; it remains possible that tofacitinib unmasked a pre-existing MS. The patient's negative CSF oligoclonal bands argue against longstanding MS. Furthermore, both reported cases occurred in individuals with other autoimmune diseases, raising the possibility of shared immunogenetic susceptibility.

The immunologic basis of JAK inhibitor-associated demyelination remains hypothetical. Experimental studies by Yoshida and hypotheses by Massoud implicate Th17/IL-17 pathway skewing.[4,7] IL-17 has a well-established role in MS pathogenesis,[7] and if tofacitinib shifts the cytokine milieu toward IL-17, it could precipitate or exacerbate autoimmunity. Alternatively, off-target effects on the JAK pathway – such as altered microglial activation or disruption of blood–brain barrier integrity – may contribute. The absence of progressive multifocal leukoencephalopathy (PML) in these cases suggests that JC virus reactivation is not the mechanism, although a single PML case has been reported with ruxolitinib.[6]

Clinically, these reports underscore the need for vigilance. Tofacitinib and other JAK inhibitors have transformed the management of autoimmune diseases, but clinicians should be alert to rare yet serious neurotoxic effects. Dermatologists and neurologists should be aware of this potential complication in patients with AA receiving tofacitinib or related agents. Baseline neurological assessment may be prudent, particularly in patients reporting subtle symptoms. At the first sign of CNS involvement – such as numbness or visual changes – prompt MRI evaluation is recommended, and corticosteroid therapy should be initiated if demyelination is confirmed, along with immediate discontinuation of the JAK inhibitor.

Regarding risk–benefit considerations, tofacitinib remains an effective treatment for refractory AA.[1,2] The incidence of CNS demyelination is extremely low, with only two published cases among thousands of users. Nevertheless, given the potential for severe disability, even rare events warrant attention. At present, there is insufficient evidence to alter general prescribing practices – no formal guidelines or label changes address demyelination specifically – but informed consent should include discussion of this emerging risk. Future pharmacovigilance studies, such as analyses of FAERS or other registries, may help quantify the risk more accurately. A recent pharmacovigilance review of 105,000

tofacitinib reports identified numerous neurological adverse events, although demyelination was not singled out.[6]

CONCLUSION

Tofacitinib-induced CNS demyelination is an emerging but potentially serious adverse effect. We report a case of multifocal demyelinating lesions in a patient with AA following 4 months of tofacitinib therapy, with clinical and radiological improvement after drug discontinuation and corticosteroid treatment. This observation adds to a previously reported case in a patient with rheumatoid arthritis and suggests a consistent pattern characterized by a temporal association between drug exposure and the onset of multiple sclerosis–like lesions, followed by stabilization after withdrawal of the offending agent. The proposed pathophysiological mechanism involves cytokine imbalance under Janus kinase inhibition, particularly enhanced IL-17/Th17-mediated immune activity. Clinicians should consider this diagnosis in patients receiving tofacitinib who develop new neurological symptoms. Further studies are warranted to identify predisposing risk factors, establish optimal monitoring strategies, and determine whether certain patient populations should avoid JAK inhibitors. Until such data are available, heightened clinical vigilance and a low threshold for neurological evaluation are recommended. Continued reporting of similar cases will be essential to better define the scope and clinical implications of this adverse effect.

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Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for their images and other clinical information to be reported in the journal. The patient understands that the patient's names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
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