

# A case report about adalimumab-induced radiologically isolated syndrome: A significant side effect of tumour necrosis factor inhibitors

SAGE Open Medical Case Reports  
JCMS Case Reports  
Volume 9: 1–3  
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DOI: 10.1177/2050313X211003057  
journals.sagepub.com/home/sco



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## Abstract

Tumor necrosis factor- $\alpha$  antagonists have become a therapeutic mainstay for various inflammatory diseases including Hidradenitis Suppurativa. Despite their clinical efficacy, these medications have been associated with the rare development of demyelinating diseases. We report a 29-year-old male who developed neurological symptoms while taking adalimumab, a tumor necrosis factor- $\alpha$  antagonist, for treatment of Hidradenitis Suppurativa. The patient was subsequently diagnosed with radiologically isolated syndrome based on magnetic resonance imaging findings. The exact temporal relationship between demyelinating disease and tumor necrosis factor- $\alpha$  antagonists is poorly understood. Also, there remain a few effective treatment options for severe inflammatory diseases like Hidradenitis Suppurativa. In cases where a patient exhibits clinical stability and structural resolution following the development of neurological symptoms after tumor necrosis factor- $\alpha$  antagonist therapy, and there is a lack of other effective treatments to control extensive inflammatory disease, restarting the tumor necrosis factor- $\alpha$  antagonist could be considered provided there is neurology approval and close monitoring.

## Keywords

Hidradenitis Suppurativa, adalimumab, radiologically isolated syndrome, demyelinating disease, tumor necrosis factor- $\alpha$  antagonists

Date received: 22 November 2020; accepted: 19 February 2021

## Introduction

Hidradenitis Suppurativa (HS) is a chronic inflammatory condition of pilosebaceous units. HS is primarily localized to intertriginous skin, especially the axillary, inguinal, submammary, and perineal regions. The primary lesions of HS are painful, inflammatory nodules.<sup>1</sup> As the disease progresses, secondary lesions including clusters of open comedones, sinus tracts, and scarring develop.

Guidelines released by the Hidradenitis Suppurativa Foundations of Canada and the United States in 2019 outline the use of different therapies for the treatment of HS including lifestyle modifications, antibiotics, and biologics. Adalimumab (Humira) was approved by the Food and Drug Administration (FDA) in 2015 and subsequently by Health Canada in 2016 for HS treatment; it is currently the only biologic approved for HS.<sup>2,3</sup>

Adalimumab is a monoclonal antibody that inhibits tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Adalimumab binds to TNF- $\alpha$  and blocks its interaction with p55 and p75 cell surface TNF receptors.<sup>4</sup> In addition to HS, adalimumab is used to treat

other inflammatory conditions including psoriasis and ulcerative colitis. The following case describes a male patient who underwent treatment with adalimumab for severe HS and developed radiologically isolated syndrome (RIS).

## Case presentation

A 29-year-old male first presented to the dermatologist in 2017 with axillary and groin inflammatory nodules. He was

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diagnosed with HS and was given a prescription for doxycycline with the intent to commence adalimumab therapy. However, the patient did not return for his follow-up appointment.

He returned in October 2019 suffering a flareup of HS that included the axillary and perineum regions and an edematous scrotum that caused significant discomfort and impeded function. Due to his symptoms, Rifampin 300 mg PO BID and Prednisone 20 mg PO BID was initiated. Clindamycin therapy was deferred due to its interactions with medications he was taking for bipolar disorder. In addition, the patient was enrolled to start adalimumab.

At reassessment, his scrotal swelling had decreased by approximately 70%. Prednisone was well tolerated; however, rifampin produced intolerable gastrointestinal symptoms and flushing. Therefore, rifampin was discontinued, and doxycycline 100 mg PO daily was started.

Adalimumab therapy began in December 2019. Simultaneously, doxycycline was discontinued, and prednisone was tapered down to 5 mg BID. The patient markedly improved while taking adalimumab 40 mg SC weekly and had only a few isolated residual lesions at the axillae and groin regions.

Three months after starting adalimumab, the patient complained of squeezing-like migraine headaches localized to the left frontal orbital region and phono- and photophobia that was worse with physical activity. A brain magnetic resonance imaging (MRI) was ordered for structural assessment. The MRI revealed white matter lesions in both cerebral hemispheres and left periventricular area morphology consistent with demyelinating lesions. Therefore, Humira was stopped. He was reviewed by a neurologist who concluded that the patient had RIS and estimated his risk of developing multiple sclerosis (MS) to be less than 50% after 15 years. The neurologist agreed with the discontinuation of adalimumab and ordered for brain, cervical and thoracic MRIs to be done in 6 months. The patient was also advised to take Vitamin D 4000 IU daily and avoid TNF- $\alpha$  antagonists.

After adalimumab was stopped, the patient's neurologic symptoms resolved, but his HS symptoms flared significantly and required an increase of prednisone to 15 mg daily. Despite evidence regarding the use of anti-IL12/23 medications in HS, this therapy was deferred because it causes headaches in approximately 5% of patients.<sup>5,6</sup> Instead, the patient sought off-label therapy with an anti-IL17 biologic.

## Discussion

Despite the positive clinical effects of adalimumab in HS treatment, there are adverse neurological side effects from its use. Adalimumab has been associated with the rare new development or exacerbation of demyelinating diseases including MS and Guillain-Barré syndrome.<sup>7</sup> Thus, significant caution must occur prior to administering adalimumab in patients with pre-existing demyelinating diseases and should be stopped if neurological symptoms develop.<sup>7</sup>

The development of demyelinating diseases such as MS following the use of TNF- $\alpha$  antagonists and specifically adalimumab has been well documented.<sup>8-15</sup> In these cases, the patients began to develop neurological symptoms several months after the initiation of adalimumab for their respective diseases. In addition, all of these patients' brain MRI's showed white matter lesions consistent with MS. RIS is a diagnosis given to patients whose brain MRI imaging reveals white matter lesions that fulfills criteria for MS, but they do not experience the typical symptoms associated with MS and do not have a history of demyelinating disease.<sup>16,17</sup> Although RIS and MS are strongly associated, the diagnosis of RIS does not mean that a patient will also develop MS. Currently, no cases have been reported regarding the development of MS or RIS in a patient undergoing therapy for HS with adalimumab.

The relationship between MS and TNF- $\alpha$  antagonists is poorly understood, although several theories have been proposed. One hypothesis suggests that TNF- $\alpha$  antagonists enhance disease activity in MS by preventing the destruction of autoreactive T-cells. Thus, by increasing the number and activity of T-cells, TNF- $\alpha$  antagonists increase autoimmune responses.<sup>18</sup> Another theory suggests that TNF- $\alpha$  antagonists deactivate TNF- $\alpha$  systemically, but not within the central nervous system (CNS) due to blood-brain barrier impermeability. TNF- $\alpha$  has been found to cause oligodendrocyte cell death, injure myelin sheath, and be a driving factor in demyelination.<sup>18</sup> Therefore, the inability of TNF- $\alpha$  antagonists to enter the CNS would prevent the inhibition of TNF- $\alpha$ -mediated demyelination in MS.<sup>18</sup> In addition, because TNF- $\alpha$  antagonists decrease TNF- $\alpha$  levels systemically but not within the CNS, this could cause an upregulation of TNF- $\alpha$  expression in the CNS, further exacerbating TNF- $\alpha$ -mediated demyelination.<sup>19</sup> A third proposed hypothesis states that TNF- $\alpha$  antagonists inhibit TNF- $\alpha$ -induced interleukin-10 and prostaglandin E2 production, resulting in increased IL-12 production which promotes IFN $\gamma$  expression; IFN $\gamma$  has been shown to exacerbate MS.<sup>18</sup> Finally, TNF- $\alpha$  antagonists may unmask a latent infection or neurologic disease that initiates an autoimmune demyelinating process.<sup>19,20</sup>

The Humira product monograph suggests the discontinuation of adalimumab if a patient develops neurological symptoms. However, there is debate as to whether TNF- $\alpha$  antagonist use and CNS demyelination are temporally related. In addition, the overall incidence of the development of neurological symptoms in patients taking TNF- $\alpha$  antagonists is low and the time interval between the initiation of TNF- $\alpha$  antagonist and CNS demyelination widely varies.<sup>19</sup> Given these uncertainties, adalimumab could be held for a 6-month period with monitoring for improvement of neurological symptoms and reimaging to assess for the resolution of demyelinating lesions. If there is clinical stability and structural resolution, resumption of adalimumab—with the approval of and close monitoring by a neurologist—may be

considered, particularly when there is a lack of other effective treatments to control extensive inflammatory disease.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### Informed consent

Informed written was obtained from the patient for publication of this case report.

### References

1. Poli F, Jemec GBE and Revuz J. Clinical presentation. In: Jemec GBE, Revuz J and Leyden JJ (eds) *Hidradenitis Suppurativa*. Berlin; Heidelberg: Springer, 2006, pp. 11–24.
2. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: part II: topical, intralesional, and systemic medical management. *J Am Acad Dermatol* 2019; 81(1): 91–101.
3. AbbVie's HUMIRA® (Adalimumab) Receives First and Only Health Canada approval for moderate to severe Hidradenitis Suppurativa, <https://www.newswire.ca/news-releases/abbvies-humira-adalimumab-receives-first-and-only-health-canada-approval-for-moderate-to-severe-hidradenitis-suppurativa-564353901.html> (accessed 15 October 2020).
4. Burness CB and Deeks ED. Adalimumab. *Drugs* 2012; 72(18): 2385–2395.
5. Montero-Vilchez T, Pozo-Román T, Sánchez-Velicia L, et al. Ustekinumab in the treatment of patients with hidradenitis suppurativa: multicenter case series and systematic review. *J Dermatolog Treat*. Epub ahead of print 21 April 2020. DOI: 10.1080/09546634.2020.1755008.
6. Ustekinumab product monograph, [https://www.janssen.com/canada/sites/www\\_janssen\\_com\\_canada/files/prod\\_files/live/stelara\\_cpm.pdf](https://www.janssen.com/canada/sites/www_janssen_com_canada/files/prod_files/live/stelara_cpm.pdf) (accessed 9 January 2021).
7. 2018 HUMIRA® (adalimumab) injection, for subcutaneous use—FDA, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/125057s4101bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s4101bl.pdf) (accessed 1 September 2020).
8. Matsumoto T, Nakamura I, Miura A, et al. New-onset multiple sclerosis associated with adalimumab treatment in rheumatoid arthritis: a case report and literature review. *Clin Rheumatology* 2013; 32(2): 271–275.
9. Bensouda-Grimaldi L, Mulleman D, Valat JP, et al. Adalimumab-associated multiple sclerosis. *J Rheumatol* 2007; 34(1): 239–240.
10. Uygunoğlu U, Uluduz D, Taşçılar K, et al. Multiple sclerosis during adalimumab treatment in a case with ankylosing spondylitis. *Rheumatol Int* 2014; 34(1): 141–143.
11. Hare NC, Hunt DP, Venugopal K, et al. Multiple sclerosis in the context of TNF blockade and inflammatory bowel disease. *QJM* 2014; 107(1): 51–55.
12. Engel S, Luessi F, Mueller A, et al. PPMS onset upon adalimumab treatment extends the spectrum of anti-TNF- $\alpha$  therapy-associated demyelinating disorders. *Therap Adv Neurol Disorder* 2020; 13: 1756286419895155.
13. Theibich A, Dreyer L, Magyari M, et al. Demyelinating neurological disease after treatment with tumor necrosis factor alpha-inhibiting agents in a rheumatological outpatient clinic: description of six cases. *Clin Rheumatol* 2014; 33(5): 719–723.
14. Alnasser Alsukhni R, Jriekh Z and Aboras Y. Adalimumab induced or provoked MS in patient with autoimmune uveitis: a case report and review of the literature. *Case Rep Med* 2016; 2016: 1423131.
15. Bellesi M, Logullo F, Di Bella P, et al. CNS demyelination during anti-tumor necrosis factor alpha therapy. *J Neurol* 2006; 253(5): 668.
16. Hosseiny M, Newsome SD and Yousem DM. Radiologically isolated syndrome: a review for neuroradiologists. *Am J Neuroradiol* 2020; 41(9): 1542–1549.
17. Radiologically Isolated Syndrome (RIS). <https://www.cedars-sinai.org/health-library/diseases-and-conditions/r/radiologically-isolated-syndrome-ris.html> (accessed 15 November 2020).
18. Robinson WH, Genovese MC and Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor  $\alpha$  antagonism: by what mechanisms could tumor necrosis factor  $\alpha$  antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? *Arthr Rheumat* 2001; 44(9): 1977–1983.
19. Kemanetozoglou E and Andreadou E. CNS demyelination with TNF- $\alpha$  blockers. *Curr Neurol Neurosci Rep* 2017; 17(4): 36.
20. Toussirot E, Pertuiset E, Martin A, et al. Association of rheumatoid arthritis with multiple sclerosis: report of 14 cases and discussion of its significance. *J Rheumatol* 2006; 33(5): 1027–1028.