Primary Progressive Multiple Sclerosis Under Anti-TNFα Treatment: A Case Report

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ABSTRACT: Antagonists of tumour necrosis factor α (TNFα) are a common therapeutic choice for autoimmune diseases. Although they are effective and relatively safe, an increasing number of immune-mediated adverse events have been reported. Among these, neurological adverse effectsm such as consisting of demyelinating events in the central and peripheral nervous system were described. Demyelination of the central nervous system is a rare complication after treatment with TNFα antagonists. Here, we report a case of multiple sclerosis under treatment with TNFα antagonists and discuss its etiopathogenesis. This 45-year-old female patient developed signs and symptoms suggestive of primary progressive multiple sclerosis during treatment with adalinumab for nodular cystic acne, and magnetic resonance imaging of the patient showed typical lesions of demyelinating disease.

KEYWORDS: Multiple sclerosis, adalinumab, anti-TNFα, demyelinating disease

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Background

Antagonists of tumor necrosis factor α (anti-TNFα) are an important therapeutic tool for various autoimmune inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, and others rheumatological diseases.

Although they are effective and relatively safe, an increasing number of immune-mediated adverse events have been reported. Among these, neurological side effects consisting of demyelinating events in the central and peripheral nervous system were described.[1]

However, it is not clear whether treatment with anti-TNFα blockers unmasks preexisting demyelinating disorders such as multiple sclerosis (MS) or induces *de novo* demyelination of the central nervous system (CNS) or peripheral nervous system.

We report the case of a 45-year-old female patient who developed signs and symptoms suggestive of primary progressive multiple sclerosis (PPMS) during treatment with adalimumab (anti-TNFα) for nodular cystic acne.

Case Report

A 45 year-old woman came to our attention due to visual problem progressive gait impairment and urinary dysfunction that slowly occurred over the last year.

Her past medical history was positive for both Basedow's and Sjogren disease. At the age of thirty, she underwent bariatric surgery and she took vitamin supplementation since then.

The patient suffered from cystic nodular acne for about 10 years. In the last 4 years she had undergone adalimumab therapy with excellent clinical response (anti-TNFα treatment, 40 mg every 2 weeks). At our first evaluation, she was able to walk without aid or rest for 500 m and neurological exam showed gait impairment due to lower limbs spasticity and mild ataxia, dysmetria, postural instability, brisk reflex and left Babinski sign, visual acuity degraded during attempted reading and visual acuity is 4/10 in both eyes with central scotoma. Moreover, the patient complained of photophobia and dyschromatospia. She had saccadic pursuits and gaze-evoked, rebound, and downbeat nystagmus, without ophthalmoparesis. Saccades had a normal latency and velocity but were inaccurate.

Brain and spinal cord magnetic resonance images (MRI) showed hyperintense lesions in T2-weighted images in subcortical and paracallosal area and lesions in cervical, dorsal and lumbar spinal cord with no contrast enhancement. These lesions are suggestive of demyelination disease (Figure 1). Furthermore, visual evoked potentials (VEPs) showed abnormal latencies in both eyes displaying a damage to the optical pathways. Routine laboratory exams including complete blood count, chemistry panel, thyroid function, Lyme titer, HIV, vitamin E, anti-GAD_{65} antibody, antinuclear antibody, paraneoplastic panel (anti-Hu, Ma1, Ma2, Yo, Ri, CV2, and Zic4), and antibodies to anti-Ro, anti-La, gliadin, endomysium, and tissue transglutaminase were unremarkable, infectious or other immunological causes were ruled out, CSF analysis was positive for oligoclonal

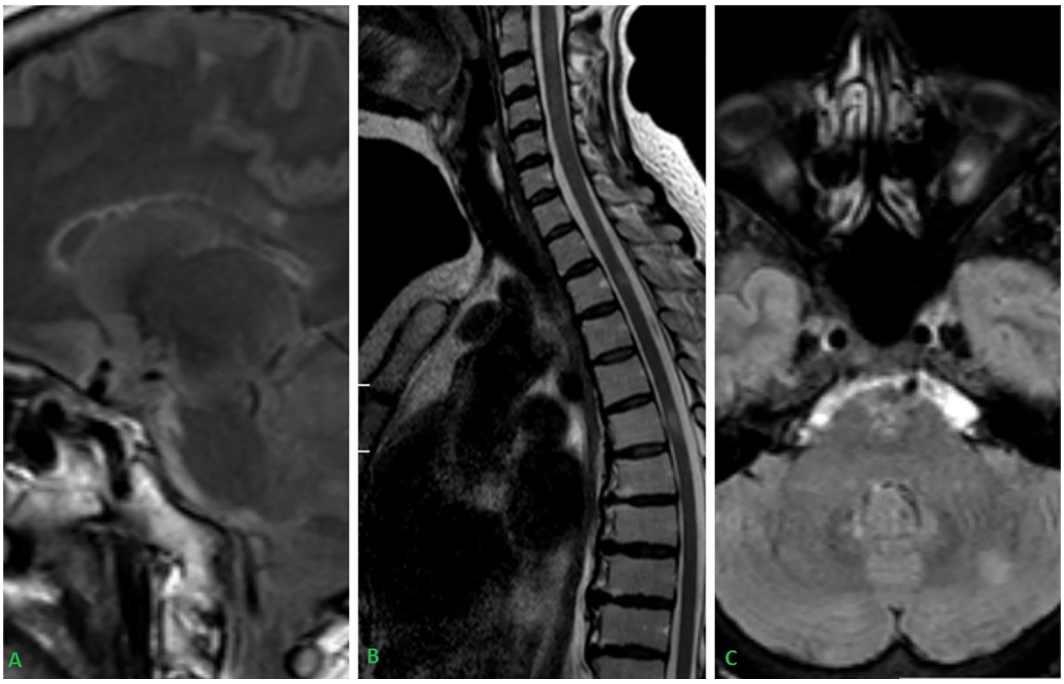

Figure 1. Brain MRI transversalT2-weighted shows hyperintense lesions in the left cerebellar hemisphere, in paracallosalareas and numerous spinal cord lesions.

bands without bands in the serum (pattern 2) and aquaporin-4 and myelin oligodendrocyte glycoprotein were negative.

As the patient fulfilled all diagnostic criteria according to the 2017 revision of the McDonald criteria (progressive neurological symptoms >12 months, MRI lesions typical for MS, positive CSF), PPMS was diagnosed.[2] Although no clear-cut recommendations have been made on the management of neurological complications associated with anti-TNFα therapy, we stopped adalimumab treatment and administered a 5-day course of high-dose steroids (1 g daily methylprednisolone). Despite these measures, the patient did not show any clinical response and relentlessly worsened over a follow-up period of 16 months. Additionally, a follow-up MRI showed increased lesion load and treatment with ocrelizumab was established.

Discussion

TNFα has a critical and complex role in MS. It is a clearly proinfiammatory cytokine during the acute phase of MS but has immunosuppressive properties in the later stage of the disease. TNFα is usually produced by macrophages, lymphocytes (T and B cells), natural killer cells, dendritic cells and monocytes while in CNS, TNFα is mainly produced by microglia, neurons, and astrocytes.[3] TNFα interacts with 2 receptors (TNFR1 and TNFR2). TNFR1, expressed by all cell types, mediates apoptosis and chronic inflammation and is involved in the pathogenesis of autoimmune demyelinating diseases. TNFR2 receptor, expressed mainly on neurons, immune cells and endothelial cells, activates genes involved in cell survival, resolution of inflammation, and myelination.[4,5] TNFα blockers are monoclonal antibodies IgG anti-TNFα receptors that act as agonists reversing the apoptosis pathway, cell activation or inhibition of cytokines production.[6,7] Adalimumab, provide considerable benefit in several autoimmune diseases. Despite its relatively safe profile, several cases of autoimmune diseases have also been described.[8,9] Central and peripheral demyelinating events have also been reported including MS, optic neuritis, Guillain-Barré and Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy. However, it is not clear if treatment with TNF blockers unmasks preexisting demyelinating disorder such as MS or induces de novo demyelinating lesion of CNS.[4]

Until now, about 20 MS case reports have been related to anti-TNFa treatment and Engel et al described the first case of PPMS under adalimumab treatment.[10] Actually, several hypotheses have been proposed to explain a potential biological relationship between TNFα blockers and demyelinating disease. TNFα blockers can exacerbate CNS demyelination by decreasing TNFR2 receptors, which are necessary for the proliferation of immature oligodendrocytes and myelin repair.[11,12]

Moreover, they could alter cytokine responses by downregulating interleukin-10 and upregulating interleukin-12 and interferon-γ, creating a profile similar to that of patients with multiple sclerosis.[13]

TNFα blockers may deactivate TNFα systemically, but not within the CNS due to the impermeability of the blood- brain barrier causing a high concentration of TNFα in the CNS.[14] Finally, they can unmask an underlying latent infection, which can lead to autoimmune demyelination.[4]

In our patient, several autoimmune diagnoses coexist. Basedow's and Sjogren disease are often associated with MS but in our knowledge, no causative relationship has never been described.[15] On the other hand, growing clinical reported

evidence, and recently, a link between the development of MS and the presence of the single nucleotide polymorphism (SNP), suggest an etiological role of anti-TNF drugs in.[10]

Observational studies and meta-analyses of randomized controlled trials and case-control study on 10 000 patients with rheumatoid arthritis treated with anti-TNF drugs have demonstrated the appearance of demyelinating disorders of the peripheral and central nervous system (CNS), underlining that anti-TNFα can increase the risk of demyelinating events by ≈30%.[16] Moreover, the short time from the start of the anti-TNFα therapy to the development of demyelinating symptoms and the improvement of symptoms on discontinuation of the biological therapy are often but not always a feature common to cases from literature reports and spontaneous surveillance. Then, in most reports, like in our case, appeared after several exposures, including long-term exposure, and did not necessarily improve after cessation of the biologic treatment.[17] Actually there are no guidelines for the management of drug induced demyelinating CNS lesions and the most common therapeutic tool is based on the administration of steroids with good short-term results, although the course of the demyelinating disease appears unpredictable.[1] However, anti-TNFα treatment should be discontinued at the onset of unexplained neurological symptoms.

Conclusion

Anti-TNFα drugs have changed the treatment of autoimmune diseases being very effective and relatively safe. However, the role of TNFα in the central nervous system is not clearly understood. To date, given the growing number of reported cases of demyelination, a causal association is conceivable rather than an accidental coexistence of 2 disorders. Follow-up of these patients is essential to diagnose the clinical course and highlight the potential differences with typical MS course. Complete remission of symptoms after discontinuation of therapy or clinical stability may prove iatrogenic causality. However, stopping treatment did not spare the patient from disease progression by suggesting the hypothesis of a trigger of a pathogenetic process instead of a toxic effect.

Although several theoretical explanations of demyelination have been proposed after TNFα blockade, the relationship of these events with the use of TNFα blockers remains to be elucidated.

However, it is recommended to avoid the use of anti-TNFα therapy in patients with a family history or onset of MS or other systemic demyelinating or autoimmune diseases. Although MRI of the brain is not recommended before starting anti-TNFα treatment, it could be useful in revealing possible silent demyelinating lesions especially in patients with systemic autoimmune diseases.[18]

Then, we suggest to pay attention in people under anti-TNFα treatment, including neurological evaluation before starting therapy and neurological monitoring to diagnose a possible demyelinating event and sooner and better.

Authors' Contribution

AI: Design and conceptualized study; acquisition and analyzed the data; drafted the manuscript for intellectual content, FA: analyzed the data; revised the manuscript for intellectual content, RD: Revised the manuscript for intellectual content, LR: Revised the manuscript for intellectual content, ST: Revised the manuscript for intellectual content, ES: Revised the manuscript for intellectual content, FM: Revised the manuscript for intellectual content, RI: Design and conceptualized study; revised the manuscript for intellectual content.

Ethics statement

This article is a clinical case study and follows the tenets of Helsinki Declaration. The findings presented on this article arise from clinical practice and did not involve any new studies of human or animal subjects performed by any of the authors. A written, informed consent was obtained from the patient to publish their medical and imaging data.

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REFERENCES

1. Bosch X, Saiz A, Ramos-Casals M; BIOGEAS Study Group. Monoclonal antibody therapy-associated neurologic disorders. *Nat Rev Neurol*. 2011;7(3):165-172.
2. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.
3. Caminero A, Comabella M, Montalban X. Tumor necrosis factor alpha (TNF-α), anti-TNF-α and demyelination revisited: an ongoing story. *J Neuroimmunol*. 2011;234(1-2):1-6.
4. Kalliolias GD, Ivashkiv LB. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. *Nat Rev Rheumatol*. 2016;12(1):49-62.
5. Kassiotis G, Kollias G. Uncoupling the proinflammatory from the immunosuppressive properties of tumor necrosis factor (TNF) at the p55 TNF receptor level: implications for pathogenesis and therapy of autoimmune demyelination. *J Exp Med*. 2001;193(4):427-434.
6. Silva LC, Ortigosa LC, Benard G. Anti-TNF-α agents in the treatment of immune-mediated inflammatory diseases: mechanisms of action and pitfalls. *Immunotherapy*. 2010;2(6):817-833.
7. Probert L. TNF and its receptors in the CNS: the essential, the desirable and the deleterious effects. *Neuroscience*. 2015;302:2-22.
8. Strangfeld A, Listing J. Infection and musculoskeletal conditions: Bacterial and opportunistic infections during anti-TNF therapy. *Best Pract Res Clin Rheumatol*. 2006;20(6):1181-1195.
9. RamosCasals M, BritoZerón P, Muñoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)*. 2007;86(4):242-251.
10. Engel S, Luessi F, Mueller A, Schopf RE, Zipp F, Bittner S. PPMS onset upon adalimumab treatment extends the spectrum of anti-TNF-α therapy-associated demyelinating disorders. *Ther Adv Neurol Disord*. 2020;13:1756286419895155.
11. 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.
12. Bellesi M, Logullo F, Di Bella P, Provinciali L. CNS demyelination during anti-tumor necrosis factor alpha therapy. *J Neurol*. 2006;253(5):668-669.
13. van Boxel-Dezaire AH, Hoff SC, van Oosten BW, et al. Decreased interleukin-10 and increased interleukin-12p40 mRNA are associated with disease activity and characterize different disease stages in multiple sclerosis. *Ann Neurol*. 1999;45(6):695-703.
14. Kaltsonoudis E, Voulgari PV, Konitsiotis S, Drosos AA. Demyelination and other neurological adverse events after anti-TNF therapy. *Autoimmun Rev*. 2014;13(1):54-58.
15. Thormann A, Sørensen PS, Koch-Henriksen N, Thygesen LC, Laursen B, Magyari M. Chronic comorbidity in multiple sclerosis is associated with lower incomes and dissolved intimate relationships. *Eur J Neurol*. 2017;24(6):825-834.

16. Bosch X, Saiz A, Ramos-Casals M, The BIOGEAS Study Group. Monoclonal antibody therapy-associated neurological disorders. *Nat Rev Neurol*. 2011;7:165-172.
17. Cruz Fernández-Espartero M, Pérez-Zafrilla B, Naranjo A, et al. Demyelinating disease in patients treated with TNF antagonists in rheumatology: data from BIOBADASER, a pharmacovigilance database, and a systematic review. *Semin Arthritis Rheum*. 2011;41(3):524-533.
18. Ding T, Ledingham J, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. *Rheumatology (Oxford)*. 2010;49(11):2217-2219.