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Case report

NMOSD with anti-MOG antibodies following anti-TNFα therapy: A case report

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ABSTRACT

Tumor necrosis factor α (TNFα) inhibitors are highly effective and a therapeutic choice for several inflammatory diseases. Their broad and long-term use is associated with a growing number of paradoxical autoimmune events including demyelinating lesions of the central nervous system (CNS). We report and discuss a case of neuromyelitis optica spectrum disorder (NMOSD) with positive myelin oligodendrocyte glycoprotein antibodies (MOG-IgG1) following anti-TNFα therapy for a pustular psoriasis.

1. Background

Tumor necrosis factor α (TNFα) blockers are highly effective and a therapeutic choice for several inflammatory diseases (e.g. rheumatoid arthritis and psoriasis). Today, five anti-TNFα inhibitors have been approved for clinical use: etanercept (soluble TNF receptor 2), infliximab, adalimumab, golimumab (IgG monoclonal antibodies) and certolizumab (PEGylated Fab1 fragment of an IgG monoclonal antibody).

The widespread and long-term use of TNF-targeted therapies is associated with a growing number of paradoxical induced autoimmune processes, including both systemic (lupus, vasculitis, sarcoidosis, antiphospholipid syndrome) and organ–specific diseases (interstitial lung disease, autoimmune hepatitis, uveitis, optic neuritis, peripheral neuropathies, multiple sclerosis, multiple sclerosis-like diseases). Although the prevalence of demyelinating events of the central nervous system (CNS) ranged between 0.05–0.2% in clinical and post-marketing studies, over 800 cases have been identified to date (Retamozo et al., 2017). Typically it includes isolated optic neuritis and transverse myelitis occurring between one month and one year after anti-TNFα initiation. In the majority of cases, the disease will not relapse after TNF inhibitor's discontinuation, however a subset of patient will develop a relapsing-remitting course despite discontinuation of the offending agent.

We report and discuss a case of neuromyelitis optica spectrum disorder (NMOSD) with positive myelin oligodendrocyte glycoprotein antibodies (MOG-IgG1) following anti-TNFα therapy for a pustular psoriasis.

2. Case presentation

A 40 year-old man with a ten-year history of pustular psoriasis was examined in March 2015 after developing right upper limb paraesthesia and Lhermitte's phenomenon. Except bilateral exaggerated knee and ankle reflexes, the neurological exam was unremarkable.

This patient had been treated for ten years with several immunosuppressive drugs for a moderate psoriasis, including azathioprine, methotrexate, etanercept and more recently adalimumab. Etanercept – 50 mg once weekly – had been administered from April 2012 to June 2013. Because of poor effectiveness, it was switched to adalimumab after three months washout. Adalimumab – 40 mg every other week – had been started 18 months before the first neurological manifestations.

Brain MRI was normal but spinal cord MRI revealed a longitudinally extensive transverse myelitis (LETM) at the bulbo-medullar junction with Gadolinium® enhancement (Fig. 1(a) and (b)). The available accumulated laboratory data did not provide evidence for infectious or systemic autoimmune myelitis. Autoimmune screening was normal (C-reactive protein, sedimentation rate, anti-thyroperoxidase antibodies, anti-neuronal antibodies, anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies, complement levels, anti-cardiolipin antibodies, anti-beta 2 glycoprotein antibodies) and plasma AQP4-IgG were not detected. Viral (Cytomegalovirus, Epstein-Barr Virus, Varicella-Zoster Virus, Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus), parasitic (Toxoplasma) and bacterial (Borrelia, Syphilis, Mycoplasma Pneumoniae, Chlamydia Pneumoniae) serologies were negative as well as QuantiFERON®-TB test. Cerebral spinal fluid (CSF) analysis

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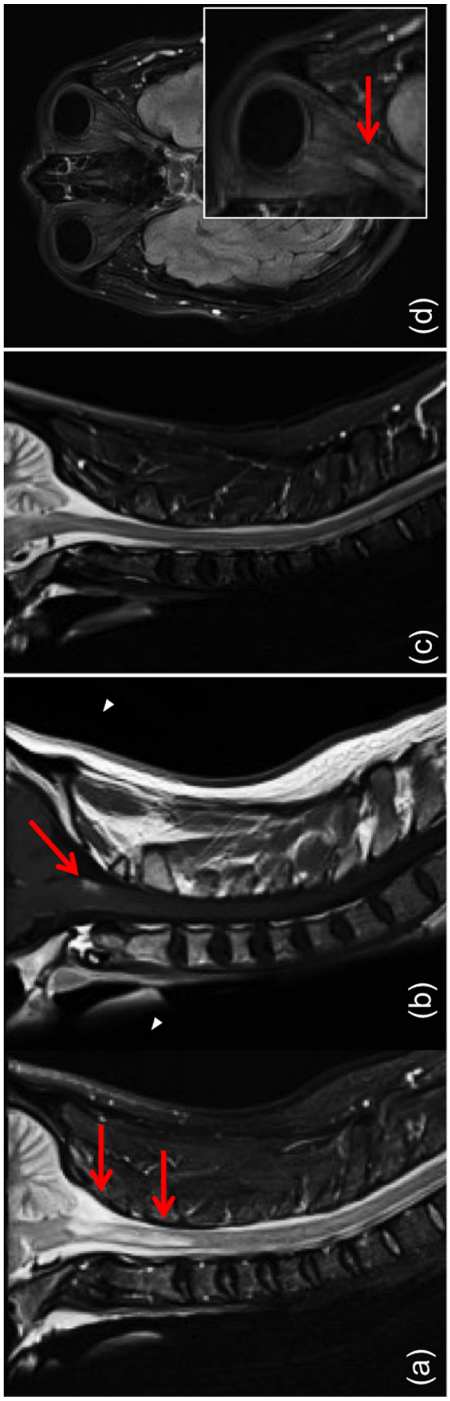

Fig. 1. Extensive T2 hyper-intense lesion at the bulbo-medullar junction (a) with Gadolinium° enhancement (b). Complete regression of bulbo-medullar lesion on T2 sequence three months after IV steroids (c). T2 hyper-intense lesion in the intra-orbital part of the left optic nerve (d).

showed lymphocytic pleocytosis (25 cells/μL; 70% lymphocytes), slightly increased total protein (680 mg/L), normal glucose level and IgG index. No oligoclonal bands were detected. The whole body FDG PET-CT was normal.

Intravenous administration of high-dose steroids resulted in a complete clinical recovery within 2 weeks. A repeat MRI performed after 3 months revealed a thorough regression of bulbo-medullar lesion on T2 sequence and no residual Gadolinium® enhancement (Fig. 1(c)). Adalimumab was discontinued and he did not receive any other treatment of psoriasis except photodynamic therapy during minor relapses.

The clinical and radiological follow-up conducted twice a year was unremarkable. However, seventeen months after the first demyelinating event, the patient presented with a painful left eye with blurred vision. Ophthalmologic examination confirmed an optic neuritis with slight papillary edema. Brain MRI showed a T2 hyper-intense signal in the intra-orbital part of the left optic nerve (Fig. 1(d)) with a discrete enhancement. Spinal cord MRI remained unchanged. We repeated the autoimmune screening. AQPA4-IgG were absent but newly described MOG-IgG1 positive. Testing for the presence of serum MOG-IgG1 was performed in the Autoimmune Neurology Laboratory in Oxford, using a cell-based assay (Waters et al., 2015). Again the patient was treated with IV steroids and rapidly recovered. Mycophenolate, at a dosage of 1 g twice daily, was started. The persistence of MOG-IgG1 after one year on immunosuppressive drug warranted continuing this treatment. Since then, the patient did not present any neurological manifestation.

3. Discussion

We report the occurrence of neurologic symptoms following TNFα inhibitors and other non-selective immunosuppressive treatments for psorias. Clinical and radiological features are consistent with demyelinating disease and patient met diagnostic criteria for NMOSD with positive MOG-antibodies (Wingerchuk et al., 2015). NMOSD has never been reported in this context neither positive MOG-IgG1. Immunosuppressants such as azathioprine, mycophenolate and rituximab are recommended to treat MOG-antibodies related disorders (Jarius et al., 2016; Ramanathan et al., 2016). However data regarding duration, efficacy and type of immunotherapy are still limited. Although patient can become antibody-negative and remain relapse free off therapy, the duration of immunosuppression after the disease onset does not seem to predict the antibody status (Jurynczyk et al., 2017).

Several factors suggest an etiological role for TNFα blockers in the development of demyelinating disorders. First, disease is temporally associated with initiation of therapy. Second, the symptomatology is suggestive of an antigen-mediated hypersensitivity process. Last, the disease most often resolves after discontinuation of therapy and/or a positive rechallenge phenomenon (reappearance or worsening of symptoms on re-exposure to the agent) is observed. However, it is still unclear whether these events are coincidental, revealed or triggered by the TNFα blockers. Even more elusive remain the underlying pathogenic mechanisms regarding the pleiotropic functions of TNFα and their contradictory effects, particularly in the CNS. TNFα and its receptors (TNRF1 and TNRF2) can either promote neuroinflammation and secondary neuronal damage, or exert neuroprotective properties under pathological conditions (Probert, 2015). However elevated TNFα production was observed in patients and animal models of MS, TNFα blockers failed to produce any beneficial effects in MS and even led to worsening the disease (The Lenercept Multiple Sclerosis Study Group, 1999). Interestingly, systemic administration of anti-TNF-α enhances antigen presenting cell function, decreases apoptosis of potentially autoreactive T-cells and induce the production of proinflammatory cytokines. As a consequence, prolonged exposure to anti-TNF-α likely promotes the activation and survival of potentially autoreactive T-cells in the periphery, which might subsequently penetrate the CNS and cause demyelination (Fromont et al., 2009).

4. Conclusion

Anti-TNFα therapies revolutionized the management of disabling inflammatory diseases but autoimmune diseases may be associated with their use. Especially, an increasing number of CNS demyelinating disorders have been reported in this context and some of them have evolved into chronic relapsing condition after discontinuation of the therapy. MOG-antibodies related disorders are so rare, that coincidental co-occurrence cannot be ruled out in this specific case. Nevertheless we propose a systematic screening of CNS side effects by regular clinical follow up during therapy and CNS MRI before its initiation. Treatment should be discontinued in the presence of any documented neurological manifestations. More generally, the risks of secondary autoimmune diseases should be considered when using treatments with potential complex effects on the immune system.

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Research ethics and patient consent

Informed consent for patient information and images to be published was provided by the patient.

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