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PPMS onset upon adalimumab treatment extends the spectrum of anti-TNF-α therapy-associated demyelinating disorders

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***Abstract*:** Since their introduction in 1999, anti-tumour necrosis factor-α (anti-TNF-α) therapies have been suspected repeatedly to be associated with the occurrence of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS). However, recent publications were restricted to descriptions of monophasic demyelinating events or cases of relapsing–remitting MS (RRMS). We here provide the first case report of primary progressive MS (PPMS) onset upon anti-TNF-α therapy as well as a literature review of previously published cases of anti-TNF-α therapy-associated MS onset. The 51-year old male patient was treated with adalimumab due to psoriasis arthritis. About 18 months after treatment initiation, he developed slowly progressing neurological deficits including gait impairment, paraesthesia of the lower limbs, strangury and visual impairment, which led to the discontinuation of adalimumab therapy. Magnetic resonance imaging of the brain and the spinal cord revealed multiple inflammatory lesions and cerebrospinal fluid examination showed slight pleocytosis and positive oligoclonal bands. Thus, PPMS was diagnosed according to the 2017 revision of the McDonald criteria. As PPMS often causes only subtle symptoms in the beginning and early treatment discontinuation of anti-TNF-α therapy seems essential to improve the patient's outcome, we think that it is important to increase the awareness of slowly progressing neurological deficits as a potential adverse event of anti-TNF-α therapy among all clinicians involved in the initiation and monitoring of these drugs. In addition, the occurrence of both RRMS and progressive MS upon anti-TNF-α therapy might suggest a shared TNF-α-mediated pathophysiological mechanism in the evolution of all MS subtypes.

Keywords: adalimumab, anti-TNF-alpha therapy, primary progressive multiple sclerosis

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Introduction

Anti-tumour necrosis factor-α (anti-TNF-α) agents such as adalimumab (Humira®) are commonly used in the treatment of rheumatological, dermatological and gastroenterological autoimmune disorders. Despite being generally considered to be well tolerated, serious autoimmune-mediated adverse events have been reported, including central nervous system (CNS) demyelinating disorders such as multiple sclerosis (MS). In formerly published MS cases associated with anti-TNF-α use, authors either diagnosed relapsing–remitting MS (RRMS) or the descriptions did not offer enough information to classify the disease course. We here describe the first occurrence of well-defined and definite primary progressive MS (PPMS) upon anti-TNF-α therapy and provide an overview of the current literature concerning this topic.

Case report

In November 2018, a 51-year old White man was first admitted to our hospital due to progressive neurological deficits. He was first diagnosed with

psoriasis vulgaris in the 1980s and was initially treated topically with steroids, dithranol and phototherapy, followed by systemic therapy with fumarate, cyclosporine, and methotrexate. Owing to signs of psoriasis arthritis, anti-TNF-α treatment with adalimumab was initiated in September 2015, leading to almost complete remission of the psoriasis.

However, in early 2017, about 18 months after treatment initiation, the patient first perceived hypesthesia of the lower limbs [corresponding to an Expanded Disability Status Scale (EDSS) score of 2.0], which progressed slowly over the following months. Adalimumab treatment was therefore discontinued in April 2017. Over the course of approximately 1 year, slowly progressive gait impairment, strangury, visual impairment and dysarthria occurred subsequently. Neurological examination in November 2018 revealed gait impairment owing to spasticity and ataxia with a restricted walking distance of about 2 km, severe pallhypaesthesia and brain stem symptoms including saccadic eye movement and dysarthria (corresponding to an EDSS score of 4.0). Visually evoked potentials (VEPs) displayed prolonged latencies of both optic nerves. Magnetic resonance imaging (MRI) of the brain and spinal cord showed numerous T2-hyperintensive lesions without contrast enhancement in periventricular, juxtacortical and spinal localization (Figure 1A–D). Cerebrospinal fluid (CSF) analysis revealed a slight pleocytosis, intrathecal immunoglobulin synthesis, and presence of CSF-specific oligoclonal bands. Tests for serum antibodies against Aquaporin-4 and MOG were negative. Infectious or other autoimmunological causes were ruled out.

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 and pathologic VEPs),[1] PPMS was diagnosed. Disease-modifying treatment with ocrelizumab was initiated and complemented by topical steroids for treating psoriatic symptoms.

The patient had no family history of multiple sclerosis or other neurological diseases. He gave written informed consent for both performing genomic sequencing and publishing its results, along with clinical data, radiological findings and results of laboratory tests in this case report.

Review of reported cases

As anti-TNF-α therapy-associated demyelinating disorders, including monophasic demyelinating events and peripheral demyelinating syndromes, have already been reviewed extensively in the past,[2–6] we focused on those reports describing a definite diagnosis of MS (Table 1).

We identified 20 cases of MS onset upon anti-TNF-α therapies, of which 9 were diagnosed with RRMS according to the McDonald criteria.[23–25] In 8 further cases, MS disease course was described as RRMS, but diagnostic criteria were not specified. One case could not be classified owing to a paucity of clinical data. There was one case description of slowly progressing neurological deficits, in which the available clinical information allowed no differentiation between secondary and primary progressive disease course,[21] and one report about the exacerbation of preexisting PPMS in a patient treated with etanercept.[22] Four patients had a positive family history for MS.[8,13,17,21]

Discussion

MS is a heterogeneous disease, which may be categorized into clinically isolated syndrome (CIS), RRMS, secondary progressive MS (SPMS) and PPMS. Lately, there have been suggestions to also include radiologically isolated syndrome (RIS), which is defined by MRI lesions suggestive for MS without clinical manifestation, as a prodrome of MS diseases since around one-third of patients with asymptomatic lesions develops neurological symptoms later on.[26] Interestingly, some RIS patients progress directly to PPMS.[27] This supports the hypothesis that all MS subtypes share some biological aspects in their pathogenesis, although it is still unknown why some patients suffer from acute relapses, whereas others progress relapse independently.

Although the possibility that the patient reported here had preexisting MS that was unmasked by adalimumab treatment, or that PPMS onset occurred coincidentally with adalimumab therapy cannot be fully excluded, our case suggests a crucial role of deregulated TNF-α homeostasis in the evolution of all MS subtypes as it offers the first description of definite PPMS onset upon anti-TNF-α therapy and thereby extends the spectrum of demyelinating diseases associated with these drugs.

Table 1. Overview of formerly published case reports of MS onset associated with anti-TNF-α therapy.

Reference	Sex/age	Primary autoimmune disease	Anti-TNF-α agent	MS disease course	According to diagnostic criteria	Family history for MS	Treatment	Disability outcome
Al Saieg and Luzar[7]	F/58	RA	Etanercept	Relapsing–remitting	Not specified	None	Discontinuation and steroids	Full recovery from relapse
Andreadou *et al.*[8]	M/17	PsA	Etanercept	Relapsing–remitting	McDonald 2010[9]	None	Discontinuation and steroids	Nearly full recovery from relapse
Andreadou *et al.*[8]	M/30	AS	Adalimumab	Relapsing–remitting	McDonald 2010[9]	Father with MS	Discontinuation and steroids	Full recovery from relapse
Andreadou *et al.*[8]	F/57	AS	Etanercept	Relapsing–remitting	McDonald 2010[9]	None	Discontinuation and steroids	Partial recovery from relapse
Davis *et al.*[9]	M/53	PsA	Etanercept	Relapsing–remitting	Not specified	None	Discontinuation and interferon-beta	Partial recovery from relapse
Davis *et al.*[9]	M/42	PsA	Etanercept	Relapsing–remitting	Not specified	None	Discontinuation	Partial recovery from relapse
Fromont *et al.*[10]	F/49	RA	Etanercept	Relapsing–remitting	McDonald 2005[8]	None	Discontinuation and interferon-beta	No data
Bensouda-Grimaldi *et al.*[11]	F/32	RA	Adalimumab	Relapsing–remitting	McDonald 2005[8]	No data	Discontinuation and steroids	Partial recovery from relapse
Matsumoto *et al.*[12]	F/68	RA	Adalimumab	Relapsing–remitting	McDonald 2010[9]	None	Discontinuation	Full recovery from relapse
Ruiz-Jimeno *et al.*[13]	F/47	PsA	Infliximab	Relapsing–remitting	Not specified	Sister with MS	Steroids and IVIGs	Partial recovery from relapse
Titelbaum *et al.*[14]	F/33	RA	Etanercept	Relapsing–remitting	Not specified	None	Discontinuation	No data
Uygunoglu *et al.*[15]	M/36	AS	Adalimumab	Relapsing–remitting	McDonald 2010[9]	None	Discontinuation and steroids	Full recovery from relapse
Pfueller *et al.*[16]	F/36	AS	Etanercept	Relapsing–remitting	McDonald 2001[7]	No data	Discontinuation	Full recovery from relapse
Alnasser Alsukhni *et al.*[17]	M/23	Autoimmune uveitis	Adalimumab	Relapsing–remitting	Not specified	Two uncles with MS	Discontinuation and steroids	Full recovery from relapse
Hare *et al.*[18]	F/26	Crohn's disease	Infliximab and adalimumab	Relapsing–remitting	Not specified	None	Discontinuation, steroids, and plasmapheresis	Partial recovery from relapse
Sicotte and Voskuhl[19]	F/21	Juvenile RA	Etanercept	Relapsing–remitting	Not specified	None	Discontinuation, steroids, and interferon beta	Full recovery from relapse
Gomez-Gallego *et al.*[20]	F/36	PsA	Etanercept	Relapsing–remitting	McDonald 2001[7]	None	Discontinuation and steroids	Partial recovery from relapse
Enayati and Papadakis[21]	F/35	Inflammatory bowel disease	Infliximab	Progressive	Not specified	Father with MS	No data	Rehabilitation necessary
Winkelmann *et al.*[22]	M/55	PsA	Etanercept	Exacerbation of preexisting PPMS	McDonald 2001[7]	No data	Discontinuation and steroids	No recovery
Cruz Fernandez-Espartero *et al.*[5]	F/67	Rheumatic Disease	Infliximab	MS, subtype not specified	Not specified	No data	Discontinuation	Recovery

AS, ankylosing spondylitis; PsA, psoriasis arthritis; RA, rheumatoid arthritis.

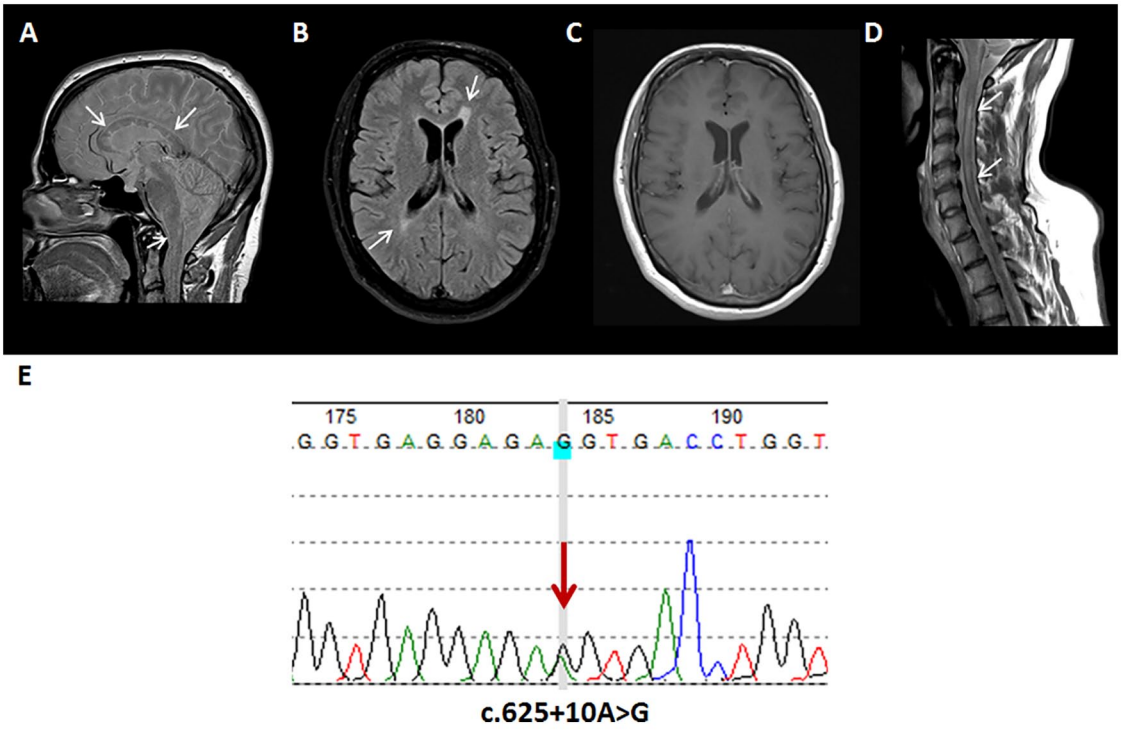

Figure 1. Magnetic resonance imaging (MRI) and sequence analysis of the TNFRSF1A gene in the patient with primary progressive multiple sclerosis upon adalimumab treatment.
T2-weighted sagittal MRI (A) and fluid attenuated inversion recovery (FLAIR) axial image (B) of the brain showed periventricular, corpus callosum and brainstem localized T2-hyperintense lesions (white arrows). No gadolinium enhancement was observed in T1Gd-weighted axial images (C). Proton density (PD)-weighted sagittal MRI of the spinal cord (D) revealed hyperintense cervical lesions (white arrows). The DNA sequence chromatogram (E) demonstrates a heterozygous A>G nucleotide change (red arrow) in intron 6 of TNFRSF1A gene (c.625+10A>G, rs1800693).

The effects mediated by TNF-α are extremely complex, not least because they can be either pro- or anti-inflammatory depending on cell type-specific interpretation of TNF-triggered pathways. There are also two biologically active variants of TNF-α, a soluble and a transmembrane form, as well as two different receptors. TNF-α-receptor 1 (TNFR1)-activation is mainly associated with pro-inflammatory and cytotoxic signalling, whereas TNF-α-receptor 2 (TNFR2)-activation evokes cytoprotective pathways.[28]

In MS, TNF-α levels were found to be increased in active MS lesions[29] and in an animal model of MS, TNFR1-deficiency led to amelioration of the disease course.[30] TNFR2-deficiency on the other hand resulted in enhanced susceptibility.[31] It is assumed that the activation of TNFR2 inhibits the pro-inflammatory activity of microglia, promotes the suppressive activity of regulatory T cells, enhances the differentiation of oligodendrocytes and stimulates remyelination.[28] It is therefore believed that in MS, in contrast to other autoimmune diseases, an imbalance in favour of pro-inflammatory TNFR1-mediated signalling pathways outweighs beneficial TNFR2-mediated effects.[32]

Furthermore, genome-wide association studies have identified a link between the development of MS and the presence of the single nucleotide polymorphism (SNP) rs1800693 in the TNFRSF1A gene, which encodes TNFR1.[33] Presence of this SNP directs the expression of a novel, soluble form of TNFR1 that can block TNF-α, thus mimicking the effects of anti-TNF-α therapies. Carriers of this SNP might therefore be genetically prone to development or exacerbation of a demyelinating disease upon anti-TNF-α treatment.[34] Supporting this hypothesis, our patient was also found to carry the rs1800693 SNP (Figure 1E). Interestingly, no such association has been described for other autoimmune conditions such as rheumatoid arthritis, psoriasis or

Crohn's disease, in which anti-TNF-α treatment has a beneficial effect.[34] In the future, genetic testing might be of use to stratify patients according to their individual propensity for developing demyelinating disease upon anti-TNF-α therapy.

We believe that this case of PPMS onset upon adalimumab treatment is of clinical importance as it extends the spectrum of demyelinating disorders associated with anti-TNF-α therapy. In PPMS, neurological deficits are often very subtle in the beginning and usually progress slowly, which may impede diagnosis. However, as early treatment discontinuation is thought to improve the patient's outcome, it is important to increase the awareness of slowly progressing neurological symptoms as a potential adverse event among all clinicians involved in the initiation and monitoring of anti-TNF-α therapies. In addition, our case supports the hypothesis of a shared pathophysiological mechanism involving dysregulation of TNF-α homeostasis in the evolution of both relapsing and progressing MS.

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Conflict of interest statement

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