Clinical and Experimental Rheumatology 2014; 32: 732-734.

Aseptic meningitis occurring during anti-TNF-alpha therapy in rheumatoid arthritis and ankylosing spondylitis

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Reprints will not be available from the author.

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Received on March 6, 2014; accepted in revised form on May 5, 2014.

Key words: aseptic meningitis, anti-TNF-α, rheumatoid arthritis, ankylosing spondylitis, brain

Competing interests: A. Tincani has received honoraria and research support from Abbvie, Actelion, BMS, Janssen, MSD, and Pfizer; F. Franceschini has received honoraria from Janssen, MSD, and Pfizer; the other co-authors have declared no competing interests.

ABSTRACT

Objective. *Aseptic meningitis is a rare and aggressive complication of rheumatoid arthritis (RA), usually histologically characterised by rheumatoid nodules and lymphocytic aggregates in leptomeninges. The aim of this study was to describe the clinical onset and evolution of aseptic meningitis occurring during anti-TNF-alpha (TNF-α) therapy.*

Methods. *we retrospectively analysed the clinical records of patients with RA or ankylosing apondylitis (AS) treated by TNF-α drugs in the last 10 years.*

Results. *Four out of 718 patients, treated with TNF-α, developed meningitis after a mean of 5 years (SD: 3.7) of TNF-α exposure (0.55%). Three subjects were affected by long-standing RA (median: 11 years, IQR:8.5–25), one patient by active AS of 8 years' duration. RA patients were treated with etanercept (2 cases) and infliximab (1 case), in association with methotrexate and prednisone. The AS patient was treated with adalimumab. Neurological onset was focal epilepsy (3 cases) and dysarthria (1 case). RM showed leptomeningeal enhancement of basal nuclei (1 case) or fronto-parietal zone (3 cases), associated in one patient with cerebritis. Bacterial, viral or parasitic infections were excluded. One patient underwent cerebral biopsy showing T and B lymphocytes' aggregates. All patients discontinued TNF-α drugs and were treated with high dose of steroids, added to methotrexate in two cases. Neurological symptoms resolved without residuals, and meningeal enhancement showed resolution with high latency.*

Conclusion. *Meningeal inflammation is a rare manifestation occurring in long-standing RA and AS in clinical remission. TNF-α therapy did not prevent this extra-articular complication.*

Introduction

Meningoencephalitis is a rare and aggressive complication of rheumatoid arthritis (RA), usually occurring in severe and long-standing disease (1-8). It's characterised by altered mental status, seizures and hemiparesis or cranial nerve deficit (3, 8). Meningeal histology shows rheumatoid nodules, lymphoplasmacellular aggregates or vasculitis (3). Some authors report high levels of IL6 in cerebral spinal fluid (CSF) and serum during rheumatoid meningitis (1), but its potential pathogenetic role has not yet been defined. Treatment with infliximab was shown to be ineffective for rheumatoid meningitis (9). Anti-TNF-alpha (TNF-α) treatment could induce the onset of infective meningitis, that must be excluded in differential diagnoses (10). However, occasional neurological complications have been described during TNF-α treatment (2, 7, 11), but without a clear direct role in the pathogenesis of aseptic meningitis.

In our paper we describe the clinical onset and treatment of meningitis occurred during TNF-α therapy in 3 patients with RA and 1 with ankylosing spondylitis (AS).

Methods

We retrospectively evaluated the clinical charts of patients affected by RA (12, 13) and one with SA (14), treated with TNF-α from 2000 to 2013. During each visit, made every 8–12 weeks, joint count, DAS28, morning stiffness duration, infection signs, Health assessment Questionnaire, and acute phase reactants were assessed. Before starting treatment and every 12 months, antinuclear antibodies (ANA), anti-dsDNA, anti-ENA, anti-cardiolipin (aCL) and anti-β2 glycoprotein I (β2GPI) were tested. Aseptic meningitis was diagnosed based on symptoms, neurological assessment, brain magnetic resonance imaging (MRI) and the exclusion of septic or neoplastic origin of meningeal involvement.

Statistical analysis

All parameters were expressed as median and interquartile range (IGR) or mean value and standard deviation (SD).

Results

Aseptic meningitis was diagnosed in 4 cases among 718 patients treated with TNF-α (0.55%), after a mean of 5 years (SD: 3.7) of TNF-α exposure. Three subjects were affected by long-standing RA (median: 11 years, IQR:

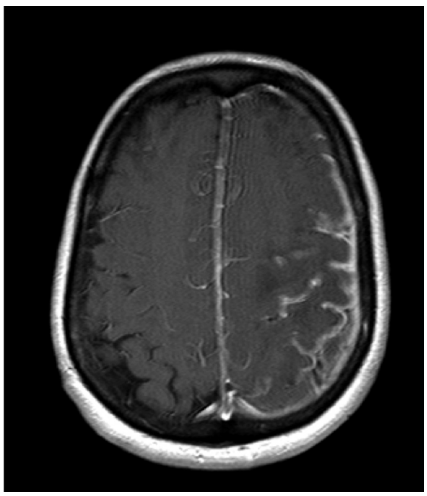

Fig. 1. T1 weighted with gadolinium showing thickening of the meninges and local cerebral enhancement at left fronto-parietal area with bulky effect on left ventricle

8.5-25), one patient by active AS of 8 years' duration. Immunological tests were negative in all cases. RA patients were treated with etanercept (2 cases) and infliximab (1 case), in association with methotrexate and prednisone. AS patient was treated with adalimumab. At the moment of meningitis onset, all cases were in clinical remission. Neurological onset was focal epilepsy (3 cases) and dysarthria (1 case). TNFA drugs were discontinued in all cases. High dose of i.v. and oral steroids were used in all the patients obtaining a rapid clinical improvement. By contrast, meningeal enhancement at RMI showed resolution with high latency (mean 1.7 years, SD:0.5) since meningitis onset. Each case deserves a brief description.

Case 1

A 50-year-old female, was affected by erosive seropositive RA since 2000, unsuccessfully treated with oral steroids, methotrexate (MTX) (10-20 mg/week), sulphosalazine (2 gr/day) and cyclosporine-A (3 mg/kg/day) since january 2001. Due to persistent disease activity (DAS28: 5.98) and the onset of new bone erosions, on 2001 she started infliximab (3 mg/kg/8 weeks), associated with MTX (15 mg) with a full control of arthritis. In December 2010, she showed focal seizure with sensitive and motor deficit at left arm and dysarthria. A brain MRI showed thickening of the meninges and local cerebral enhancement at left fronto-parietal area with bulky effect on left ventricle (Fig. 1). CSF revealed pleocytosis (40 cells, normal value <4), elevated protein level (52 mg/dL, normal value <45) without neoplastic cells or oligoclonal bands. Microbiologic tests were negative. Meningeal biopsy showed peri-vascular infiltrate of T and B lymphocytes, without vasculitis or granulomas. Infliximab and MTX were stopped. Three months later, MTX was reintroduced (15 mg) due to persistence of RMI abnormalities, that improved after 12 months. After 18 months, a relapsing RA was successfully treated with i.v. Abatacept. The last RMI (May 2013) showed minimal thickening of parietal meninges.

Case 2

A 45-year-old man with hypertension, smoking habitus and hyper-cholesterolemia was affected by seropositive, erosive RA, treated by MTX (15 mg/week), hydroxychloroquine (200 mg/day) and low dose of prednisone since 1999. In 2010 and 2011 he was admitted to hospital due to occipital ischaemic stroke and acute ischaemia at left leg, respectively. A vasculitis or hyperhomocysteinemia were excluded. On june 2012, he started etanercept (50 mg/week) due to RA flare. After 7 months, he developed a generalised seizure with downfall. A brain MRI showed thickening of lepto-meninges with cerebral enhancement at occipital-parietal right area (Fig. 2 A-B), associated with former occipital ischaemic lesion. No radiological signs of cerebral vasculitis were evident. CSF showed pleocytosis (20 cells, normal value <4), mild protein elevation (47 mg/dL, normal value <45) without neoplastic cells or oligoclonal bands. Microbiological tests were negative for bacteria, viruses and fungi. Neurologists ascribed the seizure to aseptic meningitis, and not to previous ischaemic stroke. Steroid treatment lead the resolution of neurological symptoms. The last RMI (August 2013) showed a slight reduction of cortical enhancement, and persistent meningeal thickening.

Case 3

A 52-year-old woman with seropositive RA since 2005 was treated with sulfosalazine (2 g/day), hydroxycholoquine (5 mg/kg/day) and MTX (10 mg/week). On 2007 Etanercept was added, due to high disease activity. In August 2011 she reported a focal seizure, associated with epileptic waves at EEG: CSF showed mild protein elevation (56 mg/dL, normal value <45), cell count elevation, represented by lymphocytes, rare hystiocytes and neutrophils. No oligoclonal bands were found. Microbiological tests were all negative (bacteria, BK, viruses). RMI showed thickening and enhancement of brain cortex and leptomeninges at left frontal areas, diagnosed as aseptic meningoencephailitis (Fig. 3 A-B). An anti-epileptic drug was added to MTX (10 mg/week) and prednisone. A further RMI (4 months later) showed a reduction of meningeal inflammation. The last MRI (one year later) was normal.

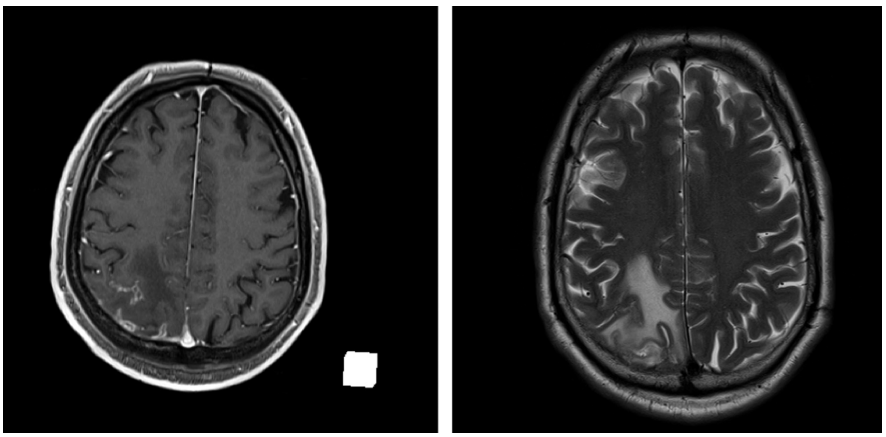

Fig. 2A. T1 weighted showing thickening of occipital meninges; **B**: T2 weighted showing parenchimal oedema.

Case 4

A 49-year-old man who had been affected by AS since 2004, was treated with NSAIDs and sulphosalazine (2 g/day) for 3 years. In 2007, adalimumab (40 mg every other week) was added, due to persistent active disease (BASDAI: 4.95). In April 2011, he was admitted to hospital due to acute aphasia. CSF showed high protein level (144 mg/dL, normal value <45). Microbiological tests were negative for viruses, bacteria, BK and fungi. MRI showed thickening of leptomeninges at parietal and occipital right area and slight enhancement of caudate nucleus. He was successfully treated with a high dose of prednisone. A waxed-and-waned aphasia was shown depending on the steroid dose taken (minimum: 12.5 mg/day). However, in 2012 a positron emission tomography showed reduced metabolic activity at temporal zone and cerebellar hemispheres: a higher prednisone dose (50 mg/day) induced clinical improvement and a significant improvement of the caudate nucleus and absence of inflammation at leptomeninges. Since 2012 he has been treated with i.v. pamidronate due to a flare of backpain, but without clinical improvement.

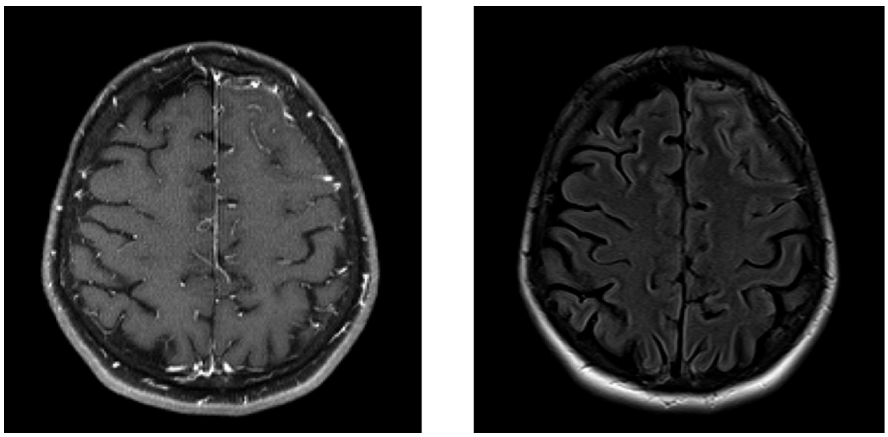

Fig. 3A. T1 weighted showing thickening of frontal meninges; **B**: flair image showing cortical thickening.

Discussion

Aseptic meningitis is found in 0.55% of patients treated with TNF-α drugs, while no cases in patients treated with classical DMARDs or other biologicals have been found in our cohort, up to now. Neurological symptoms onset in a long-standing active RA, confirming other reports (1-8). Our patients were younger than those previously reported (8), with a low disease activity of RA at the moment of the neurological event. Rheumatoid meningitis seems to develop independently of disease activity (1), however, an association with small-vessel vasculitis has been described (1), but was not evident in our cohort. The pathogenesis of rheumatoid meningitis is still unknown, but a role of inflammatory cytokines has been supposed (1). The onset of aseptic meningitis during TNF-α treatment has already been described (2, 7, 9, 10) in single cases. Up to now, the selective blocking of TNF-α does not seem to have a role in the pathogenesis of meningeal inflammation. However, an MRI study has shown brain integrity loss during infliximab treatment, demonstrating a haematoencephalic barrier passage of monoclonal antibodies to TNF-α (15).

All RA patients were treated with MTX for a mean of 13 years (SD: 11) before meningitis onset. The role of MTX in inducing meningitis is not known. MTX is known to be associated with the onset of cutaneous or pulmonary rheumatoid nodules, but not at the meningeal site. In these cases, no signs of granulomas at RMI were found.

A prompt and complete neurological improvement was achieved when patients were treated with high dose of steroids (1). By contrast, a non-complete or slow radiological response was evident, as frequently described (2, 4, 5).

In conclusion, the onset of severe meningitis during TNF-α treatment could suggest that these drugs do not protect from meningeal inflammation. However, they could represent a risk factor for the development of this severe complication.

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