

Hypertrophic Pachymeningitis in Rheumatoid Arthritis After Adalimumab Administration

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ABSTRACT. Tumor necrosis factor- α (TNF- α) inhibition, used in the treatment of rheumatoid arthritis (RA), is associated with central nervous system (CNS) events including new onset and/or exacerbations of pre-existing demyelinating neurological diseases. We describe a patient with refractory RA where adalimumab, a fully humanized IgG1 monoclonal antibody against TNF- α , may have contributed to the development of meningoencephalitis, with brain biopsy suggestive of hypertrophic pachymeningitis, a rare complication of this disease. The patient had recurrence of neurological symptoms upon repeated administration of adalimumab, and resolution of symptoms after withdrawal. (J Rheumatol First Release Sept 15 2006)

Key Indexing Terms:

ADALIMUMAB
TUMOR NECROSIS FACTOR ALPHA

RHEUMATOID ARTHRITIS
PACHYMENINGITIS

Hypertrophic pachymeningitis is a clinical disorder characterized by localized or diffuse thickening of dura mater, with or without associated inflammation. It has been associated with infections, systemic autoimmune and vasculitic disorders, neurosarcoidosis, malignancy, and intracranial hypotension¹.

We describe a patient with refractory RA where adalimumab, a fully humanized IgG1 monoclonal antibody against TNF- α , may have contributed to the development of meningoencephalitis, with brain biopsy suggestive of hypertrophic pachymeningitis, a rare complication of this disease.

CASE REPORT

A 77-year-old Caucasian man was admitted in early October 2004 with a history of recurrent episodes of diffuse headache, expressive dysphasia, involuntary movements of upper extremities, and confusion. The patient was diagnosed with rheumatoid arthritis (RA) in 1994 and was being treated with multiple disease modifying antirheumatic drugs (DMARD) including methotrexate (MTX, 15 mg/wk), hydroxychloroquine (200 mg twice a day),

sulfasalazine (1.5 g twice a day), minocycline (100 mg twice a day), and leflunomide (10 mg once daily). In August 2004, he was diagnosed with community-acquired pneumonia and leflunomide was withheld. This led to an RA flare, and he was started on adalimumab 40 mg subcutaneously twice a month in addition to continuing the above-mentioned DMARD (except leflunomide).

He received his first dose of adalimumab in September 2004 without any adverse events. During his second administration, he developed severe headache, expressive dysphasia, involuntary movements of upper extremities, and confusion that lasted for 4 hours with complete resolution to baseline mental status. This episode was not reported to the treating physician and he administered another injection 2 weeks later. Within hours, he noted recurrence of neurologic symptoms similar to above but which were persistent and he was admitted to the neurology unit of the University of Cincinnati Medical Center. There was no history of concurrent seizures, visual or auditory disturbances, or extremity weakness. There was no history of falls or trauma to the head.

Examination showed normal vital signs. He was disoriented in time and place and had expressive dysphasia. There were involuntary, unsustained, irregular movements of upper extremities. There was no evidence of cranial neuropathies or cerebellar involvement, and funduscopic examination was unremarkable. A clinical diagnosis of meningoencephalitis was made. Laboratory investigations including complete blood count with differential, renal panel, liver panel, angiotensin converting enzyme, and urinalysis were normal. Urine and blood cultures were negative. Tests for anti-nuclear antibody and anti-neutrophil cytoplasmic antibodies were negative. Magnetic resonance imaging (MRI) of the brain revealed abnormal, predominantly bifrontal leptomeningeal hyperintense fluid-attenuated inversion recovery (FLAIR) signal and contrast enhancement. White matter also showed mild ventricular dilatation and scattered hyperintense FLAIR signal (Figure 1, upper panel).

Cerebrospinal fluid (CSF) analysis showed 88 white blood cells/mm³, 67% lymphocytes, and 14% neutrophils. The CSF protein was 67 mg/dl, glucose was 48 mg/dl (with serum glucose of 76 mg/dl) and myelin basic protein was negative. Oligoclonal bands or IgG synthesis index were not performed. Cytological examination of the CSF did not show any malignant cells. Serology and cultures for bacteria, mycobacterium, fungi, protozoa, West Nile virus, herpes zoster, and enteroviruses were negative and so was the polymerase chain reaction for herpes simplex virus.

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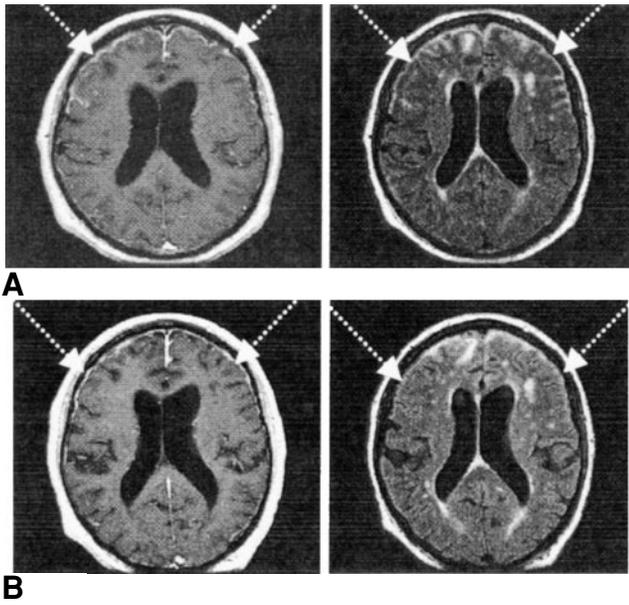


Figure 1. Upper panel. Admission MRI. Post contrast T1-weighted axial image (left) and corresponding FLAIR image (right) show abnormal predominantly bifrontal leptomeningeal enhancement and FLAIR hyperintensity (arrows). Also noted, mild ventricular enlargement and scattered non-specific hyperintense FLAIR signal white matter insults. Lower panel. Followup MRI. Post contrast T1-weighted axial image (left) and corresponding FLAIR image (right) show interval regression in predominantly bifrontal leptomeningeal enhancement and FLAIR hyperintensity (arrows).

During his hospital stay, he was treated initially with intravenous acyclovir, which was discontinued after 5 days following negative viral results. A frontal lobe meningeal biopsy was performed due to persistent neurologic abnormalities that showed mild lympho-histiocytic inflammation and calcifications of dura mater consistent with pachymeningitis (Figure 2). Stains for microorganisms for bacterial, fungal, and acid fast bacillus and amyloid were negative.

A diagnosis of RA associated pachymeningitis was entertained in light of

negative infectious disease investigations in concert with the positive MRI and histopathologic findings. Prednisone at a dose of 60 mg/day was initiated and the patient was discharged home on tapering dose regimen of prednisone over the ensuing 3 months.

The patient gradually returned to his baseline mental status within 3 months. On followup (last visit was February, 2006) the patient was doing extremely well. His mental status has remained normal and RA is well-controlled with traditional DMARD therapy. A repeat MRI performed one and a half months after the admission MRI revealed regression in leptomeningeal abnormalities (Figure 1 lower panel).

DISCUSSION

The majority of patients with hypertrophic pachymeningitis present with chronic headache with or without associated neurologic manifestations such as cranial neuropathies, cerebellar ataxia, and neuro-ophthalmic complications such as papilledema, optic neuropathy, visual field defects, and in some cases, blindness^{2,3}. High dose corticosteroid therapy, treatment of the underlying disease, and/or withdrawal of the offending agent (adalimumab in this case) is considered the mainstay of therapy^{1,2}. However, disease progression may continue in some cases despite the above measures and these patients may require longterm corticosteroid therapy with or without immunomodulating agents^{1,4}. There have been reports of various neurological disorders in association with the use of tumor necrosis factor- α (TNF- α) antagonists⁵. All 3 agents have been associated with demyelination or multiple sclerosis (MS)-like syndrome, peripheral neuropathy, and optic neuritis^{5,6}. Also, in a randomized, double-blind study conducted among patients with MS, lenercept (a soluble p55 TNF-receptor-Ig fusion protein) was associated with more clinical exacerbations of MS than placebo⁷. Neurological deficits also worsened in patients receiving lenercept.

Assessing the likelihood of a causal connection between an environmental exposure and an adverse event is referred to as attribution analysis. Many methods have been proposed to

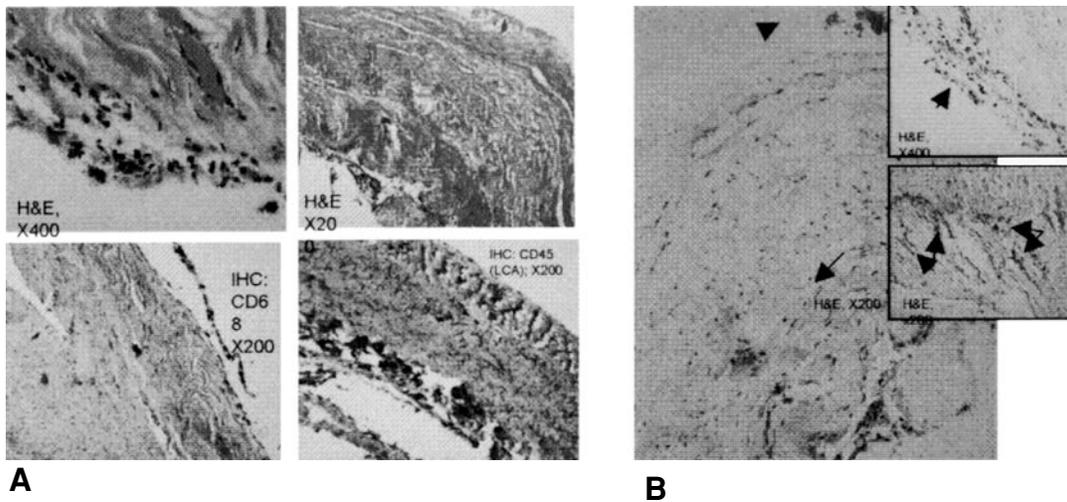


Figure 2. A. Photomicrographs of dura (hematoxyline and eosin) with mild, lympho-histiocytic inflammation and calcifications. B. Microphotographs of hematoxylin and eosin stained dura with mild mononuclear (long arrows) and calcifications (short arrow).

substantiate such an association. Components of attribution analysis have been classified into primary and secondary elements as described by Miller, *et al*⁸. The specified primary attribution elements are more critical than secondary attribution elements and include temporal association, the lack of likely alternative explanations, dechallenge (improvement in symptoms following the discontinuation of the agent), rechallenge (reappearance or worsening of the symptoms on re-exposure to the agent), and biologic plausibility (the likelihood of the agent causing the manifestations, based on *in vivo* and/or *in vitro* effects). Secondary attribution elements include analogy (prior published or unpublished reports of a similar disorder developing after exposure), dose responsiveness (dose of the agent related to the likelihood developing the disorder), and specificity (similar manifestations and lab features in previous patients after exposure to the same agent). For a possible causal relationship between an environmental exposure (drug) and a clinical syndrome, at least 4 of the 8 attribution elements and at least 3 of the 5 primary elements should be present^{8,9}.

Our patient showed all 5 primary elements of attribution analysis. Although his hypertrophic pachymeningitis could be due to RA, the diagnosis of rheumatoid pachymeningitis is ominous as most patients die within 6 months of onset of neurological symptoms, and the use of corticosteroids and immunosuppressants have not been shown to have any significant effect on this^{4,10}.

The other differential diagnosis in this patient with meningoencephalitis includes CNS vasculitis and atypical infections such as *Mycoplasma pneumoniae*. However, diagnostic studies such as angiogram of the CNS and cultures for atypical microorganisms were not performed. Clinical and radiological improvement of our patient after stopping adalimumab points against these diagnoses. Also, the presence of cortical gliosis without microglial activation indicates an unspecific and probably reversible process. As the lesions did not enhance on the MRI and pathologically only perivascular chronic inflammation was found, it is unlikely to be an acute vasculitic or demyelinating process.

In summary, our patient with RA developed clinical meningoencephalitis with brain biopsy suggestive of hypertrophic pachymeningitis after 3 doses of adalimumab. To our knowledge, there are no published case reports of development of hypertrophic pachymeningitis after the use of TNF- α antagonists. It is imperative to critically monitor the patients receiving TNF- α antagonist therapy for neurological manifestations and to stop these agents at the first signs of such manifestations in order to prevent more widespread CNS damage.

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