Successful treatment of neuro-Behçet's disease with infliximab: four years follow-up

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Abstract

Neuro-Behçet's disease (NBD) is a rare but severe manifestation of Behçet's disease. Patients with NBD tend to have high morbidity and mortality. Some patients do not respond adequately to conventional therapy (corticosteroids and immunosuppressants). This has led to treatment gaps in the therapy of NBD. There are reports in the literature of patients with Behçet's disease responding to anti-TNF therapy. We present a case of a male patient with biopsy proven cerebral vasculitis presenting as NBD who has been in remission with near resolution of cerebral magnetic resonance imaging lesions for 4 years following treatment with infliximab and azathioprine.

Introduction

Behçet's disease (BD) was first described by a Turkish dermatologist, Hulusi Behçet, in 1937 as a triad of recurrent oral and genital ulcers and uveitis.[1] Neuro-Behçet's disease (NBD), arthritis, gastrointestinal lesions, arterial occlusion or aneurysms, superficial thrombophlebitis and deep vein thrombosis are some of the other manifestations of the Behçet's disease.[2] Behçet's disease is now known to be a multisystem disease that may include in its spectrum vasculitis. It can affect the blood vessels of any organ, including the central nervous system.

The mean age of Behçet's syndrome onset is third decade of life. Young male patients tend to have a more severe disease course with regards to the eye, vascular and neurological disease.[1]

Neuro-Behçet's disease is a serious complication of Behçet's disease associated with high morbidity and mortality. NBD usually shows three clinical patterns: a brainstem syndrome, a meningomyelitic syndrome and an organic confusional syndrome.[3] The most common sites of central nervous system (CNS) involvement on magnetic resonance imaging (MRI) scan, reported by Lee *et al*., are the brainstem, white matter, basal ganglia, internal capsule and thalamus. On pathology, the common features throughout the courses of NBD appear to be areas of inflammation with perivascular infiltration of T-lymphocytes and activated monocytes/macrophages.[4] However, the cause of Behçet's disease, and why some patients are prone to NBD, remains unknown.

Conventional therapy for Behçet's disease includes corticosteroids, colchicine and immunosuppressants. Corticosteroids are commonly used during acute exacerbations for rapid suppression of the inflammatory process. For severe disease, including NBD, immunosuppressants such as azathioprine, cyclophosphamide, and methotrexate may be used, both as induction therapy, and in the case of azathioprine and methotrexate, as maintenance therapy to prevent exacerbations and complications. Even though, there is no evidence to support or refute the benefit of biologics, colchicines, corticosteroids, immunosuppressive and interferon-alpha for the treatment of patients with NBS, in recent years there has been increased interest in evaluating the efficacy of biologics for NBD.[2] Some cases of off-label use of biologics such as rituximab, etanercept, and infliximab have been reported.[5-12] We present a case of a male patient with neuro-Behçet's disease and cerebral vasculitis who had remission induced 4 years before. He has remained in remission on infliximab along with azathioprine.

Case Report

The patient is a 39-year-old male with a history of Behcet's disease that was manifested by recurrent aphthous oral ulcers, genital ulcers and arthritis, since age 21. Patient was tested positive for human leukocyte antigen-B51 antigen at the time of diagnosis. Patient's prior separate courses of medications included methotrexate up to 20 mg weekly, cyclosporine 300 mg daily, cyclophosphamide IV, and etanercept 50 mg weekly with continued relapses. The patient was experiencing recurrent arthritis, multiple skin lesions, headaches and neurological deficits on maintenance therapy. Patient had received corticosteroids during disease flares multiple times; however, patient was never placed on maintenance steroid therapy.

Two months prior to admission, the patient was evaluated at an outside hospital and was found to have an abnormal MRI/MRA of his brain. At that time, the dose of azathioprine was increased to 150 mg daily and patient was started on prednisone 10 mg daily by his rheumatologist. The patient continued to experience progressive left weakness/numbness, balance problems, memory impairment, headaches, neck pain and back pain resulting in admission at our hospital. At presentation, patient endorsed recent oral ulcers and double vision with floaters. A comprehensive metabolic panel, complete blood count, urinalysis and infectious workup were unremarkable with the exception for an elevated sedimentation rate (50 mm/hr) and C-reactive protein (202 mg/L). A computed tomography (CT) of the head showed right frontal lobe hypodensities with an associated right to left midline shift. Follow up MRI of the brain showed bilateral homogeneous white matter parietal lobe lesions measuring approximately 6.0×3.4 cm and 4.0×1.4 cm without brainstem involvement (Figure 1A-C). MRA head and neck was normal.

On day 1 of admission, he experienced status epilepticus and had to be intubated. Continuous electroencephalograph showed slowing and occasional spikes without any clinical seizures. Brain biopsy was performed before patient was started on loading dose of pulse steroids with methylprednisolone 1 mg daily for three days followed by prednisone 60 mg daily for a period of four weeks and it was tapered off over months. Brain biopsy showed multifocal perivascular inflammation and acute vasculitis (Figure 2).

Ophthalmology was consulted for concern of episcleritis or retinal vasculitis. However, no ocular involvement was found on ophthalmo-

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scopic exam. Since his prior courses of medications included methotrexate, cyclosporine, cyclophosphamide IV, and etanercept, without much clinical benefit to prevent relapse, he was considered an appropriate candidate for infliximab infusion. He was started on infliximab 5 mg/kg infusion at weeks 0, 2 and 6 and every 8 weeks thereafter. A repeat follow-up MRI at 81 days from the previous MRI, showed almost complete resolution of previously described lesions and midline shift, and marked improvement in white matter disease (Figure 1D-E). It has been 4 years since induction, and patient remains in full remission of the skin lesions, neurological disease and vision involvement while on infliximab 5 mg/kg every 8 weeks along with azathioprine 2 mg/kg daily, and carbamazepine 200 mg BID.

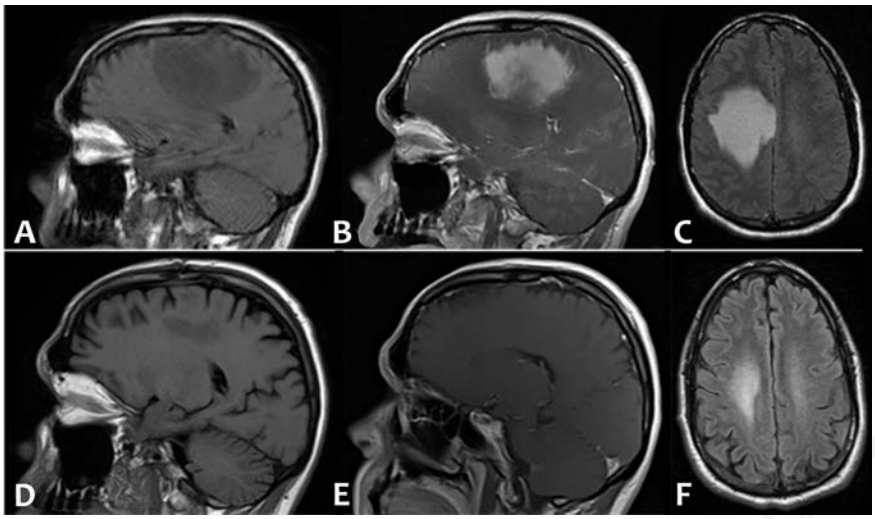

Figure 1. A-C) Pre treatment sagittal T1 magnetic resonce (MR) image (A) demonstrate a large hypointense mass within the right parietal lobe white matter. Sagittal T1 post contrast MR image (B) demonstrates moderate patchy enhancement associated with this lesion. Axial flair MR image (C) demonstrates this lesion to be hyperintense with associated vasogenic edema and no significant mass effect on the adjacent cerebral parenchyma. D-E) Post treatment - sagittal T1 pre (D) and post contrast (E) MR images demonstrate complete resolution of the previously seen enhancing white matter right parietal lobe lesion. Axial flair MR image (F) demonstrates a small area of residual vasogenic edema within the right parietal lobe.

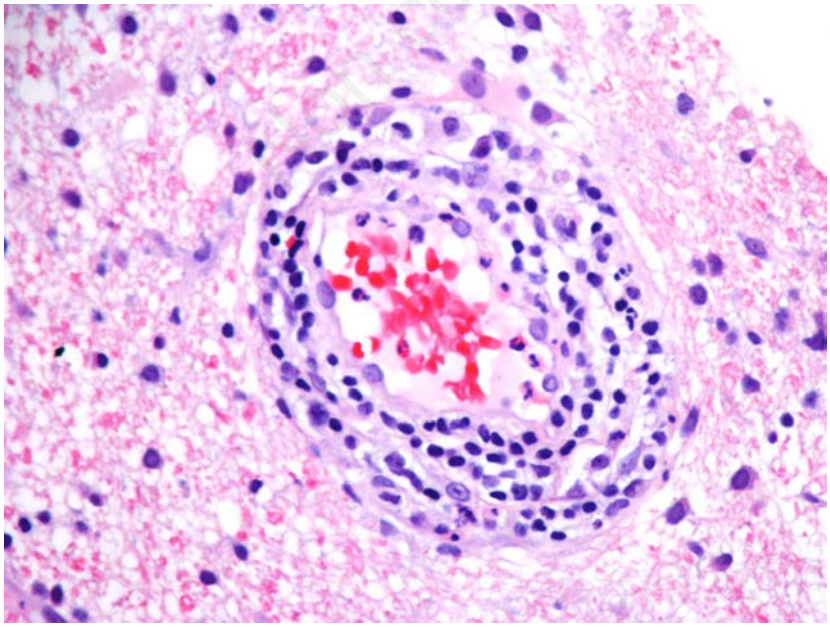

Figure 2. Infiltration of polymorphonuclear cells and lymphocytes through vessels wall (Hematoxylin & Eosin, 40×).

Discussion

The use of infliximab was first described in 2001 for patients with BD and relapsing ocular inflammation.[7] In these patients, perivascular inflammation mediated by T-lymphocytes and monocytes is the hallmark of BD.[4] Overproduction of proinflammatory cytokines, interferon- , TNF-α, IL-6, IL-18, and IL-12 in patient with BD most likely contribute to neutrophil and endothelial cell activation and induction of apoptosis of neurons.[4,13] Increased levels of TNF, soluble TNF receptors, and TNF-producing cells were found in the peripheral blood of patients with active BD. Infliximab was found to be capable of interfering with γ+T cell function in BD resulting in suppression of innate immunity and restoration of circulating T cell function. A rapid and dramatic improvement of visual acuity and decrease of ocular inflammation starting 24 hours after infliximab infusions has been reported and is most likely secondary to anti-TNF-α property of infliximab.[10,13] In 2007, infliximab was approved to be used for refractory uveoretinitis in Japan.[14]

A number of anecdotal case/series reports and small scale randomized controlled trails have been published of infliximab being used off-label for NBD.[5-12] While the data on infliximab use for NBD remains limited, the therapeutic decisions about when to use infliximab are being made based on personal experience, anecdotal case/serial reports and studies in patients with systemic BD.[6] Infliximab may be considered in patients who do not satisfactorily respond to high doses of steroids, azathioprine methotrexate or cyclophosphamide.[15] Since our patient had continued to relapse on steroids and immunosuppressants, we felt it necessary to start our patient on infliximab infusions to prevent further neurological damage. Our patient has made significant improvement in his neurological deficits and currently remains symptom free.

Conclusions

This is the first case to document MRI improvement in conjunction with clinical remission, and brain pathology based on biopsy. Our patient has been in remission from more than 4 years. Given infliximab's effect on the immunopathogenesis of Behçet's disease and resolution of symptoms within days and improvement of laboratory and imaging findings, infliximab can be an effective strategy for treatment of NBD. Since the data on long-term safety, efficacy and side effect profile of infliximab for NBD is limited, further long-term large scale, multi center studies are needed.

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