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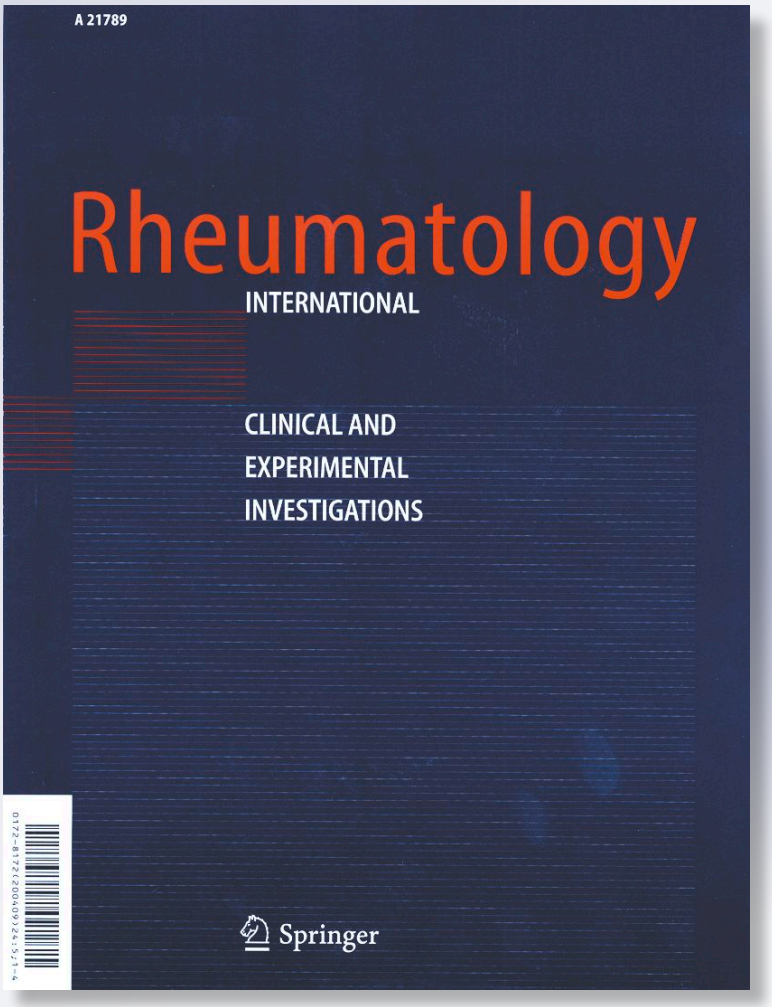

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SHORT COMMUNICATION

Atypical presentation of Behçet's disease with central nervous system involvement successfully treated with infliximab

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Abstract Central nervous system involvement is a rare and serious complication of Behçet's disease (BD). Herein, we describe a patient with an atypical central lesion, who experienced progressive hypesthesia of the right arm and sensory loss of the trigeminal nerve together with intense headache. A repeated biopsy was necessary to conclusively establish the diagnosis of BD. Therapy with infusions of infliximab led to a remarkable full remission. TNFα-blocking therapy was successfully replaced by azathioprine. The present well-illustrated case demonstrates the difficulty of establishing the diagnosis of BD with central nervous system involvement, the dramatic benefit of short given TNF-α-blocking agent, and the long-term remission with azathioprin.

Keywords Behçet's disease · Central nervous system involvement · Infliximab · Azathioprine

Introduction

The original description of Behçet's disease (BD) included the classical triad of oral, genital, and eye ulcers [1]. Since then, it has been recognized that BD is a systemic inflammatory vasculitis with recurrent episodes of oral and genital aphthosis, ocular inflammation, skin lesions, oligoarthritis and, late in the course of the disease, involvement of the central nervous system [2]. Recognized clinical criteria for BD are recurrent bipolar aphthosis, eye lesions, skin lesions like pseudofolliculitis, and papulopustular eruptions as well as the positive pathergy test [3]. Behçet's disease occurs primarily in young adults with the prevalence being highest in countries of the eastern Mediterranean, the Middle East, and East Asia, thus the name Silk Road disease. Little is known about etiologic factors. Genetic studies have shown a strong association with HLA-B51; however, the exact role of this gene in the development of BD is uncertain. Management of BD remains largely empirical. For mucocutaneous manifestations, colchicine is used, whereas effective control of uveitis is achieved by cyclosporine. Azathioprine has shown a beneficial effect on arthritis, deep venous thrombosis, and long-term prognosis [4]. Glucocorticoids are useful in acute phases of the disease but insufficient to treat severe manifestations such as uveitis or brain tissue involvement. Since increased serum levels of tumor necrosis factor α (TNFα) have been noted in active BD, use of TNFα blockers in the therapy of various manifestations of BD has been considered. A first report of TNFα blockade in neurological manifestation of BD in the published literature summarized the findings of 12 patients [5].

The present case involves a patient with BD who presented with an atypical localization of central nervous system (CNS) involvement. Magnetic resonance imaging (MRI) revealed a single ring-enhancing lesion in the left

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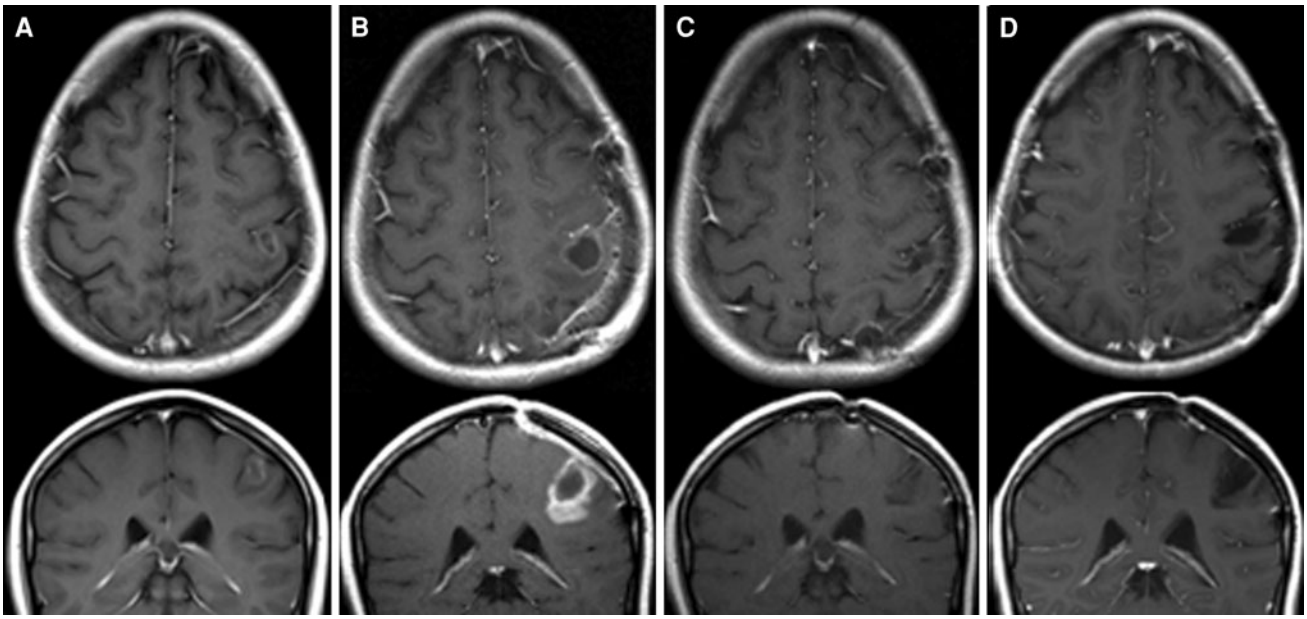

Fig. 1 Contrast-enhanced T1-weighted axial and sagittal cranial MRI imaging studies. **a** Initial finding of a ring-enhancing lesion in the postcentral gyrus before craniotomy. **b** Imaging study after craniotomy and before infusions of infliximab. **c** Finding after 3 infusions of infliximab. **d** Follow-up 5 months after stopping infliximab and under therapy with azathioprine

postcentral gyrus involving the cortex and subcortex. Immunohistochemistry showed a perivascular infiltration with a majority of T lymphocytes and relatively scarce B lymphocytes. The patient experienced a dramatic improvement of her condition under TNFα blockade.

Case report

A 32-year-old woman was hospitalized with progressive hypesthesia of the right arm over several days, accompanied by a sensory loss of the second and third branch of the right trigeminal nerve. The patient reported a strong headache of varying intensity over the past few months. Two weeks before admission, she had experienced an episode of bloody diarrhea over 3 days. She described night sweats as well as anorexia and weight loss of 3 kg over the past 2 weeks. There were no episodes of fever or shivering, no trauma, and no tick bite. No concomitant diseases were known, and her only medication was acetaminophen as occasional pain treatment. When further questioned about her medical history, the patient reported having had contact with a case of open pulmonary tuberculosis within her family approximately one year earlier. The patient was of Indian descent, originated from Kenya and had emigrated to Switzerland many years before. She was married and had three healthy children. Her last trip to Kenya had taken place 4 months earlier with continuous anti-malarial prophylaxis using mephaquine.

Her general condition was good. Clinical investigation showed no abnormalities other than the above mentioned neurologic deficits. Laboratory testing showed a normal full blood count, normal liver function tests, and normal creatinine, electrolyte and C-reactive protein levels. Serologic testing for HIV, TPHA, and borrelia burgdorferi was normal. A lumbar puncture revealed a normal cell count with a slight protein elevation (0.75 g/L). Both blood and cerebrospinal fluid cultures remained sterile, including cultures for mycobacteria. PCR testing of the cerebrospinal fluid for mycobacteria, herpes simplex, varizella-zoster, and cytomegalovirus was negative. Gram and Ziehl-Neelsen staining of the cerebrospinal fluid showed no microorganisms. Isoelectric focusing disclosed no intrathecal synthesis of immunoglobulins. Elevated serologic anti-Epstein-Barr-virus and anti-toxoplasma IgG antibody levels in the absence of IgM documented past infections and serological investigations for tick-borne encephalitis, cysticercosis, and schistosomiasis were negative.

Cranial magnetic resonance imaging (MRI) revealed a 1.5-cm lesion at the cortico-subcortical junction in the postcentral gyrus of the left parietal lobe. There was slight peripheral enhancement and minor diffusion impairment and edema in the surrounding brain tissue. No signs of elevated intracranial pressure or midline shift were present (Fig. 1a).

At this stage, a wide range of differential diagnoses was considered. These included inflammatory or autoimmune diseases such as multiple sclerosis, vasculitis, or neurosarcoidosis; neoplastic diseases such as glioma, primary brain

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lymphoma, or a brain metastasis; or an infectious disease such as a brain abscess, tuberculoma, or parasitosis. The patient was referred to the Department of Neurosurgery at the tertiary center for brain biopsy.

Craniotomy and partial exstirpation of the lesion were performed. The surgical specimen submitted for histopathological study consisted mostly of necrotic brain tissue, wherein only a small number of viable blood vessels encircled by small lymphocytes as well as foamy macrophages were seen (Fig. 2a). While no conclusive diagnosis was issued and a comment regarding the possibility of a "sampling error" was made, it was felt that the material could originate from a devitalized area of a neoplasm. As the cerebral process worsened, neurosurgical re-exploration was undertaken. After re-craniotomy, a navigated partial resection of the residual lesion was performed. This time, microscopic examination revealed—in addition to further zones of necrosis—a bona fide vasculitic picture composed of moderately cellular lymphocytic cuffs around blood vessels, mostly venules (Fig. 2b). Dominated by T lymphocytes, these also included B cells as well as copious amounts of macrophages, which tended to diffusely infiltrate the adjacent parenchyma (Fig. 2c and d–f). Neither granulomatous nor leukocytoclastic patterns were seen. A neoplastic or infectious etiology was further ruled out by Spectro-MRI and whole body positron-emission tomography/computer tomography. Finally, a detailed medical history regarding possible autoimmune diseases was undertaken. Surprisingly, it revealed recurrent episodes of oral and genital ulcers for years, recurrent inflammations of the eyes, recurrent arthropathies of the hand, finger and knee joints, a pseudofolliculitis, and intermittent abdominal cramps with hematochezia. Together with the immunohistochemistry, we hypothesised a presentation of BD with cerebral involvement, despite the lesion's atypical localization, and the absence of HLA-B51. Based on reports on Neuro-Behçet's disease, we started immunosuppression with infliximab 5 mg/kg body weight after pre-treatment with isoniazid 300 mg daily for 2 weeks. Prednisolone could be tapered successively from 50 to 0 mg/d after 4 infusions of infliximab. After 3 administrations of infliximab, a reduction in size of the lesion and T1-weighted peripheral enhancement was demonstrated in magnetic resonance imaging (Fig. 1c). Clinically, the hypesthesia and paresis of the right arm persisted, whereas the sensory loss of the second and third branch of the right trigeminal nerve recovered. Simple partial seizures, that first became manifest after brain biopsy, were continuously treated with levetiracetam.

Additional 5 infusions of infliximab every 6 weeks revealed no further improvement of the lesion and T1-weighted peripheral enhancement, so treatment was switched to azathioprine 3 mg/kg body weight. Follow-up by MRI after 2 and 5 months upon beginning azathioprine showed a stable remission (Fig. 1d). Azathioprin was reduced to 1.5 mg/kg body weight. Clinical follow-up showed no sign of reactivation.

Discussion

Neurological involvement in Behçet's disease has been documented in prospective studies in about 9% of cases, both as parenchymal or non-parenchymal lesions [6–10]. Parenchymal involvement of the CNS mainly presents as inflammation of the brainstem, basal ganglia and the white matter [11] causing ataxia, cognitive or pychiatric disturbances, and corticospinal tract signs. Non-parenchymal manifestations such as meningoencephalitis can lead to headache, central vein thrombosis, cranial nerve palsies, and epilepsia [10]. Neurological manifestations as presented in this case with a single subcortical ring-enhancing lesion, however, are highly uncommon and entail a thorough diagnostic assessment to cover a broad differential diagnosis.

Therapeutic strategies in Neuro-Behçet's disease are not well established as no prospective randomised controlled trials have been published so far. Parenchymal disease is generally treated with intravenous infusions of methylprednisolone followed by a slowly tapered course of oral steroids. However, as serum levels of tumor necrosis factor α (TNFα) are increased in active Behçet's disease, TNF α-blocking agents have been suggested to play a role in the treatment of neurological manifestations. Pipitone et al. [5] first published a case series of 12 patients treated with infliximab at a dose of 5 mg/kg body weight. All 12 patients experienced a satisfactory clinical response, and brain MRI showed at least a partial regression of the parenchymal lesions in the 10 patients who underwent MRI examination before and after infliximab treatment. At follow-up, all patients were in remission. Similarly to this report, we observed a very rapid and satisfactory response to infliximab therapy in our patient, with clinical remission and regression of the brain lesion on imaging studies (Fig. 1c–d).

The efficacy of monoclonal antibodies such as infliximab might be surprising, as the blood–brain barrier does not allow the passing of immunglobulins. However, the detectable impact of infliximab on Neuro-Behçet's diesease may point to the fact that the blood–brain barrier is affected by the surrounding inflammation and malfunctioning. The slight elevation of the protein level in the cerebrospinal fluid may be explained in this context. We detected a reduction in size of the lesion and peripheral enhancement in our patient after 9 infusions of infliximab, whereas additional infusions revealed no further improvement. This may sug-

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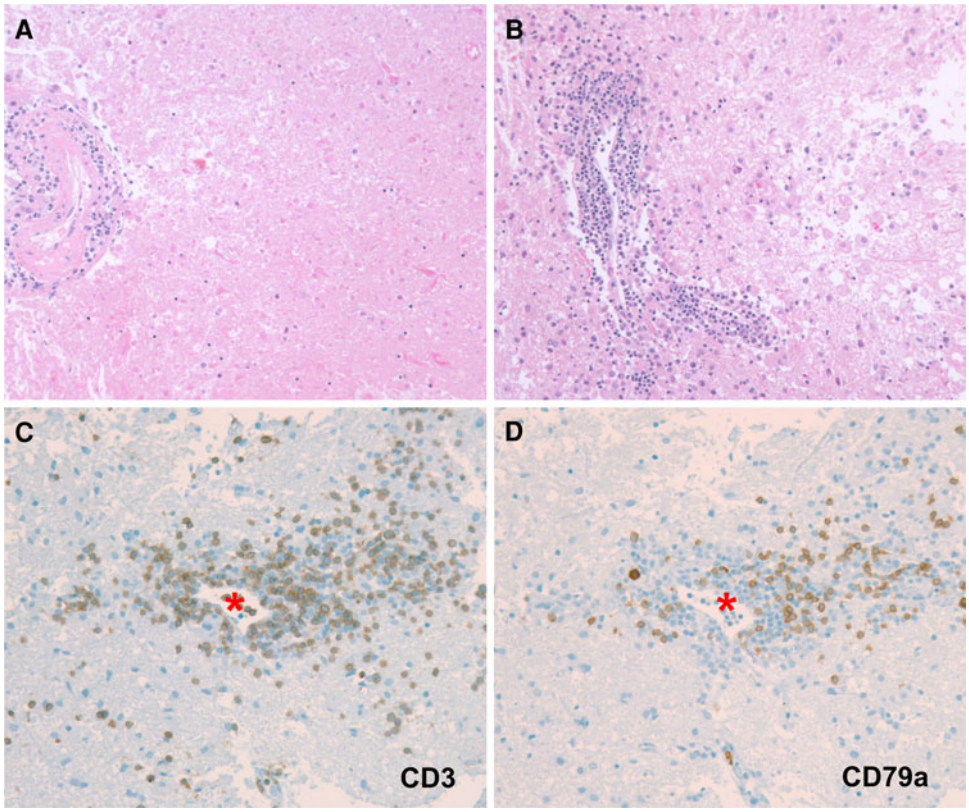

Fig. 2 Histology and immunophenotype of cerebral involvement by Behçet's disease. **a** Infarctoid necrosis of brain parenchyma punctuated by an occasional viable blood vessel was the predominant finding in both the first and the second biopsy specimen. **b** Nonnecrotic inflammatory focus composed of a perivascular cuff of small lymphocytes with vigorous reactive gliosis of the adjacent neuropil. **c** and **d** Contiguous serial sections of the same inflammatory focus stained by immunohistochemistry to show perivascular infiltrate to include a majority of T lymphocytes (**c**), while B lymphocytes (**d**) are relatively scarce. Cross-sectioned profile of blood vessel (*asterisk*) is used as a landmark to identify region of interest on consecutive section planes. Microphotographs not labeled otherwise represent hematoxylin and eosin staining. Immunoreactions were developed with polymer-bound horseradish peroxidase (Envision+; Dako, Glostrup, Denmark) and 3,3′-diaminobenzidine as chromogen. Original magnification: **a** through **d**—×200

gest an increasing loss of efficacy of the agent as the blood–brain barrier regains its full function. Therefore, after induction of remission with immunoglobulin therapy, a change to an immunosuppressive agent such as azathioprine might represent a good alternative for further treatment.

The risk of causing harm by anti-TNF-α therapy such as CNS demyelination or weakened innate immune control of tuberculosis should always be weighed against its advantages. However, appropriately used, anti-TNF-α monoclonal antibody therapy is in many respects better tolerated than conventional disease modifying anti-rheumatic drugs. In contrast to cyclosporine for instance, infliximab does not cause dermal malignoma, gingival hyperplasia, or renal toxicity. Lastly, in each case, it has to be addressed whether the high cost of a biological therapy is justified and if it translates to long-term health economic benefits.

In summary, we conclude that infliximab presents a highly effective therapy in active parenchymal Neuro-Behçet's disease, and subsequent treatment with disease modifying anti-rheumatic drugs seems a safe option to maintain remission.

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Conflict of interest None.

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