

## Severe neuro-Behcet's disease treated with a combination of immunosuppressives and a TNF-inhibitor

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### ABSTRACT

Behcet's disease (BD) is a multisystem inflammatory disorder characterized by recurrent oral and genital ulcers, skin lesions and uveitis. The nervous system involvement of BD, neuro-Behcet's disease (NBD), is one of the important causes of mortality of the disease. Herein, we present a 29-year-old male with parenchymal NBD who has progressed rapidly and was managed with an uncommon aggressive immunosuppressive combination therapy. The patient first presented six years ago with vertigo and difficulty in talking and walking. On examination, he had oral ulcers, acneiform lesions on the torso, genital ulcer scar, dysarthria, and ataxia. Along with the magnetic resonance imaging (MRI) findings, the patient was diagnosed as NBD. After pulse methylprednisolone (1g/day, 3 days) and 8 courses of 1g/month iv cyclophosphamide therapy, he was put on azathioprine and oral methylprednisolone. On the 4th year of the maintenance therapy, he was admitted with NBD relapse which was treated with 3 days of iv 1g pulse methylprednisolone. One year after the last relapse, the patient voluntarily stopped medications and presented with global aphasia, right hemihypoesthesia and quadriparesis. MRI findings were suggestive of NBD relapse. After exclusion of infection, pulse methylprednisolone was started but no improvement was observed. Considering the severity of the NBD, the patient was put on methylprednisolone (1mg/kg/day), iv cyclophosphamide (1g) and adalimumab 40 mg/14 days subcutaneously with appropriate tuberculosis prophylaxis. Neurological exami-

nation and MRI findings after 4 weeks showed dramatic improvement however patient developed pulmonary tuberculosis. Methylprednisolone dose was decreased (0.5mg/kg/day) and quadruple antituberculosis therapy was started. Patient was discharged with 5/5 muscle strength in extremities without any respiratory symptoms 2 months after the first presentation. Prompt introduction of immunosuppressive therapy is crucial in NBD. Although combination of TNF inhibitors and cyclophosphamide is a rare therapeutic approach, it may be life-saving. However a higher awareness is required for opportunistic infections.

**Keywords:** TNF inhibitors; Neurologic involvement; neuro-Behcet's disease

### INTRODUCTION

Behcet's disease (BD) is a multisystem inflammatory disorder of unknown aetiology characterized by recurrent oral and/or genital aphthosis, vascular and ocular involvement in combination with variable skin lesions<sup>1</sup>. Other manifestations are arthritis, a positive pathergy test, thrombophlebitis, central nervous system disease and gastrointestinal ulcerations. The nervous system involvement of BD is called neuro-Behcet's disease (NBD) which has two main subtypes: parenchymal, an inflammatory meningo-encephalitic process and non-parenchymal, a condition secondary to vascular involvement such as dural sinus thrombosis<sup>1</sup>. The clinical presentation can be as corticospinal tract and brainstem involvement, venous sinus thrombosis, increase in intracranial pressure secondary to aseptic meningitis, isolated headache or isolated behavioural changes. Rarely aneurysmal rupture, peripheral neuropathy, optic neuritis and vestibular involvement can also be observed. NBD is defined as a constellation of neuro-

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logic manifestations with characteristic neuropathologic findings, usually confirmed by ancillary investigations, in patients who meet the diagnostic criteria for BD<sup>1,2</sup>. The prevalence of neurological manifestations in BD is highly variable (5.3-59%) depending on diagnostic criteria and ethnic populations<sup>3</sup>. In a two-decade retrospective study of 387 patients with BD in Turkey, the frequency of NBD was 13% in men and 5.6% in women<sup>4</sup>. Parenchymal, brainstem, cerebellar involvements, abnormalities in cerebrospinal fluid (CSF), and presentation with paresis were associated with worse prognosis<sup>5</sup>. Although there is no well-established treatment protocol for NBD, prompt introduction of immunosuppressive treatment is necessary to ameliorate morbidity, disability and consequently mortality. Herein, we present a NBD case with parenchymal involvement, which has progressed rapidly and was managed with an aggressive immunosuppressive combination therapy. The reason we report this case was the severe relapsing nature of the disease, which caused quadriplegia, was unresponsive to very high doses of glucocorticoids and finally necessitated an uncommon aggressive immunosuppressive treatment. So far, concomitant use of a TNF inhibitor (TNFi) and cyclophosphamide (CyP) with high dose glucocorticoids has never been reported for NBD.

## CASE PRESENTATION

A 29-year-old male patient first presented six years ago

with vertigo and difficulty in talking and walking. He had recurrent oral (24-30/year) and genital ulcers on his history. On examination, he had active oral ulcers, acneiform lesions on the torso of the body, genital ulcer scar, dysarthria, left-sided hypoesthesia and ataxia. Magnetic resonance imaging (MRI) of the brain showed contrast-enhanced lesion at the right pontocerebellar peduncle and a haemorrhagic lesion in the right basal ganglia (Figure 1). Diffusion-weighted MRI and MR venography excluded acute infarction and dural sinus thrombosis. With the exclusion of infectious causes by examination of the CSF, the patient was diagnosed as parenchymal NBD according to International Consensus Recommendation (ICR) criteria for NBD diagnosis. Treatment with pulse methylprednisolone (1g/day, iv for 3 days) and CyP were initiated. With the pulse steroid treatment, neurologic findings dramatically improved. After 8 months of CyP (1g/month iv) treatment, the therapy was continued with azathioprine (AZA) (150mg/day) and oral methylprednisolone (initial dose of 1mg/kg/day with gradual tapering until 4 mg/day). The patient was in remission with the maintenance therapy for 4 years. However, while on maintenance therapy, 2 years ago, he was admitted with nausea and loss of vision in the right eye. He had no signs of uveitis but MRI revealed recurrence of the brain stem lesions. This relapse was treated with 3 days of iv 1g pulse methylprednisolone. The maintenance therapy was set as AZA (150mg/day) and methylprednisolone (tapered to 4mg/day), and colchicine. However, at the end of the first year of this



**FIGURE 1.** Retro-patellar space and granular synovitis

treatment, due to clinical remission, the patient voluntarily stopped taking medications. Ten months after cessation of the drugs, he was admitted to another hospital with diplopia, absent gag reflex, dysarthria, right hemihypoesthesia and quadriparesis. Diffusion-weighted MRI revealed hyper intense lesions at left mesencephalon and central pons with hypo-isointense signal changes on apparent diffusion coefficient maps. The lesions were considered as acute ischemia due to a vasculitic process, which was consistent with parenchymal NBD. CSF examination (35 white blood cells/ $\mu\text{l}$  with normal glucose and protein) was not suggestive of infection and the lesions were regarded as relapse of NBD. For the acute NBD attack, considering the severity of the neurologic findings, treatment with pulse methylprednisolone (1g/day iv) was started. Seven days of pulse steroid therapy did not result in significant neurological improvement and the patient was referred to our institution.

On neurologic examination, the patient was alert, partially cooperative and oriented. He had dysarthria, horizontal gaze palsy (left one-and-a-half syndrome), mild tetraparesis and right hemihypoesthesia. The findings were in favour of aggressive NBD. The patient was treated with 2 pulses of high dose iv CyP 500mg/2 weeks, methylprednisolone 60 mg/day iv and adalimumab 40 mg/14 days subcutaneously. He had no previous tuberculosis (TB) contact, the QuantiFERON TB gold test was negative, and chest X-ray was normal. Nevertheless, prophylactic isoniazid (INH) was administered due to the aggressive immunosuppressive treatment. Neurological examination after 2 weeks of treatment revealed nystagmus, dysarthria, 4/5 motor strength and wide based ataxic gait. Computed tomography (CT) of thorax was performed to assess pulmonary vascular involvement of Behcet's disease 4 weeks later. Thorax CT showed 2.5 cm pleural effusion and atelectasis on right hemithorax without any vascular changes. Bronchoscopy and pleural sampling were performed to exclude infectious and other causes. Pleural effusion was exudative with lactate dehydrogenase of 715U/L, and total protein of 3.1g/dL. Total cell count was 6110/ $\mu\text{l}$  with a predominance of polymorphonuclear cells (78%). Cultures for bacteria and acid-fast stain of the effusion were all negative. Bronchoalveolar lavage fluid polymerase chain reaction (PCR) was positive for *Mycobacterium tuberculosis* and culture was positive for methicillin resistant *Staphylococcus aureus* (MRSA). As the clinical presentation was not pneumonic, culture positivity for MRSA was con-

sidered as colonization. Since the patient was severely immunosuppressed, vancomycin was initiated. For TB, quadruple anti-TB treatment (INH, rifampicin, pyrazinamide, and ethambutol) was started. Due to the elevation of liver enzymes, quadruple anti-TB treatment was switched to the combination of ethambutol and moxifloxacin. Methylprednisolone dose was decreased to 32 mg/day. Therapy for MRSA was continued with trimethoprim-sulfamethoxazole (two months). When levels of liver enzymes returned to normal, INH was added to anti-TB treatment (with a plan of 2 months quadruple anti-TB and 7 months INH and rifampin combination). One month later, the patient was discharged with 5/5 muscle strength in 4 extremities, without any respiratory symptoms.

## DISCUSSION

NBD is a serious complication of BD, which has no proven curative treatment yet. Patients with NBD have a poor long-term outcome. In a study of the 820 BD patients, 275 had neurologic symptoms and 68 (24.7%) were diagnosed as having nonparenchymal CNS involvement. Of these with NBD, 25% became dependent (were unable to perform activities of daily living) or died during follow-up, and the mortality rate was 10.4%<sup>3</sup>.

Considering the high disability, morbidity and mortality rates of NBD, prompt introduction of immunosuppressive treatment is crucial. Despite treatment, severe relapses can occur during the disease course. In this report, we presented a patient with severe relapsing NBD, which caused quadriparesis, was unresponsive to high-dose glucocorticoids and finally necessitated an uncommon aggressive immunosuppressive treatment. So far, concomitant use of TNFi and CyP with high dose glucocorticoids has never been reported for NBD. This combination was only used in a phase 2 trial of adalimumab in severe ANCA-associated vasculitis<sup>5</sup>. Although that study reported similar rates of adverse events with adalimumab and CyP combination compared to standard therapy, the follow-up duration, and sample size were small<sup>5</sup>. Regarding the severe course of our patient, despite all the risks, this aggressive combination therapy was started as other treatment options failed.

Although there is no well-established treatment protocol exists for NBD, immunosuppressives like interferon (IFN) alpha, AZA, CyP and methotrexate have

been reported to be efficacious in controlling NBD. Additionally there are positive studies with infliximab and adalimumab which are TNFi mainly used for ocular BD<sup>6-8</sup>. In a case by Leccese et al ocular BD treated with infliximab and cyclosporine progressed to NBD and after 2 months of adalimumab therapy, there was an unexpected improvement of the neurological symptoms with complete regression of the active lesions in MRI<sup>8</sup>. In a pediatric case, treatment with adalimumab resulted in resolution of systemic and neurological signs, along with improvement of MRI abnormalities<sup>9</sup>. In another NBD case report by Belzunegui et al, after insufficient responses to sequential pulse CyP, glucocorticoids and infliximab, lesions disappeared with adalimumab<sup>10</sup>. Case notifications with tocilizumab and etanercept have also been reported<sup>11,12</sup>. In our case, considering the severity of the relapses, inability of previous maintenance AZA therapy in full suppression of relapses and unresponsiveness to high-dose glucocorticoids, instead of starting CyP alone, other immunosuppressives, a relatively rapid-acting agent, adalimumab, was added to the treatment regimen. Inflammatory reaction in BD arises from disruption of homeostasis resulting in altered innate and adaptive immune responses, pathogenic T cell activation in the peripheral blood, and in inflammatory sites. Researches have shown that both Th1 and Th17 expansions were present, while regulatory T cell response was suppressed<sup>13</sup>. Although the exact immunological and molecular pathways in NBD have not been fully understood yet, it is suggested that release of interleukin (IL)-1, -6 and -8, and TNF- $\alpha$  and IFN- $\gamma$  into CSF were increased in NBD patients<sup>14</sup>. This reflects a nonspecific inflammatory pattern compatible with auto-inflammatory disease pathways. The potential beneficial effects observed with TNFi, anti-IL6 and anti-IL1 also support these findings. Recently, encouraging responses with anti-IL1 agents, anakinra, canakinumab and, gevakizumab, especially in difficult and multi-resistant cases of BD have also been reported<sup>15,16</sup>. Cantarini et al. showed rapid resolution of disease activity with anakinra in eight of nine drug-resistant BD patients<sup>17</sup>. Only one of those cases had neurologic involvement and anakinra improved ocular involvement of that patient<sup>17</sup>. Although there are no data about effects of anti-IL1 agents in NBD, in difficult relapsing cases like ours, anti-IL1 agents may also be an alternative after failure of standard therapy or TNFi. However, there are currently no randomized controlled trials (RCT) in BD with these biologic agents, therefore in order to understand benefits and risks or

steroid sparing effects of these drugs, well-designed multi-center RCTs are needed.

Another noteworthy issue related to the treatment applied in this patient is infections. It is well known that biologic agents, especially TNFi, are associated with reactivation of latent TB and serious infections. In this case although the tests for latent TB was negative and prophylactic INH was started, the patient developed pulmonary TB. A recent multicenter Turkish study reported 73 new TB cases among 10.434 TNFi-exposed patients with rheumatic diseases (0.69%). In this research, the frequency of TB was the highest among TNFi-exposed BD patients (5 of 124; 4%). TB was more frequent in patients exposed to adalimumab compared with etanercept, but the difference was statistically insignificant ( $p = 0.08$ ). The median time for occurrence of TB since the initiation of infliximab, adalimumab, or etanercept was 13 months (range 1–96), 13 months (range 3–36), and 7 months (range 4–60), respectively<sup>18</sup>. However, in our case the interval between the initiation of CyP and adalimumab combination therapy and development of TB was relatively low. In this case, concomitant high-dose, long-term glucocorticoid therapy could probably have a significant role in the increased risk of infection with the treatment mentioned earlier. Although the risk of infections with TNFi or CyP has not been well examined yet in BD as in other rheumatic diseases, the literature from RA and systemic lupus suggest that concomitant use of glucocorticoids either with TNFi or CyP significantly increases the risk of serious infections, including TB<sup>19-20</sup>. Therefore in our case, each of the medications probably contributed to the development of infections.

In conclusion, we describe a patient with serious NBD refractory to conventional immunosuppressive therapy. In this case, due to serious clinical course, CyP and adalimumab were given together. Although this treatment led to a good clinical response, TB developed as a complication of immunosuppressive treatment. In cases of severe clinical course, with close follow-up, adalimumab can be considered for the treatment of NBD. However, a high awareness is required for opportunistic infections.

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