CASE REPORT

Treatment of myelitis in Behçet's disease with rituximab

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SUMMARY

Behçet's disease (BD) is a chronic inflammatory disorder that involves the parenchymal central nervous system (neuro-BD, NBD) approximately in 5–49% of patients, causing lesions rarely located in the spinal cord (SC). We report the first case of NBD-myelitis treated with intravenous rituximab. A 41-year-old man affected by BD presented with mild paraparesis with a miliary involvement and a 'net-like' gadolinium enhancement (Gde) of the SC. After a therapeutic attempt with pulsed cyclophosphamide and intravenous methylprednisolone, the clinical and neuroradiological course worsened. A progressive improvement was observed after rituximab administration associated with low doses of oral prednisone. No disease activity was detected and the patient reported no adverse event. After six rituximab cycles, cervical MRI was normal while thoracic MRI showed a slight T2-weighted hyperintensity of D4–D10 spinal tract without Gde. A combined use of rituximab and oral steroids resulted in a long-term suppression of NBD activity without any safety concern.

BACKGROUND

Behçet's disease (BD) is a chronic relapsing, inflammatory disorder of unknown aetiology,¹ more common in Mediterranean, Middle East and East Asian countries. It is known that BD affects several organs. The involvement of the parenchymal central nervous system (neuro-BD, NBD) is one of its serious complications and occurs in approximately 5–49% of patients with BD.^{1–3} MRI is helpful to reveal mass-like lesions, isolated brain stem and basal ganglia lesions or spinal cord lesions.³ We report the first case of NBD myelitis treated with intravenous rituximab with optimal response and no adverse event.

CASE PRESENTATION

The patient was a 41-year-old man with no familial history of neurological disorders. He presented with a slight onset of paresthesias and slowly progressive hyposthenia at the lower limbs, more on the right side; he also reported increasing difficulty in walking and was unable to run or climb stairs rapidly. In 2008 a diagnosis of BD was made.⁴ The patient had a history of recurrent oral and genital ulceration since adulthood, episodes of migrant arthralgia and a previous anterior uveitis in his right eye. Human leucocyte antigen (HLA) typing for HLAB27 and HLAB51 were negative.

INVESTIGATIONS

On admission to our department the patient had a mild paresis at the right lower limb. His gait was paretic on the right leg and ataxic. He did not take any medication and had no exposure to neurotoxic agents.

DIFFERENTIAL DIAGNOSIS

Blood tests including coagulation, liver function, C reactive protein and thyroid-stimulating hormone were within normal ranges. Viral serology (herpes simplex virus, herpes zoster virus, Venereal Disease Research Laboratory, treponema pallidum haemagglutination, borrelia, *Mycobacterium tuberculosis*, HIV, hepatitis B virus, hepatitis C virus, toxoplasma and cytomegalovirus) showed negative findings. Antinuclear antibody, antineutrophil cytoplasmic antibody, antiSjogren's syndrome antigen, anti Sjogren's syndrome B, anticardiolipin, anti-transglutaminase antibodies, lupus-like anticoagulant, rheumatoid factor and levels of ACE were normal. Neuromyelitis optica-IgG and antibodies for paraneoplastic syndrome were negative as well. Esophagogastroduodenoscopy revealed no mucous abnormalities suggesting Whipple disease. Cerebrospinal fluid (CSF) contained 14 cells/ μ L and protein level 49 mg/dL, without oligoclonal IgG bands. Visual and somatosensory-evoked potentials showed a bilateral increased latency. Brain MRI was normal, while spinal cord (SC) MRI disclosed a miliary involvement of the whole SC. Almost all the lesions showed gadolinium enhancement (Gde) on T1-weighted images (figure 1A, B) and a leptomeningeal enhancement was observed as well.

TREATMENT

The patient was first treated with oral prednisone, gradually tapered with reduction of the lesion volume and improvement of Gde. Owing to the miliary SC involvement, intravenous pulsed cyclophosphamide was infused (14.2 g total dosage). However, after an initial improvement, hyposthenia at the right lower limb worsened and MRI showed multiple Gde at the entire SC. So the patient was treated with intravenous methylprednisolone (MP) 1 g for 5 days, then intravenous rituximab 1 g was administered for off-label use. The same dose of monoclonal antibody was repeated after 15 days and then every 6 months for a further 7 times, with associated oral prednisone (7.5 mg/day), leading to an initial recovery of the symptoms followed by a clinical stable course.

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Figure 1 MRI. (A) Sagittal T2-weighted image of the dorsal spinal cord. Multifocal and diffuse intra-axial hyperintensities (B). Sagittal T1-weighted image after contrast. Multiple punctate foci of enhancement within the spinal cord (C). Sagittal T1-weighted image after treatment. Almost complete disappearance of multifocal enhancement.

OUTCOME AND FOLLOW-UP

The clinical course remained unchanged since then. After only one cycle, SC MRI detected a significant reduction of Gde. A further reduction of the number of T2 and Gde enhancing lesions was detected following the third infusion. Besides, after six cycles MRI detected no Gde (figure 1C) and only a doubtful T2-weighted hyperintensity of D4–D10 spinal tract that presented subtly thinned. Cervical MRI was normal. Neurological examination actually showed a slight paresis at the right lower limb with a right parietic gait.

DISCUSSION

BD does not have a specific diagnostic marker. Diagnosis is made on the basis of criteria proposed by the International Study Group for BD.⁴ HLAB51 has been reported to be present in only 10–20% of European patients, who have a six-time increased risk of BD and a more severe course.⁵ Isolated myelitis is an uncommon presentation of NBD³ and usually does not respond well to treatment. As SC involvement is a bad prognostic factor in parenchymal NBD,⁶ its early detection in the disease process should be emphasised. Case reports of NBD with myelitis remain rare, literature describes cases with non-contiguous multifocal lesions^{7–9} and only one case refers to a longitudinal myelitis involving the entire SC.¹⁰ Myelitis is caused by many other diseases that we tried to exclude by laboratory data. Despite the whole SC involvement, our patient reported mild clinical symptoms, with a clinicoradiological dissociation. This is probably due to the larger role of inflammation and oedema more than degeneration, also supported by the clinical response. However, considering the bad prognostic role of NBD myelitis, a prompt therapeutic choice was mandatory. Owing to the lack of data, there is no established treatment protocol for NBD myelitis. Corticosteroids were reported to be effective for the acute phase. Other immunosuppressants such as azathioprine, methotrexate, cyclophosphamide, novel targeted therapies and TNF-blockers may be used. Actually, no patient with NBD myelitis was treated with rituximab. Rituximab has been infused in one case of retinal vasculitis until now.¹¹ This chimeric monoclonal antibody acts against CD20, a specific B-cell antigen expressed on immature, pre and memory B cells, but not on plasma cells.¹² Some mechanisms by which rituximab depletes B cells have been suggested, including complement activation, cytotoxicity via antibody action and inhibitory effect on B-cell proliferation,¹² but CD20 function is not exactly known so far. It is suggested that it acts as a calcium

channel subunit.¹² Recently, autoimmune diseases that are considered as being predominantly T-cell mediated have been treated successfully with rituximab.^{12 13} So the real mechanism of rituximab remains debated.

Learning points

- ▶ Rituximab administration associated with oral steroid therapy was efficacious in reducing neuro-Behçet's disease (NBD) activity and in maintaining a steady state during a long-term follow-up.
- ▶ No safety concern has been detected until now.
- ▶ It is very difficult to assess the efficacy of rituximab on NBD due to variation in treatment regimens and heterogeneity of the few studied patients.
- ▶ Although such reports are promising in NBD, further studies are required to evaluate the efficacy and safety of this treatment.

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Competing interests None.

Patient consent Obtained.

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