Transverse myelitis in Behçet's disease: a series of four cases and review of the literature

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ABSTRACT

Objectives. *Transverse myelitis (TM) is an uncommon neurologic condition characterised by the segmental involvement of the spinal cord. Although its etiology is unknown, a well established list of associations have been described, many items of which point towards an autoimmune and vasculitic process. TM is also a rare complication of Behçet's disease (BD), an autoimmune process. Herein we present 4 cases of TM associated with BD.*

Methods. *Retrospective chart reviews of 104 patients were done. Diagnosis of BD was established in each case according to the diagnostic criteria established by the International Study Group for Behçet's Disease. Demographic data, clinical and radiologic presentations of TM, treatment strategies and outcomes were obtained from hospital records.*

Results. *Among the 15 patients with neurological involvement, four cases (3 male, 1 female) of acute TM associated with BD were confirmed. TM associated with BD affected cervical and thoracic levels of the spinal cord. Myelitis involved multiple segments (4 cases). TM developed at any stage of the disease, even as a dramatic initial presentation, leading to the diagnosis of BD (1 case). The longest time elapsed since the diagnosis of BD prior to the development of TM was 10 years. A major association was the history of panuveitis in all four cases. Cyclophosphamide and steroid therapy were the mainstay of the treatment once the TM had developed. Treatment outcomes were variable, depending mostly on the severity of the neurologic involvement at presentation, timing of the initiation of the therapy and patients adherence with the treatment. Two of 4 cases recovered without major sequela.*

Conclusion. *Although rare, the presented association and its detailed clinical discussions would serve to enhance our understanding of both TM and the spectrum of neurologic complications that BD may harbour. Early recognition and initiation of therapy are crucial for successful outcome.*

Introduction

Transverse myelitis (TM) is not in itself a pathological entity. It is characterised by segmental inflammation of the spinal cord which results in axonal demyelination and necrosis. It is an uncommon condition with an approximate incidence of 1 to 5 cases per million annually (1). The inflammation is generally restricted to one or two segments, especially in the thoracic (Th) cord. If the inflammation is in 3 or more segments, it is known as longitudinally extensive TM (2). Clinical presentation is usually with an acute attack followed by a remission, but, unfortunately, mostly with sequelae. It might also be associated with a secondary progressive course in some patients. Its pathogenesis remains unknown and many cases are idiopathic. However, TM has many associations. The most common ones are neurological diseases such as multiple sclerosis (MS) and neuromyelitis optica (3). MS is especially important since TM may be the first sign of it. Among the connective tissue diseases, systemic lupus erythematosus and Sjögren's disease are well recognised (4-5). Some degree of persistent disability is seen in many of the cases (6). Glucocorticoids and immunosupressants are the mainstay of the therapy (7).

The neurological involvement in Behçet's disease (BD) is not uncommon and seen in about 5% of patients (8-9). The term 'neuro-Behçet' (NB) is often used to categorise those patients with any form of neurological involvement.

Among neuro-Behçet cases, spinal cord involvement is about 10% (9) and TM in neuro-Behçet's is found about 4% (10). In this report, we present 4 cases of TM associated with BD.

Patients and methods

One hundred and five patients, who were diagnosed with BD in our clinic between 2008 and 2012 and fulfilled the International Study Group for Behçets Disease diagnostic criteria, were included (11). Their medical records were retrospectively reviewed. Fifteen patients (11 male, 4 female) were found to have NB and 4 of them (3 male, 1 female) had isolated TM. The demographic, clinical, laboratory and radiologic presentations of these four cases, treatment protocols and outcomes were obtained. These patients were evaluated by a multidisciplinary team of physicians (rheumatologist, ophthalmologist, neurologist, neuroradiologist, physical therapist, psychiatrist) and followed up at our rheumatology clinic since 2008. There were no evidence of spinal cord compression in any patient. The serological markers of autoimmune diseases, including anti-nuclear antibody, anti-neutrophil cytoplasmic antibody were negative in all patients. Cerebrospinal fluid examination (CSF) was done in 2 patients.

Case 1. A 24-year-old woman with a history of oral and genital ulcers presented with inflammatory back pain. Methotrexate 10 mg per week, sulfasalazine 1 gr b.i.d. and colchicine were started. Two years later she developed bilateral panuveitis. The therapy was switched to interferon (IFN)-α 3μ three times per week and oral steroid in tapering doses. Two years after panuveitis, she developed progressive paraparesis and urinary incontinence. She had a spinal MRI showing gadolinium enhancement in segments between Th 2–6 and between Th 8–10. She was lost to follow-up with her rheumatologist, but continued to use IFN-α in the following year and then stopped using it on her own decision. Two years after the onset of neurological symptoms, she presented to the rheumatology clinic, she was paraplegic and had neurogenic bladder. Her CSF analysis was normal. She had atrophic spinal cord on the MRI (Fig. 1). Azathioprine therapy was started to prevent another attack. Over the course of 5 years, she was relapse free with azathioprine.

Case 2. A 28-year-old man with a diagnosis of BD for four years presented with bilateral panuveitis in 2007. Cyclosporine 100mg b.i.d. and methylprednisolone (MP) 1mg/kg/day were initiated. Steroid dosage was tapered over 3 months. In 2009, he admitted to emergency department with paraparesis and urinary incontinence for twelve hours duration. He had hypoesthesia below thoracic Th 12 and hyperactive deep tendon reflexes (DTRs) in lower extremities. Babinski sign was positive bilaterally. The MRI performed on the day of admission showed T2-weighted hyperintense areas between Cervical (C) 5–6 and an extended hyperintensity between Th 2–12. Gadolinium enhancement was seen between C5 and 6 and between Th 5–6 (Fig. 2). Intravenous pulse MP 1 gram/day for 7 days followed by oral MP were given. The steroid therapy induced a remarkably rapid clinical recovery in the first week. Then intravenous cyclophosphamide (CTX) 500 mg every 2 weeks for 6 doses, followed by 1 gr/monthly for 5 months were administered. During his follow-up a year later, his motor strength and sensory examination were normal except slight hyperactivity in DTRs and minimal spasticity in his legs. Azathioprine 50 mg t.i.d. was started as a maintenance therapy. He had left occlusive retinal vasculitis in May 2012. His medical therapy was switched to IFN-α 6μ thrice a week. His disease has been under good control at the time of the latest follow-up in October 2012.

Case 3. A 32-year- old man with a family history of BD had recurrent oral ulcers and pseudofolliculitis in his back for 12 years. His father died from neurological complications of Behçet's disease. Three years ago, he presented with bilateral panuveitis, paraparesis and difficulty in urinating. He was diagnosed with ocular and neurological involvement of Behçet's disease and received pulse MP and CTXYX 1 gr monthly along with interferon α. MP and CTX were discontinued after 1 year, but he remained on IFN-α. At his follow-up visit one year ago, his muscle strength and sensory exam were normal. He was able to walk without assistance. He only had spasticity in lower extremities. He was on IFN-α 6μ twice a week. After his visit, he stopped IFN-α injections on his own and two months later he had recurrence of dif-

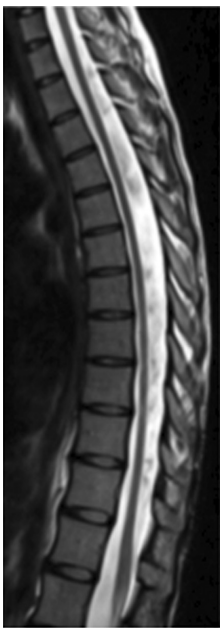

Fig. 1. Sagittal T2-weighted sequences through the thoracic cord demonstrate marked atrophy without any intramedullary signal abnormality.

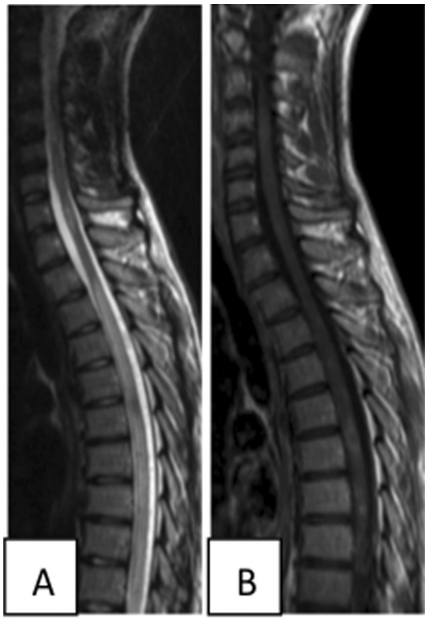

Fig. 2. Sagittal T2 weighted (**A**) and gadolinium enhanced T1 weighted (**B**) sequences through the cervicothoracic spine demonstrate cord expansion and T2 hyperintensity extending from C5-6 to Th10-12, with patchy and ring-like areas of enhancement.

ficulty in walking and urinary incontinence. Ten days after the onset of these symptoms, he presented with paraparesis, urinary incontinence and hypoesthesia below Th 12 level. CSF examination showed neutrophilic pleocytosis and elevated protein level. Viral markers and oligoclonal bands were negative in. On spinal MRI, T2 weighted images showed increased signal intensities between C 4–5 and between Th 5–9 (Fig. 3). These lesions did not show any enhancement after gadolinium injection. He received intravenous pulse MP 1 gr per day for 7 days followed by oral MP. There was no recovery following pulse steroid therapy. Plasmapheresis was performed every other day for 10 days and then he was started on CTX 500mg every two weeks. However, there was still no clinical recovery. The MRI performed 3 months after the initiation of therapy, revealed thinning of the spinal cord in the cervical and thoracic segments, but no new lesions.

Case 4. A 34-year-old male patient with a history of BD for 3 years presented with bilateral panuveitis while on colchicine. He was started on cyclosporine 100 mg b.i.d. and oral MP 1mg per kg a day and gradual tapered. The therapy was switched to IFN-α 3μ thrice a week, just after a second panuveitis attack 9 months later. One month later, he developed paraparesis, neurogenic bladder and, hypoesthesia below Th 10. He had hyperactive DTRs and extensor plantar reflexes. The MRI on the day of admission showed extensive diffuse hyperintensity from C2 through Th12 (Fig. 4). MP 1 gr/day was initiated within 12 hours of symptom onset and continued for 7 days. After the first week of steroid therapy he had complete functional recovery. He received 6 doses of intravenous CTX, 500 mg every 2 weeks for 3 months, then, 1 gr monthly. On his last examination, he had hyperactive DTRs in lower extremities and hypoesthesia below Th 10, without any impact on activities of daily living, which were accepted as sequelae.

Fig. 3. Sagittal T2-weighted MR imaging sequences through the thoracic cord demonstrate T2 hyperintensity extending from C 4–5 to Th 8–9 without expansion.

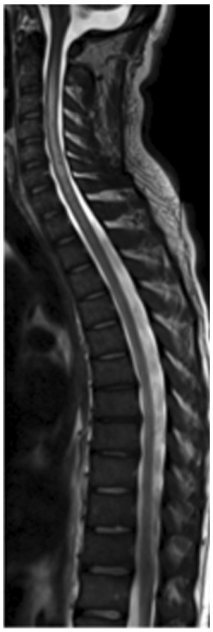

Fig. 4. Sagittal T2-weighted MR imaging sequences through the cervicothoracic spine demonstrate cord expansion and T2 hyperintensity extending from C2 to T12.

Discussion

In this paper, we presented 4 cases of BD with TM who had long-term follow-up. Frequency of TM among our BD patients was 3%. Although such cases had been presented before, up to date, there is no well established guideline for this clinical scenario. All four cases in our mini-series have presented to the emergency department with acute onset neurologic symptoms. Three patients had a history of BD and panuveitis at the time of presentation and they were already on medications such as colchicine, methotrexate, interferon. It is an interesting finding that these medications had no preventive role in the development of TM. One patient was diagnosed with BD at the time of emergency consultation. Although he had a suggestive history, he was not presented or diagnosed earlier. It is another interesting observation that TM can be the initial presenting scenario in BD. This subset of patients is especially hard to diagnose, since BD is responsible only from a small fraction of TM cases. Therefore it is advisable to question every patient with TM for Behçet's symptomatology. Another interesting observation is about the timing of TM onset in relation to the onset of panuveitis. Alhough it can be coincidental, in three patients TM developed 2 years after the diagnosis of panuveitis. This time period can be indicative of a "risk window" for the development of TM after panuveitis. In these four patients presented, TM associated with BD affected single or multiple segments in the cervical and thoracic spinal cord. The acute phase reactants and complements (c3, c4) were normal in all patients at the time of presentation with TM.

The autoimmune markers (ANA, Anti ds DNA, Anti-SSA, Anti-SSB, Anti-SM, Anti-Sm-RNP) were negative in all patients. Since TM may be the first presentation of multiple sclerosis and neuromyelitis optica, magnetic resonance imaging (MRI) of the brain and ophthalmological examination were done for differential diagnosis. Both were normal in all 4 patients. It is well known that spinal cord involvement had a worse prognosis than other forms of neuro-Behçet diseases. For the currently presented cases, our observation is that immediate initiation of intravenous pulse steroid therapy, once the symptoms of TM have developed, is the main determinant of a favourable outcome. Two patients had pulse steroid therapy within 24 hours of symptom onset and had the best outcome. The other two patients' admissions to the hospital were delayed and also compliance with the medication was poor. Three patients were given azathioprine as a maintenance therapy. One patient (Case 1) had primary progressive, one patient (Case 3) had secondary progressive course. The other two patients were cured with a little neurological sequelae.

Isolated spinal cord involvement in BD

is uncommon (9-10, 12). Most of the data come from case reports in the literature (13-15). Spinal cord involvement in BD was initially reported in autopsy series in 1950s (16). Since it is difficult to have a biopsy, spinal MRI and CSF analysis are currently the only tools to determine the presence of inflammation within the spinal cord. Yesilot *et al*. (9) evaluated 24 patients with spinal cord involvement amongst 216 patients with parenchymal disease. Six cases had an isolated spinal cord involvement. Kidd *et al*. (17) reported that 2 of 50 patients with NB presented with acute TM. Tohmé *et al*. (18) reviewed 170 patients with BD and found 12 of 21 NB patients with meningoencephalitis and/or transverse myelitis. Deshpande *et al*. (19) reported a patient with BD who developed TM immediately after lumbar steroid injection for radicular pain. Since the pathergy phenomenon is a unique dermatological feature of BD, they suggested that acute myelitis in this patient might be due to spinal pathergy reaction.

It is not feasible to conduct a prospective clinical study in TM, due to the rarity of TM cases associated with BD. There is no treatment protocol or guideline for TM associated with BD. In cases of acute episodes of parenchymal neuro-Behçet's, pulse corticosteroids should be given as infusions of 1 gr/day methylprednisolone for 3–7 days, followed by a slowly tapering course of oral steroids (20). Maintanence therapy should be started in this group of patient since primary or secondary progressive course can be seen. It is well known that maintanence therapy should be continued for a period of time, because early relapse is not uncommon. Monthly pulses of cyclophosphamide or azathioprine may be used as a maintanence therapy (8). Since cyclosporine is known to be neurotoxic, it should not be used in NB (21). Ait Ben Haddou *et al*. (22) retrospectively analysed 40 patients with NB who received 5 doses of pulse steroids and cyclophosphamide as initial bolus of 600 mg/m^2, followed by a bolus of 600 mg/m^2 every 2 months for 2 years. They reported a good prognosis with immediate therapy with steroids and cyclophosphamide. Çalguneri *et al*. (23) reported a favourable outcome with combination of interferon, cyclophosphamide and steroid in a patient with TM associated with BD. Successful treatment of resistant NB cases with infliximab have been recently reported (24-27). Coulter *et al*. (28) used infliximab in a patient with TM associated with BD and reported a good prognosis.

The most important step in the treatment of TM in association with BD is the immediate administration of i.v. pulse steroid therapy. This recommendation is beeing supported by the observation that the best outcomes were achieved in those who received the earliest intervention. Although maintenance theraphy is important as well, neither our experience nor the literature provides evidence regarding the superiority of any known drug therapy. However, our limited experience is inclined to favour cyclophosphamide as a maintenance option, since 2 of our patients who have received this drug were found to be relapse free at the end of a 2-year follow-up.

Conclusion

In conclusion, although rare, physicians caring for BD patients should be alert against the neurological symptoms of TM, since early initiation of immunosuppressive therapy is the major determinant of prognosis. Patients should be educated to comply with treatment, since premature discontinuation of immunosuppressants is associated with relapses, neurological sequela and long-term morbidity.

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