Longitudinally extensive transverse myelitis as the sole presentation of neuro-Behçet's disease responding to infliximab

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Context: Isolated involvement of the spinal cord is an uncommon presentation of neuro-Behçet's disease (NBD) and it is associated with a poor prognosis for functional recovery.

Method: A case report of an 18-year-old Turkish man who presented with a progressive paraparesis and bladder dysfunction secondary to a longitudinally extensive transverse myelitis as the sole presentation of NBD.

Findings: Examination revealed a spastic paraparesis and a T7 sensory level. Magnetic resonance imaging revealed multiple enhancing lesions throughout the thoracic cord and cerebrospinal fluid showed intense neutrophilia. On further enquiry a family history of Behçet's disease was elicited. The patient subsequently reported a history of recurrent oral ulceration and intermittent ocular inflammation. A diagnosis of NBD was made and intravenous high-dose steroids commenced with poor response. In view of the poor prognosis for functional recovery associated with spinal NBD the patient was treated with infliximab, an anti-tumour necrosis factor-alpha monoclonal antibody, leading to excellent recovery of function.

Conclusion/clinical relevance: Early treatment with infliximab may facilitate a favourable functional recovery and should be considered in cases of NBD with spinal cord involvement.

Keywords: Behçet's disease, Infliximab, Myelitis, Spinal cord, Paraparesis

Case report

An 18-year-old man of Turkish descent was admitted with a 3 month history of progressive lower-limb weakness associated with intermittent paresthesia extending to his abdomen and urinary urgency. He also reported intermittent fever and generalized malaise. He had a past medical history of epididymitis. The patient had lived in the UK for 10 years, but prior to this had resided in Turkey. Although his immediate family did not speak English, no family history of neurological disease was noted. On admission the patient was pyrexial (38°C). Examination demonstrated a spastic paraplegia with pyramidal weakness (hip flexors 2/5, Medical Research Council grading), and a T7 sensory level. A post void residual volume of 150 ml was noted on urinary bladder ultrasound. Further examination of the neurological system was unremarkable.

The following blood tests were negative or within normal limits; routine haematology, biochemistry (including vitamin B₁₂ and folate), autoimmune screen, serum angiotensin-converting enzyme levels, and aquaporin 4 antibodies. Screening for tuberculosis, human immunodeficiency virus, syphilis, *Borrelia burgdorferi*, herpes simplex viruses 1 and 2, and *Brucella* was negative. C-reactive protein was normal but the erythrocyte-sedimentation rate was elevated at 41 mm/hour (0–7 mm/hour). HLA-B51 serotype positivity was noted. Cerebrospinal fluid (CSF) analysis demonstrated <5 red blood cells/mm³, 438 white blood cells/mm³ (90.0% polymorphs), protein 0.95 g/l, and a CSF glucose of 2.5 mmol/l. Paired serum glucose was 6.0 mmol/l (41.7%). Microscopy and culture were negative. The CSF Ig G index was normal and oligoclonal bands were absent. Cytological examination revealed a dense aggregate of polymorphonuclear cells. Magnetic resonance imaging (MRI) with gadolinium contrast of

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Figure 1 MRI spine sagittal view: T1 pre (A) and post (B) gadolinium contrast demonstrating several abnormal lesions with signal enhancement in the upper thoracic cord (arrow) and (C) T2, high signal within the thoracic cord (arrow).

the spine demonstrated oedema within the cord and expansion extending from T3-T6 with abnormal signal continuing throughout the remainder of the cord to just above the conus (Fig. 1). Multiple areas of gadolinium contrast enhancement were observed in the thoracic cord (Fig. 1). MRI of the brain and a chest X-ray were unremarkable.

Closer questioning revealed a history of recurrent oral ulceration and intermittent eye inflammation. A history of genital ulceration and skin lesions was denied. With the aid of a translator, it was determined that the patient's mother, paternal uncle, and grandmother had Behçet's disease (BD). Subsequent pathergy testing was positive and slit lamp examination confirmed an intermediate uveitis. We concluded that a diagnosis of neuro-Behçet's disease (NBD) with spinal cord involvement was likely. The patient was commenced on a 10-day course of methylprednisolone (1 g/day). The patient's neurological condition failed to improve and an interval MRI scan demonstrated progression of cord oedema and evolving areas of contrast enhancement. The tumour necrosis factor- α (TNF α) antagonist infliximab was commenced at a dosage of 3 mg/kg. The treatment course was complicated by herpes zoster infection (treated with aciclovir) and a mild hypersensitivity reaction both of which resolved without adverse sequelae.

The patient improved neurologically and an MRI scan 1 month following the first dose of infliximab demonstrated significant resolution of the enhancing lesions. Further doses were administered at 2, 6, and 14-week intervals with gradual reduction of the oral prednisolone. The patient's clinical condition continued to improve with neurorehabilitation and at 3 months he was able to walk 10 m unaided. The patient's bladder dysfunction also resolved. Further doses of infliximab have been scheduled for administration every 8 weeks for a total of 6 months. It is our intention to gradually convert to

a steroid-sparing agent such as azathioprine or methotrexate for long-term maintenance.

Discussion

Initial differential diagnoses considered for this patient included post viral transverse myelitis, demyelination, neuromyelitis optica, neurosarcoidosis, malignancy, and tuberculosis. The Turkish ancestry, positive pathergy test, uveitis, oral ulceration, previous epididymitis, HLA-B51 serotype (confers a six-times increased risk of developing BD, and of having more severe manifestations),¹ and neutrophilic pleocytosis led us to conclude that this was an unusual isolated spinal cord presentation of NBD. The patient fulfilled the International BD Study Group criteria for the diagnosis of BD.²

BD is eponymously credited to the Turkish dermatologist Hulusi Behçet³ who first described the classical clinical triad of uveitis and recurrent oral and genital ulceration. BD is a multisystem inflammatory perivascularitis which may arise in a multitude of tissues including the central nervous system (CNS). CNS involvement is recognized as a serious cause of long-term morbidity and mortality in BD.^{4,5} Parenchymal neurological involvement in BD is atypical of the condition but usually manifests as a meningoencephalitis.⁴ The prevalence of spinal cord involvement in NBD ranges between 2.5 and 30% with a particular predilection for the cervical and thoracic cord.^{6,7} Isolated spinal cord involvement is unusual. In a series of 200 cases of NBD only 10 patients had isolated spinal cord involvement⁸ and myelitis in general is recognized as a poor prognostic factor in NBD.⁴

The treatment of NBD remains largely empirical with corticosteroids forming the mainstay.⁴ In our patient this conferred minimal, if any therapeutic benefit. Other conventional immunosuppressive medications

such as methotrexate and cyclophosphamide were considered but deemed unsuitable due to the former's slow onset of action and the latter's well recognized toxic side effect profile. Taking into account the patient's age and neurological deterioration the decision to administer infliximab was made following careful discussion with the patient and his family. Serum levels of TNF α have been found to be increased in active BD implicating a role in the condition's pathogenesis.⁹ Although further controlled studies are required there is a growing body of evidence to suggest TNF α antagonists such as infliximab, etanercept, and adalimumab have a significant role in the treatment of BD, in particular those cases with severe manifestations including ocular,¹⁰ gastrointestinal,¹¹ and CNS involvement.¹² Anti-TNF α agents have also been found to have a therapeutic role in patients with a resistance or intolerance to the standard BD immunosuppressive regimens.¹³

Evidence for the efficacy of TNF α antagonists in NBD is so far based on the results of a few case reports and case series. Piptone *et al.*¹² presented a case series of eight patients with NBD treated with infliximab all of whom demonstrated a favourable response with no adverse effects reported. Borhani Haghighi *et al.*¹⁴ reported their observations in the treatment of four NBD patients with infliximab and found that patients receiving the higher dosage of 5 mg/kg with adjuvant immunosuppressive therapy exhibited a good clinical response compared with those patients receiving only 3 mg/kg. One patient in their series developed varicella zoster infection. In the largest case series to date, Al-Araji *et al.*¹⁵ reported a favourable outcome in 17/18 patients with NBD treated with infliximab. The emerging evidence supports the use of infliximab as an efficacious treatment for NBD. While a delayed response to corticosteroids may have been a possibility in our patient, the poor prognosis associated with spinal cord involvement in NBD^{4,7} influenced our decision to commence infliximab. Following administration our patient exhibited gradual neurological improvement and at 3 months was functionally able to walk short distances unaided.

Conclusions

Isolated spinal cord involvement in NBD is a rare, but important, condition that should be considered as a

differential diagnosis in cases of acute myelitis. It is important to enquire specifically about a history of uveitis and orogenital ulceration in suspected cases. The prompt initiation of treatment with immunotherapy, including anti-TNF α medications such as infliximab, appears effective and should be considered as a treatment of NBD with spinal cord involvement, especially if corticosteroids have proved ineffective.

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