

## Case report

# Refractory neuro-Behçet treated by tocilizumab: a case report

P. Urbaniak, P. Hasler, S. Kretzschmar

Rheumaklinik und Institut für  
Physikalische Medizin und Rehabilitation,  
Kantonsspital Aarau AG, Aarau,  
Switzerland.

Piotr Urbaniak, MD  
Paul Hasler, MD  
Samuel Kretzschmar, MD

Please address correspondence to:  
Piotr Urbaniak, MD,  
Rheumaklinik und Institut für  
Physikalische Medizin und Rehabilitation,  
Kantonsspital Aarau AG,  
Tellstrasse,  
CH-5001 Aarau, Switzerland.  
E-mail: piotr.urbania@usz.ch

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### ABSTRACT

*A patient with central nervous system involvement of Behçet's disease was refractory to conventional immunosuppressive therapy and showed secondary failure of the anti-TNF agent infliximab. This presented as a progressive weakness of the legs and reduction in walking distance. The cerebrospinal fluid showed signs of inflammation including a vastly elevated IL-6 concentration. Given this result, the anti-IL-6 receptor antibody tocilizumab was administered and a good improvement of inflammatory parameters and a satisfactory increase of the walking distance were achieved.*

### Introduction

In 1937 Hulusi Behçet first described the eponymous entity of a systemic vasculitis affecting veins and arteries of all sizes. The inflammation in the venous and arterial blood vessels of different sizes explains the manifold signs and symptoms of Behçet's disease. Apart from recurrent oral and genital ulcers, these include inflammation of the eyes, several types of skin lesions, arthritis, central and peripheral nervous system damage, gastrointestinal and, rarely, cardiac involvement (1, 2). The severity of disease manifestations typically fluctuates. Morbidity and mortality are associated with gastrointestinal disease, ruptured central and peripheral aneurysms, neurologic lesions and amyloidosis. Immunosuppression with glucocorticoids, azathioprine, cyclophosphamide, cyclosporine and TNF inhibitors are established therapies (3). Due to elevations in IL-6 levels in Behçet patients with active inflammation, a beneficial effect of inhibiting IL-6 signalling by the monoclonal antibody directed against the IL-6 receptor, tocilizumab, can be postulated (4-8). This assumption led us to treat

a patient with secondary failure of infliximab by inhibition of IL-6. Tocilizumab is established for the treatment of rheumatoid arthritis refractory to conventional disease-modifying drugs and anti-TNF- $\alpha$  agents at a dose of 8 mg/kg as an infusion every four weeks. In Japan it is registered as an orphan drug for Castleman's disease and as a first line therapy for juvenile idiopathic arthritis. Descriptions of individual cases and small series have reported an effect in Crohn's disease, polymyalgia rheumatica, giant cell arteritis, remitting seronegative symmetrical synovitis with pitting oedema, systemic sclerosis, polymyositis and systemic lupus erythematosus.

### Case report

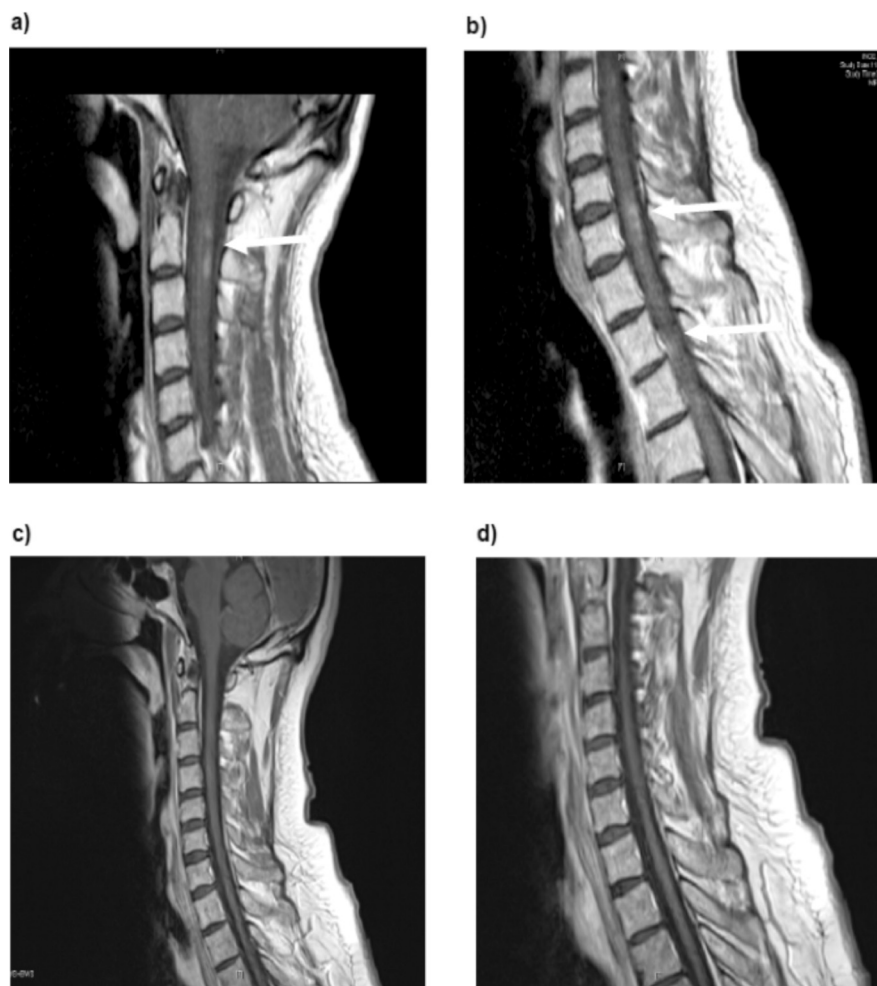
A 46-year old male patient was referred for further treatment of Behçet's disease. At the age of 25 he experienced deep venous thrombosis of the left leg and pelvic veins and was placed under transient oral anticoagulation. At 31 years of age recurrent oral and genital ulcers and bilateral thrombophlebitis of the lower leg were noted. Eight years later, deep venous thrombosis recurred, and continuous oral anticoagulation was begun. Colchicine 1-1.5 mg daily improved the genital, but not the oral ulceration. Erythema nodosum of the right calf occurred. Repeated ophthalmologic examinations failed to detect eye involvement.

At the age of 43 the first episode of urinary retention was recorded. Subsequently, subfebrile temperatures with general malaise and polyarthralgias appeared if colchicine was interrupted. Glucocorticoids, baclofen and tamsulosin 400 $\mu$ g were started to treat the neurogenic bladder dysfunction and newly apparent pyramidal disturbances with numbness distal to the sensory level of Th 7/8, gait disturbance pre-

Competing interests: none declared.

dominantly of the right leg with paraparesis and spasticity, hyperreflexia of the arms and low back pain. Under this regimen, the disease continued to progress with flares. MRI showed signal intensification and atrophy of the spinal cord at the mid and distal thoracic level (Fig. a-b). The sensory evoked potentials were pathologic, and lymphocytes in the spinal fluid were increased, indicating lymphocytic meningitis. Intravenous pulse glucocorticoids and azathioprine 150 mg daily were started, with improvement of the lumbar pain, but not of the gait disturbance. Four months later, infliximab was added at a dose of 400 mg every 4 weeks, corresponding to 5mg/kg, leading to a distinct improvement.

Sixteen months later, after a total of 9 infusions and continuous prednisone 40 mg daily, there was marked worsening of the gait disturbance with limitation of the walking distance to 30–50 m, weakness of the legs and lumbar pain. The MRI of the spine showed no clear changes compared with the previous examination, while the spinal fluid showed a marked pleiocytosis of 38 cells/mm<sup>3</sup> (normal <5) and a raised total protein of 0.62 g/l, both compatible with a relapse of the myelitis. The ESR was 15 mm in the first hour and the serum C-reactive protein 10 mg/l (normal range <3mg/l). The IL-6 in the serum was within the normal range of ≤3.3 ng/l, which was highly discordant with the spinal fluid level of 910 ng/l. There were no signs of an opportunistic infection of the central nervous system. Methylprednisolone was administered at a dose of 500 mg iv twice daily for three days followed by 1 mg prednisone/kg daily. The alternatives of cyclophosphamide, increasing the dose of infliximab, switching to another TNF-α blocking agent and the anti-IL-6 receptor antibody tocilizumab were considered and discussed with the patient. Cyclophosphamide and increasing the dose of infliximab were unattractive due to chronic urinary tract colonisation with extended spectrum beta-lactamase resistant *E. coli* (ESBL) and chronic neurogenic bladder. On the other hand, the secondary failure of infliximab spoke against trying another anti-TNF-α agent.



**Fig.** Panels a–d were sagittal T1 weighted images with *i.v.* gadolinium. Cervical spine and thoracic spine from C1-C7 (a) and C3-Th4 (b) under IFX. Cervical c) and thoracic spine d) after 6 infusions with TCZ. Arrows in a) and b) point to enhancing areas of the spinal cord, that were no longer present in c) and d).

After weighing the advantages and disadvantages of these options and considering the massively elevated IL-6 in the cerebrospinal fluid, the humanised IL-6 receptor blocking antibody tocilizumab 8 mg/kg was infused the day after the three-day methylprednisolone pulse, and the clinical signs and symptoms improved rapidly with an increase of the walking distance to 100 m. During tapering of the prednisone to 10 mg daily and a delay of the second infusion of tocilizumab planned after 4 weeks due to reimbursement issues the walking distance decreased to 30–50 meters, but improved again after the prednisone dose was increased to 40 mg daily and the second infusion with tocilizumab was administered.

Azathioprine 150mg daily was continued and prednisone tapered further to

15 mg daily. After the fourth tocilizumab infusion a scrotal abscess due to ESBL of the same resistance pattern as the bladder agent occurred. The abscess required surgical drainage, and tocilizumab was discontinued. The course was further complicated by extensive inguinal condyloma accuminata, for which surgical intervention was scheduled. Four months after discontinuation of tocilizumab, the patient was stable, and the MRI of the spine showed no lesions (Fig. b-c). The serum CRP and IL-6 were normal, the ESR 16 mm/1h. In the spinal fluid there were 6 cells/mm<sup>3</sup> and the IL-6 was 4.3 ng/l. Tocilizumab was started again, and the walking distance remained at 50–60 m.

### Discussion

The elevated cytokines released by

leukocytes in Behçet's patients are potential therapeutic targets (9, 10). There have been many reports on the use of TNF- $\alpha$  blocking agents in Behçet's disease, and they have become standard when conventional immunosuppressives have failed. In the case of failure of an anti-TNF- $\alpha$  agent, the options are limited. A switch to another anti-TNF- $\alpha$  agent or more stringent conventional immunosuppression are possibilities. So far, we have not identified any other cases of the treatment of nervous system manifestations of Behçet's disease with tocilizumab.

In our case with secondary progression of myelitis despite 4-weekly infliximab in combination with glucocorticoids and azathioprine, more stringent conventional immunosuppression, e.g. with cyclophosphamide, was unattractive because of the bladder dystonia and colonisation with ESBL. Switching to another TNF- $\alpha$  blocker did not seem promising. Based on previous reports of elevated IL-6 in the spinal fluid and the high levels measured in our patient, we decided to administer tocilizumab to treat the spinal cord inflammation in conjunction with glucocorticoids and continued azathioprine (8). This regimen led to a satisfactory response as judged by the improvement of the gait disturbance, inflammatory parameters in the serum and of the cell count, protein and IL-6 levels in the spinal fluid. On the other hand,

the well known effect of high dose glucocorticoids on nervous system involvement of Behçet's disease could explain the improvement. The walking distance did not improve substantially, so that the preservation rather than the improvement of the functional ability was achieved. Further follow-up will be necessary to determine whether the effect will be long-lasting.

Since IL-6 levels have previously been reported to be markedly elevated in Behçet's disease cases with central nervous involvement, further evaluation of spinal fluid IL-6 levels may provide an answer to the question whether they are of value in assessing such involvement and predicting a response to selective inhibition of this or other cytokines.

Concerning the initial therapy in this case before appearance of the neurological symptoms, it was inadequate according to current practice. The deep vein thrombosis would have required administration of glucocorticoids alone or with initiation of continuous oral anticoagulation.

The development of a scrotal abscess with the same ESBL strain responsible for chronic cystitis and the extensive spread of condyloma accuminata raise serious safety concerns. They illustrate that careful patient instruction and monitoring and, if necessary, rapid diagnostic and therapeutic intervention are essential for early detection and management of infections.

## References

1. MENDES D, CORRECIA M, BARBEDO M, VAIO T, MOTA M: Behçet's disease – a contemporary review. *J Autoimmun* 2009; 32: 178-88.
2. KOSEOGLU E, YILDIRIM A, BORLU M: Is headache in Behçet's disease related to silent neurologic involvement? *Clin Exp Rheumatol* 2011; 29 (Suppl. 67): S32-7.
3. LECCESE P, D'ANGELO S, ANGELA P, CONIGLIO G, LIVIERI I: Switching to adalimumab is effective in a case of neuro-Behçet's disease refractory to infliximab. *Clin Exp Rheumatol* 2010; 28 (Suppl. 60): S102.
4. EVEREKLIOGLU C, ER H, TÜRKÖZ Y, CEKEMEN M: Serum levels of TNF- $\alpha$ , sIL-2R, IL-6, and IL-8 are increased and associated with elevated lipid peroxidation in patients with Behçet's disease. *Mediators Inflamm* 2002; 11: 87-93.
5. HAMZAOUI K, HAMZAOUI A, GUÉMIRA F *et al.*: Cytokine profile in Behçet's disease patients. Relationship with disease activity. *Scand J Rheumatol* 2002; 31: 205.
6. KULABER A, TUGAL-TUTKUN I, SIBEL P *et al.*: Pro-inflammatory cellular immune response in Behçet's disease. *Rheumatol Int* 2007; 27: 1113-8.
7. HIROHATA S, OKA H, MIZUSHIMA Y: Streptococcal-related antigens stimulate production of IL6 and interferon- $\gamma$  by T cells from patients with Behçet's disease. *Cell Immunol* 1992; 140: 410-9.
8. HIROHATA S, ISSHIKI K, OGUCHI H *et al.*: Cerebrospinal fluid interleukin-6 in progressive neuro-Behçet's syndrome. *Clin Immunol Immunopathol* 1997; 82: 12-7.
9. EVEREKLIOGLU C: Current concepts in the etiology and treatment of Behçet disease. *Surv Ophthalmol* 2005; 50: 297.
10. MEGE JL, DILSEN N, SANGUEDOLCE V *et al.*: Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease. A comparative study with familial Mediterranean fever and healthy subjects. *J Rheumatol* 1993; 20: 1544-9.