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Infliximab for the Treatment of Refractory Adamantiades-Behçet Disease with Articular, Intestinal, Cerebral and Ocular Involvement

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Key Words

Adamantiades-Behçet disease • Monoarthritis • Oral and genital ulcerations • Ileocaecal bleeding • Cerebral vasculitis • HLA-B51 • Retinal vasculitis • Infliximab

Adamantiades-Behçet disease (ABD) is a chronic relapsing multisystem inflammatory vascular disorder with a broad spectrum of clinical manifestations, some of them being associated with high morbidity and mortality [1–4]. Tumour necrosis factor α (TNF- α) is a potent pro-inflammatory cytokine playing an important role in the pathogenesis of several inflammatory diseases, including ABD [4–7]. Therefore, TNF- α -inhibiting therapy has been used successfully for severe and/or acute cases of ABD [7–29].

We report a case of ABD presenting with bipolar aphthous lesions, relapsing monoarthritis, cerebral vasculitis and complicated by haemorrhagic terminal ileitis resulting in potentially life-threatening anaemia. The clinical course was refractory to a corticosteroid- and azathioprine-based immunosuppressive therapy with appearance of retinal vasculitis despite treatment. A complete, lasting remission was achieved with infliximab (IFX).

Case Report

In spring 2003, a 17-year-old young man of Albanian (Kosovo) origin started to complain about recurrent swelling and pain in his left knee; he was taken in charge by a rheumatologist who ruled out an infectious agent as well as a collagenosis by performing several joint punctures and serological tests. HLA-B27 was negative.

The monoarthritis showed further relapses, which led to a radiosynovitis in May 2004, and finally to a surgical synovectomy in January 2007. Four days after discharge from the orthopaedic clinic, the patient was referred to our Department because of very painful scrotal necrotic lesions, which started to appear as he came back home after knee surgery. At clinical examination, 2 distinct ulcerative lesions were present on the scrotum, with diameters of 4 and 5 cm, central necrosis, fibrin-rich ground and elevated borders (fig. 1a). A sexually transmitted disease was ruled out. Haematological analysis showed microcytic hypochromic anaemia (Hb 10.7 g/dl) and elevation of C-reactive

protein at 81 mg/dl, without leucocytosis. An empirical antibiotic treatment with amoxicillin/clavulanic acid, 1 g twice daily, was started. Histological examination of a skin biopsy specimen taken on an ulcer border described dermal massive neutrophilic infiltration without granulomas. Giemsa, Warthin-Starry and Gram staining showed no presence of bacteria, hence also excluding donovanosis.

After targeted asking, the patient mentioned more than 10 episodes of painful oral ulcerations starting to appear about 13 months before the genital lesions, thus leading to suspicion of ABD. Clinical, neurological and ophthalmological assessment was normal. Considering its prognostic value [2, 30], we ordered an HLA-B51 test, with a positive result. Colchicine 0.5 mg twice daily was started.

Persistent headache motivated a cerebral magnetic resonance scan (fig. 1c) which was consistent with focal (micro)vasculitis. Following the revised criteria for the diagnosis of ABD [2], the diagnosis of incomplete ABD could be formulated after detection of cerebral involvement. Lumbar puncture permitted to rule out infectious encephalomeningitis and multiple sclerosis. Cardio-angiological assessment including echocardiography, ECG, arterial Doppler sonography of the lower extremities, cyclo-ergometry and magnetic resonance angiography of the whole aorta was normal.

Five days after hospitalization, the patient developed abdominal pain with abundant bloody diarrhoea and rapidly worsening anaemia (Hb from 10.5 to 6.9 g/dl in 4 days). Endoscopy evidenced deep ileocaecal mucosal ulcerations (fig. 1b) with massive arterial bleeding after biopsy, requiring haemostasis with a metallic clip. Histological analysis showed a neutrophilic non-granulomatous infiltration, hence excluding Crohn's disease. This acute manifestation led us to introduce a middle-dosed immunosuppressive treatment, administering intravenous methylprednisolone 125 mg twice daily for 3 days and then switching to oral prednisone 50 mg/day. We added oral azathioprine 150 mg daily and a primary vascular prevention with acetylsalicylic acid 100 mg daily. Eight weeks later, cerebral magnetic resonance imaging showed total regression of the cerebral vasculitic lesions.

Prednisone was slowly tapered: in September 2007, the patient still had oral prednisone 15 mg daily, azathioprine 150 mg once and colchicine 0.5 mg twice daily. Two weeks later, the patient reported a right superior central scotoma and visus loss. Funduscopy and retinal angiography supported the diagnosis of retinal artery vasculitis (fig. 1d). Prednisone was increased to 50 mg daily, and the administration of IFX (5 mg/kg as slow intravenous infusion) was started. Two days later all ophthalmological symptoms had completely resolved, as confirmed by retinal angiography. IFX was repeated every 6 weeks until September 2008 without drug-induced complications, then every 7 weeks until March 2009 and finally every 8 weeks, while slowly decreasing prednisone to 10 mg/day and keeping azathioprine at 150 mg daily. At present, no further relapses of ABD were observed, including mucosal and skin manifestations.

Fig. 1. **a** Painful ulcerative lesions on the scrotum. **b** Endoscopy: ileocaecal mucosal ulcerations, with metallic clip after biopsy. **c** Cerebral magnetic resonance imaging: enhancement in the periventricular region (arrows), predominantly on the right side and in the basal ganglion region. **d** Retinal angiography of the right eye: typical setting of retinal artery vasculitis (arrow).

Discussion

ABD is a Th1-mediated chronic relapsing multisystem inflammatory vascular disease of complex, yet not entirely known aetiopathogenesis [2, 4, 5]. As summarized by Kalayciyan and Zouboulis [4] in 2007, there seems to be a vasculitic reaction where IgM-type anti-endothelial cell antibodies [31], heat shock proteins, Toll-like receptors, IL-12, IL-8 and $\gamma\delta$ T lymphocytes are involved, in a setting of different immune responses to environmental antigens such as commensal or pathogenic micro-organisms or to self-antigens [4, 32]. After being first described by Hippocrates of Kos [33], the disease was defined by the Greek ophthalmologist Benedict Adamantiades [34] in 1931 and subsequently in 1937 by the Turkish dermatologist Hulusi Behçet [35] as a triad of uveitis, oral and genital ulcerations. The prevalence is predominant in the countries along the ancient silk route [36] (hence the old description 'silk route disease' [37]), namely from Japan and the Turkmen areas in Mongolia through the Middle East to Turkey and Greece, with current epidemiological data suggesting a clear genetic background [38]. It remains an essential clinical entity, not being associated with any elevation of an auto-antibody titre; the current diagnostic criteria accepted worldwide were established in 1990 by the International Study Group for ABD, based on a multicentric study on 914 patients

from 12 centres in 7 countries [1], and have recently been revised [2]. This disease can also affect the gastro-intestinal tract (mimicking Crohn's disease), the cardiovascular system, the joints, the kidneys and the central nervous system (neuro-ABD) [1–3, 36].

For mucosal and skin involvement, the treatment is essentially based on colchicine. Thalidomide, dapsone and α -interferon are good alternatives. Systemic corticosteroids associated with other immunosuppressive agents (most often azathioprine) are necessary in case of ocular or other extramucosal involvement. Treatment alternatives include cyclophosphamide and cyclosporine A [2, 7, 36]. In 2007, after reviewing the literature, Sfrikakis et al. [7] formulated general recommendations for the use of IFX in ABD, defining posterior segment intra-ocular inflammation as the only indication for IFX as first-line treatment. Currently, there are no official guidelines regarding treatment regimen and duration, with reported cases ranging from a single dose to a total of 30, for a maximal duration of 5 years. Table 1 summarizes the published cases of acute and/or severe ABD treated with IFX [8–29] and shows how satisfactory the response to the TNF- α inhibitor is, with 76/99 patients experiencing complete remission, 15 patients with partial remission and only 8 patients showing no response. Further, IFX has also been reported as a successful

Table 1. Reported cases of severe and/or acute ABD treated with IFX

Authors	Year	Number of patients	Major involvement	Regimen	Number of doses/duration of treatment	Outcome
Muñoz-Fernández et al. [9]	2001	1	ocular	5 mg/kg	3/6 weeks	marked, lasting improvement
Sfikakis et al. [10]	2001	5	ocular	5 mg/kg	1	complete remission
Takamoto et al. [11]	2007	1	ocular	10 mg/kg, then 5 mg/kg	14 and 30, resp./5 years	complete remission, recurrence after discontinuation
Niccoli et al. [12]	2007	12	ocular	5 mg/kg	9/1 year	complete, lasting remission in 75%; partial remission in 8%; no response in 17%
Benitez-del-Castillo et al. [13]	2005	5	ocular	5 mg/kg	3–8/6 weeks to 21 months	complete, lasting remission in 100%
Sayarlioglu et al. [14]	2004	1	ocular	5 mg/kg	8/10 months	complete, lasting remission
Sfikakis et al. [15]	2004	25	ocular	5 mg/kg	1	complete remission in 100%
Lanthier et al. [16]	2005	4	ocular	5 mg/kg	3–16/2–29 months	partial response in 50%; no response in 50%
Tognon et al. [17]	2007	7	ocular	3–5 mg/kg	3–20/4 weeks to 30 months	complete remission
Olivieri et al. [18]	2008	1	ocular	5 mg/kg	3/6 weeks, then every 8 weeks	complete remission
Olivieri et al. [19]	2009	1	ocular	5 mg/kg	13/22 months	complete, lasting remission
Al-Rayes et al. [20]	2008	10	ocular	5 mg/kg	2/2 weeks	complete lasting remission in 30%; recurrence in 70%, with complete remission after beginning of scheduled infusions every 8 weeks
Lee et al. [21]	2007	1	intestinal	5 mg/kg	2/4 weeks	complete, lasting remission
Naganuma et al. [22]	2008	6	intestinal	5 mg/kg	3/6 weeks, then every 6–8 weeks in 4 patients; 3/6 weeks in 1 patient; 1 in 1 patient	complete, lasting remission no response no response
Ju et al. [23]	2007	1	intestinal	300 mg	1	complete remission
Baki et al. [8]	2006	1	vascular	5 mg/kg	unknown/14 months	complete, lasting remission
Ribiet al. [24]	2005	1	CNS	5 mg/kg	3/6 weeks, then every 8 weeks	partial improvement, relapse after discontinuation
Kikuchi et al. [25]	2008	5	CNS	5 mg/kg	4/14 weeks	marked improvement in 3 patients; no response in 2 patients
Fujikawa et al. [26]	2007	1	CNS	3 mg/kg	3/6 weeks	marked improvement
Sarwar et al. [27]	2005	1	CNS	3 mg/kg	3/6 weeks	complete, lasting remission
Licata et al. [28]	2003	1	CNS	5 mg/kg	3/6 weeks	complete remission
Pipitone et al. [29]	2008	8	CNS	5 mg/kg	3/3–6 weeks, then every 6–8 weeks in 7 patients; 3/6 weeks in 1 patient	marked improvement in 6 patients; complete, lasting remission in 1 patient; complete, lasting remission in 1 patient

treatment option in refractory pyoderma gangrenosum [39, 40], thus underlining its effectiveness in neutrophilic processes.

The clinical course of ABD is mostly unpredictable, with possible relapses even despite adequate therapy. The main cause of morbidity and disability is visus loss following uveitis, and possible lethal outcomes can be the consequence of arterial thrombosis and aneurysm rupture [41], as well as intestinal bleeding.

The reported case exhibits several of the typical complications mentioned in ABD. Monoarthritis was the only symptom during the first 3 years: joint involvement represents the initial manifestation in about 7% of patients with ABD [42] and has proved to be

associated with delayed diagnosis in the absence of other suggestive symptoms [43]. This case bears an epidemiological interest, as this is the fourth ever reported patient with ABD originating from Kosovo [44]. The lack of reported cases is even more surprising if we consider the neighbourhood of Kosovo and Albania with countries with a high prevalence, namely Greece, Turkey, Italy and Serbia. This fact, in addition to the severe course in the reported Albanian patients, could indicate that ABD is still 'unknown' in the country or that less severe cases could be misdiagnosed. Further, neuro-ABD is a rarely diagnosed manifestation but it could be underestimated, if cerebral radiological imaging is

not performed [3, 24, 25, 45]. Last, this case emphasizes the unpredictability of ABD even with combined immunosuppression (development of an ocular involvement despite therapy) and corroborates the evidence of efficacy and a favourable safety profile of TNF- α inhibitors in the treatment of ABD refractory to conventional immunosuppressive drugs, as already reported by other authors. Whether the absence of recurrence is due to a protective effect of IFX or to the natural course of the disease remains unclear. Furthermore, many questions still remain unanswered regarding the total duration of TNF- α -inhibitor-based treatment; unfortunately, there are currently no protocols that could solve this problem. We think that large-scale, long-term studies are surely needed to establish accepted guidelines for this kind of treatment of ABD.

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