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SHORT REPORT

Successful treatment with adalimumab in a familial case of gastrointestinal Behcet's disease

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Abstract

We present here two siblings with a history of recurrent oral and genital ulcers, neurological and gastrointestinal manifestations. The diagnosis of Behçet's disease in a context of familial aggregation was assumed. Facing repeated steroid-dependent flares and failure of maintenance therapies with colchicine and intolerance to pentoxifilline and disulone, adalimumab was started. Rapid response was observed in both patients, with clinical remission after induction therapy, which currently sustains under maintenance schedule. This case report suggests the effectiveness of adalimumab as first anti-TNFα in case of steroid-dependent/resistant gastrointestinal BD.

1. Introduction

Behçet's disease (BD) is a rare systemic vasculitis characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, skin and ocular lesions.[1] It can affect other systems including neurological and gastrointestinal systems.[2] In case of gastrointestinal involvement a spectrum of symptoms may appear, the most frequent being diarrhea and abdominal pain.[3] This disease is mainly prevalent in the countries from the Mediterranean area to the Far East, where it is often associated with the major histocompatibility complex (MHC) antigen HLAB51 allele.[4]

Differential diagnosis between BD and Crohn's disease (CD) may be difficult particularly in Western people, who are frequently HLA B51 negative.[4] CD can also manifest with oral and genital ulcers.[5] Extraintestinal lesions are typical of both diseases, as well as positivity for anti-*Saccharomyces cerevisiae* antibodies (ASCA).[6,7] The histopathology can be resolutive, but is rarely specific. Therapy of both diseases is grossly similar and is based on steroids and immunosuppressors. In CD, cumulative evidence suggests that anti-TNFα

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agents might change the natural history of the disease, supporting their early use in severe cases.[8] In BD, anti-TNFα have been recently experienced but are considered as rescue therapy in recurrent or refractory cases.[9]

We report the case of two siblings presenting with muco-cutaneous ulcerations and ileocolitis in whom adalimumab led to complete remission of the disease. To our knowledge this is the first report of adalimumab used as first anti-TNFα in a case of gastrointestinal BD.

2. Case Report

A 21-year old girl consulted in our center in 2008 for advice regarding a differential diagnosis between CD and BD in the context of abdominal pain and ileitis and a history of bipolar ulcers. She had suffered from severe oral ulcers since the age of 3 months, that evolved on a relapsing and remitting mode during childhood and youth, associated with sporadic genital ulcers (Fig. 1). A diagnosis of BD was made on the basis of her bipolar recurrent ulcers in accordance with the criteria for BD.[10–12] She was HLA B51 negative and ASCA positive (34 UI; n<10 UI). The presence of abdominal pain, thickening of the ileo-caecum at entero-CT, pharyngeal, gastric (Fig. 2) and colonic ulcers at endoscopy without granulomas on biopsies, and 2 ulcers in the jejunum and terminal ileum at wireless capsule endoscopy allowed to pose a diagnosis of gastrointestinal BD. Resistance to long-term and high doses of colchicine, development of corticosteroid-dependency, cutaneous intolerance to pentoxifilline and disulone and the necessity of a rapid acting treatment urged us to propose an anti-TNF treatment. Because of the severity of genital lesions, leading to permanent disability, adalimumab was empirically started at an induction dose of 160 mg subcutaneously, followed by 80 mg 2 weeks later and a maintenance schedule of 40 mg every other week. Clinical response was dramatic with complete remission after induction therapy, allowing progressive tapering of corticosteroids; the patient remains currently symptoms- and steroid-free under maintenance schedule at a 2 months of follow-up.

Her 17-year old brother also presented since the age of 3 months a history of very severe recurrent oral ulcers, requiring several hospitalisations due to almost complete aphagia. At the age of 15 he had also developed a fourth degree transient peripheric facial nerve paralysis, with enhancement of the external auditory segment of the facial nerve at cerebral MRI, compatible with neuro-Behçet. A diagnosis of BD was thus retained, considering the oral and neurological manifestations and the familial character of the disease. Abdominal ultrasound showed wall thickening of the

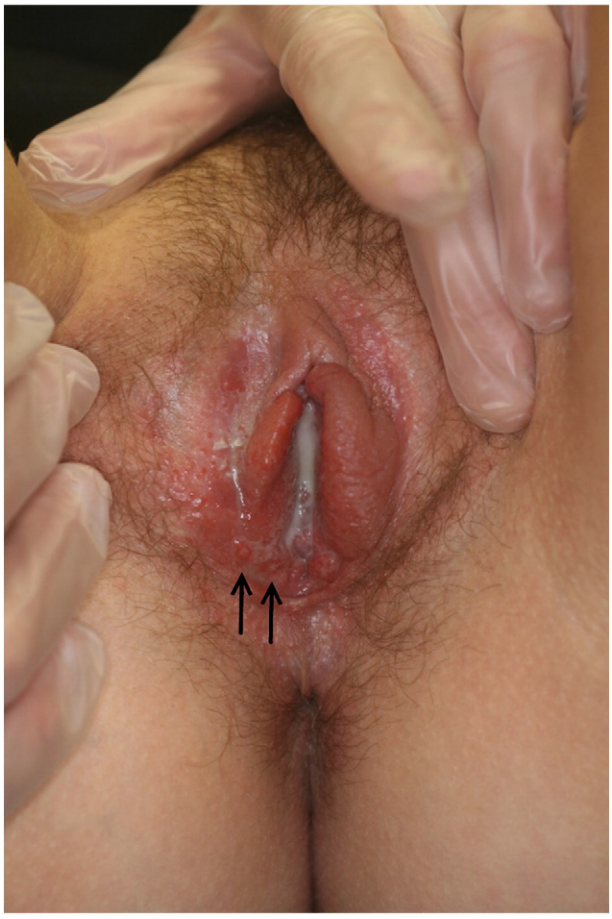

Figure 1 Genital ulcers in a 20-year old female patient with a history of bipolar ulcers and ileitis. Arrows indicate ulcers in the vestibular fossa.

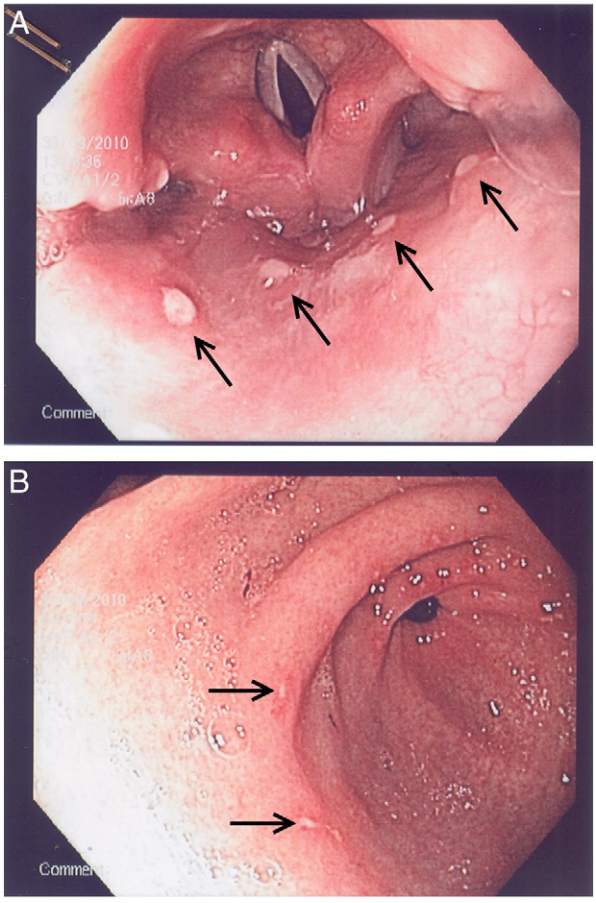

Figure 2 Pharyngeal and gastric ulcers in the same female patient. Arrows indicate lesions seen at gastroscopy (A) in the posterior wall of the pharynx and (B) in the gastric angulus.

Table 1 Previous experience with adalimumab in Behcet's disease.

	N of patients	Indications for antiTNFα	Previous use of infliximab	Schedule of ADA	Duration of ADA treatment (weeks)	Results
Sànchez-Cano D et al.[16] Clin Exp Rheumatol. 2006	1	Arthritis and cutaneous vasculitis lesions	No	40 mg every other week	10	Partial response and interrumption because of drug-related urticaria and angioedema
Mushtaq B et al.[23] Eye 2007	3	Uveitis	Yes	40 mg every other week	n.d.	Maintenance of remission after switch to da and co rticosteroid/immunosuppressor sparing effect
Van Laar JA et al.[22] Ann Rheum Dis. 2007	6	Uveitis, CNS disease, colitis, severe oral ulcers, and arthritis	Yes	40 mg every other week	61	Complete (free of symptoms) or incomplete (subjective response and reduction in frequency of symptoms) response in all patients and corticosteroid/immunosuppressor sparing effect.
Belzunegui J et al.[21] Clin Exp Rheumatol. 2008	1	Neuro-behcet	Yes	40 mg every other week	104	Improvement of symptoms and of magnetic resonance imaging
Callejas-Rubio JL et. al[15] Med Clin 2008	5	Ocular disease, cutaneous vasculitis and refractory ulcers	No	40 mg every other week	48,8	Complete remission in 5 out of 6 patients
Takase K et al.[20] Rheumatol Int. 2009	1	Uveitis	Yes	40 mg every other week	24	Remission (no ocular flares)
Olivieri I et al.[19] Clin Exp Rheumatol. 2009	1	Oral and genital ulcers	Yes	40 mg every other week	n.d.	Complete resolution of genital and oral lesions
Lee SW et al.[14] Clin Rheumatol. 2010	1	Pulmonary artery aneurysm	No	40 mg every other week	10	Decrease in size of pulmonary artery aneurysm on chest radiography and corticosteroid sparing effect
Bawazeer A et al.[13] Ocul Immunol Inflamm. 2010	11	Ocular disease	In 1 patient	40 mg every other week	43,2	Improvement of visual acuity and corticosteroid/ immunosuppressor sparing effect in 10 out of 11 patients
Leccese P et al.[17] Clin Exp Rheumatol. 2010	1	Neuro-behcet	Yes	40 mg every other week	n.d.	Improvement of symptoms and resolution of lesions on magnetic resonance imaging
Atzeni F et al.[18] Clin Exp Rheumatol. 2010	1	Leg ulcers	Yes	40 mg every other week	40	Improvement of leg ulcers with adalimumab alone and resolution after combination with methotrexate 10 mg weekly
Our case	2	Severe oral and genital ulcers, CNS disease, gastrointestinal disease	No	Induction therapy[a] + 40 mg every other week	60	Complete resolution of genital and oral lesions and gastrointestinal disease; maintenance of remission of CNS disease

n.d.: not documented, CNS: central nervous system.

[a] Induction therapy: Female patient: 160 + 80 mg 2 weeks later. Male patient: 80 + 40 mg 2 weeks later.

terminal ileum that was confirmed by small bowel computed tomography. Ileocolonoscopy was macroscopically normal but biopsies displayed evidence of non specific inflammation without granulomas. The patient received numerous successive treatments including various topical treatments and systemic colchicine at increasing doses. Recurrence of flares and neurological manifestation led to adjunction of systemic corticosteroids, with complete resolution of the neurological symptoms. The patient developed steroid-dependency with severe recurrence of oral ulcers below a daily dose of 50 mg of prednisone. Adalimumab (at induction dose of 80 mg subcutaneously, followed by 40 mg 2 weeks later and a maintenance schedule of 40 mg every other week) was started. Clinical response was dramatic with complete remission after induction therapy, allowing progressive tapering of corticosteroids; after 1 year of treatment, the patient remains currently, symptoms- and steroid-free under maintenance schedule.

3. Discussion

To our knowledge this is the first time that adalimumab has been used as first anti-TNFα in the context of gastrointestinal BD. In case of gastrointestinal BD, there is no clear evidence-based recommendation. Immunosuppressors should be used first, except if a perforation occurs, requiring emergency surgery. In patients who failed 2 previous immunosuppressors and who require equivalents of prednisolone >7.5 mg/day, infliximab may be used.[9] The experience of adalimumab in BD is limited. It has sporadically been used as first anti-TNFα in ocular and pulmonary vessel manifestations of the disease and in case of cutaneous vasculitis and recalcitrant ulcers in 16 patients[13–16] or after stopping, failure or allergy to infliximab in 15 patients.[13,17–23] Results and tolerability were good in all patients (Table 1), except for one case of severe urticaria and angioedema.[15,16] In case of gastrointestinal BD adalimumab has been used as second anti-TNFα in only 3 patients (colitis/oesophageal ulcers),[22] leading to complete remission in 1 patient and response but not remission in 2 patients. In our cases, the choice to use anti-TNFα rather than immunosuppressors was based on the severity of the lesions and the need of an immediate improvement in the context of a severely altered quality of life. Adalimumab was preferred to infliximab for patients' convenience (subcutaneous administration allowing self-medication). Considering the positive experience as first anti-TNFα in extra-gastrointestinal manifestations and as second anti-TNFα in gastrointestinal manifestations, we assumed it might also be effective as first anti-TNFα in the gastrointestinal tract. Indeed, both patients experienced a dramatic clinical response already after induction therapy, that was performed at the doses of 80+40 mg in the male patient and of 160+80 mg in the female, according to the severity of their clinical symptoms. Both patients are now on maintenance schedule of 40 mg every other week and sustain clinical remission after a mean time of 60 weeks.

Differential diagnosis between BD and CD is difficult. Difficulties come from the fact that localisation, symptoms, extra-intestinal manifestations, endoscopic and histopathologic aspect, serology as well as treatments are similar in both diseases. Some authors suggest that they are part of the same spectrum of diseases,[24] as corroborated by their similar pathogenesis,[25,26] while others that both may coexist.[27–29] Gastrointestinal involvement in BD is rare, with a different prevalence according to geographical areas. Curiously it is more frequent in countries with low prevalence of BD, as UK (disease prevalence of 0.64/100,000,[30] with 38–50% of gastrointestinal manifestations),[31] rather than in countries of the ancient "silk road", as Turkey, where prevalence of BD is up to 421 per 100,000 adults[32] but where gastrointestinal manifestations are present in only 3% of patients.[33] Alternatively, genital ulcers in CD are rare but they represent the most frequent (18.1%) manifestation of "non contiguous cutaneous" spectrum in adults, while in children they represent only 2.5%.[5] HLA B51 positivity, vasculitis of the small veins and venules with deep ulcerations, absence of cobblestoning and granulomas may help in affirming BD.[3] On the other hand the strongest risk factor for BD, HLA B51, has a high prevalence among patients who live in areas along the "silk road" (up to 81%),[4] but its role is less significant in white people of western countries, where only 13% of BD patients present this allele. In our cases, HLA B51 was negative in both patients but this is not incompatible with BD because of their European origin. ASCA positivity is present in 50–80% of patients with CD[7] but it can be present also in BD with a prevalence between 0 and 48%,[6,34–37] and with a significant trend when gastrointestinal involvement is present,[6] as was observed in our patients.

Another particularity of our case report is the familiar character. Familial aggregation is known both for CD and BD. For what concerns BD, the majority of cases have been described in Turkey[36] and in Japan,[37] in patients with HLA B51 positivity. However, HLA B51 genetic association is present in only 20% and 31% of the siblings respectively in Turkish[38] and Japanese[37] population. HLA A26 has already been correlated with BD in Japanese population.[37] Other genetic factors are probably implicated[39] but further studies are needed, especially in not "silk road" populations, as our patients, to understand their genetic background.

In conclusion we presented a case of familial BD, posing problem in differential diagnosis with CD, that showed a good response to adalimumab, suggesting its effectiveness as first anti-TNFα in case of gastrointestinal localisation.

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CDC wrote the manuscript with contributions from BDV, CD and JFC; JFC, EH and SB were involved in the patients' care. All authors read and approved the final manuscript. Consent for publication was obtained from the patients.

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