LETTER TO THE EDITOR

AN INCOMPLETE FORM OF CHILDHOOD BEHÇET'S DISEASE TREATED WITH INFLIXIMAB

S. CAPORUSCIO[1], G. PRANTEDA[2], S. NISTICÒ[3], T. MAUCIONE[4], M. CANZONI[1], A. STEFANI[1], M. MUSCIANESE[1], M. FANTÒ[1] and M. SORGI[1]

[1]Division of Rheumatology, Department of Medicine, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy; [2]Division of Dermatology, Department of Medicine, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy; [3]Unit of Dermatology, University of Catanzaro, Italy; [4]Sapienza University of Rome, Rome, Italy

Received May 6, 2014 – Accepted July 3, 2014

Behçet's disease (BD) is a multi-systemic vasculitis characterized by the possible presence of cutaneous, ocular, articular and neurological manifestations. In this report, we examine the case of a fifteen-year-old boy with an incomplete form of juvenile Behçet's disease which began with joint involvement and developed into a complete form only after several years. The patient showed a rapid response to anti-TNF-alpha (infliximab) with an improvement of mucocutaneous lesions (oral and genital ulcers, pseudofolliculitis) and arthritis.

Behçet's disease (BD) is a chronic inflammatory disorder characterized by recurrent oral aphtae and any of several systemic manifestations including genital ulcers, ocular disease, skin lesions, neurological disease and arthritis (1). As its clinical course is heterogeneous, pharmacotherapy is variable depending on the organ involvement and severity of the disease (2). Treatment is based largely on anecdotal case reports, case series, and scarce randomized clinical trials (3, 4).

The criteria for BD diagnosis were published in 1990 and require the presence of recurrent oral aphtae plus two of the following: recurrent genital ulcers, uveitis, typical skin lesions (erythema nodosum, folliculitis, papulopustular rash) or positive pathergy test.

The disease is rare in childhood and its frequency is estimated as between 0.9% and 7.6% with the mean age of onset between 10 and 12 years. In some cases, a possible delay in diagnosis of up to five years has been reported. HLA class I polymorphism shows the presence of HLA B51 and HLA B5 at the same frequency in childhood BD. It seems therefore, that B27 could be associated with an incomplete form of the disease in children (5).

The pathogenesis of Behçet disease is still unknown, but some studies demonstrate an increased expression of Th1 type cytokines in active disease. Particularly high levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1 and IL-8 (5) have been found.

Clinical aspects of BD in children (6) are different from those in adults:

- Oral aphtosis is the most common manifestation at the beginning in both adults and children but the frequency of genital ulcers in

Key words: Childhood Behçet's disease, incomplete form of Behçet's disease, juvenile idiophatic arthritis, joint involvement, infliximab

Mailing address:
Prof. Steven Nisticò,
Associate Professor in Dermatology,
University of Catanzaro,
Viale Europa,
Germaneto, CZ, Italy
steven.nistico@gmail.com

0394-6320 (2014)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

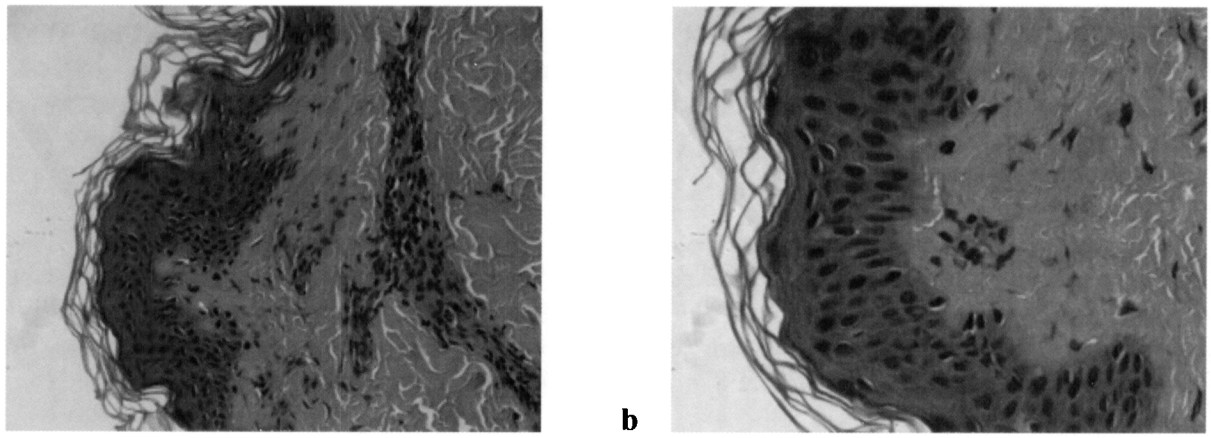

Fig. 1. *Histology in hematoxylin-eosin magnification (**a**) x 200 and (**b**) x 400 of skin samples show typical dermal sclerosis associated with lymphomononuclear infiltrate.*

childhood is controversial. Previous studies of juvenile onset BD reported a high incidence of genital ulcers, whilst, in contrast, recent studies demonstrated that children had less ulcers than adults. However, it seems likely that in children the incidence of genital ulcers might increase with age (7).

- Skin lesions are more frequent in childhood (8) and may include papulae, pustules, pseudofolliculitis, palpable purpura and purulent bullae. However the hypersensitivity demonstrated by a positive Pathergy test is more common in adults.
- Joint involvement is the most frequent minor expression of childhood BD and the most commonly involved joints are knees, ankles and hips. Children are more likely than adults to have joint manifestations and polyarthritis involvement.
- Gastrointestinal symptoms seem prevalent in children and are represented by abdominal pain and diarrhea, sometimes bloody.
- Uveitis is less frequent than in adults but it seems to be associated with a poor prognosis, especially in male patients, because children more frequently develop ocular complications such as cataracts, maculopathy and retinal detachment.

Below we present a case that highlights the difficulty in the diagnosis of an incomplete form of juvenile BD.

Case report

In this report we present the case of a fifteen-year-old boy who was seen in our clinic in July 2010 presenting oro-genital aphtosis, pseudofolliculitis and swelling of the second and third proximal interphalangeal joint of the left hand and the third and fifth interphalangeal joint of the right hand.

At three years of age, he was diagnosed with B 27 positive juvenile idiophatic arthritis characterized by the involvement of hands, right hip and elbows. Laboratory tests revealed an elevated ESR 50 mm/h and CRP 2 mg/dl whilst antinuclear antibodies and rheumatoid factor were negative. In his family history, the father and maternal grandmother were affected by rheumatoid arthritis and the mother was celiac. The patient had been treated initially with NSAIDs and methotrexate until May 2005, followed by etanercept at a dose of 50mg/week. Methotrexate was discontinued in 2005 for poor clinical control and was replaced by sulfasalazine. In May, 2009 the patient complained of bloody diarrhea. The patient underwent a colonoscopy which resulted without significant alterations. In January, 2010 treatment with etanercept was suspended owing to the resolution of articular symptoms. After the discontinuation of this therapy the patient complained of the development of oral and genital ulcers, pseudofolliculitis, headaches and rectal bleeding. The study of HLA class I and II polymorphism was carried out on the patient and his parents, revealing the presence of B27 and CW6 allele in the patient, as well as in his father. As orogenital ulcers appeared the patient was treated with colchicine, which was suspended after two

months for inefficacy.

Following our examination, in July, 2010, laboratory tests showed an increased value of CRP 1.2 mg/dl and ESR 40 mm/h and negative antinuclear antibodies, rheumatoid factor and anti-citrulline antibodies.

A cutaneous biopsy was performed to investigate the origin of pseudofollicolitis, which showed dermal sclerosis associated with lymphomononuclear infiltrate with perivascolar distribution (Fig. I a and b). We also carried out a Pathergy test that resulted positive.

Diagnosis of BD was made according to the International criteria (orogenital aphtosis, positive Pathergy test, pseudopfolliculitis). Corticosteroid therapy was started (prednisone 10 mg/day) and, in view of the inefficacy of the previous drugs, treatment with infliximab was started (5mg/kg).

The patient showed a rapid response to infliximab characterized by an improvement of mucocutaneous lesions (oral and genital ulcers, pseudofolliculitis) and of arthritis. The patient was treated with infliximab for only one year, which was then suspended due to his improved clinical conditions.

DISCUSSION

BD is a rare immune-mediated small-vessel systemic vasculitis. Although the usual onset is in adulthood, the disease can occur in children. The diagnosis is difficult in children due to the variability of the clinical manifestations at the onset and the low sensitivity of diagnostic criteria in the pediatric population.

Treatments for pediatric patients usually consist of corticosteroids and immunosuppressants, but some of them are ineffective, as reported widely in the literature. Recently, it has been shown that TNF-alpha appears to play an important role in the immunopathogenesis of BD (5). The present case report represents a form of incomplete BD debuted with joint involvement.

In literature, it has been known that in childhood BD the diagnosis can be delayed for some years and furthermore joint involvement is a frequent event. It is possible that the treatment with Etanercept started at the beginning of joint involvement could have prevented the appearance of the entire clinical features, according to the increased levels of TNF-α observed in BD.

We decided to start infliximab in our patient as he had already undergone etanercept therapy during childhood. Furthermore, some cases of mucocutaneous BD have been successfully treated with infliximab, as reported in recent literature (9-12), with results that are comparable to other dermatosis (13-22).

This case report suggests that in case of joint involvement in children, in addition to juvenile idiopathic arthritis, BD should be considered in the differential diagnosis. Furthermore, anti-TNFα agents, and in particular infliximab, are effective in the treatment of articular and mucocutaneous manifestations of BD and, in our opinion, should be considered in the case of recalcitrant form of BD.

REFERENCES

1. Wallace GR. HLA-B*51 the primary risk in Behcet disease. Proc Natl Acad Sci 2014; 111(24):8706-7.
2. Hatemi G, Merkel PA, Hamuryudan V, Boers M, Direskeneli H, Aydin SZ, Yazici H. Outcome measures used in clinical trials for Behcet syndrome: a systematic review. J Rheumatol 2014; 41(3):599-612.
3. Saleh Z, Arayssi T. Update on the therapy of Behcet disease. Ther Adv Chronic Dis 2014; 5(3):112-34.
4. Li J, Fernando S, Herkes G. Use of infliximab and other biologics in Behcet disease. Intern Med J 2014; 44(1):96-100.
5. Krause I, Uziel Y, Guedj D, Mukamel M, Harel L, Molad Y, Weinberger A. Childhood Behçet's disease: clinical features and comparison with adult-onset disease. Rheumatol 1999; 38(5):457-62.
6. Gül A. Cytokines in Behçet's disease. In: Zierhut M, Ohno S, eds. Immunology of Behçet's Disease. Lisse, The Netherlands: Swets & Zeitlinger Publishers 2003; p. 73-80.
7. Laghmar M, Carim A, Allali F, et al. Childhood Behçet's disease: clinical and evolutive aspects. About 13 cases. J Fr Ophtalm 1999; 25(9):904-08.
8. Borlu M, Ukİal Ü, Ferahbaİ A, Everekliogl u C. Clinical features of Behçet's disease in children. Int J Dermatol 2006; 45:713-16.
9. Tugal-Tuktun I, Urgancioglu M. Childhood-onset

uveitis in Behçet disease: a descriptive study of 36 cases Am J Ophtalmol 2003; 13(6):1114-19.
10. Zhou ZY, Chen SL, Shen N, Lu Y. Cytokines and Behçet's disease. Autoimmun Rev 2012; 11(10):699-704.
11. Robertson LP, Hickling P. Treatment of recalcitrant orogenital ulceration of Behçet's syndrome with infliximab. Rheumatol 2001; 40(4):473-74.
12. Almoznino G, Ben-Chetrit E. Infliximab for the treatment of resistant oral ulcers in Behçet's disease: a case report and review of the literature. Clin Exp Rheumatol 2007; 25(S):S99-102.
13. Specchio F, Saraceno R, Chimenti S, Nisticò S. Management of non-melanoma skin cancer in solid organ transplant recipient. Int J Immunopath Pharmacol 2014; 27(1):21-24.
14. Muscoli C, Lauro F, Nisticò S, et al. Olea europea-derived phenolic products attenuate antinociceptive morphine tolerance: an innovative strategic approach to treat cancer pain. J Biol Reg Homeost Agents 2014; 28(1):117-28.
15. Specchio F, Carboni I, Chimenti S, Tamburi F, Nisticò S. Cutaneous manifestations in patients with chronic renal failure on hemodialysis. Int J Immunopath Pharmacol 2014; 27(1):1-4.
16. Chiricozzi A, Pitocco R, Saraceno R, Nistico SP, Giunta A, Chimenti S. New topical treatments for psoriasis. Exp Op Pharmacother 2014; 15(4):461-70.
17. Nisticò SP, Saraceno R, Chiricozzi A, Giunta A, Di Stefani A, Zerbinati N. UVA-1 Laser in the treatment of palmoplantar pustular psoriasis. Photomed Laser Surg 2013; 31:434-38.
18. Chiricozzi A, Zhang S, Dattola A, Gabellini M, Chimenti S, Nisticò S. Role of Th17 in the pathogenesis of cutaneous inflammatory diseases. J Biol Regul Homeost Agents 2012; 26(3):313-18.
19. Chiricozzi A, Zhang S, Dattola A, Cannizzaro MV, Gabellini M, Chimenti S, Nisticò S. New insights in the pathogenesis of cutaneous autoimmune disorders. J Biol Regul Homeost Agents 2012; 26(2):165-70.
20. Nisticò S, Chiricozzi A, Saraceno R, Schipani C, Chimenti S. Vitiligo treatment with monochromatic excimer light and tacrolimus: results of an open randomized controlled study. Photomed Laser Surg 2012; 30:26-30.
21. Saraceno R, Nisticò SP, Capriotti E, Chimenti S. Monochromatic excimer light 308 nm in monotherapy and combined with topical khellin 4% in the treatment of vitiligo: A controlled study. Dermatol Ther 2009; 22:391-94.
22. Saraceno R, Nisticò SP, Capriotti E, de Felice C, Rhodes LE, Chimenti S. Monochromatic excimer light (308 nm) in the treatment of prurigo nodularis. Photodermatol Photoimmunol Photomed 2009; 24:43-45.