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Case Report

Incomplete Behcets' Disease in a Teenager

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Abstract: *Background:* Behçets' disease (BD) is a multisystemic vasculitis with various manifestations: mucocutaneous, articular, ocular, gastrointestinal, musculoskeletal, neurological, cardiac and pulmonary, the most common of which is the presence of painful ulcers lasting more than 14 days that occurs at east 3 times in a year, either alone or in combination with other lesions. Association with HLA-B51 has been described and sometimes have a positive pathergy test. Histopathologic evaluation reveals a neutrophilic vascular reaction or leukocytoclastic vasculitis. Clinical case: We report the case of a 14-year-old teenager with a past medical history of allergic rhinitis diagnosed, but with a 3-year history of painful oral ulcers that present more than 3 times per year; he presented oral ulcers, he did not present at the ocular and genital level. The biopsy samples of oral lesions did consistent with BD (showed narrowing of the vascular lumen due to neutrophil and lymphocyte infiltrate that completely affects the vascular wall) and HLA B 51 positive. Immunosuppressive treatment was started with mycophenolate 400 mg/ BSA for one year and 50 mg of prednisone OD followed by a gradual taper with good response to therapeutic approach and decrease of oral ulcers until they disappear. We present the case of a patient with an incomplete type of BD, with recurrent aphthous ulcers that present more than 3 times during a 12-month period as well as Indian descent, a biopsy with neutrophilic vascular reaction and positive HLA B51. BD is more likely to develop in children aged 11.7 to 14.5 years with diagnosis based on the presence of oral ulcers in 87 to 98% of the cases. Genital ulcers are far less common in children that in adults; BD is also more frequent among males. BD prognosis is dominated by ocular, neurological and vascular damage, with a poor functional and/or vital prognosis. Ocular involvement is severe and frequent, rapidly involving the visual prognosis. Treatment must be individualized according to the organ involved, good response has been described with intravenous steroids, which represent the mainstay of treatment, immunosuppressive the most commonly. *Conclusions:* Recurrent oral ulcers with more than three occurrences in one year must be considered as a sign to rule out BD. We must carry out an interrogation and when suspected, it must be confirmed with histopathological study and HLA B 51, regardless of the age of the patient. The diagnosis of BD is a challenge for the clinician.

Keywords: Behçets' Disease, Oral Ulcers, Pathergy Test

1. Introduction

Behçets' disease (BD) was first described by Hulusi Behçet in 1937. It is a multisystemic vasculitis with various clinical manifestations: mucocutaneous, articular, ocular, gastrointestinal, musculoskeletal, neurologic, cardiac and pulmonary with aphthous ulcers being the most common physical finding. [1, 2].

The incidence and prevalence of Behçets' disease is higher in the Mediterranean area, especially in Turkey, and extends to

the Middle Eastern populations as well as Korea and Japan where the highest HLAB-51 distribution is found [3].

The International team review of the International Diagnostic Criteria of Behçets' Disease proposed special criteria for diagnosis in pediatric population (Table 1). [4] It is worth mentioning that a positive pathergy test is not mandatory for diagnosis in adults and it is not considered as a criterion for children [3, 4]. Association with HLA-B51 has been described [5].

Table 1. *2015 International Study Group for Behçets' Disease in Children Diagnostic Criteria.*

Criteria	Definition	Points
Recurrent aphthous oral ulcers	At least 3 occurrences in 12 months	1
Recurrent genital ulcers	Genital aphthous ulcerations or scarring	1
Eye lesions	Anterior and posterior uveitis, retinal vasculitis	1
Skin lesions	Erythema nodosum, folliculitis, papulopustular lesions, acneiform nodules	1
Neurological manifestations	Except isolated cephalea	1
Vascular manifestations	Arterial or venous thrombosis, aneurism	1
Diagnosis of Behçets' disease requires a score of 3 points		

2. Clinical Case

A 14-year-old male of Indian descent (grandfather born in India) with a past medical history of allergic rhinitis diagnosed on February 2015 currently in treatment with allergen specific immunotherapy (*Dermatophagoides* mix) complaining of painful, chronic oral ulcers that have been presenting for the last 3 years (more than 3 episodes per year). He denies occurrence of ulcers in different anatomical sites as well as other symptoms. He received treatment in an outpatient facility with systemic steroid (1 mg/kg/day of prednisone) with partial improvement of lesions. His mother also comments about recurrent episodes of red eye that coincide with the emergence of oral ulcers. Patient was sent to this hospital for multidisciplinary approach by pediatric immunology, dermatology and ophthalmology.

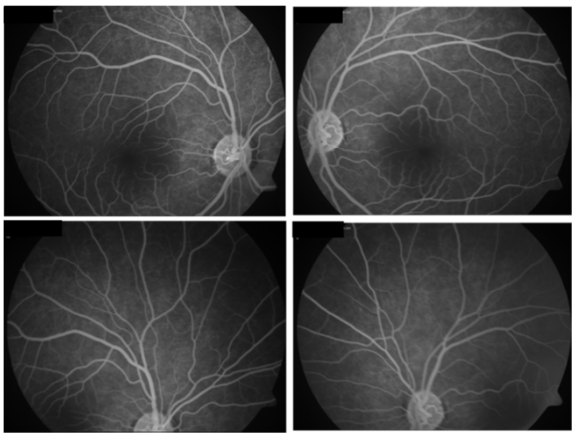

Figure 1. *Aphthous ulcers with well-defined erythematous halos and central yellowish gray bases.*

Physical examination: Two painful aphthous ulcers of approximately 0.3 to 0.6 cm with well-defined erythematous halos and central yellowish gray bases were observed in the sublingual mucosa of the oral cavity, three ulcers with the same characteristics of approximately 0.3 to 0.5 cm were found in the inferior lip. Patient denies presence of recent or past genital ulcers (Figure 1), the rest of the physical examination was normal. Ophthalmologic examination showed conserved visual acuity in both eyes, right eye (RE) 20/20, left eye (LE) 20/20, inferior tarsal conjunctiva with papillae, clear cornea, wide and well-formed anterior chamber, normo-reflective iris with granulomatous configuration, round pupil and transparent lens in both eyes.

Fundoscopy of both eyes revealed clear vitreous, orange disk with sharp margins, cup to disk ratio 4/10, central emergence of blood vessels with normal course, attached retina, shiny appearance of the macula and present foveal reflex in both eyes (figure 2).

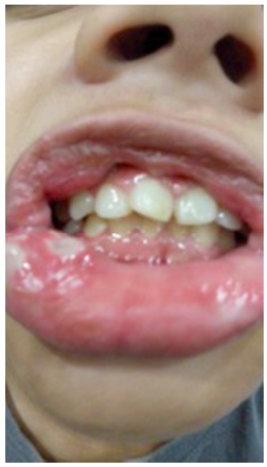

Figure 2. *Right eye and left eye fluorescein angiography.*

Laboratory tests: Hemoglobin: 13.10, hematocrit: 40, leukocytes: 7730, neutrophils: 2480, lymphocytes: 3990, monocytes: 400, platelets: 244 000, eosinophils: 560, rheumatoid factor test: <12 (negative), C-reactive protein: <0.35 (negative), erythrocyte sedimentation rate: 26 mm/h, complement (C3) 1.17 g/L, complement (C4) 0.3 g/L, immunoglobulin E: 206 (0-87), aspartate transaminase: 16 mg/dl, alanine aminotransferase: 25 mg/dl, urinalysis: normal, anti-nuclear antibodies: negative, anti-neutrophil cytoplasmic antibodies (anti-myeloperoxidase MPO/PR3): negative, HIV test: not reactive, pathergy test: negative, HLA B 51: positive.

Biopsy of lingual lesions with hematoxylin and eosin stain showed narrowing of the vascular lumen due to neutrophil and lymphocyte infiltrate that completely affects the vascular wall, inflammation and necrosis.

Histiocytes affecting the walls of small caliber vessels compatible with BD were also observed (figure 3).

Patient was started on systemic steroid 50 mg PO daily, methotrexate 15 mg once a week and folic acid without improvement and persistence of oral lesions, treatment was modified to mycophenolic acid 1 g daily and oral steroid with amelioration of oral ulcers. Until now, he continues with mycophenolic acid and no steroid with disease remission.

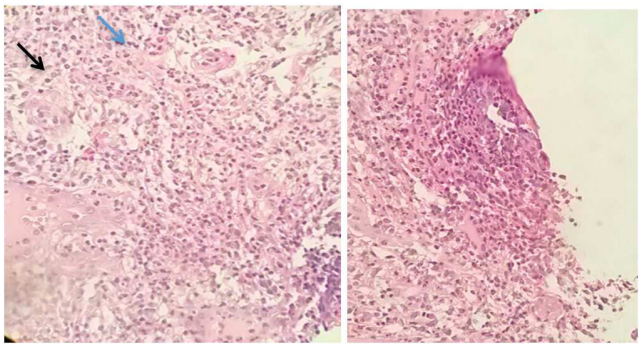

Figure 3. *(A) Dense inflammatory infiltrate (bilobulate and trilobulate neutrophils are pointed by the blue arrow; lymphocytes are pointed by the black arrow). (B) Vessel with narrowed lumen by neutrophil and lymphocyte infiltrate that completely affects the blood vessel wall.*

3. Discussion

We present the case of a patient with an incomplete type of BD, with recurrent aphthous ulcers that present more than 3 times during a 12-month period as well as Indian descent, a biopsy with neutrophilic vascular reaction and positive HLA B51.

Behçets' disease is more likely to develop in children aged 11.7 to 14.5 years with diagnosis based on the presence of oral ulcers in 87 to 98% of the cases. Genital ulcers are far less common in children that in adults; BD is also more frequent among males [3, 6, 7]. In this patient, diagnosis was made at age 14.

Involvement of the eyes presents in 80% of cases. Uveitis is the most common manifestation characterized by recurrent inflammatory crises that may affect the anterior segment in the form of nongranulomatous anterior uveitis with or without hypopyon (2 to 15% of cases) or the posterior segment, presenting as panuveitis (4 to 80% of cases) with vitritis, retinal infiltration and/or occlusive vasculitis; which was ruled out in our patient [6].

Ocular involvement is common in BD and is potentially severe, as it is sight-threatening. BD uveitis may be responsible for a large number of cases of blindness or low vision in countries where BD has a high prevalence [8]

Among neurological manifestations, repeated cephalea has been reported as the first symptom in up to 25% of cases, as well as venous thrombosis and paralysis of the sixth cranial nerve. Gastrointestinal symptoms such as abdominal pain, ulcers or bleeding present in up to 40% of the cases. Joint involvement occurs in as many as 20 to 40% of pediatric patients [3].

Clinically, BD is characterized by exacerbations and a relapsing/remitting course with sudden onset crises followed by spontaneous resolution.

BD prognosis is dominated by ocular, neurological and vascular damage, with a poor functional and/or vital prognosis. Ocular involvement is severe and frequent, rapidly involving the visual prognosis. The incidence of ophthalmological impairment in BD patients is close to 70%. [9]

During periods of remission, the eyes are calm or mildly inflammatory. The objectives of therapeutic management of BD uveitis are to rapidly and effectively control inflammation in order to preserve visual function and limit irreversible structural damage, but also to treat the chronic subclinical inflammation, to prevent relapses and ocular complications, to limit ophthalmological and general side effects of iatrogenic causes and to control the associated systemic manifestations [10, 11].

Treatment must be individualized according to the organ involved, good response has been described with intravenous steroids, which represent the mainstay of treatment, immunosuppressive the most commonly used conventional treatment agents are antimetabolites (azathioprine), mycophenolate mofetil, methotrexate), T-cell inhibitors (cyclosporine-A, tacrolimus), and alkylating agents (cyclophosphamide, chlorambucil) [8].

Azathioprine, in a large placebo-controlled trial, led to significantly reduced hypopion uveitis relapses and new eye disease after 24 months. In the azathioprine group, no serious adverse events were reported, whereas in the placebo group, one patient died of pulmonary artery aneurysm [12]. And biologics agents such as Tocilizumab (TCZ) is a humanized anti-interleukin-6 (IL-6) receptor mAb, inhibiting IL-6 pathway to prevent IL-6 from binding to its receptor. TCZ is authorized worldwide for various inflammatory diseases, such as rheumatoid arthritis, giant cell arteritis and Still's disease. IL-6 inhibitors may be effective in the management of posterior uveitis and macular edema in BD uveitis [13].

Three anti-interleukin-1 (IL-1) agents have been studied in BD treatment: anakinra, an IL-1 receptor antagonist protein; canakinumab, a human anti-IL-1β mAb; and gevokizumab, a humanized anti-IL-1β mAb. Their place in the management of BD uveitis remains unclear, based on contradictory findings in the literature [14].

Secukinumab, the only anti-IL-17 agent studied in uveitis management to date, is a fully human mAb. Nevertheless, a prospective study suggested the efficacy of intravenous secukinumab in active chronic non-infectious uveitis which required systemic immunosuppression in 16 patients, including one BD uveitis [15, 16].

Rituximab, B cell targeted therapy, is a chimeric mAb against CD20. Davatchi et al., in 2010, successfully tested, in a single blind randomized control study, the efficacy of rituximab associated with methotrexate vs. a combination of pulse cyclophosphamide and azathioprine in improving BD ocular involvement; no significant difference was observed between groups [17].

Abatacept, T cell targeted therapy, is a recombinant fusion protein which can block CD-80 and CD-86 on

antigen-presenting cells, necessary for its activation. Short-term efficacy was described in a case report of refractory BD-associated scleritis [18].

Tofacitinib is an anti-Janus Kinase (JAK) 1/3 inhibitor, appeared to be a potential new treatment option for refractory, non-infectious idiopathic uveitis or scleritis [19].

Behcets' disease course is recurrent, unpredictable and unfortunately death is associated with younger patients [3].

4. Conclusions

Recurrent oral ulcers with more than three occurrences in one year must be considered as a sign to rule out BD, especially among young males in whom this entity is more common, clinical course is more severe and prognosis is worse.

The diagnosis of BD is a challenge for the clinician.

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