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Clinical report

Behçet's syndrome: Literature review and clinical case report

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ABSTRACT

Behçet's disease (BD) is a multi-systemic vascular disorder characterized by oral and genital ulcers, as well as cutaneous, ocular, arthritic, vascular, central nervous system and gastrointestinal involvement. It usually affects young adults, and its pathological origin is unknown. The case of a 47-year-old woman with recurrent ulcers in the oral cavity is presented. She linked the pain with sitting and during the sexual act, with vaginal and oral cavity pain, due to the lesions present at those sites, as well as swelling and pain in the knees, making walk painful. The patient was kept under observation and underwent multidisciplinary treatment with prescription of topical and systemic drugs to improve quality of life. Dentists should be aware of BD and the need of multidisciplinary treatment to increase the patient's quality of life.

Síndrome de Behçet: Revisión de la literatura y presentación de Caso Clínico

Palabras clave:
Úlceras orales
Síndrome de Beçhet
Manifestaciones genitales

RESUMEN

La Enfermedad de Behçet (EB) es un trastorno vascular multi-sistémico caracterizado por úlceras orales y genitales, cutáneas, oculares, artritis, y afectación vascular, sistema nervioso central y gastrointestinal. Por lo general afecta a los adultos jóvenes y la etiopatogenia es desconocida. Se presenta un caso de mujer de 47 años de edad que presenta úlceras recorrentes en la cavidad oral. Ella ha relacionado com el dolor al sentarse, durante el acto sexual, dolor vaginal y oral, cavidad, debido a las lesiones presentes en los lugares mencionados, hinchazón y dolor em las rodillas causando dificultad para caminar. El paciente se mantuvo em observación y se sometió a través de untratamientomultidisciplinariocon la prescripción de produtos farmacéuticos tópicos y sistémicos para mejorar la calidad de vida. El

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conocimiento del clínico sobre EB ayuda en el tratamento multidisciplinario de promoción de la calidad de vida para el paciente.

Introduction

Behçet's disease was described by Hulusi Behcet in 1937 as an inflammatory process of unknown etiology, characterized by recurrent aphthous ulcers, genital ulcers, uveitis and cutaneous lesions. It is also associated with other less frequent systemic manifestations, such as gastrointestinal, central nervous system, vascular and joint infections.[1]

In 1990, the *International Study Group for Behçet's Disease*[2] established the existence of recurrent mouth ulcerations and at least two additional clinical manifestations, which may consist of recurrent genital ulcers, ocular lesions, arthritis, thrombophlebitis, neurological abnormalities and cutaneous lesions or positive pathergy test, which occurs in 40–80% of the cases and is exclusive to this disease (sterile pustule cutaneous reaction after the injection of an inert substance) as key points for diagnosing Behçet's disease.[3]

The specific criteria proposed by the International Study Group for Behçet specifies those recurrent ulcers: smaller naphtha's, larger naphtha's or herpetiform ulcers observed in a minimum of three episodes during a period of 12 months, and two of any of the following manifestations: recurrent genital ulcers (ulcers or genital ulcer scars); joint manifestations; ocular lesions (anterior or posterior uveitis, or presence of cells on the vitreo during ocular exam, or also retinal vasculitis); cutaneous lesions (erythematosus nodules, pseudofolliculitis, papular-pustulous lesions or also acneiform nodules observed in post-adolescent patients not treated with corticosteroids); analysis of the pathergy signal test (for 48 h).[2–4]

It seems to preferentially occur in individuals in their third decade of life, although there is increasing rate of the disease in children and there is no proof of hereditary factor. Men are more frequently affected than women. This condition's prognosis is severe especially in young men, without, however, an explanation for this. The severity of the disease seems to decrease while people age.[5]

The etiopathogeny seems to be related to an alteration of the immunoregulation set off by one or various infectious agents in genetically susceptible individuals. Some histopathologic studies support the existence of an immunologic mechanism mediated by cells, in which the infiltrates consist mainly of cooperative T lymphocytes and macrophages in association with NK cells (Natural Killer cells), in which the participation of both cell and humoral immunity is suggested where, in response to the increase in the number of cells, a reaction of hypersensitivity type III occurs.[6] Recent findings have both supported the significance of genetic factors and better defined the nature of inflammation in Behçet's disease.[7]

The evolutionary history of the disease is marked initially by oral, followed by genital ulcers, ocular lesions skin disorders and arthritis.[3]

The involvement of major importance in this syndrome, also being the first manifestation perceived in between 25 and 75% of cases, are the oral lesions, which are manifested in the same location during the entire course of the disease in almost all patients. Such lesions are similar to the typical aphthous ulcers that are characteristically presented in a great number of lesions (six or more), occurring mainly on the soft palate, lips, tongue, gingiva, oral mucosa and oropharynx, while the larynx and the nasal mucosa are rarely affected. When these lesions are individually present, they generally vary in size, measuring from 2 to 10 mm in diameter, and present with a yellowish necrotic base, raised edges and a diffuse erythematosus area. Some studies have demonstrated prevalence in the occurrence of larger aphthae in almost 40% of the patients with this syndrome.[8] There may also be herpetiform ulcers, which occur with greater frequency in women. These ulcers persist for several days or even weeks, and heal without leaving scars. Some studies have shown that the oral severity of the lesions is not directly related to a more severe systemic involvement.[4,8]

The genital ulcers appear to be the second frequent manifestation in the disease's cases and are found in a large majority of patients. The perianal lesions are found in both gender and their evolution is similar to what occurs in the mouth. Lesions on the penis and scrotum are rarely observed. In women, lesions occur mostly on the lips, vulva and vaginal wall, and may have painless manifestations that go unobserved, and in these cases, the diagnosis is made through pelvic examination.[4,8]

Skin lesions are present in forms of erythematosus nodules, erythematosus papules, vesicles, pustules, pyoderma, folliculitis and acneiform eruptions and are positive in the pathergy test, developing a reaction one or two days after injection of a cutaneous lesion hyper-reactivity similar to a sterile pustule that is present in 40 and 80% of affected patients.[4]

Posterior uveitis, retinal vasculitis, conjunctivitis, optic neuritis and retinal arthritis are frequent ocular manifestations, but anterior uveitis with hypopyon (presence of pus in the anterior chamber of the eye) is the classical manifestation in the beginning of the Behçet's syndrome. These ocular lesions may be reversible, but they may evolve to a cataract or glaucoma. The recurrence and gravity of these manifestations lead to a high rate of patients becoming blind, which makes necessary to perform an energetic and aggressive treatment for this disease.[9]

The articular manifestations are present in over 50% of the patients and may precede, accompany or follow other manifestations of the Behçet's syndrome. It is characterized as monoarthritis or polyarthritis of an inflammatory and non-erosive nature. Generally, the arthritis or arthralgia is asymmetrical and polyarticular, and more frequently attacks the large joints such as knees, ankles, elbows and wrists, but

the small joints may also be affected. Patients may relate multiple recurrent episodes of acute inflammatory arthritis, similar to arthropathy associated with inflammatory intestinal disease, although, in some cases the arthritis may become chronic.[10]

Neurological manifestations occur due to inflammation of the central nervous system and are not very frequent, due to vascular involvement at the location or because of peripheral polyneuropathy. The most frequent forms occur due to meningoencephalitis, caused by inflammation and not by an infection. The neurological deficits are characterized by sensitive disturbances, pyramidal syndrome, convulsions, cerebellum syndrome, vestibular syndrome and oculo-motor paralysis. The thrombosis of small cerebral vessels, or large venous sinuses is manifested by endocranial hypertension. Polyneuritis are not often and when they occur, they are manifested by mental confusion, psychiatric symptoms and dementia.[11]

Vascular manifestations are presented as superficial thrombophlebitis, venous thromboses or as arteritis. These arteritis are manifested by occlusive-thrombotic and aneurismatic phenomena that preferentially affect the aorta, pulmonary artery, popliteal artery, femoral artery, subclavia artery and less frequently, the carotid artery. Thus, they are responsible for heart attack or hemorrhagic phenomena in different organs.[12]

Gastrointestinal manifestations preferentially attack the intestines and esophagus, and are manifested through abdominal pain, diarrhea and occasionally by perforations.[5]

The authors consider that the main differential diagnoses of Behçet's syndrome are erythema multiforme or Stevens Johnson Syndrome and Crohn's disease, showing lesions in oral and genital mucosa.[5]

The important point about Behçet's syndrome is related to its manifestations, which increases the importance of a multi-disciplinary treatment, as there are several treatment possibilities, including highly toxic approaches or physical conditions that restrict the use of certain drugs.[13] Currently treatment varies according to the seriousness of each patient's manifestations, starting with simply informing, explaining and reassuring the patient.

Due to the absence of longitudinal studies and the reduced number of control groups, it is not possible to answer questions such as: what is the ideal moment to start a treatment, duration and intensity of it, and what is the effect of a long term treatment, which compels a proposal based on evidence (Cochrane Collaboration).[14]

For oral manifestations in patients which present complex aphthous ulcers, therapeutic management must be started with topical pharmaceutics of the colchicine and dapsone type. If no response occurs with these drugs, orally administered thalidomide, prednisone and methotrexate may be used, always bearing in mind the degree of toxicity and the adequate physical condition for the use of such drugs. In more severe cases, a combination of corticosteroides with immunosuppressors, such as cyclosporin, azathioprine, cyclophosphamide, interferon-alfa 2a or chlorambucil, may be used; however, the need for multidisciplinary treatment is required because this is a systemic infirmity.[13,14]

Case report

The present report is of a female patient, 47 years old, referred to Center for Study and Care of Special Patients (CEAPE) – Paulista University – Indianapolis Campus – São Paulo – Brazil, for the diagnosis and treatment of recurrent ulcers in the oral cavity. The main complaint reported was pain when sitting, during the sexual act, vaginal and oral cavity pain, due to the clinical lesions present at those sites, with a duration of approximately five months, with the condition of these manifestations becoming exacerbated. She also reported that she had five children and had ligation of the fallopian tubes performed 20 years ago, and a hysterectomy 3 years previously due to the formation of uterine myoma. In the anamnesis she related that for the past 2 years she had suffered episodes of oral and genital lesions, had sought medical attention and had been treated for sexually transmittable disease.

On clinical intraoral exam, multiple ulcers were observed, measuring approximately 0.5–1.2 cm in diameter, with the presence of an erythematous halo and fibrinolytic bed on the edge and back of the tongue, lips and bilateral jugal mucosa (Fig. 1a–f). An incisive biopsy was performed, and material was collected for pathologic anatomy. The material collected was located on the lateral edge of the tongue, fixed in 10% formol, and on macroscopic exam, the material showed a fragment of irregular shaped tissue, measuring 0.4 cm × 0.2 cm × 0.2 cm, of grayish color, with an irregular surface and a firm elastic consistency. On microscopic examination, the cuts revealed an ulcerated lesion located in mucosa partially coated by parakeratinized stratified pavementous epithelium with signs of hyperplasia and proliferation at the margin of the ulceration. The subjacent tissue to the ulcer showed intense inflammatory infiltrate, rich in neutrophils close to the surface of the lesion, where necrosis and a fibrinous crust were noted. Deeper down, mononuclear cells of unspecific chronic inflammation were present, which also infiltrated the muscular fibers present at the deep base of the lesion which was well vascularized. No histologic signs of malignity were observed. The result was: larger and smaller recurrent aphthas (Sutton or Mikulicz). The patient was medicated with Dexametasone Elixir mouthwashes twice a day for 8 days. There was regression of the oral lesions, but by this time, she reported that the genital manifestations and the condition of edema and pain in the knees had intensified, making it very difficult for her to walk.

The patient was referred to the Specialized Butantã Attendance Service of the Municipal Secretary for Health of São Paulo, where a clinical gynecological exam was done, and it was reported that the patient presented multiple ulcerations in the posterior vaginal wall of 1.5–2 cm in diameter, with a hyperemia halo, painful during palpation, with abundant white liquid discharge (Fig. 2a–c). Oncologic cytology of the vaginal cupula, colposcopy and pathological anatomy was performed, and the macroscopic material collected consisted of 3 irregular fragments of tissue measuring 0.1–0.4 cm, with a smooth elastic appearance and brownish color. The material was fixed in 10% formol and submitted to the B1 and F3 exam, and the result was: chronic unspecific colpitis in an acute attack on the side of the fibrino leukocytic

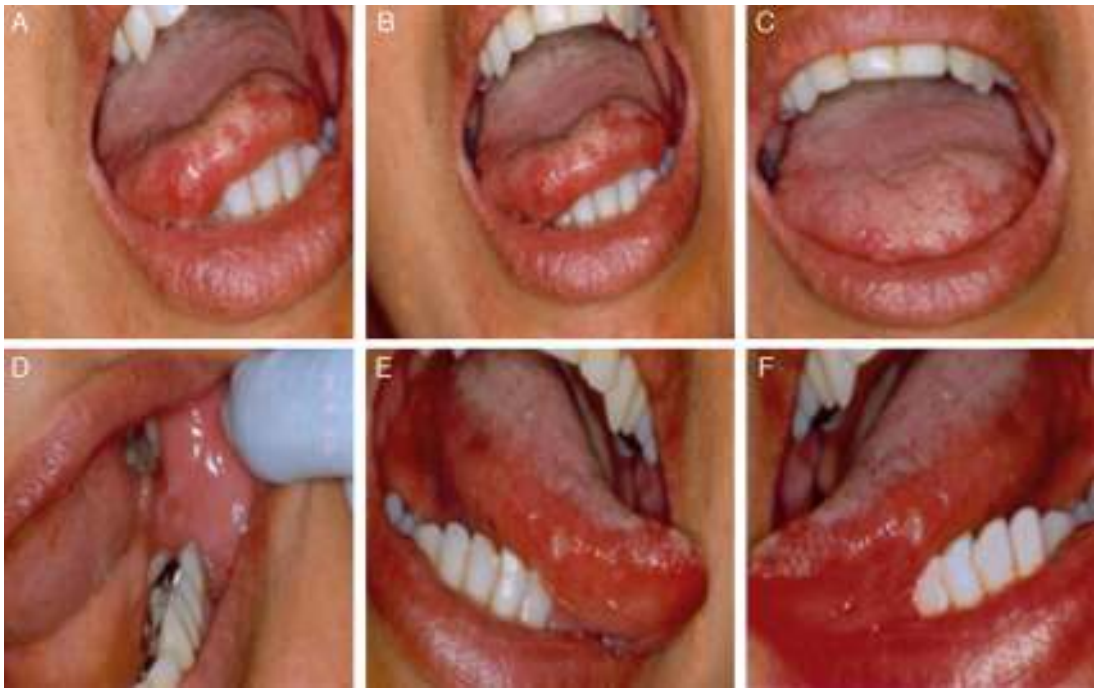

Fig. 1 – (a–f) Clinical intraoral exam, multiple ulcers measuring approximately 0.5–1.2 cm in diameter, with an erythematous halo and fibrinolytic bed on the edge and back of the tongue, lips and bilateral jugal mucosa.

crust, outcrops of erosion, exocytosis and spongiosis; positive vaginal and urethral culture for enterococcus sp, negative FAN/anti DNA and rheumatoid factor lower than 20. Non-reagent serology for syphilis (VDRL) and anti HIV 1 and anti HIV 2 also non-reagent, was performed. Seric dosage of T3 (triiodothyronine = 1449 ng/dL), T4 (thyroxine = 7.9 ng/dL), TSH (thyrostimulant hormone = 3.4 mUI/ml), free T4 (free thyroxine fraction = 1.1 ng/dL), LH (luteinizing hormone = 8.0 mUI/ml), and FSH (follicle stimulant hormone = 4.4 mUI/ml) was performed and all the results presented were within the normality parameters. The seric dosage of alpha-1 acid glycoprotein resulted in a confirmed value of 234 mg/dL (reference value 30–120 mg/dL).

The patient also reported that when having sexual relations in this phase of the treatment, she presented dyspareunia and afterwards the uterine cervix wall ruptured, and surgical intervention was required to repair it. The patient was medicated with 20 mg/day prednisone for 15 days and then doses of 15 mg/day for a further 15 days, followed by 10 mg/day for 1 month. The pre-existent condition of all the symptoms having disappeared, the patient was kept under observation.

After the treatment was interrupted and the patient was kept under observation, 5 months later, the patient presented new less aggressive episodes of oral and genital lesions, but at this time the joint pains had intensified, making it difficult for her to walk, and ophthalmic lesions began to occur.

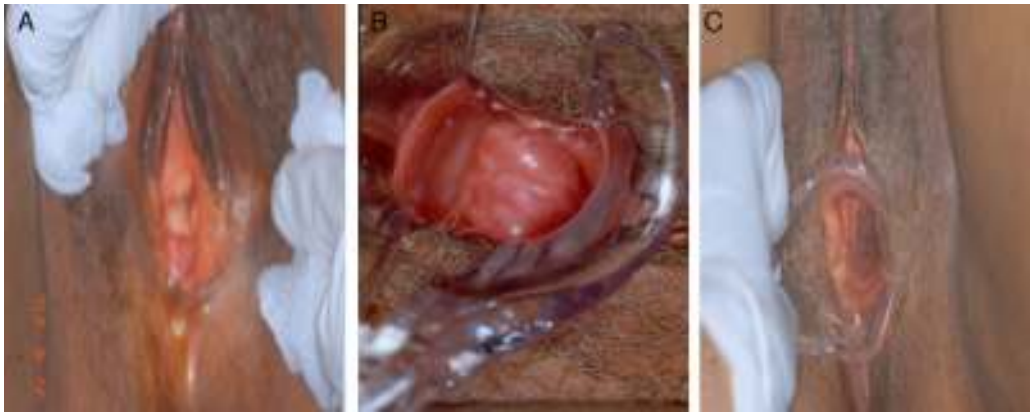

Fig. 2 – (a–c) Multiple ulcerations of the posterior vaginal wall of 1.5–2 cm in diameter, with a hyperemia halo, painful on palpation, with abundant white liquid discharge.

The patient complained of a discreet loss of visual acuity and reddened, burning eyes. On clinical ophthalmologic exam the patient presented with non-granulomatose bilateral intra-ocular inflammation characterizing the condition of retinitis and non-exuberant intra-retinal hemorrhages in the depth of the eye, confirming the diagnosis as uveitis. Soon afterwards, blister-like vesico lesions, erythematosus and extremely painful multiple lesions, measuring approximately 0.4–0.8 cm in diameter appeared unilaterally in the infra-mammary and intercostal region and were diagnosed as Herpes Zosters.

At this time, the use of prednisone was started with 60 mg/day on the first day, 50 mg/day on the second day, 40 mg/day on the third day, 30 mg/day on the fourth day, 20 mg/day on the fifth day and kept at 10 mg/day up to the present time. Concomitantly aciclovir (Zovirax – 200 mg/day) was also administered, with complete remission of the lesions, but the painful reactions to touch at the sites that manifested Herpes Zosters lesions were still present.

In accordance with the criteria of the International Group for diagnosing the Behçet's syndrome, the patient fits in with the criteria, with the presence of oral, genital, ophthalmic and orthopedic manifestations, her diagnosis being compatible with the said syndrome.

Discussion

The SB is a chronic inflammatory disease characterized by genital, ocular, cutaneous, orthopedic, gastrointestinal and neurological manifestation. The International Study Group for Behçet's Disease recommends that in the diagnosis of the disease it is necessary to present oral lesions (recurrent oral ulcers) associated with two more manifestation: ocular, genital, and cutaneous or rheumatoid arthritis (arthralgia), and thus need to be investigated properly through good anamnesis and multidisciplinary involvement to confirm the diagnosis, which implies a broader dentists's knowledge of the characteristics of oral and systemic disease.[2,3,10]

Behçet's syndrome is a disease that can reach serious proportions, may lead the patient to blindness and even death due to the complications of systemic manifestations mainly ophthalmological, neurological and pulmonary.[11,12,15]

Both for diagnosis and treatment, the multidisciplinary is essential because treatment can include medications in high doses and criteria should be thoroughly evaluated to establish patterns between benefits and risks, leading the patient to the disappearance of lesions, keeping it under stable conditions, evaluating the drug toxicity and physical conditions.[13,14]

The dentists should establish the best treatment in sync with the physicians involved in patient care, so that they can effectively improve the oral complications without causing serious injury or interfere with the syndrome's systemic treatment.[8,11,13,14]

Conclusion

Emphasis is laid on the importance of the dentist knowledge about the Behçet's syndrome, its characteristics and its forms of oral and general manifestations, as in view of the seriousness of this pathology and its similarity to other diseases, it is difficult to diagnose and treat. Due to its broad clinical spectrum, multi-disciplinary treatment is important to make an early and efficient diagnosis, so as to prevent aggravation and installation of the more significant and mutilating manifestations and to provide adequate treatment, in order to offer the patient an improved quality of life.

Ethical responsibilities

Protection of people and animals. The authors declare that procedures conformed to the ethical standards of the responsible committee on human experimentation and in accordance with the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Conflict of interest

The authors declare no conflict of interest.

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