Behçet's disease: part of the differential diagnosis of the ulcerative vulva

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Summary

Background: Behçet's disease is a heterogeneous pathological entity of unknown etiology, most of the time affecting many organs concurrently.

Cases: We report two cases of women who presented with ulcerations of the vulvar area as the first symptom, highlighting the diagnostic difficulties that were encountered until the diagnosis of Behçet's disease was confirmed.

Conclusion: Behçet's disease should be kept in mind as a part of the differential diagnosis of vulvar ulcers.

Key words: Behçet's disease; Vulva; Ulcers.

Introduction

Behçet's disease (BD) is a heterogeneous pathological entity of unknown etiology, most of the time affecting many organs concurrently.

In 1990, the International Study Group for Behçet's disease set the criteria for the diagnosis of this disorder. Recurrent oral ulcerations – at least three annual episodes – along with two of the following must be present in order to set the diagnosis of BD: skin lesions, eye lesions, genital ulcerations and positive pathergy test [1]. The most common primary manifestation of BD is recurrent aphthous stomatitis, which sometimes may precede the other symptoms by a number of years. Genital ulcers are also a frequent symptom of BD, but not a presenting one.

We report two cases of women who presented with ulcerations of the vulvar area as the first symptom, highlighting the diagnostic difficulties that were encountered until the diagnosis of BD was confirmed.

Cases report

First case

A 49-year-old woman, gravida 2, para 2, presented at the Colposcopy Unit complaining of severe pain due to vulval ulcerations.

Her past history was unremarkable apart from an appendectomy performed 13 years prior. The patient reported that four days earlier she noticed a small papular lesion on the perineum, tender to palpation, which eventually ruptured and became elcotic. Gradually, the lesion extended onto the adjacent vulval area along with the onset of other similar ulcerative lesions on the upper vulva. She did not report being febrile during the days before or at the time of examination.

On examination there was marked inflammation and ulcers of the whole vulvar area from the perineum to the clitoris, involving the labia minora and extending laterally to both labia majora. There were spaces of "healthy skin islands" between the ulcers. The latter varied in size and depth with the larger ones being deeper, and characterized by erythematous halos and fibrinopurulent bases showing no clearly defined borders. The lesions were extremely tender. No clinically palpable inguinofemoral nodes were noted. Colposcopy of the cervix and vagina was negative. The patient was otherwise free of symptoms and was placed under acyclovir, 1 g per day orally, and topical application of clindamycin phosphate cream, 2% twice a day.

Cultures for bacteria, fungi, viruses and spirochaetes were negative. A series of serological tests including herpes, hepatitis B and C, HIV and syphilis were also negative. Four days later, she presented painful oral ulcerations, less than 1 cm in diameter, on the tongue and the lower lip along with two dark nodules located above her ankles. After consultation with a dermatologist and a positive pathergy test 48 hours later, the patient was diagnosed with Behçet's disease and was transferred to the dermatology ward. She did not develop lesions on any other organs. One week from diagnosis and while she was under colchicine, 1 mg per day orally, and betamethasone ointment topically applied three times per day, she was discharged with complete remission of the genital ulcers.

Second case

A 31-year-old woman, gravida 3, para 1, presented to our Unit reporting a painful vulval ulcer on her left labium minor and a smaller one in the middle of her right labium minor.

Her medical history included two elective abortions and a laser conization of the cervix for a moderate intraepithelial neoplasia (CIN II) two years before. The rest of her past medical history was free and she was not on any medication.

Colposcopy revealed a well-defined ulcer approximately 2-3 cm in diameter, with an erythematous border and a granulating base covered by a purulent exudate, originating from her left labium minor and extending upwards and laterally, affecting part of the left labium majus. Additionally, a smaller ulcer (1 cm in diameter) with the same characteristics was noted in the middle of her right labium minor. The lesions were very tender on palpation. Colposcopy of the cervix, vagina and anus was negative. Palpation of the inguinofemoral nodes was also negative and the patient was not febrile. Cultures for haemophilus

Revised manuscript accepted for publication May 22, 2002

ducreyi, spirochaetes, fungi and bacteria were taken and the patient was placed under acyclovir, 1 g per day orally, and acyclovir cream locally applied to the lesions. She returned three days later with a slight enlargement of both lesions, suffering from severe pain of the area. Two colposcopically directed biopsies, one from each side, were obtained and she was admitted to the gynecology clinic. All the previously taken cultures were negative and all blood tests apart from a mild increase of the sedimentation rate (25 mm/h) were normal. While a number of serological tests were obtained, the treatment was changed to doxycycline, 400 mg per day orally, metronidazole 1 g per day orally, and betamethasone valerate, 0.1% ointment, locally applied three times per day. Two days later, she presented multiple oral ulcerations, photophobia and eye pain. The consultant opthalmologist diagnosed anterior uveitis of the left eye. The serological tests obtained for syphilis, granuloma venereum and herpes simplex turned out negative.

Pathology report

The vulvar biopsy revealed a non-specific ulceration with marked vascular response and extensive endothelial injury (Figure 1).

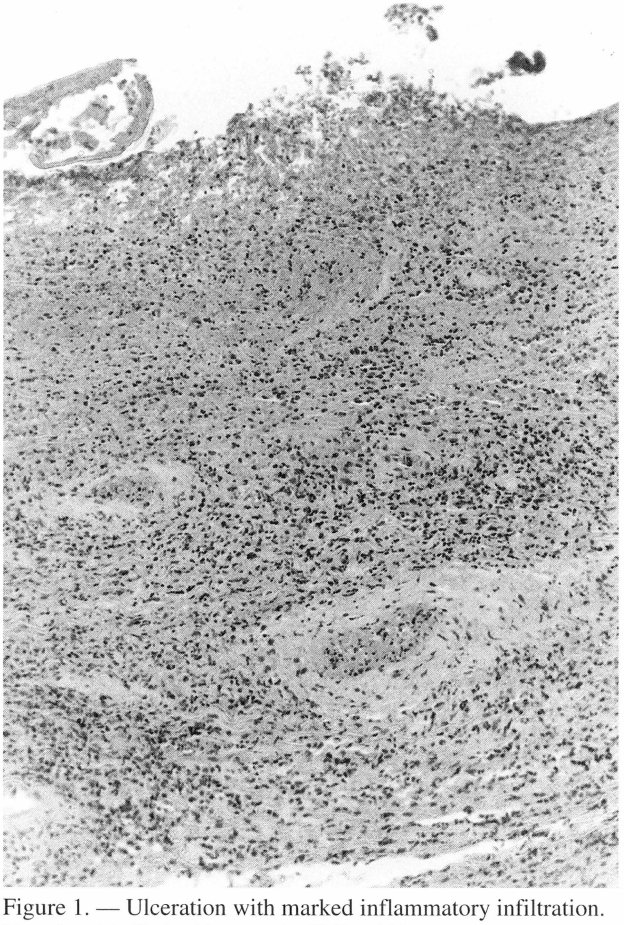

Figure 1. — Ulceration with marked inflammatory infiltration. Vessels with fibrinoid necrosis. H-E x 100.

The surface epithelium was covered with a fibrinopurulent exudate. The vessel wall had been replaced by fibrin and was infiltrated by polymorphonuclear and mononuclear leucocytes. Mural thrombosis as well as thrombotic emboli in the lumen were noted (Figure 2).

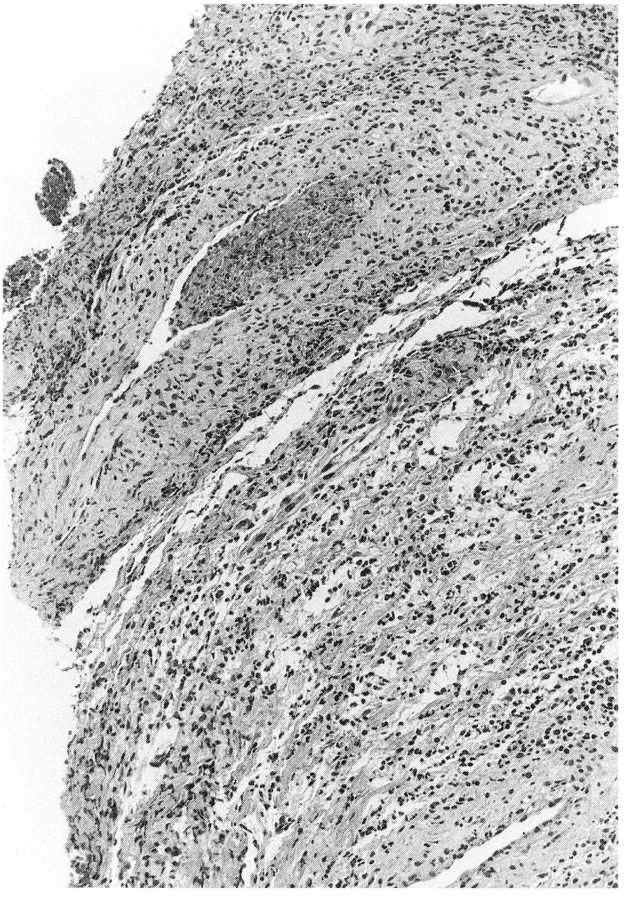

Figure 2. — Arteriole with inflammation of the wall and thrombosis. H-E x 100.

The definitive diagnosis was ulcerative inflammation of the vulva with necrotizing vasculitis. The above histologic findings are consistent with Behçet's disease if the clinicolaboratory findings agree (clinical correlation should be considered).

The consultation of a rheumatologist and a positive pathergy test read two days later confirmed the diagnosis of BD. Treatment consisted of 1 mg colchicine per day orally, betamethasone drops 3 times daily topically for the anterior uveitis and continuation of the betamethasone ointment for the genital lesions. The response was dramatic and the patient was dismissed four days later with the genital ulcers almost completely healed.

Discussion

Behçet's disease is a multisystemic disorder of unknown origin. The disease is more prevalent in the Eastern and Mediterranean countries with Turkey and Iran having the highest number of cases. Of particular interest is the observation that cases from these countries seem to exhibit a more severe course than patients from Northern America or Britain.

It seems that BD is triggered by an inflammation caused by a disorder of the cellular and humoral immunity of the affected individuals, thus leading to hyperfunction of the neutrophils, autoimmune response and

injuries of the small vessels (vasa vasorum). The latter feature thrusted several authors to propose that BD is essentially a vasculitis. Due to the lack of specific abnormal laboratory findings or pathognomonic symptoms, the diagnosis of the syndrome is based on the criteria that have been set by the International Study Group for the disease and have already been mentioned [1].

Recurrent oral aphthous ulcerations seem to be the most frequent symptom of BD presenting in 95% of the patients. The ulcers are usually multiple, more often localized on the anterior than the posterior parts of the mouth, and less than 1 cm in diameter. In our cases, the first patient developed apart from the oral ulcerations and the genital lesions, erythema nodosum which represents one of the skin involvement manifestations. It usually appears as painful papules surrounded by a peripheral halo, most of the time affecting the back, the face and the extremities of the patient. Erythema nodosum has been reported to occur in 5-55% of the patients. The second woman suffered from anterior uveitis, a rather serious symptom included in the group of ocular lesions seen in about 60% of the patients. Involvement of the retinal vessels and cumulative damage of the optic nerve may progressively lead to blindness. Moreover, both women were positive for the pathergy test which is a skin reaction presenting as a papule after insertion of a needle to the skin of the patient. Although the pathergy test is not pathognomonic, it shows very high specificity and is considered to be an important parameter for the diagnosis of BD [2]. Other manifestations include musculoskeletal findings seen in about 50% of the patients during the course of the disease, involvement of arteries and veins of any diameter (10-40%), gastrointestinal findings and central nervous system involvement (5-29%) which is the main cause of death from the disease. BD may also produce infrequent manifestations from the genitourinary system, the lymph nodes, the heart and the lungs.

Vulval ulcers are not a common finding in gynecological practice. The most usual cause of genital ulcers in industrialized countries is herpes simplex virus infection (HSV) [3]. The actual clinical manifestation of herpes with rupture of the vesicles and the formation of painful ulcers may mimic the genital manifestations caused by BD and can pose a diagnostic dilemma. The morphology of the ulcers is similar – even the "herpes halo", a characteristic finding of HSV consisting of an erythematous border to the erosive herpetic lesion may resemble a BD ulceration – the lesions can be multiple, both might be associated chronologically with the menstrual cycle and both conditions are characterized by recurrent episodes, which could make diagnosis more difficult. The two cases reported in this paper were treated primarily as suffering from genital herpes. It should be noted that neither of our patients had inguinofemoral node enlargement or fever, two parameters that might be present in primary infection by HSV and could help in the differential diagnosis of BD. Final diagnosis of HSV infection should be based on viral cultures of blister fluid or exudate from a fresh erosion. Antigen tests are available but are not as reliable as a tissue culture [3]. Exclusion of other causes of painful genital erosions should also be ascertained. On the other hand, it seems that when the ulcers are due to BD, one or more organs will be affected shortly after the initial symptom, thus directing the gynecologist to the systematic nature of the disease.

There are numerous other conditions, not as frequent as HSV infection, with which BD ulcerations can be misinterpreted. Chancroid, an acute sexually transmitted infection caused by Haemophilus ducreyi, produces an initial pustule, which rapidly progresses to a painful ulcer with the same characteristics as HSV and BD ulcers. Isolation of the bacterium from the ulcer will establish the diagnosis. In patients with syphilitic ulcers, the lesions are not usually painful and along with the serological tests (VDRL and rapid plasma reagin are positive in 70 and 80% of the patients, respectively) and the cultures from the erosions, which will identify Treponema pallidum, will finally establish the diagnosis.

Other uncommon conditions exhibiting genital ulcerations with almost the same clinical features as BD are granuloma inguinale or donovanosis, caused by the bacterium Calymmatobacterium granulomatis, lymphogranuloma venereum, an infection attributed to Chlamydia trachomatis, amoebiasis, caused by Entamoeba histolytica, and extreme cases of candidosis, a common yeast infection caused by Candida albicans. Differential diagnosis should be based on the bacteriological cultures [4].

The variety of conditions that present with vulval ulcerations and their resembling morphology, predispose gynecologists and often dermatologists towards potential diagnostic pitfalls. Although not as frequent as other disorders of the vulva, and given the fact that general obstetricians/gynecologists are not familiar with vulval lesions, Behçet's disease should always be kept in mind as a part of the differential diagnosis of vulvar ulcers.

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