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Case Report
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A Rare Self-Limiting Adamantiades Behcet Diseasen in A Woman: A Case Report

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ABSTRACT

Background: Adamantiades–Behçet is a genetically determined disorder with a probable environmental triggering factor and is an inflammatory disease representing vasculitis. Chronic relapsing progressive course, Dapson prevents problems in other organs. **Case Report:** A 31-year-old woman with chief complaints of a progressive painful ulcer on her genitalia in the last month, covered by pus and with a bad odor, and also recurrent tongue sores that healed spontaneously. Multiple partner sexual intercourse, joint pain, and an eye complaint were denied. Her husband has no history of previous sexually transmitted diseases. The labia majora region showed a solitary ulcer, sharply marginated, and covered with pus. The *Haemophilus ducreyi*, pathergy, VDRL, TPHA, and rapid test HIV all came back negative. *Enterococcus faecalis*, found in bacterial culture, is sensitive to Penicillin and glycopeptide. Histopathologically recited vasculitis with thrombus in the blood vessel marks Behcet disease. The patient was given Mefenamic Acid (3x500mg), doxycicline (2x100 mg), and a wet dressing. The ulcer decreased in size after 3 weeks of treatment. **Discussion:** Adamantiades-Behçett disease is characterized by chronic, recurrent oral aphthous ulcers, genital ulcers, skin lesions, ocular lesions, and arthritis or arthropathy. Viral and bacterial infections have been implicated in initiating immunopathologic pathways. The pathergy test is pathognomonic, but it is not specific and often gives a negative result. Histopathological examination is still the best option to establish the diagnosis. **Conclusion:** Self-limiting and relapsing episodes of clinical manifestations represent a hallmark of Behcet's disease. Since it is not a life-threatening disease and some other complaint has never been diagnosed, a careful history-taking, physical examination, and supporting laboratory examination will lead to a prompt diagnosis.

Keywords*:* adamantiades–behçet, inflammatory disease, sexually transmitted disease, human and disease.

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BACKGROUND

Adamantiades- Behcet's disease (BD) is a genetically determined disorder with a probable environmental triggering factor. Inflammatory disease characterized by a neutrophilic vascular reaction, often known as vasculitis. Recurrent oral aphthous and genital ulcers, skin lesions, and iridocyclitis/posterior uveitis, occasionally accompanied by arthritis and vascular, gastrointestinal, neurologic, or other manifestations characterize the condition clinically. It is a chronic, relapsing and progressive disease with a potentially poor prognosis. This disease is not considered contagious, as no horizontal transmission has ever been reported. Gastrointestinal involvement is one of the most serious occurrences in Behçet disease and can potentially end with severe complications. Although venous thrombosis is found primarily in the lower extremities, it may affect many different sites, including the inferior and superior vena cava, pulmonary artery, suprahepatic vessels, and cardiac cavities.[1–3]

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The prevalence is 80 to 370 cases per 100,000 people in Turkey, 10 per 100,000 in Japan, and 0.6 per 100,000 in Yorkshire. BD has MHC class I associations. HLA-B51 is the most strongly associated known genetic factor with BD. It is also commonly found in akylosing spondylitis and psoriatic arthropathy. The male to female ratio is 7:1 in symptomatic forms, but women has fewer systematic symptoms. BD occurs mainly between 18 and 40 years of age.[3,4] This case reveals a specific dermatological lesion of BD. This report aimed to describe the importance of careful history-taking because Adamantiades-Behcet disease can be very severe and can cause organ damage if it is recurrent; an early definite diagnostic test is really necessary to prevent the non-cutaneous lesion that may cause high morbidity and mortality; and also to recognize the symptom as one component of the BD disease.

CASE REPORT

A 31-year-old woman visited to the outpatient clinic after complaining about a painful large ulcer on her genital area in the previous month. The ulcer is single, with pus covering the surface; it is also painful. The ulcer is minor at first, but it grows larger and more painful until she can't walk properly. She had previously examined the ulcer at primary care and was given medication; she couldn't recall the name of the medication, although she was told they were painkillers and antibiotics. Despite taking the prescription, the patient's complaint has not improved. Even though she was given medicine to heal the ulcer on her genital, it grew larger. She consumes mefenamic acid almost every day for the pain. Beside the ulcer on her genital area, she also complained of an indolent aphthous on her tongue. The aphthous on her tongue had been recurrent for a year. She never took any medicine for her tongue complaint. She sometimes had fever recurrently since she had the ulcer, but she never any complain about joint sore or eye complaints. From the historical anamnesis, there was no history of previous ulcers on her genitalia before this, she never had any sexual intercourse with multiple partners; no complaint of vaginal discharge; no history of long-term medication use; no history of diabetes mellitus before, her husband never had any sexual intercourse with multiple partners before marriage.

A physical examination of her general state showed her blood pressure was in the normal range of 120/90, her heart rate was in normal range of 100 times per minute, her temperature was $37,3^0$ Celsius. From the head and neck, there were no signs of anemia, cyanosis, icterus, or dyspnea. On thoracic examination, the heart and lungs were normal. On the abdomen examination, the liver and spleen were not palpable. From her upper and lower extremities there were no edema, and there was warmth on palpation. There was no enlargement of the cervical, axillary, inguinal, or genital lymph nodes.

Dermatological examination on the left labia majora area revealed oedematous lesions and a solitary ulcer in 2-3cm of diameter with a clean base, no necrotic area or necrotic edges, sharp margin, covered with pus and no blood. On her tongue were found an aphthous clean base with no necrotic area and no white membrane.

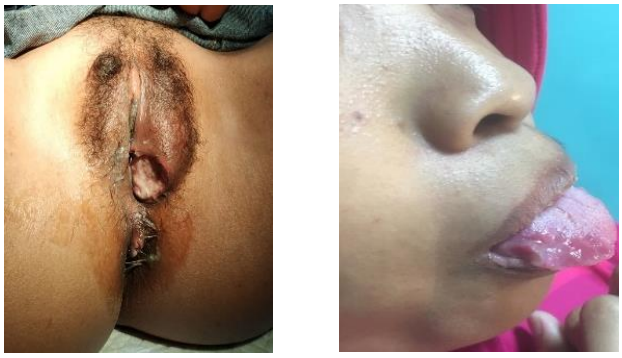

Figure 1. The dermatology state before treatment. (left) On the labia majora region, there was a solitary ulcer, sharp a marginated, covered by pus, and there was no blood. (right) Single aphthous ulcer, clean base, no white membrane.

Table 1. The diagnostic examination results

Test	Results
STS* (VDRL**, TPHA***)	Non-reactive
HIV**** test	Non-reactive
Microscope Examination	*Una ducreyi* negative.
Vaginal Swab	NSGI (Non-Specific Gonococcal Infection)
Culture pus from ulcer	*Enterococcus faecalis*
Consult opthalmology	No uveitis
Histopathology	*Behcet* disease
Pathergy test	Negative

*STS: Serologic Test for Syphilis, **VDRL: Venereal Disease Research Laboratory, ***TPHA: Treponema Pallidum Hemagglutination Assay, ****HIV: Human Immunodeficiency Virus

We initially suspected the patient suffered an ulcer that was caused by a sexually transmitted disease such as ulcus molle. To eliminate the sexually transmitted infection in this patient, we examined the patient with several laboratory tests, include syphilis test, an HIV test, a culture of pus from the ulcer ulcus, a consultation with ophthalmology, histopathology, and a pathergy test. For the biopsy, a 5-mm punch biopsy was taken from the patient's ulcer and also involving the skin that is still intact, and this size of biopsy was chosen to achieve a representative sample. All test results will be shown in Table 1 below.

Since this patient has already consumed several kinds of antibiotics, the consideration of giving other antibiotics were based on the results of the culture. The culture results for this patient were sensitive to ampicillin, penicillin G, theicoplanin, linezolid, fosfomycin. The patient refuses to be hospitalized; the sensitive antibiotics were intended to be provided through infusion and injection in the hospital ward. Because the patient declined to be hospitalized, she was given doxyciclin 2 x100mg for 10 days, mefenamic acid 3 x 500mg and a wet dressing with normal saline 0,9%. Doxycicline was chosen to be the therapy because the patient also has NSGI (Non-Specific Gonococcal Infection). Two weeks after being given therapy with doxycycline, the ulcer size began to reduce, and she has been in complete remission for 3 weeks since her first visit to the hospital and after being given antibiotics. The ulcer that appeared on her tongue also disappeared together at the same time as of ulcer on her labia major.

The pathergy test was done on the patient and observed in 48 hours, but the result was negative. The patient was consulted by the ophthalmic department to make sure that there was no eye anomaly. The result was that there was no sign of deformity in her eyes that had a connection to the disease she had. The result of the culture that was taken from the pus was *Enterococcus faecalis,* which is sensitive to Ampicillin and Penicillin G.

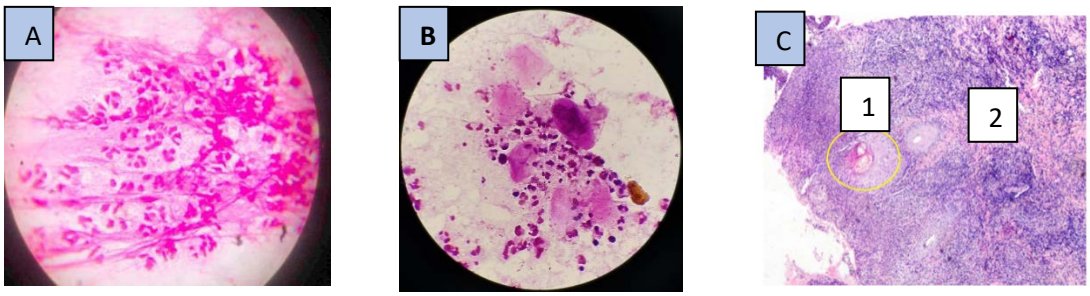

Figure 2. Gram staining from the pustules at 40x magnification. (A) There were polymorphonuclear cells without any basil or coccus bacteria. (B) Gram staining from the vaginal swab at 40x magnification. The result was leucocytes 50-60, epithelia 4-6, and gram-positive coccus. (C) Histopathology examination of the patient. (1) There was an infiltration of lymphocytes and lots of inflammation cells. (2) There was a thrombus in the blood vessel, and it is compatible with Behcet disease. Hematoxylin and eosin staining with the original magnification of 40x.

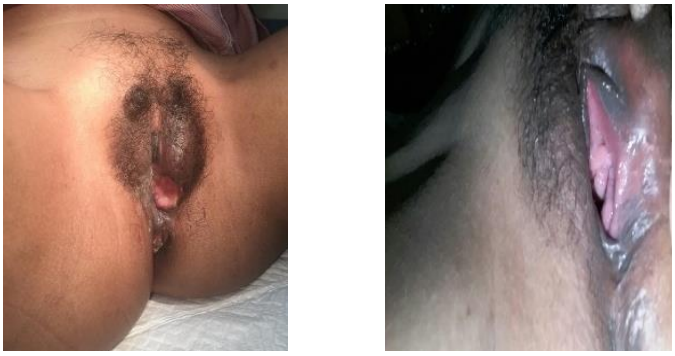

Figure 3. Treatment progress. after therapy for 10 days, the pus had gone, the ulcer was clean, and the base depth was decreasing (left). The ulcer has been in complete remission for 3 weeks since she first came to the hospital (right).

DISCUSSION

Adamantiades–Behçet disease is a multisystem inflammatory disease of unknown etiology, classified as systemic vasculitis involving all types and sizes of blood vessels and characterized clinically by recurrent oral aphthous and genital ulcers, skin lesions, and iridocyclitis/ posterior uveitis, occasionally accompanied by arthritis and vascular, gastrointestinal, neurologic, or other manifestations. In BD patients, altered fibrinogen structure and impaired fibrinogen function are associated with neutrophil activation and enhanced reactive oxygen species production, whose primary source is represented by neutrophil NADPH oxidase.[1,4]

In the early stages of the disease, both Th1 and Th17 cells drive inflammation, leading to mucosal damage via abnormal and long-lasting cytokine production as well as via both perforin- and Fas–Fas ligand-mediated cytotoxicity. Finally, all the T cells at mucosal level were able to produce a large amount of TNF-a, suggesting that its production is a property of intestinal T cells in patients with early active intestinal disease. The antibodies with the best-defined role in BD are the anti-endothelial cell antibodies; these have been reported to be present in 18-50% of BD patients and found to be associated with disease activity related to vascular involvement.[2,5]

Thrombosis is the most frequent vascular manifestation in BD patients; its prevalence ranges from 14% to 39%, and venous involvement is characteristically more common and makes up 75% of all vascular complications.[6] Venous thrombosis occurs more frequently in males with active disease during the early years, sometimes at the onset of disease, and tends to recur. Deep vein thrombosis (DVT) and superficial vein thrombophlebitis (SVT) of the lower extremities are the typical manifestations, but thrombosis may occur anywhere in the venous system, and the involvement of atypical sites such as hepatic veins, superior and inferior vena cava, and cerebral sinus veins is also observed.[4,7] Ocular involvement is frequent and severe, often bilateral, compromising visual function rapidly. A variety of eye lesions have been found, including anterior uveitis, cataracts, glaucoma, posterior segment involvement with vasculitis, vitritis, retinitis, panuveitis, retinal edema, cystoid macular degeneration, venous or arterial occlusion, disc edema, and retinal detachment.[8,9]

Oral aphthae occur in 98% of cases and are mandatory in the international criteria for classification. The typical lesion is round with a sharp, erythematous, and elevated border, mostly 1 to 3 cm in diameter, but larger lesions can also occur. The surface is covered with a yellowish pseudo-membrane. Genital ulcers occur in 60 to 65% of cases and are very suggestive of the diagnosis of BD. Thrombosis is the most frequent vascular manifestation in BD patients; its prevalence ranges from 14% to 39%, and venous involvement is characteristically more common and makes up 75% of all vascular complications. Arthralgia and/or arthritis occur in 45% of cases. Up until now, a wide variety of diagnostic criteria have been developed for the diagnosis of BD. Currently, the ISG (International Study Group) and ICBD (International Criteria for Behcet's Disease) criteria are among the most widely used diagnostic tools for BD.[10,11]

The simple test that can help diagnose DB is pathergy test. Pathergy is a non-specific hypersensitivity reaction to skin trauma that can occur in patients with Behçet’s disease. In this patient, the pathergy test was negative. The skin pathergy test is one of the minor diagnostic criteria for BD. Its diagnostic sensitivity increases during exacerbations, but there is considerable ethnic variation. Pathergy is a feature of most of the other neutrophilic dermatoses, including pyoderma gangrenosum and Sweet’s syndrome.[12,13]

There are scoring criteria to help diagnose BD. The score itself is based on the symptoms of BD. For recurrent ocular and oral lesions and genital aphthae, each score were 2 points. Meanwhile, recurrent skin lesions, central nervous system involvement, vascular manifestations, and positive pathergy test each scored 1 point. A total score ≥ 4 indicates BD disease.[14,15]

In an observational, multicenter study including 17 BD patients (70.6% male, with a median age of 39.3 [24–60] years) that were refractory to immunosuppressants and treated with anti-TNFα (infliximab 5 mg/kg or adalimumab). Complete remission was defined by the disappearance of all neurological symptoms and the improvement of radiological abnormalities at 12 months. Musculoskeletal symptoms are managed with various analgesics, including non-steroid anti-inflammatory drugs (where appropriate), as well as physical therapy. The inflammatory symptoms are suppressed with oral DMDs, escalating to biologics (typically TNF inhibitors).[16]

Fibromyalgia is frequently observed in BD. It requires an approach of graded physical activity, pain-modifying medications (eg., amitriptyline, pregabalin), and cognitive behavioral therapy. Inflammation may be amenable to local steroid injections, physical therapy, and, if not, DMDs. Immunopathogenesis in BD is a rapidly evolving field, although the exact picture is yet to be fully established. However, recent breakthroughs have shed new light on novel cell mediators and cytokine axes, which have provided novel treatment rationale. Overall, a shift from general drugs to highly specific agents has occurred in recent years. Among them, the IL-23/IL-17 axis is emerging as a pivotal disease player, but further research is needed.[17–19]

Behcet's disease is often mistaken for other sexually transmitted infections that have a manifestation of an ulcer in the genital area similar to Lipshutz ulcer, which is symptomatic, usually self-limiting, and disappears spontaneously within 1–2 weeks without recurrences, but the cause of Lipschutz ulcer is bacterial, therefore it can be differentiated from BD by doing a culture examination. HIV screening is also important is diagnosing BD since mucocutaneous lesions are one of the first clinical presentations of immunosuppression in HIV seropositive patients, manifest at different stages of the infection, and require early diagnosis and prompt treatment.[20–22]

Self-limiting and relapsing episodes of clinical manifestations represent a hallmark of Behcet's disease. BD is also often mixed with non-specific gonococcal infection. In 2015, the CDC stated that doxycycline is one of the options in treating NSGI. Recurrent symptoms may decrease the quality of life. Since it is not a life-threatening disease, some other complaint has never been diagnosed. In this patient a recurrent painful lesion ulcer in the genital area, and also tongue aphthous in the past year, but the swab result didn't contain *Haemophilus ducreyi*, the negative result of TPHA and VDRL, and we can use the BD scoring as our clinical guideline.[24]

A careful history, physical examination, the scoring criteria are very helpful in diagnosing BD and supporting laboratory examination will lead to a prompt diagnosis. A correct diagnosis will lead to prompt treatment that will help patients improve their quality of life.[23-24]

Table 1. Diagnostic criteria for Behcet Disease

International Criteria for Behçet Disease	
Symptom	**Symptom Points**
Ocular lesions (recurrent)	2
Oral aphthosis (recurrent)	2
Genital aphthosis (recurrent)	2
Skin lesions (recurrent)	1
Central nervous system	1
Vascular manifestations	1
Positive pathergy test	1

*BD scoring: score ≥ 4 indicates Adamantiades–Behçet disease.

*Though the main scoring system does not require the pathergy test, if it is conducted, a positive result may be included for 1 extra point.

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