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Ann. Acad. Med. Siles. (online) 2025; 79: 70–74
eISSN 1734-025X
DOI: 10.18794/aams/199833
www.annales.sum.edu.pl

OPIS PRZYPADKU
CASE REPORT

An interdisciplinary diagnostic approach successful in diagnosing rare diseases using Behçet's disease as an example

Interdyscyplinarne podejście diagnostyczne sukcesem w rozpoznawaniu chorób rzadkich na przykładzie choroby Behçeta

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ABSTRACT

Behçet's disease (BD) is an inflammatory and autoimmune disorder that develops in individuals with a genetic predisposition who are simultaneously exposed to certain environmental factors. It is believed that mediators of the inflammatory response, by initiating the migration of inflammatory cells into tissues, trigger an autoimmune response. This response leads to a systemic inflammatory process, resulting in the clinical manifestations of BD.
We present the case of a 39-year-old female patient referred to the internal medicine department with non-specific systemic symptoms and high levels of inflammatory parameters in her blood. She had a history of recurrent oral aphthae, genital ulcers on admission, as well as skin and musculoskeletal lesions of an upper limb. Following an extensive differential diagnosis, a diagnosis of BD was made. The paper describes the diagnostic difficulties and the multidisciplinary approach that is crucial in making an accurate diagnosis, especially in rare diseases.

KEYWORDS

diagnosis, treatment, Behçet's disease, skin lesions, oral ulcers, hepatitis C

Received: 03.11.2024 **Revised:** 11.11.2024 **Accepted:** 07.01.2025 **Published online:** 17.03.2025

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Publisher: Medical University of Silesia, Katowice, Poland

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STRESZCZENIE

Choroba Behçeta (*Behçet's disease* – BD) to schorzenie o charakterze zapalnym i autoimmunologicznym, rozwijające się u osób z predyspozycją genetyczną, które jednocześnie narażone są na działanie określonych czynników środowiskowych. Uważa się, że mediatory reakcji zapalnej, inicjując migrację komórek zapalnych do tkanek, wyzwalają odpowiedź autoimmunologiczną. Reakcja ta prowadzi do ogólnoustrojowego procesu zapalnego, skutkując pojawieniem się objawów klinicznych BD.

W pracy przedstawiono przypadek 39-letniej pacjentki skierowanej na oddział internistyczny z nieswoistymi objawami ogólnoustrojowymi i wysokim poziomem parametrów zapalnych we krwi. W wywiadzie nawracające afty jamy ustnej, owrzodzenia narządów płciowych przy przyjęciu, a także zmiany w zakresie skóry i układu mięśniowo-szkieletowego kończyny górnej. Po szerokiej diagnostyce różnicowej postawiono rozpoznanie BD. Opisano trudności diagnostyczne oraz multidyscyplinarne podejście, które jest kluczowe w postawieniu trafnej diagnozy, zwłaszcza w chorobach rzadkich.

SŁOWA KLUCZOWE

diagnoza, leczenie, choroba Behçeta, zmiany skórne, afty jamy ustnej, zapalenie wątroby typu C

INTRODUCTION

Behçet's disease (BD) is a chronic multisystem inflammatory syndrome. It is characterized by recurrent oral and genital ulcers, skin and ocular lesions. In addition, there are disorders of the musculoskeletal system, vascular, central nervous system (CNS) and gastrointestinal tract [1].

In Europe, there are approximately 0.1–7.5 new cases per 100 000 citizens per year. It occurs mainly between the ages of 20 and 30, with equal incidence in both sexes in European countries and a male predominance in Middle Eastern countries [2]. The incidence in Poland is estimated at 0.5/1 million people per year [3]. The pathogenesis is still unknown, and infections, both bacterial and viral, as well as genetic and environmental factors, are mainly cited as potential causes. They cause activation of the immune system, resulting in inflammation and clinical symptoms [1]. Genetic background correlates strongly with the risk of developing BD and is significantly higher among first-degree relatives, especially in twins. The most significant genetic factor is the presence of the HLA-B51 allele. In recent years, variations in non-HLA genes such as the endoplasmic reticulum aminopeptidase enzyme (ERAP1), interleukin 10 (IL-10) and interleukin 23 receptor/interleukin 12 receptor beta 2 (IL23R/IL12RB2) have also been identified as being associated with the occurrence of BD [4,5]. The diagnosis of BD is usually made on the basis of clinical symptoms and a score of $\geq$ 4 pts according to the International Behçet's Disease Criteria [6] (Table I), which are mainly based on mucocutaneous manifestations due to their high sensitivity and specificity [7]. The primary aim of treatment is to control the inflammatory process and prevent irreversible damage to the organs involved, especially at an early stage of the disease.

Table I. International criteria for Behçet's disease

Criteria	Definition	Point value	Does the patient meet the criteria?
Ocular changes	retinal vasculitis, anterior uveitis, posterior uveitis	2 pts	NO
Lesions in the oral cavity	recurrent, painful aphthous ulcers in the mouth, recurring at least three times in the last 12 months, healing spontaneously within 1–3 weeks	2 pts	YES
Genital lesions	recurrent ulcers of the vulva in women and of the penis and scrotum in men	2 pts	YES
Skin lesions	aphthous skin ulcers, erythema nodosum, pseudofolliculitis or papulopustular lesions or acne nodules observed by a physician in patients after puberty who are not taking GCS	1 pt	YES
Positive pathergy test	assessed by at least three skin pricks; a positive result is the appearance of a pustule surrounded by erythema within 24–48 hours after irritation	1 pt	YES
Neurological changes	lesions assessed by a neurologist based on clinical examination and CT, MRI and/or CSF	1 pt	NO
Vascular lesions	thrombosis of arteries or large veins, deep or superficial phlebitis	1 pt	NO

GCS – glucocorticosteroids; CT – computed tomography; MRI – magnetic resonance imaging; CSF – cerebrospinal fluid.

CASE REPORT

A 39-year-old female patient was admitted to the internal medicine ward in moderate general condition due to recurrent fevers. She had a history of hepatitis C virus (HCV) infection 5 years ago. At the time she was not taking any medication. The examinations on admission were notable for their high inflammatory markers (CRP 309 mg/l, leukocytosis 23.8 th), with negative procalcitonin (PCT 0.19) and a normal chest X-ray. Owing to the additionally reported difficulties in concentration, speech and dizziness, a computed tomography (CT) scan of the head was performed followed by lumbar puncture with cerebrospinal fluid (CSF) examination. After consultation with an infectious disease physician, a neurologist, and based on the negative CSF results, neuroinfection was ruled out. Blood and urine cultures taken at the start of the study were ultimately found to be sterile. However, the presence of local ulcer-like lesions on the thumb of the left hand and on the external surface of the genitalia was noted. As the patient had unprotected sexual contact 2 weeks earlier, a suspicion of sexually transmitted diseases (STDs) was raised. Tests for human immunodeficiency virus (HIV, negative), hepatitis B surface antigen (HBs, negative), HCV (reactive), herpes simplex virus (HSV, negative), venereal disease research laboratory test (VDRL, negative) were sent and the patient was consulted dermatologically and gynaecologically – ruling out local inflammation and STD. The proteinogram was also inconclusive as elevated alpha-1 and alpha-2--globulins indicated an acute disease process, while beta-2-globulins with a mild reduction in albumin and hemoglobin indicated a chronic disease process. In addition, on the following day, the patient reported a sore throat and muscle pain, most severe in the left upper limb with restricted mobility in the shoulder joint. The diagnosis was expanded to include tests for rheumatological diseases, which were also initially suggested by the infectious diseases doctor: antinuclear antibody (ANA1, negative), rheumatoid factor (RF, slightly elevated), anti-cyclic citrullinated peptide antibody (anti-CCP, negative), complement components C3 and C4 normal, immunoglobulins (IgA, IgM, IgG) normal. An X-ray of the shoulder joint did not show any changes and after an orthopedic consultation, non-steroidal anti-inflammatory drugs (NSAIDs) were added to the treatment. Ear, nose, and throat (ENT) causes of the fever including cytomegalovirus (CMV, negative) and Epstein-Barr virus (EBV, negative) infection were also ruled out (Table II). During this consultation, the patient additionally reported that she had a history of frequent recurrent oral aphthae, which was resolved with topical antiseptics.

Table II. Test results

Inflammatory markers	CRP 309 mg/l leukocytosis 23.8 K PCT 0.19
Sexually transmitted diseases	HIV – negative HBs – negative HCV – reactive HSV – negative VDRL – negative
Microbiological tests	blood culture – negative urine culture – negative
Proteinogram	alpha-1-globulins – elevated alpha-2-globulins – elevated beta-2-globulins – elevated albumin – mildly decreased
Rheumatology panel	ANA1 antibodies – negative RF – slightly elevated anti-CCP – negative complement components C3, C4 – normal immunoglobulins – normal
Infection panel	CMV – negative EBV – negative

CRP – C-reactive protein; PCT – procalcitonin; HIV – human immunodeficiency virus; HBs – hepatitis B surface antigen; HCV – hepatitis C virus; HSV – herpes simplex virus; VDRL – venereal disease research laboratory test; ANA1 – antinuclear antibody; RF – rheumatoid factor; anti--CCP – anti-cyclic citrullinated peptide antibody; CMV – cytomegalovirus; EBV – Epstein-Barr virus.

The treatment included broad-spectrum empirical antibiotic therapy and NSAIDs, with a resolution of the complaints and a decrease in the inflammatory parameters (CRP 18, PCT and leukocytosis normal). On the basis of the clinical symptoms and the International Behçet's Disease Criteria (6 pts), a diagnosis of BD was made and hospitalization in the rheumatology department was planned, after prior exclusion of HCV recurrence (HCV RNA testing by PCR), with a view to possible immunosuppressive treatment.

DISCUSSION

Most patients with BD develop periodic fever, malaise and elevated inflammatory parameters. Nevertheless, these symptoms are uncharacteristic, hence inflammatory foci in the patient were sought first. Even before the administration of a broad-spectrum antibiotic, cultures were taken, which made it possible to rule out sepsis and urinary tract infections with relative reliability. The rarer the disease, the harder it is to receive a quick diagnosis and the tests usually give inconclusive results. Early diagnosis and effective treatment can prevent severe complications and reduce mortality. Symptoms of BD include oral ulcers, which are painful aphthous lesions of the oral mucosa. The difficulty in diagnosis lies in the similar morphology of lesions in the course of recurrent aphthous stomatitis (RAS) [7] and HCV infection [8].

In the case described here, oral aphthae had appeared in the past and were recurrent, but were at the time absent. The differential diagnosis excluded herpes and other viral diseases, in addition to recurrent aphthous stomatitis. Based on the determined levels, iron, vitamin B12 and folic acid deficiency were ruled out, and with negative ANA1 antibodies as well as no gastrointestinal symptoms, inflammatory bowel disease was also excluded. Nonetheless, attention was drawn to mild anemia suggesting a chronic process. Another important symptom of BD is genital ulcers, which often leave scars resulting from the deeper location of the lesions [7]. Due to the embarrassing nature of the lesions, it is often overlooked by patients in their history. In the search for inflammatory foci, a gynecological consultation in women, and a urological consultation in men, should be the primary diagnostic element. The history additionally indicated the possibility of infection with STDs, but this was not confirmed in the study, and the ulcers themselves were the patient's main reported problem. The diagnostic, but not pathognomonic for BD, symptom of pathergy, i.e. the formation of an erythematous papule or pustule at the site of a needlestick usually after 24–48 hours in the case described, was not present. It is estimated to affect 60% of patients with BD. Rare skin lesions include the patient's thumb ulceration. Much more common are papulopustular lesions on the basis of raised erythema or folliculitis.

BD usually presents with mild joint inflammation; the process mainly involves large joints, rarely small joints, while the sacroiliac joints are almost non-existent. In the case described here, the aggravated musculoskeletal complaints required an extended orthopedic diagnosis. After ruling out autoimmune causes of the complaints, suspected inflammation of the shoulder joint (the so-called frozen shoulder) was finally diagnosed. These lesions involve the joint capsule and synovial membrane, and their cause, once trauma is ruled out, is usually unknown. Slightly elevated levels of the RF in the patient's tests are not characteristic of BD, as they, like serum ANA antibodies, are usually absent in patients [9]. The so-called MAGIC syndrome (mouth and genital ulcers with inflamed cartilage) coexists with BD, in which oral and genital ulcers as well as polyarthritis occur simultaneously [10]. The diagnosis of BD in the patient may also be indicated by muscle pain in the upper extremities. Myositis occurs in some patients and is local; generalized myositis has been described only in isolated cases. Infectious diseases and fever can give similar complaints but they are most often generalized. In the patient, the creatine kinase and myoglobin levels were normal. The patient did not present with ocular changes, while the initial neurological symptoms in the form of pain and stiffness in the neck muscles were considered secondary to the muscle symptoms. A head CT scan, lumbar puncture and CSF analysis were performed, in addition to a neurological consultation – finding no abnormalities. Similar symptoms of neck muscle stiffness were described by Komatsumoto et al. [11], indicating that it may precede other BD symptoms. Treatment of BD focuses on two goals. The first is to prevent irreversible damage caused by repeated exacerbations of inflammation. The second goal is to prevent skin, mucosal and joint lesions, which usually do not lead to serious damage, but can significantly reduce patients' quality of life (QOL). Therapy should be tailored to the severity of the disease, the organs involved, the individual characteristics of the patient and his preferences [2]. The main role in the treatment of the disease is played by immunosuppressive and/or immunomodulatory drugs [12]. Because of their rapid anti-inflammatory effect, glucocorticosteroids (GCS) are the most commonly used [1]. Owing to the reactive anti-HCV antibodies found and the gradual improvement during symptomatic treatment in addition to empirical broad-spectrum antibiotic therapy (fluoroquinolone + cephalosporin III generation), the patient was not treated with GCS. It is worth mentioning at this point that despite the suspected influence of viral infections (including HCV infection) on the development of BD, its association with the disease has not been confirmed to date [11,12]. In clinical practice, prednisolone is used at a dose of 40–60 mg/d (reducing the dose after 4–6 weeks of treatment) [7]. As first-line treatment for mucocutaneous and articular symptoms, colchicine could also be used in our patient, either as monotherapy or in combination with benzathine penicillin, which accelerates the effect of colchicine [13]. We associate the improvement in our patient with the use of NSAIDs in support of broad-spectrum antibiotic therapy. In the maintenance treatment phase, the first-line drug is azathioprine [1]. However, it reaches maximum blood levels after 8–12 weeks of use, thus it is used in combination with NSAIDs to bridge acute attacks of the disease. The second-line drug is interferon alfa (IFN-α) and cyclosporine. In a randomized, placebo--controlled trial, the use of IFN-α2a significantly reduced the duration of exacerbations and pain [7]. Cyclosporine is usually preferred for conditions associated with ocular involvement. Due to its neurotoxicity, it is not recommended for use in patients with nervous system involvement [14].

CONCLUSIONS

BD is a multisystem disease, the diagnosis of which is often made more difficult by the different timing of symptoms. A multidisciplinary approach plays a key role in diagnosing patients. The patient's stay in the internal medicine ward contributed to a quicker

diagnosis because of the holistic view of the disease picture, and the numerous specialized consultations contributed a range of relevant information to the diagnosis. The diagnosis lacked an endoscopic examination of the gastrointestinal tract, but the patient was transferred to the Department of Rheumatology for further follow-up and diagnosis, and this will most likely be performed in the outpatient setting. As outlined above, making the diagnosis required a series of medical consultations ranging from neurology, ENT, gynecology, infectious diseases, dermatology and orthopedics. Owing to the unclear clinical picture, and in accordance with the recommendations of physicians from other specialties, a differential diagnosis was made for rheumatologic, autoimmune, bacteriologic (including sepsis), viral and STD diseases. The involvement of the skin, mucous membranes and joints is often less severe because of the low to moderate risk of permanent organ dysfunction. The key role is to control the inflammatory process, which can be achieved, as in the case presented here, by using NSAIDs in the cover of broad-spectrum antibiotics. This represents an interesting observation, however, the exact confirmation of such therapy, due to the small number of patients, may be difficult to achieve. Ocular involvement, CNS involvement and vasculitis have a worse prognosis and usually lead to significant disability, including blindness and even death, thus also requiring more aggressive treatment [15]. Most clinicians tailor BD treatment to the severity of the disease by assessing the risk of permanent organ damage and QOL considerations. The most common treatments are GCS, which in our case were limited by the possible recurrence of HCV infection, as well as disease-modifying drugs such as azathioprine, cyclosporine and interferon alfa. Unfortunately, even despite optimal treatment, relapses are common [1]. That is why it is so important to make an appropriate diagnosis and promptly initiate treatment to reduce the ongoing inflammatory process, which requires a multidisciplinary approach.

Authors' contribution

Study design – K. Gołojuch, P. Major, J. Smyk, A. Kamińska, W. Kosiba
Manuscript preparation – K. Gołojuch, P. Major, J. Smyk, A. Kamińska
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