Behçet's disease – diagnostic problems

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Abstract: Behçet's disease, rare in Poland, has been described in a 47-year-old woman with mucocutaneous lesions and gynecological pathology, persisting for 4 years before establishing the correct diagnosis. The criteria, course and principles of treatment were reminded in hope it may be useful for the physicians of various specialities.

Key words: Behçet's disease

INTRODUCTION

Behçet's disease (BD) is a systemic inflammation of blood vessels, involving recurrent painful mucosal sores in the oral cavity and on the genitals, skin lesions, and, frequently, eye inflammation. The disease was for the first time described in 1937 by Hulusi Behçet, a Turkish dermatologist [1-8]. The etiology of BD is unknown. Genetic factors are considered as its possible causes. The relationship between BD and the presence of histocompatibility antigens, HLA-B_{51} and HLA-B_{12}, has been demonstrated [1,3,6]. A role of disturbances in the immune system has been pointed out, i.e. an increased production of proinflammatory cytokines, circulating immunological complexes, antibodies against mucosal or endothelial cells [1,6,9]. A contribution of infectious factors to the BD development has not been confirmed [1,3,6,9]. Behçet's disease is most common in the Middle and Far East and in Mediterranean countries [1,3,7,9]. Depending on the geographic region, the incidence in the adult individuals amounts to 380/100,000 in Turkey, 100/100,000 in Japan, 1–2/100,000 in the USA, and 1/300,000 in northern Europe [3,9]. About a dozen cases have till now been described in Poland [1,4,10-16]. The most important clinical manifestations of BD are: ulcers in the oral cavity (97–99%) and on the genitals (85%), acne-like papulopustular skin lesions (85%), erythema nodosum (50%), positive pathergy test (60%), ocular symptoms (50%). Other symptoms that may occur include arthritis (44%), vein thrombosis (24%) and, more rarely, gastrointestinal complications (30%), inflammation in the central nervous system (CNS) (5%), kidneys (3%), lungs, or cardiovascular system (4%) [1-5,7,9]. Laboratory examinations are not specific. Anemia, leucocytosis, increased erythocyte sedimentation rate (ESR), elevated levels of C-reactive protein (CRP), immunoglobulins (Ig), mainly IgA, and components of the complement system may also occur. Antinuclear antibodies (ANA) and rheumatoid factors are usually absent. Coagulant abnormalities predisposing to thrombosis may appear [1,13]. No specific laboratory tests nor histopathologic findings confirming the disease are known. The diagnosis is being made based exclusively on typical signs and symptoms [1,3,6]. Criteria for diagnosing BD, established in 1990 by the International Study Group for Behçet's disease, include [8]:

1) main criterion: recurrent erosive lesions in oral mucosa occurring at least three times in a 12-month period
2) additional criteria:
   a) ocular involvement – anterior or posterior iritis, retinitis
   b) positive allergy test (pathergy reaction) – observed at 24–48 hours
   c) recurrent genital ulceration
   d) erythema nodosum, papulopustular lesions or those resembling inflammation of the hair follicles, acneiform nodules in postadolescent patients not on corticosteroids.

For the diagnosis of BD, criterion 1 and at least two of group 2 should be satisfied. No standards for pharmacological treatment of BD have been established. Each patient is treated on an individual basis depending on the clinical course of a particular case. Most often prescribed medication includes glycocorticosteroids (GCS), systemic and topical, nonsteroidal anti-inflammatory drugs (NSAIDs), azathioprine, cyclosporine, sulphasalazine, colchicine, antiplatelet drugs, anticoagulants, cyclophosphamide, dapsone, recombined α-2a and α-2b interferons. Studies on the use of anti-CD52 antibodies are under way [1,3,5-7]. In severe BD cases, in particular those with concomitant eye lesions and CNS involvement, treatment with TNF-α (tumor necrosis factor α) inhibitors has been initiated in preliminary studies. [2,4,17,18].

CASE REPORT

A 47-year-old woman admitted to the hospital had a 4-year history of recurring painful oral ulcerations with concomitant

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skin eruptions resembling erythema nodosum and subfibrile state. The patient complained also of periodic dyspareunia and bloody vaginal discharges. Prior to admission she was treated with antibiotics, antifungoids, and with antiinflammatory drugs administered topically without any improvement. On admission numerous shallow erosions of oral and tongue mucosa were found. Lesions resembling erythema nodosum were noted on the right lower extremity. In the genital area an ulceration with a diameter of 2 cm was noted, with hard heaped-up edges and bleeding crater-like bottom (two months earlier no pathology had been observed during gynecological examination). The ulceration was differentiated from neoplastic lesions. Histopathological examination (No. R4031554) revealed the presence of fragments of inflammatory granules containing numerous macrophages, granulocytes, lymphocytes, plasmacytes, necrotic core, stimulated swollen fibroblastic stroma, and moderately increased dilatated capillary vessels. After 10 days another ulceration appeared in the perivulval area. Laboratory examinations showed increased ESR (24 mm), elevated CRP level (26.45 mg/l, normal <5.0 mg/l), and leucocytosis in peripheral blood. Other laboratory results were normal (general urinanalysis, aminotransferases, electrolytes, creatinine, urea, coagulation tests). Rheumatoid factor, ANA against the native DNA (dsDNA), antibodies against smooth and skeleton muscles were absent. The X-ray of the chest was normal. Ultrasonography of the abdomen did not show abnormalities apart from isolated deposits in both kidneys. A trace dicrotic wave through the mitral valve, insignificant hemodynamical, was found on echocardiography. Ophthalmological examination showed slightly constricted retinal vessels with increased retinal reflection and Gunn's sign (+). Neurological checkup did not show any abnormalities.

The diagnosis of Behçet's disease was made based on the entire clinical presentation. The medication used included GCSs, initially prednisolone at a dose of 75 mg/d (1 mg/kg b.w.), followed by prednisone (50 mg/d), NSAIDs (ketoprophen), omeprasole, Aspargin (magnesium hydroaspartate + potassium hydroaspartate), and topical treatment. A complete regression of mucosal lesions and a partial of genital ulceration was achieved. Erythema nodosum and subfebrile state subsided. continued treatment with prednisone at tapered doses was recommended. After three weeks a complete regression of mucocutaneous lesions was observed. However the patient began complaining of eyeball pains which aroused a suspicion of secondary glaucoma. The medication was supplemented with dorzolamide and azatioprine at a dose of 150 mg/d (2 mg/kg b.w.). The dose of prednisone was reduced to 30 mg daily. After four weeks the complete regression of skin and mucosal lesions persisted, inflammatory markers were normal, but intraocular pressure was still increased. Therefore metipranolol was administered topically and the dose of prednisone was further reduced to 20 mg/d. After eight weeks, exacerbation of the disease occurred, manifested by mucosal symptoms and erythema nodosum, which required an increased dosage of prednisone (30 mg/d). Due toinefficacy, azatioprine was discontinued. Modifications in the treatment resulted in clinical improvement. During next few months mucocutaneous lesions occurred periodically, but being less diffuse leading to alterations in the therapy. Relapsing symptoms resulted in the combination of continued GCS medication with azatioprine, which stabilized the patient condition. For 7 months no full-blown relapse of the disease has been observed and the regression of skin and genital lesions persists. However, isolated small aphtha-like erosions occur in the oral mucosa.

DISCUSSION

The case described satisfied criterium 1 (main) and three additional criteria (b–d) for the recognition of BD. Small aphtha-like painful ulcers in the oral cavity, recurring many times during 12 months, were observed. Relapsing genital ulceration was also noted. Cutaneous lesions were diagnosed as erythema nodosum. No ocular complications, e.g. iritis or retinitis, were found, although observed in 50–70% of patients with BD. The later development of glaucoma was probably associated with GCS therapy. There were no serious systemic complications of BD. Laboratory examinations revealed increased ESR, raised CRP level and transient leucocytosis in the peripheral blood.

The diagnosis was established after 4 years from the first pathological signs, which reflects the diagnostic problems. Behçet's disease with a atypical course or incomplete set of criteria satisfied may not be diagnosed. In the differential diagnosis of BD, oral and genital inflammation, venereal diseases, collagen diseases, spondyloarthropathies, reactive arthritis, Stevens-Johnson or Lyell's syndrome, inflammatory bowel diseases, and cancer should be considered [1,3,9]. Behçet's disease generally begins with one or two signs. Other manifestations may occur within years. First symptoms tend to appear between 20 and 35 years of age [7], although they can happen at any age; in our patient at the age of 40. They tend to subside and recur spontaneously. Remission periods last for weeks, months and even years, exacerbations from several days to several months [6,7]. The activity of BD decreases in time and the prognosis is generally favorable. The treatment is individual, depending on the course of the disease. In view of its unpredictable course, diversified clinical manifestations, multi-organ involvement, spontaneous exacerbation and remission, the treatment of BD is difficult and requires coordination between different specialists. This was confirmed by the case described herein, in which irrespective of correct diagnosis being made there were difficulties in the effective management of the disease. Optimal improvement was achieved as a result of GCS treatment. Considering the multitude of symptoms, the need for long-term therapy using several agents and used on an individual basis, the report of BD, rare in Poland presented in this article seems valuable.

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