Adamantiades-Behçet Disease

3

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Key Points

- Rare disease with a worldwide distribution but strongly varying prevalence; certain ethnic groups are mainly affected.
- A genetically determined disorder with a probable environmental triggering factor.
- Multisystem occurrence, with oral aphthous ulcers, genital ulcers, papulopustules, erythema nodosum-like lesions, uveitis, and arthropathy as most common signs.
- Inflammatory disease representing a neutrophilic vascular reaction or vasculitis.
- Diagnosis is defined by new clinical criteria.
- Chronic relapsing progressive course and potentially poor prognosis (especially in males with systemic presenting signs; mortality, 0–6%).

Definition and Epidemiology

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 (McCarty et al. 2003; Suzuki Kurokawa and Suzuki 2004).

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Historical Aspects

The disease is named after Benediktos Adamantiades, a Greek ophthalmologist, and Hulûsi Behçet, a Turkish dermatologist, who, in 1931 and 1937, respectively, described patients with the characteristic clinical complex insisting for a single clinical entity (Zouboulis and Keitel 2002).

Epidemiology

Adamantiades-Behçet disease presents a worldwide occurrence with varying prevalence, being endemic in the eastern and central Asian and the eastern Mediterranean countries (along the so-called Silk Road) and rare in northern European countries, central and southern Africa, the American continent, and Australia (Zouboulis 2003). A prevalence of 80–420 patients per 100,000 inhabitants has been reported in Turkey (Azizlerli et al. 2003), whereas only 1.5 to 7.5:100,000 in southern Europe and 0.12 to

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1.18:100,000 in Northern Europe and the United States (Zouboulis 2003). Its annual incidence is low; 0.75–1.0 new cases per 100,000 inhabitants were assessed in Japan (1990) and Germany (2005) (Altenburg et al. 2006, 2012).

Adamantiades-Behçet disease most often affects patients in their 20 s and 30 s; however, early and late onsets (first year of life to 72 years) have been reported. Both genders are equally affected; a male predominance is still observed in Arab populations, whereas female predominance is evident in Korea, China, some northern European countries, and the United States.

Etiology and Pathogenesis

The etiology of the disease remains unknown, although genetic factors, infectious agents, environmental pollution, immunologic mechanisms, and endothelial and clotting factors have been implicated and studied intensively (Zouboulis and May 2003; Hirohata and Kikutchi 2003). The endemic occurrence along the historical Silk Road, the major involvement of certain ethnic groups (mostly of Turkmen and Mongol descent), and associated immunogenetic data support the hypothesis that the disease followed the migration of these old nomadic tribes. On the other hand, the wide variation of the disease prevalence in the same ethnic group in association with different geographic areas of residence indicates an additional environmental triggering factor. Therefore, transfer of genetic material and/or of an unknown exogenous agent may have been responsible for the expansion of the disease.

There is no specific mode of Mendelian transmission in Adamantiades-Behçet disease (Zouboulis and May 2003; Hirohata and Kikutchi 2003). Familial occurrence with regional differences has been reported. A significant association exists between the disease and human leukocyte antigen (HLA)-B_{51} in Japan, the Middle East, and the Mediterranean countries (de Menthon et al. 2009). The allele also seems to be associated with a more severe prognosis (Zouboulis et al. 2003a). Its exact role in the disease mechanism is still unknown; however, it may be involved in the disease development through specific antigen presentation, molecular mimicry with microbial antigens, or participation in linkage disequilibrium with a presently unknown susceptibility gene (Fietta 2005; Durrani and Papaliodis 2008). Among the 24 currently described alleles, HLA-B_{5101} and B_{5108} have most frequently been associated with Adamantiades-Behçet disease (Zierhut et al. 2003). Shared amino acid residues (defining the B_{w4} epitope) are crucial for antigen binding and natural killer cell interactions (Remmers et al. 2010), and B_{W4} was also reported to contribute to the severity of the disease (Papoutsis et al. 2010). Genes possibly associated with the disease have been localized on chromosome six in the region between the tumor necrosis factor gene and HLA-B or HLA-C genes, including the major histocompatibility complex class I chain A gene (A_6 allele) and genes for heat shock proteins (Hirohata and Kikutchi 2003; Fietta 2005; Zierhut et al. 2003; Escudier et al. 2006).

Adamantiades-Behçet disease is not considered contagious, as no horizontal transmission has ever been reported. However, viral and bacterial infections have been implicated in initiating immunopathologic pathways, leading to the onset of the disease (Zouboulis and May 2003; Hirohata and Kikutchi 2003).

Immunologic mechanisms are considered to play a major role in the pathogenesis of Adamantiades-Behçet disease (Zouboulis and May 2003; Hirohata and Kikutchi 2003; Zierhut et al. 2003; Escudier et al. 2006). The disease has been classified among the autoinflammatory disorders (Gül 2005), which are caused by primary dysfunction of the innate immune system.

Clinical Presentation

Adamantiades-Behçet disease is a chronic, recurrent, multisystem, and, occasionally, life-threatening disorder (McCarty et al. 2003; Altenburg et al. 2006). Recurrent oral aphthous ulcers, recurrent genital ulcers, skin manifestations, ocular lesions, and arthritis/arthropathy are the most frequent clinical manifestations. Vascular, gastrointestinal, neurologic, psychiat-

ric, pulmonary, renal, and cardiac manifestations, epididymitis, and other findings can also occur. The clinical picture usually develops within a few months after the presenting sign; both an acute multisystem presentation and long-term development of the disease over years are possible.

Approach to the Patient

Diagnosis of Adamantiades-Behçet disease is based on clinical signs, as pathognomonic laboratory test or histologic characteristics are absent. There are several sets of diagnostic criteria, the most popular of them being the criteria of the International Study Group (International Study Group for Behçet's Disease 1990) and those of the Behçet Disease Research Committee of Japan (Kaneko et al. 1999). However, there have been several problems with these criteria, including their performance in selectivity and specificity, so that both of them have currently been revised (International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) 2014) (Table 3.1).

Mucocutaneous Lesions

Recurrent oral aphthous and genital ulcers are the most frequently observed mucosal manifestations. Oral aphthous ulcers are the presenting sign in more than 80% of the cases (McCarty et al. 2003; Altenburg et al. 2006). Although recurrent aphthous stomatitis is a common disorder, only a few patients progress to Adamantiades-Behçet disease, and it is not possible to determine in whom or when the transition may occur (Oh et al. 2009). Typically, lesions are multiple, painful, 1–3 cm in diameter, and sharply margined with a fibrin-coated base and surrounding erythema (Fig. 3.1). Oral aphthous ulcers usually heal without scarring (92%). Genital ulcers may not recur as often and usually heal with a characteristic scar (64–88%; Fig. 3.2). Spontaneous healing of aphthae occurs within 4 days to 1 month; genital ulcers may persist longer. Large oral ulcerations can also be associated with problems such as pharyngeal involvement, dysphagia, and dyspnea or fistulae involving the pharynx, larynx, trachea, or esophagus. Genital ulcers can occur on the penis, scrotum, vagina, labia, and urethra, and also in the anal, perineal, and inguinal regions.

Skin lesions that should be accepted as diagnostically relevant in Adamantiades-Behçet disease should be confined to pustular vasculitic lesions (including pathergy lesions), erythema nodosum-like lesions, Sweet-like lesions, pyoderma gangrenosum-like lesions, and palpable purpuric lesions of necrotizing venulitis (Fig. 3.3). All of these lesions are characterized in their early stages by a neutrophilic vascular reaction (Jorizzo et al. 1995). Acneiform lesions or follicle-based pustules should not be considered relevant.

Table 3.1 Revised international criteria for Behçet's disease (International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) 2014)

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[a]	1

Scoring: score ≥4 indicates Adamantiades-Behçet disease

[a]Though the main scoring system does not include pathergy test, where pathergy testing is conducted, a positive result may be included for one extra point

Systemic Lesions

Ocular involvement is the major cause of morbidity in patients with Adamantiades-Behçet disease. The most diagnostically relevant lesion is posterior uveitis (also called *retinal vasculitis*), which can lead to blindness (Fig. 3.4). Other ocular lesions include anterior uveitis, hypopyon (pus in the anterior chamber of the eye, which is now—due to early treatment—uncommon), and secondary complications such as cataract, glaucoma, and neovascular lesions (Krause 2005).

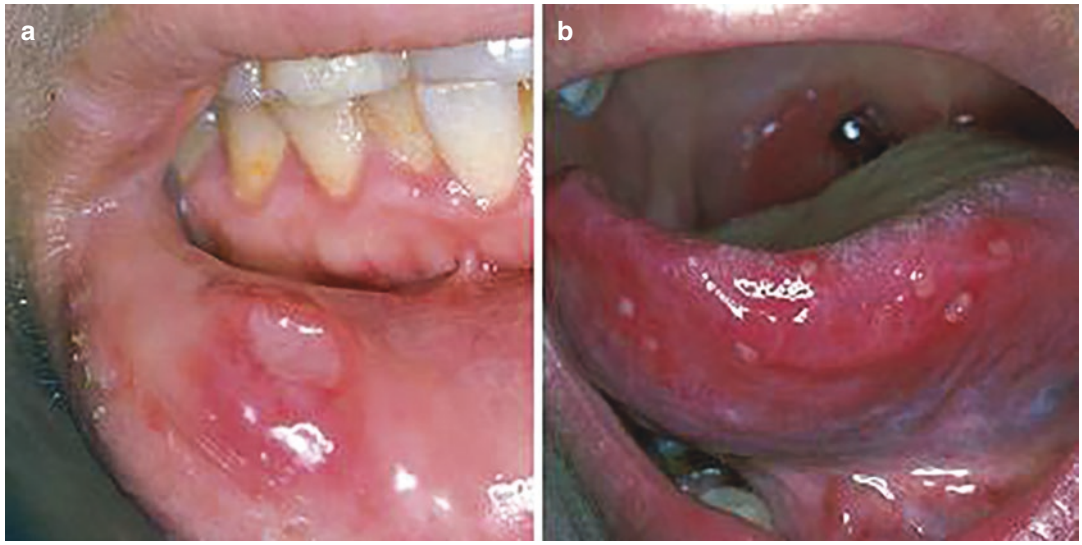

Fig. 3.1 Single (**a**) and multiple (**b**) oral aphthous ulcers ((**a**) from Altenburg et al. (2006), with permission)

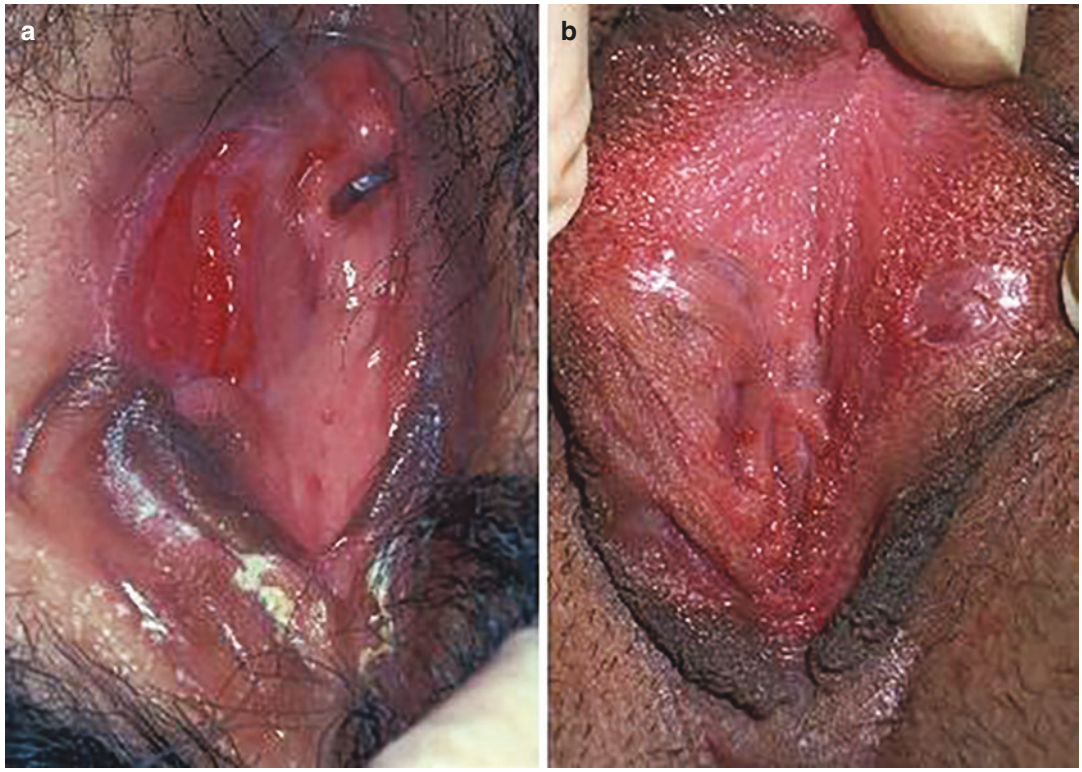

Fig. 3.2 Genital ulcer (**a**) healing with a demarcated flat scar (**b**)

Retinal inflammation can lead to vascular occlusion and, ultimately, tractional retinal detachment. Severe vitreous involvement, chronic cystoid macular edema, and possible—presumably also vasculitic—involvement of the optic nerve can result in vision loss. Recurrent vasculitic changes can ultimately lead to ischemic optic nerve atrophy.

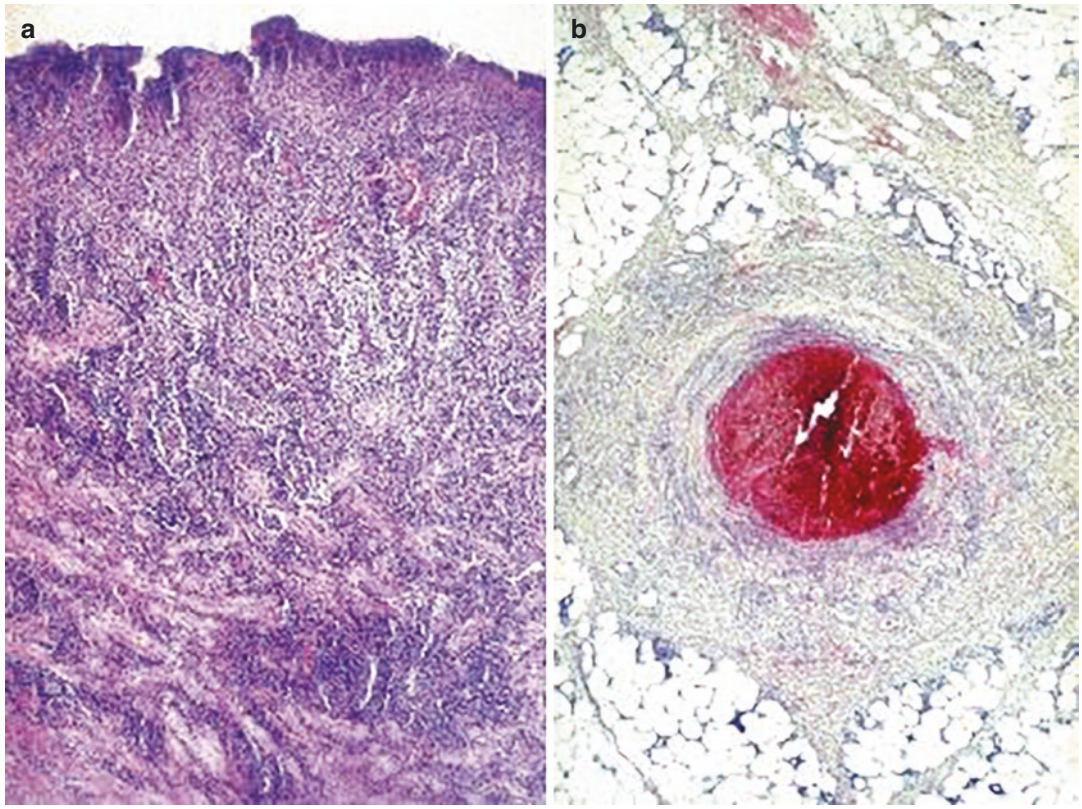

Fig. 3.3 (**a**) Abundant mixed inflammatory infiltrate dominated by neutrophils in an oral ulcer of Adamantiades-Behçet disease. (**b**) Vessel thrombosis in an erythema nodosum-like lesion

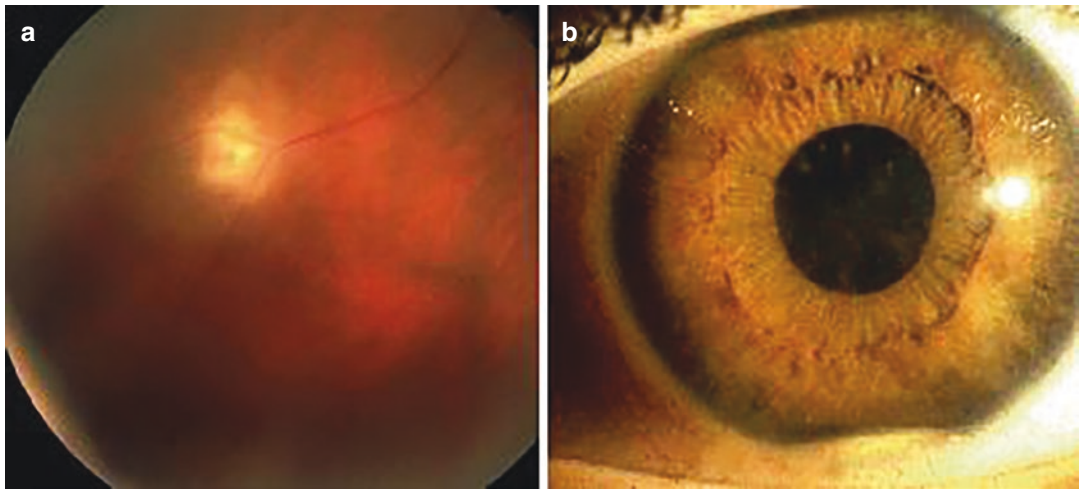

Fig. 3.4 (**a**) Posterior uveitis. (**b**) Hypopyon iritis. (From Altenburg et al. (2006), with permission)

The characteristic arthritis is a nonerosive, asymmetric, sterile, seronegative oligoarthritis; however, symmetric polyarticular involvement is common. Joint manifestations frequently occur first in one knee or ankle and then the other as migratory monoarthritis, then in both joints simultaneously, and finally affecting nearly all joints (Vaiopoulos et al. 2019). An HLA-B27-positive, erosive sacroiliitis has to be excluded.

Systemic vascular involvement can be significant and includes venous occlusions and varices, arterial occlusions, and aneurysms, often being migratory. Cases of large-vein thrombosis (inferior vena cava, cranial venous sinuses) or large-artery aneurysms are potentially fatal (McCarty et al. 2003; Altenburg et al. 2006). Arterial involvement is rather rare and usually presents in the form of thromboses and, less often, of aneurysms, resulting from multicentric arteritis. Pulmonary artery aneurysms are the principal feature of pulmonary involvement in Adamantiades-Behçet disease, occasionally resulting in coughing and hemoptysis. Cardiac involvement can include myocarditis, coronary arteritis, endocarditis, and valvular disease. A wide spectrum of renal manifestations can occur, varying from minimal change disease to proliferative glomerulonephritis and rapidly progressive crescentic glomerulonephritis. Immune complex deposition is thought to be responsible for the underlying pathogenesis in some cases of glomerulonephritis. Gastrointestinal complaints can be a symptom for aphthae throughout the gastrointestinal tract and can rarely result in perforation and peritonitis (0.5%). Inflammatory bowel disease has to be excluded. Sterile prostatitis and epididymitis can be present in male patients without genital ulcers.

Significant neurologic manifestations occur in approximately 10% of patients and may be delayed in onset. Meningoencephalitis, cerebral venous sinus thrombosis, benign intracranial hypertension, cranial nerve palsies, brainstem lesions, and pyramidal or extrapyramidal lesions have been described. Poor prognosis is associated with a progressive course, relapses after treatment, repeated attacks, and cerebellar symptoms or parenchymal disease. Neurologic manifestations usually present with severe headache. Further symptoms include gait disturbance, dysarthria, vertigo, and diplopia as well as hyperreflexia, epileptic seizures, hemiplegia, ataxia, or a positive Babinski reflex. Psychiatric symptoms, such as depression, insomnia, or memory impairment, are also signs of neurologic involvement.

Histopathology

Characteristic histopathologic features of Adamantiades-Behçet disease are vasculitis and thrombosis (Fig. 3.3). Biopsies from early mucocutaneous lesions show a neutrophilic vascular reaction with endothelial swelling, extravasation of erythrocytes, and leukocytoclasia or a fully developed leukocytoclastic vasculitis with fibrinoid necrosis of blood vessel walls (McCarty et al. 2003; Altenburg et al. 2006). Although there are reports of lesions that consist primarily of a lymphocytic perivasculitis, most of these lesions are likely older. The neutrophilic vascular reaction should be considered the predominant histopathologic finding (Jorizzo et al. 1995). Aneurysms can also develop in large arteries as a result of vasculitis of the vasa vasorum with penetration of the lamina elastica.

Special Tests

Pathergy Test

A positive pathergy test (hyperreactivity reaction) manifests within 48 h as an erythematous papule (>2 mm) or pustule at the site of a skin needle prick or after intracutaneous injection of 0.1-ml isotonic salt solution using a 20-gauge needle without prior disinfection of the injection site. The skin prick is generally placed at an angle of 45° 3–5 mm intracutaneously on the volar forearm. Erythema without infiltration is considered a negative finding. Provoked oral aphthae and genital ulcers after injection or injury (such as chorioretinitis in the corneal region of the eye after photocoagulation of the ocular fundus region) can also be considered as positive pathergy phenomenon. Broader pathergy phe-

nomena also include the occurrence of aneurysms around vascular anastomoses as well as local recurrence of ulcers after resection of affected bowel segments. Although a positive pathergy reaction is a sign of Adamantiades-Behçet disease, it is not pathognomonic, as it can also occur in patients with pyoderma gangrenosum, rheumatoid arthritis, Crohn disease, and genital herpes infection.

Radiologic Findings

Scintigraphic evidence of arthritis is found in 50% of the patients (Altenburg et al. 2006). Cranial magnetic resonance imaging allows documentation of hypodense or atrophic changes in the brain. Electroencephalographic detection of diffuse α waves is considered a positive finding. Vascular lesions can be detected by angiography.

Differential Diagnosis (Table 3.2)

Table 3.2 Differential diagnosis of Adamantiades-Behçet disease

Oculocutaneous/mucocutaneous syndromes
Erythema multiforme exudativum and variants, including Stevens-Johnson syndrome
Vogt-Koyanagi-Harada syndrome
Reiter disease
Bullous autoimmune diseases: pemphigus vulgaris, cicatricial mucous membrane pemphigoid, epidermolysis bullosa acquisita
Viral infections (herpes, coxsackie, echo)
Syphilis
Articulomucocutaneous syndromes
Systemic lupus erythematosus
MAGIC syndrome (*m*outh *a*nd *g*enital ulcers with inflamed *c*artilage)
Yersiniosis
Arthropathic psoriasis
Gastrointestinal/mucocutaneous syndromes
Ulcerative colitis, Crohn disease
Tuberculosis
Bowel-associated dermatitis-arthritis syndrome
Aphthae
Recurrent aphthous stomatitis (RAS)
Cyclic neutropenia
Herpes simplex infection
Genital ulcers
Ulcus vulvae acutum (Lipschütz ulcer)
Herpes simplex infection
Sexually transmitted infections
Uveitis
Other forms of uveitis
Arthritis
Ankylosing spondylitis
Juvenile rheumatoid arthritis
Central nervous system manifestation
Multiple sclerosis
Neuro-sweet disease
Lung manifestation
Sarcoidosis

Adapted from Altenburg et al. (2006)

Clinical Course and Prognosis

The clinical course of Adamantiades-Behçet disease is variable. There can be a delay of up to several years before the diagnosis is made, and this may influence the prognosis. Mucocutaneous and joint manifestations usually occur first. Recurrent erythema nodosum and $HLAB_{51}$ positivity are risk factors for the development of superficial thrombophlebitis and vision loss (Zouboulis et al. 2003a, b; Sakamoto et al. 1995), and superficial thrombophlebitis, ocular lesions, and male gender are risk factors for the development of systemic vessel involvement (Zouboulis et al. 2003a, b; Coskun et al. 2005; Bonitsis et al. 2015). A severe course, including blindness, meningoencephalitis, hemoptysis, intestinal perforation, and severe arthritis, occurs in approximately 10% of patients. Blindness can often be prevented with early aggressive therapy of posterior uveitis. Lethal outcome has been seen in 0–6% of affected patients in different ethnic groups. Central nervous system and pulmonary and large vessel involvement, as well as bowel perforation, are the major life-threatening complications; death may also result as a complication of immunosuppressive therapy. Markers of severe prognosis include $HLA\text{-}B_{51}$ positivity, male gender, and early development of systemic signs (Zouboulis et al. 2003a). Onset in childhood does not necessarily predict a poor prognosis (Vaiopoulos et al. 2016). Spontaneous

remissions of certain or all manifestations of the disease have been observed. Ophthalmic and neurologic sequelae are leading causes of morbidity, followed by severe vascular and gastrointestinal manifestations, and their effects on morbidity may be cumulative.

General Principles of Treatment

The choice of treatment for patients with Adamantiades-Behçet disease depends on the site and severity of the clinical manifestations of the disease. Recurrent aphthae are most often treated with palliative agents, such as mild diet, avoidance of irritating agents, and potent topical glucocorticoids and local anesthetics (Zouboulis 2003a; Alpsoy 2005); however, a series of different treatments according to the severity of the aphthae has been proposed (Table 3.3) (Altenburg et al. 2007, 2014). For the topical treatment of genital ulcers and skin lesions, corticosteroid and antiseptic creams can be applied for up to 7 days. Painful genital ulcerations can be managed by topical anesthetics in cream. Corticosteroid injections (triamcinolone acetonide, 0.1–0.5 ml/lesion) can be helpful in recalcitrant ulcerations. They can also be beneficial on panuveitis and cystoid macular edema as a single intravitreal injection (triamcinolone acetonide 4 mg) (Atmaca et al. 2007; Tuncer et al. 2007).

Patients with mucocutaneous lesions resistant to topical treatment, those with systemic involvement, and patients with markers of poor prognosis are candidates for systemic treatment (Zouboulis 2003a; Pipitone et al. 2006; Altenburg et al. 2014; Hatemi et al. 2018). Several compounds have been found effective in randomized, double-blind, placebo-controlled trials (Aktulga et al. 1980; Yazici et al. 1990; Davies et al. 1998; Yurdakul et al. 2001; Alpsoy et al. 2002; Sharquie et al. 2002; Matsuda et al. 2003; Mat et al. 2006; Davatchi et al. 2009; Jaffe et al. 2016; Mohammadi et al. 2017; Hatemi et al. 2018, 2019) (Table 3.4). Additional treatments have been successful in studies with a lower grade of evidence (BenEzra et al. 1988; Davies et al. 1988; Hamuryudan et al. 1998; Masuda et al. 1989; Ozyazgan et al. 1992; Moral et al. 1995; Zouboulis and Orfanos 1998; Zouboulis 2003a, b; Suzuki Kurokawa and Suzuki 2004; Melikoglu et al. 2005; Guillaume-Czitrom et al. 2007; Sfikakis et al. 2007; Nanke et al. 2008; Krause et al. 2008; Kiliç et al. 2009) (Table 3.5). Oral and intravenous prednisolone can be combined with other immunosuppressants, colchicine, dapsone, sulfasalazine, or interferon-α. A synergistic effect with cyclosporine A has been described in patients with

Table 3.3 Topical treatment of oral aphthous ulcers

Mild diet
Avoidance of hard, spicy, or salty nutrients and irritating chemicals, such as toasted bread, nuts, oranges, lemons, tomatoes, spices (pepper, paprika, curry), alcohol- or CO_2-holding drinks, mouthwashes, toothpastes containing sodium lauryl sulfate[a]
Topical treatment of the aphthous oral ulcers includes
Caustic solutions (silver nitrate, 1–2%; tinctura myrrha, 5–10% weight/volume; H_2O_2, 0.5%; methyl violet, 0.5%) 1–2×/day
Antiseptic and anti-inflammatory preparations (amlexanox, 5% in oral paste[a]; triclosan, 0.1% mouthwash solution and in toothpastes[a]; amyloglucosidase- and glucose oxidase-containing toothpastes[a]; hexetidine, 1%, chlorhexidine, 1–2% mouthwash solutions; benzydamine; chamomile extracts) 3% diclofenac in 2.5% hyaluronic acid[a]; hyaluronic acid 0.2% gel; tetracycline mouthwash (as glycerine solution 250 mg/5 mL glycerine) 2 min 4–6×/day [a] (caveat: pregnancy); doxymycine in isobutyl cyanoacrylate[a]
Corticosteroids (triamcinolone mucosal ointment, dexamethasone mucosal paste, betamethasone pastilles) 4×/day or during the night (ointment/paste) or intrafocal infiltrations with triamcinolone suspension 0.1–0.5 mL per lesion
Anesthetics (lidocaine, 2–5%; mepivacaine, 1.5%; tetracaine, 0.5%–1% gels or mucosal ointments) 2–3×/day (caveat: Allergy)
5-Aminosalicylic acid (5% cream) 3×/day (reduces the duration of lesions and the pain intensity)
Cyclosporin A, 500-mg solution for mouthwash 3×/day (effective as topical immunosuppressive drug)
Sucralfate suspension, 5 mL × 4/day [a] (for oral aphthous and genital ulcers)
A close association of smoking with a decrease of recurrences of oral aphthous ulcers has been described

[a] Small, randomized, double-blind, placebo-controlled trial against placebo

Table 3.4 Systemic treatment of Adamantiades-Behçet disease

Drug	Dose	Indication
Apremilast	30 mg/2×/d PO for 16 months (caveat: mild gastrointestinal symptoms)	Oral aphthae (improvement and prevention)
Rebamipide	300 mg/day PO (caveat: pregnancy, lactation)	Oral aphthae
Colchicine	1–2 mg/day PO (caveat: pregnancy, lactation—induces oligozoospermia)	Oral aphthae, genital ulcers, folliculitis, erythema nodosum
	1.5 mg/day	Erythema nodosum, arthritis, genital ulcers (oral aphthae in females)
		Ineffective
Methylprednisolone	40 mg/every 3 weeks IM	Erythema nodosum (but not orogenital ulcers)
	1000 mg/d IV for 3 days (in addition to cyclophosphamide, azathioprine, and prednisolone IV for 6 months	Posterior uveitis and/or retinal vasculitis – Improvement of visual acuity
Dapsone	100 mg/day PO (caveat: pregnancy, lactation—methemoglobin increase: ascorbic acid, 500 mg/day)	Oral aphthae, genital ulcers, skin lesions, pathergy test
Interferon-α 2a	6×10^6 IU/3×/week SC (caveat: pregnancy, lactation—induces psychotic signs, psoriasis, myopathy)	Oral aphthae, genital ulcers, papulopustular lesions
Thalidomide	100 mg/day or 300 mg/day (caveat: pregnancy, lactation—induces polyneuropathy: minimized at 25 mg/day)	Oral aphthae, genital ulcers, papulopustular lesions
Etanercept (anti-TNFαR-ab)	25 mg/2×/week PO (caveat: pregnancy, lactation)	Oral aphthae, nodular lesions, papulopustular lesions (not pathergy test)
Azathioprine	2.5 mg/kg/day (caveat: pregnancy, lactation, severe liver disease, bone marrow depression, severe infection, children)	Recent onset ocular disease
Cyclosporine A	10 mg/kg/day PO (against colchicine, 1 mg/day PO) (caveat: lactation, renal insufficiency—contraindicated in central nervous system involvement)	Ocular manifestations, oral ulcers, skin lesions, genital ulcers
	5 mg/kg/day PO (against cyclophosphamide pulses)	Visual acuity
	5 mg/d PO (against conventional treatment)	Ocular attacks
Azapropazone	900 mg/day PO over 3 weeks	Arthritis
Adalilumab (anti-TNFα-ab)	160 mg SC day 0, 80 mg day 14, 40 mg day 28 and every 2 weeks	Uveitis (any type, different etiology)
Acyclovir	5 × 800 mg for 1 week +2 × 400 mg/day for 11 week	Ineffective
Interferon-α	1000 and 2000 IU/day PO	Ineffective
Secukinumab (anti-IL17A-ab)	Initial loading, secukinumab 300 mg/2 weeks SC	Ineffective
Gevokinumab (anti-IL1-ab)	60 mg/month SC	Ineffective
Anticoagulants	Meta-analysis	Ineffective against thrombosis, but no use may increase the risk of post-thrombotic syndrome

Evidence grade A—randomized, double-blind, placebo-controlled trial (RCT) against placebo except otherwise mentioned

Table 3.5 Systemic treatment of Adamantiades-Behçet's disease

Drug	Dose	Indication
Pentoxifylline	300 mg × 1–3/day PO	Oral aphthae (partic, in children)
Oxpentifylline	400 mg × 3/day PO	
Irsogladine	2–4 mg/day PO	Recurrent aphthae
Indomethacin	100 mg/day PO	Mucocutaneous lesions, arthritis
Interferon-α	9×10^6 IU × 3/week/3–9×10^6 IU × 5/week SC ($3\ 10^6$ IU × 3/week maintenance dose) (caveat: pregnancy, lactation—induces psychotic signs, psoriasis, myopathy)	Ocular lesions, long-term visual prognosis, arthritis, vascular lesions (peg-IFN-α-2b: reduces the need of long-term systemic corticosteroids)
	1.5–3 × 10^6 IU × 3/week according to body weight	Corticodependent uveitis in children
Corticosteroids	5–60 mg/day prednisolone equivalent PO	Active disease
	100–1000 mg/day IV over 1–3 days (alone or in combinations) (can induce diabetes or psychosis)	Acute exacerbation (partic. uveitis, neurological manifestations)
Cyclosporine A	3–6 mg/kg/day PO (serum levels: 100–150 ng/ml) (caveat: lactation, renal insufficiency—induces pathologic CNS findings)	Uveitis, mucocutaneous signs, thrombophlebitis, acute hearing loss
Tacrolimus	0.05–0.2 mg/kg/day PO (serum levels: 15–25 ng/ml)	Refractory uveitis
Cyclophosphamide	1 g/month IV bolus (caveat: hemorrhagic cystitis: mesna 200 mg)	Uveitis, neurologic manifestations
Chlorambucil	0.1 mg/day PO (2 mg/day maintenance dose) (caveat: cumulative toxicity)	Neurologic manifestations, uveitis, thrombosis, mucocutaneous lesions
Methotrexate	7.5–20 mg/1× week PO (caveat: pregnancy, lactation, severe bone marrow depression, liver dysfunction, acute infections, gastrointestinal ulcers, kidney insufficiency)	Severe mucocutaneous lesions, arthritis, progressive psychosis, or dementia
Infliximab (anti-TNFα-ab)	5 mg/kg IV days 1, 7, 14, and 28 or days 1, 14/1, 30/1, and 45 (caveat: pregnancy, lactation)	Acute uveitis, refractory posterior uveitis, neurologic manifestations, vascular manifestations, intestinal involvement
Adalimumab (anti-TNFα-ab)	160 mg SC day 0, 80 mg day 14, 40 or 80 mg day 28 and every 2 weeks	Refractory ocular lesions, intestinal manifestation—individual optimization reduces side effects
Sulfasalazine	1.5–3 g/day PO	Gastrointestinal ulcers
Thalidomide	2 mg/kg/day PO; increased to 3 mg/kg/day if necessary or decreased to 1–0.5 mg/kg/day according to the response (caveat: neurotoxicity)	Intestinal involvement (in children)
Gevokinumab (anti-IL1-ab)	30 mg/month IV or 60 mg/month SC	Ineffective
		Control of acute ocular exacerbation

Evidence grade B—well-conducted open clinical trial

ocular involvement. Prednisolone is one of the few medications that can be used during pregnancy. Colchicine can be combined with immunosuppressants and interferon-α. Apremilast for the treatment of oral aphthous ulcers and adalimumab for the improvement of uveitis/retinitis have been recently added in the treatment of the disease (Jaffe et al. 2016; Hatemi et al. 2019). A rapid relapse often occurs after discontinuing cyclosporine A, interferon-α, dapsone, or infliximab (BenEzra et al. 1988; Davies et al. 1988; Hamuryudan et al. 1998; Hatemi Get al. 2018, 2019).

Prevention

- Patients with severe or progressive recurrent aphthous stomatitis should be followed up for years as potential candidates for Adamantiades-

Behçet disease, particularly those patients with familial occurrence of the disease.
- Patients with suspected Adamantiades-Behçet disease should be referred early for specialist advice.
- Male patients with systemic involvement as a presenting sign and/or an early age of onset should be treated systemically because of the poor prognosis.

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