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19.11.10 Behçet’s syndrome 4579 immunosuppressants, both conventional and biologic, have been used in refractory cases. MAGIC syndrome: Mouth and genital ulcers with inflamed cartilage MAGIC syndrome describes an overlap between relapsing polychondritis and Bechet’s disease. Clinical presentation includes chondritis, oral aphthous ulcers, ocular inflammation, genital ulceration, and arthritis. Aneurysms occur in about 20% of cases. Treatments that have been used include prednisolone, colchicine, azathioprine, methotrexate, and cyclophosphamide. Cogan’s syndrome Cogan’s syndrome is a rare disease of unknown cause that mainly affects young adults and characteristically presents with nonspecific systemic features and ocular (interstitial keratitis) and inner ear (vertigo, tinnitus, hearing loss) symptoms. It may be associated with a large vessel vasculitis. Inflammatory markers are raised; im- munological tests are typically negative; corneal biopsies may show a lymphocytic and plasma cell infiltrate; vessel histology resembles giant cell arteritis. Treatment is with topical or oral steroids; add- itional immunosuppressive therapy may be needed for resistant dis- ease. Deafness is the commonest long-term complication. FURTHER READING IgA vasculitis Audemard-Verger A, et al. (2015). IgA vasculitis (Henoch-Schönlein purpura) in adults: diagnostic and therapeutic aspects. Autoimmun Rev, 14, 579–85. Gonzalez-Gay MA, Blanco R, Pina T (2014). IgA vasculitis (Henoch- Schönlein purpura). In: Ball GV, et al. (eds) Oxford textbook of vasculitis, pp. 528–46. Oxford, Oxford University Press. Cryoglobulinaemia vasculitis Cacoub P, et al. (2015). Cryoglobulinaemia vasculitis. Am J Med, 128, 950–5. Ramos-Casals M, et al. (2012). The cryoglobulinaemias. Lancet, 379, 348–60. Hypocomplementaemic urticarial vasculitis Jachiet M, et al. (2015). The clinical spectrum and therapeutic man- agement of hypocomplementaemic urticarial vasculitis. Arthritis Rheum, 67, 527–34. 19.11.10 Behçet’s syndrome Sebahattin Yurdakul, Izzet Fresko, and Hasan Yazici ESSENTIALS Behçet’s syndrome is an inflammatory disorder of unknown aeti- ology that involves arteries and veins of all sizes. Most cases are from the countries around the Mediterranean basin, the Middle East, and East Asia, with

the highest prevalence in Turkey. Clinical features—typically presents in the second and third decades with recurrent oral ulcers (98% of cases), genital ulcers (85%), acneiform lesions (85%), pathergy reaction (60% in some countries), erythema nodosum (50%), uveitis (50%), arthritis (50%), thrombo- phlebitis (30%), and less commonly with arterial occlusion/an- eurysm, central nervous system involvement, or gastrointestinal lesions. A relapsing/remitting course is usual. Disease is more se- vere and mortality is higher in men. The diagnosis is clinical, labora- tory findings are nonspecific, and there is no specific diagnostic test for Behçet's syndrome. Management and prognosis—elderly people, and women with mild mucocutaneous lesions, can be managed symp- tomatically. Young people and men need a more aggressive treatment approach, typically as follows (1) mucocutaneous lesions—colchicine and local measures (i.e. corticosteroids); (2) acute severe eye involvement—ciclosporin with or without steroids, an anti-tumour necrosis factor agent, or solo inter- feron is the first agent to use, often replaced by azathioprine to maintain remission; (3) thrombophlebitis—typically man- aged with aspirin and azathioprine; (4) severe vascular disease— cyclophosphamide, steroids and anti-tumour necrosis factor agents are the preferred treatments (5) parenchymal central nervous system disease—management remains problematic:
steroids, immunosuppressives, and tumour necrosis factor α antagonists have all been tried. Major vessel disease and neuro- logical involvement are the main causes of death. About 10–15% of male patients who have eye disease lose useful vision despite treatment. Fig. 19.11.9.6 Auricular cartilage inflammation in a patient with relapsing polychondritis. Reproduced from Watts RA et al. (eds) (2013). Oxford Textbook of Rheumatology, 4th edn, by permission of Oxford University Press.

section 19 Rheumatological disorders 4580 Introduction Hulusi Behçet, a Turkish dermatologist working in Istanbul, de- scribed three patients with oral and genital ulceration and uveitis with hypopyon in 1937; it soon became apparent that many other organ systems were involved and that the condition was a wide- spread vasculitis. Aetiology, genetics, pathogenesis, and pathology Behçet's syndrome is an inflammatory disorder of unknown aeti- ology. HLA B51 is the genetic marker which had consistently been shown to be associated with the condition. This is now confirmed in several whole-genome studies. However, non-HLA loci may also be operative, such as IL-10, IL-23R IL-12RB2, CCR1, STAT4, KLRC4, IL-1A-IL-1B, IRF8, CEPBP-PTPN1, and GIMAP (GTPases of immunity associated protein). An interaction between ERAP1 and HLA-B51 has also been showed. Various microRNAs have also been implicated in the pathogenesis. Both the adaptive and innate immune systems are activated in Behçet's syndrome. The evidence for the former is the Th1 and Th17 predominant cytokine profile, and a Th1 type tissue infil- tration in cutaneous and intestinal tissues; the evidence for the latter is the primed state of neutrophils and the presence of polyclonal γδ T cells in the sera. The absence of classical autoimmune features such as specific antibodies and the intermittent nature of the clinical findings have led some to include Behçet's syn- drome among the autoinflammatory syndromes. However, this generalization is not justified when one considers the monogenic autoinflammatory disorders (see Chapter 12.12.2), but can be more justified when one compares Crohn's disease with patients with Behçet's syndrome with mainly intestinal inflammation. In considering the pathogenesis of Behçet's syndrome it might prove useful to consider particular variants of disease expression. One notable cluster of patients is those with acne and arthritis; an- other is those with superficial and deep vein thrombosis, and a pro- pensity to dural sinus thrombi. These differing manifestations of what we now regard as Behçet's syndrome might indicate more than one disease mechanism. Behçet's syndrome involves arteries and veins of all sizes, but there are some lesions where direct evidence of injury to the

vessel wall cannot be demonstrated. Among these are the acne lesions of the skin, where histology is no different from ordinary acne, and, in the brain, where evidence for direct vessel wall injury is difficult to find. There is no specific cell type that dominates in vasculitic le- sions and immune complex deposition can be seen only in some. Thrombophilic factors seem not to be the primary event in explaining the hypercoagulability of Behçet's syndrome: hypertriglyceridaemia might be a risk factor. Epidemiology Behçet's syndrome has a distinct geographical distribution, with most cases being from the countries around the Mediterranean basin, the Middle East, and East Asia. The prevalence ranges from 0.07/104 in Spain to 8 to 42/104 in Turkey. The Silk Route has been suggested as the mechanism through which an aetiological agent (genetic or environmental) was spread. A study performed in North African and Asian immigrants in Paris showed that (by contrast with the native population) Behçet's syndrome was nearly as frequent as the primary vasculitides among them, and the increased prevalence was not related to the age of immigration, suggesting a genetic rather than environmental explanation. The condition can affect every age group, but onset before puberty or after the sixth decade is relatively rare. Changes in disease expres- sion such as older age at diagnosis and more frequent joint, gastro- intestinal, and central nervous system manifestations have been reported in Korea, probably due to changing patterns of medica- tion, hygiene, and disease awareness. Alterations in annual preva- lence rates have also been reported. Clinical findings Clinical manifestations are protean (Table 19.11.10.1) and the disease course is characterized by unpredictable periods of recur- rences and remissions. Although skin and mucosal lesions are most common, the ocular, central nervous system, and large-vessel manifestations are more serious. Mucocutaneous Oral ulceration is generally the first, as well as the most frequent, manifestation of Behçet's syndrome. Smoking may decrease the frequency. Table 19.11.10.1 Clinical manifestations of Behçet's syndrome Manifestation Features Recurrent oral ulcers (97–99%) Usually the first and most recurrent manifestation Mostly minor ulcers; heal without scarring Usually indistinguishable in appearance and histology from recurrent aphthae Genital ulcers (c.85%) Mostly on the scrotum or both labiae Less frequent on the penis Large ulcers (>1 cm) heal with a scar Papulopustular lesions (c.85%) Indistinguishable from ordinary acne On face and back as well as unusual acne sites (extremities) Erythema nodosum (c.50%) Mostly on lower extremities Similar to primary erythema nodosum Confused with superficial thrombophlebitis Pathergy reaction (60%) 60–70% positivity in Turkey or Japan Rarely positive in northern Europe or the United States Uveitis (c.50%) Chronic, relapsing, bilateral panuveitis Hypopyon indicates a grave prognosis Joints (50%) Mono- or oligoarticular yet symmetrical Nondeforming, nonerosive, and self-limited Mostly knees, ankles, elbows, and wrists Thrombophlebitis (30%) Frequently superficial or deep veins of the legs Thromboembolism is rare Arterial occlusion/ aneurysm (c.4%) Entire arterial tree Pulmonary artery aneurysms present with haemoptyses CNS involvement (5–10%) Parenchymal (80%) and dural sinus thrombi (20%) Peripheral neuropathy uncommon Gastrointestinal lesions (1–30%) Rare in Turkey and 30% in Japan Mimicking inflammatory bowel diseases

 Genital ulcers cause pain and discomfort (Fig. 19.11.10.1), with the presence of genital scarring being quite useful for diagnosis. Urethritis is not observed, in contrast to that seen in Reiter's disease or sexually transmitted infections. Papulopustular or acneiform lesions are usually indistinguishable from ordinary acne vulgaris, both in appearance and in histology. They are usually seen on the face, upper chest, and back, but they can also affect sites not typically affected by acne vulgaris, such as the arms and legs. The lesions of erythema nodosum can be diffi- cult to differentiate from superficial thrombophlebitis by the naked

eye: ultrasound examination may obviate the need for a biopsy. Less common forms of skin lesions are papules, palpable purpura, skin ulcers, Sweet's syndrome, and pyoderma gangrenosum. The pathergy phenomenon is defined as a nonspecific hyperre activity to simple trauma. Typically, a papule or a pustule forms in 24–48 h after skin puncture with a needle (Fig. 19.11.10.2). This is quite specific for Behçet's syndrome, but although found in 60 to 70% of patients in Turkey or Japan, it is rarely observed in northern Europe or the United States of America. A global decrease in its rate of posi- tivity has been noted during the last decade. It can be observed in organs other than the skin, such as attacks of uveitis after eye surgery, synovitis after arthrocentesis, or development of an aneurysm after puncture of an artery. However, wound healing is normal.

Ocular Eye involvement takes the form of a relapsing panuveitis that gen- erally starts within the first two years of disease onset. It is more frequent (70%) and has a more severe course in men, and in young people (aged less than 25 years). Hypopyon uveitis, an intense in- flammation in the anterior chamber that can be seen by the phys- ician without any ophthalmological aids in 20% of patients with ocular disease, is associated with severe retinal disease. Posterior uveal inflammation with retinal vasculitis causes retinal exudates, haemorrhages, venous thrombosis, papilloedema, and macular disease. Smooth layered hypopyon, superficial retinal infil- trates with retinal haemorrhages and branch retinal vein thrombosis seem pathognomonic. Recurrent attacks of eye inflammation lead to structural changes such as synechiae and retinal scars, which are the main determinants of eye prognosis. Episcleritis, conjunctivitis, cor- neal ulcerations, and lid lesions are occasionally seen. Multimodal imaging using color fundus photography, angiography and optical coherence tomography increases the diagnostic precision. Musculoskeletal Arthritis is mono- or oligoarticular, usually resolves in a few weeks, and is associated with acneiform lesions.

A subgroup with acne and arthritis has increased enthesopathy when examined by ultrasonog- raphy. Chronic synovitis with erosions and deformity can be seen, but is rare. Back pain and sacroiliac joint involvement are not part of the clinical picture. Synovial fluid is commonly inflammatory, with a predominance of neutrophils, but it has a good mucin clot forma- tion. Local myositis of the legs, or generalized similar to polymyo- sitis, is infrequently seen, as is osteonecrosis. Vascular Behçet's syndrome involves both veins and arteries. Around a third of patients have thrombophlebitis, most frequently in the superfi- cial or deep veins of the legs. Venous claudication is occasionally observed. Obstruction of the superior and/or inferior vena cava are less frequent, and occlusion of the suprahepatic veins (Budd– Chiari syndrome) is rare but carries a high mortality especially in patients with symptomatic liver disease. Thromboembolism is rare, most probably due to the tight adherence of thrombi to the diseased vein. The entire arterial tree can be affected by arterial aneurysms and/or occlusion: the abdominal aorta is the most frequent site, followed by the iliac, femoral, popliteal, carotid, and subclavian vessels. Pulmonary artery aneurysms are associated with thrombophlebitis of leg veins and inferior vena cava in 90% of patients. They present with haemoptyses, which can be fatal, with the typical finding on chest radiography being noncavitating single or multiple shadows (Fig. 19.11.10.3). Computed tomography (CT) scans confirm the diagnosis. Neurological Disease of the CNS is also more common and more severe in male patients. Most of those affected (80%) have parenchymal disease, which causes pyramidal, cerebellar, and sensory signs and symptoms, sphincter disturbances, and behavioural changes alongside with cognitive impairment. The remaining 20% have nonparenchymal involvement in the form of intracranial hyper- tension due to dural sinus thrombosis presenting with headaches Fig. 19.11.10.1 Genital ulcers in a patient with Behçet's syndrome. Fig. 19.11.10.2 The pathergy reaction induced by needle pricks to the forearms.

section 19 Rheumatological disorders 4582 and papilloedema. Both types of involvement rarely occur in the same patient. Cerebrospinal fluid examination shows nonspecific findings, but a high protein or cell count implies a grave prognosis in the long run. Peripheral neuropathy, which is frequently seen in other vasculitides, is uncommon in Behçet's syndrome. Gastrointestinal Gastrointestinal involvement shows geographical variation, being rare among people who live in the Mediterranean countries al- though frequent among those in Japan. Mucosal ulceration, primarily in the ileum and colon, presents with colicky abdominal pain and diarrhoea that mimic inflammatory bowel diseases. It usually follows a fluctuating course, with exacerbations and remissions, and it tends to perforate. Lack of mucosal healing and the use of immunomodulators during the maintenance of remission are pre- dictors of relapse. Hepatic involvement is uncommon except for the rare Budd– Chiari syndrome. A slightly enlarged spleen can be found in men. Cardiac There have been sporadic reports of many types of conduction problems, valvular disease, and aortitis, as well as ventricular an- eurysms and coronary vasculitis, and endomyocardial fibrosis with intracardiac thrombi. However, the overall frequency of cardiac disease was no different from that seen in controls in a prospective controlled study. Other features Renal involvement, seen infrequently, ranges from IgA nephropathy to rapidly progressive glomerulonephritis. Immune complexes are not usually found in the kidneys. Amyloidosis of the AA type occasion- ally occurs, as observed in other chronic inflammatory states, usu- ally presenting in men with a nephrotic syndrome, which has a grave prognosis. Epididymitis is a well-recognized feature, reported in up to 20% of cases. Voiding disturbances have also been described. Differential diagnosis The two conditions that most commonly cause problems in diag- nosis are inflammatory bowel disease, especially Crohn's dis- ease, and multiple sclerosis. Intestinal and especially ileocaecal ulcers are both observed in Crohn's disease and Behçet's syn- drome, but fistulization and perianal ulcerations are rare in the latter. Furthermore, the eye inflammation of Behçet's syn- drome is most often a panuveitis, compared with the anterior chamber disease seen in Crohn's disease. With regard to mul- tiple sclerosis, optic neuritis is rare in Behçet's syndrome, and the characteristic MRI lesions of Behçet's syndrome are situated in the basal ganglia and diencephalon, whereas those in mul- tiple sclerosis are usually seen as white matter lesions in the periventricular areas. Clinical investigation Laboratory findings are nonspecific. A mild anaemia of chronic disease and leucocytosis are seen in some patients. The erythro- cyte sedimentation rate and C-reactive protein may be moderately elevated, and the latter may correlate with erythema nodosum and acute thrombophlebitis, although these inflammatory markers generally do not mirror clinical activity. Autoantibodies such as rheumatoid factors and antinuclear antibodies are absent and tests for antineutrophil cytoplasmic antibodies and anticardiolipin anti- bodies are usually negative. Criteria for classification In 1990 the International Study Group for Behçet's syndrome pro- posed a set of classification criteria that are sensitive (95%) and specific (98%) (Box 19.11.10.1). A revised version that takes into account the vascular and neurological findings has a 94% sensitivity and a 92% specificity. Management Treatment depends on the type and severity of symptoms, disease duration, and the age and sex of the patient. Those who are eld- erly, and women with mild mucocutaneous lesions, can be man- aged symptomatically, while young people and men need a more Fig. 19.11.10.3 Chest radiograph showing pulmonary artery aneurysms in a patient with Behçet's syndrome. Box 19.11.10.1 International Study Group Criteria for diagnosis of Behçet's disease • Recurrent oral ulceration (recurrent at least three times in one 12-month period) plus any two of the following findings: • Recurrent genital ulceration • Eye lesions • Skin lesions • Positive pathergy test Reprinted from The Lancet, 335, International Study Group for Behçet's Disease, Criteria for diagnosis of Behçet's disease, 1070–80, 1990, with permission from Elsevier.

19.11.10 Behçet’s syndrome 4583 aggressive approach. A EULAR based recommendation set for management is available (Table 19.11.10.2). Controlled trials show that colchicine 1 to 2 mg/day is effective for genital ulcers, erythema nodosum, and arthritis in women. It is beneficial only for arthritis in males. Thalidomide at 100 mg/day is effective for orogenital ulceration, but its well-known adverse ef- fects, in particular as a teratogen, hinder its more widespread use. Dapsone 100 mg/day is also beneficial in mucocutaneous lesions. A recent phase 2 trial has shown that the phosphodiesterase in- hibitor apremilast is effective in oral and most probably genital ulcerations. Azathioprine (2.5 mg/kg per day) helps preserve visual acuity in established eye disease and prevents the emergence of new eye disease. It also has salutary effects on oral–genital ulcers and arthritis, and its use early in the course of disease is asso- ciated with a more favourable outcome. A drawback is its slow onset of action—usually taking around four months for full effect. Ciclosporin 3–5 mg/kg per day acts within weeks and is the first agent to use in acute and severe eye involvement. It decreases the frequency of mucocutaneous lesions as well. Adverse effects are hypertension, renal impairment, and neurotoxicity, which require close monitoring. Ciclosporin and azathioprine are frequently combined, with the former used to induce remission and the latter as a remission-maintaining agent. Corticosteroids are widely used in managing Behçet’s syndrome, but in the only controlled study methylprednisolone acetate (40 mg intramuscularly every three weeks) was useful only in controlling erythema nodosum lesions in women. Cyclophosphamide (2– 2.5 mg/kg per day orally, or 500–1500 mg as monthly intravenous boluses) is the preferred treatment for severe vascular disease, with steroids usually added for the initial few months. The management of the parenchymal type of CNS disease is prob- lematic: steroids, immunosuppressives, interferon-α, and tumour necrosis factor (TNF)-α antagonists have all been tried. Dural sinus thrombosis is managed with brief courses of high dose steroids. Gastrointestinal involvement is initially managed by sulfasalazine at a dose of 2 to 6 g/day, but sometimes bowel resection is required. Anti-TNF agents have been useful in selected cases. There is debate about whether or not to use heparin or oral anti- coagulants for the thrombophlebitis of Behçet’s syndrome. As stated previously, pulmonary embolism is seldom observed, so antiplatelet drugs (i.e. aspirin) are probably sufficient. We also use azathioprine to generally suppress disease activity in the thrombophlebitis of Behçet’s syndrome. Surgical correction of peripheral arterial aneurysms is usually successful (in appropriate cases), with immunosuppressives given before surgical intervention to prevent recurrence. However, sur- gical correction of pulmonary arterial aneurysms should not be at- tempted because of high surgical mortality. Data on α-interferon and the TNFα blockers from open studies have shown that they are also beneficial in patients who are resistant to conventional treatments and they are used with increasing frequency worldwide. Interferon-α (3–6 MU/day) was reported to cause a partial or complete response in patients with resistant posterior uveitis. Side effects such as flu-like symptoms were frequent and dose dependent. The TNFα blocker infliximab 5 mg/ kg was useful in controlling severe and resistant uveitis, and other severe manifestations such as gastro- intestinal and neurological Behçet’s syndrome and major arterial dis- ease. A double-blind, placebo-controlled study with the TNFα blocker etanercept found it to be useful in controlling most mucocutaneous lesions of Behçet’s syndrome when used at 25 mg twice a week for a period of 4 weeks. Adalimumab, interleukin 1 antibodies gevokizumab

Table 19.11.10.2 2018 EULAR recommendations for the management of Behçet’s syndrome

Manifestation	Recommendation
Eye disease	Any patient with inflammatory eye disease affecting the posterior segment should be on a treatment regimen that includes azathioprine ciclosporin, IFN-α or TNF antagonists. Systemic glucocorticoids should be used only in combination with immunosuppressives. Severe eye disease—Patients presenting with acute sight threatening uveitis should be treated with high dose glucocorticoids, infliximab or IFNα. Intravitreal glucocorticoid

injection is an option in selected patients. Arterial and/or venous disease There is no firm evidence to guide the management of major vessel disease. For acute deep vein thrombosis, immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide, or ciclosporinA are recommended. For pulmonary and peripheral arterial aneurysms, cyclophosphamide and corticosteroids are recommended. TNFα blockers are alternatives especially in resistant cases. There are no controlled data on, or evidence of benefit from uncontrolled experience with anticoagulants, antiplatelet or antifibrinolytic agents in the management of deep vein thrombosis, or for the use of anticoagulation for arterial lesions. Gastrointestinal disease There is no evidence-based treatment that can be recommended for the management of gastrointestinal involvement. Agents such as sulfasalazine, corticosteroids, azathioprine, TNFα antagonists and thalidomide should be tried before surgery, excepting in emergencies. Arthritis Can be managed with colchicine in most cases. Azathioprine, IFNα and TNFα inhibitors can be used in recurrent and chronic cases. CNS disease There are no controlled data to guide management. For parenchymal involvement agents to be tried include corticosteroids, IFNα, azathioprine, cyclophosphamide, methotrexate and TNFα antagonists. For dural sinus thrombosis corticosteroids are recommended. Ciclosporin A should not be used in central nervous system involvement unless necessary for intraocular inflammation. Skin and mucosal disease The decision to treat will depend on the perceived severity by the doctor and the patient. Mucocutaneous involvement should be treated according to the dominant or codominant lesions present. Topical measures (i.e. local corticosteroids) should be the first line of treatment for isolated oral and genital ulcers. Acne-like lesions are usually of cosmetic concern only, hence topical measures as used in acne vulgaris are usually sufficient. Colchicine should be preferred when the dominant lesion is erythema nodosum. Azathioprine, TNFα antagonists, IFNα and apremilast may be considered in resistant mucocutaneous disease. Leg ulcers in BS might be caused by venous stasis or obliterative vasculitis. Treatment should be planned with help of a dermatologist and a vascular surgeon.

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