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Behçet's Disease

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Certification of Supervisor

I certify that this project entitled "BEHCETS DISEASE " was prepared by Shahad Salah under my supervision at the college of dentistry/university of Baghdad in partial fulfillment of the requirements for the degree of B.D.S.

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Dedications

“To my father and mother who guided my steps and provided love , support and appreciation all the way through ..
To my guardian angel , my brother ” ahmed” who’s soul was present with me , lighted my way until this very moment…
All love, gratitude and respect to my friends , they have been a constant source of inspiration, a special thanks is offered to them…”

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Introduction

BEHÇET'S disease is an inflammatory disorder of unknown cause, characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions **(Kaklamani *et al* , 1998).** All these common manifestations are self-limiting except for the ocular atacks . Repeated attacks of uveitis can cause blindness **(Nussenblatt , 1997).** Behçet's disease is ,persistent inflammatory disease, but rather one consisting of recurrent attacks of acute inflammation **(Cetişli A ,2008)** . The disease rarely onsets at childhood and an early diagnosis is often challenging **(Hu et al , 2021)** . Behçet's disease (BD) was first described in 1937 , Behçet's disease differ due to the fact that the disease is detectedat different rates in different geographical regions and ethnic groups and is rare. It is mostly seen in the Eastern Mediterranean and the Far East (along with the Silk Road). The incidence in Turkey is 0.3% whereas it is 0.02% in Japan, Korea, Iran, Iraq, and Saudi Arabia . It is a chronic inflammatory disease that is more severe among young men and exhibits prolonged remission periods and relapses of decreasing severity as the age increases. The onset is severe and progression is fast in 30 to 40-year-old males (male/female ratio 3:1). Mortality varies according to ethnicity, geographic and genetic characteristics **(Leccese et al , 2017)** . There is ocular involvement in approximately half of all cases. Ocular findings generally emerge in the first 5 years after the onset of the disease, and those cases comprise 70–80% young males and the remainder are females and elderly **(Tugal-Tutkun et al , 2004)** . Besides considerable morbidity, the disease confers an increased mortality, mainly because of neurological, pulmonary and other large vessel involvement as well as bowel perforation. It has long been implicated that increased morbidity and lethal outcome are often due to delayed diagnosis and treatment **(Alpsoy E et al ,2004)** .

The disease has a wide clinical spectrum of mucocutaneous lesions and ocular, vascular, articular, neurologic, gastrointestinal and cardiac involvement. Although the number of effective drugs used in the disease's treatment has increased in recent years. Many factors are associated with a more serious course, such as male gender and a younger age of onset. While the severity of the disease is more pronounced in the first years of the disease, it decreases in most patients after the age of forties. The primary goal treatment should be the prevention of irreversible organ damage. Therefore, early diagnosis and appropriate treatment and close follow-up are mandatory to reduce the morbidity and mortality of the disease. Treatment varies depending on the organ involved and the severity of the involvement. For all these reasons, the treatment should be personalized and arranged with a multidisciplinary approach according to the organs involved. Treatment is mainly based on suppression of the inflammatory attacks of the disease using local and systemic immunomodulatory and immunosuppressive drugs **(Alpsoy E et al , 2021)** . Since the first description of the disease triad in the 1930s, infectious microbial agents have always been speculated to be involved in the pathogenesis of BD, however, so far, no single pathogenic etiology has been found. Recent studies have investigated the association between the composition of the microbiomes and BD, which may provide a useful insight to the role of the microbiome in the disease process**(Mehmood et al , 2021) .**

Review of literature

Behçet's disease (BD) is a systemic variable vessel vasculitis that involves the skin, mucosa, joints, eyes, arteries, veins, nervous system and gastrointestinal system, presenting with remissions and exacerbations. It is a multifactorial disease, and several triggering factors including oral cavity infections and viruses may induce inflammatory attacks in genetically susceptible individuals **(kone-paute et al. ,2021).**

1. Epidemiology of Behçet's disease

Behçet's disease (BD) has significant epidemiological aspects to keep in mind, because they may have implications for the diagnosis **(Kone-Paut et al. , 2021) .** BD exists worldwide although there are significant regional differences, with the highest number of incidences in the Mediterranean, the Middle East, and the Far East **(Levine & Godeau , 1993) .** The association of BD with the ancient trading route known as the "Silk Road" which extends from eastern Asia to the Mediterranean basin and the distribution of HLA-B5 and its HLA-B*51 subtype provides important clues to its origin. BD occurs most frequently between the latitudes 30º and 45º N in Eurasian populations **(Bang & Lee , 2011)** . The incidence of BD varies according to geographical location. Turkey demonstrates the highest prevalence in the world, with up to 420 per 100,000 persons affected. Iran, Israel, northern China, and Korea follow with the next highest prevalence **(Cho et al , 2012)** . The countries with the lowest prevalence are the United Kingdom, Spain, Sweden, Portugal, and the United States, ranging from 0.3 to 6.4 per 100,000 persons **(Davatchi et al , 2010)** . The onset of BD typically occurs

in the third or fourth decade of life, and it is rarely seen in children or patients above the age of 50. The clinical courses of childhood-onset BD and late-onset BD are relatively benign **(Bang et al , 2011)** . BD shows a male preponderance in Middle Eastern countries and the Mediterranean; however, women are more commonly affected in Japan and Korea **(Yesudian et al , 2007) .** Men and women may be affected by BD, the sex ratio of which is close to 1 on the international scale. There are, however, some uncertain- tie concerning a possible greater gender-related predisposition to developing BD in certain geographical zones. Data giving the preferential occurrence of BD as a function of gender rely on the fact that gender is a determining factor in the severity of BD. Indeed, men present a more severe disease course, particularly a greater fre- quency of major vascular and ocular events. It is thus conceivable that the variation in sex ratio observed in the studies reflects a greater or lesser disposition to diagnose less severe forms of BD **(Kone-Paut et al , 2012).**

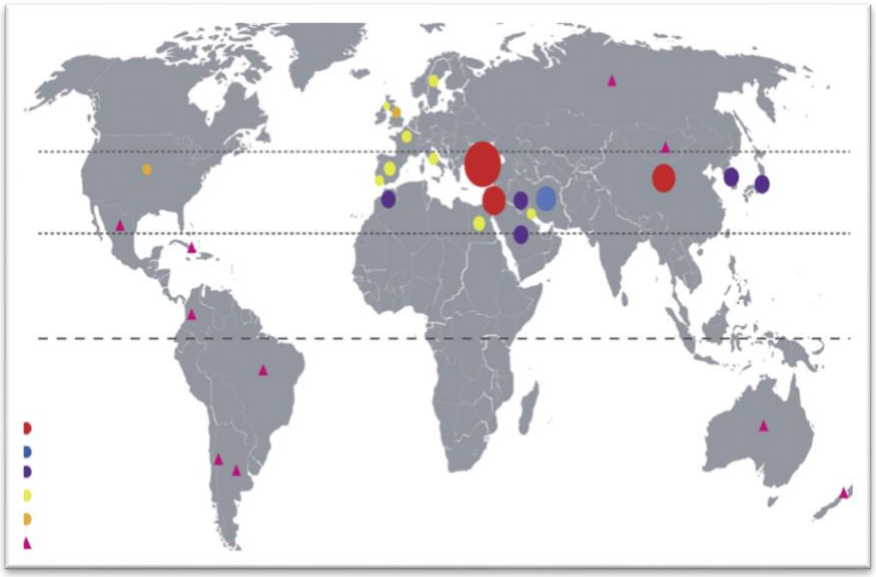

Figure 1 : distribution of Behçet's disease . (Cho et al , 2012)

2. Etiopathology

The cause of BD is unknown. It is believed to be due to an autoimmune process triggered by an infectious or environmental agent in a genetically predisposed individual **(pay et al , 2007).**

2.1 Genetic theory

The unusual geographic distribution of BD and pathology association with the allele of the major histocompatibility complex (MHC) locus, HLA-B51, may be the strongest indicator that certain genes are directly responsible for BD . HLA-B51 allele located in the MHC locus, on chromosome 6p has been the most strongly associated risk factor for BD in areas along the Old Silk Route, with a stronger association in Turkish and Japanese patients in comparison to

Caucasians **(Verity et al , 1999).** Studies have shown that HLAB*51 is associated with BD, with more than 60% of patients testing positive for HLA-B*51 **(Wallace & Niemczyk , 2011).** Other genes present in the MHC locus have been studied like HLA-B5701, associated with disease susceptibility and MICA (MHC class I related gene) and TNF genes, however, their participation is considered to be due to linkage disequilibrium with HLA-B51 gene **(Marshall S , 2004)** . Several other genes, located outside the MHC region have been proposed to be involved in BD pathogenesis. Meta-analyses identified that common variants of the IL10 and encoding interleukin 23 receptor (IL23R)-encoding interleukin 12 receptor beta (IL12B2) genes were strongly associated with BD **(Remmers et al , 2011).** IL23 is a proinflammatory cytokine that stimulates Th17 proliferation, increases the production of inflammatory cytokines, and increases the expression of IL-23 p19 mRNA in erythema nodosum-like skin lesions in patients with active BD **(Lew et al , 2008).** IL10 is known as an anti-inflammatory cytokine that inhibits the action of proinflammatory cytokines, and the up-regulation of the CD4+ CD25+ T-regulatory cells in a BD-like mouse model improved the inflammatory symptoms via IL10 **(shim et al , 2011)**. Therefore, the IL10 and IL23R-IL12B2 genes may play major roles in thepathogenesis of BD. Factor V gene, also called factor V Leiden (FVL), have been associated with thrombosis and ocular involvement in BD with controversial results **(Chamorro et al , 2011).**

2.2Infection theory

Individuals from endemic areas who have immigrated to areas with low prevalence of the disease have an intermediate risk for developing the disease, which points that environment has some role in BD **(Zouboulis et al , 1997)**. Several microorganisms have long been postulated as possible environmental triggers of BD, specially Herpes simplex virus-1 and Streptococcus Sanguis **(Direskeneli , 2011).** The most commonly investigated microorganism in the pathogenesis of BD is Streptococcus. The relationship between streptococcal infections and BD is suggested by clinical observations such as a higher incidence of infections such as tonsillitis and dental caries, aggravation of BD and the beneficial effect of antibacterial treatments on mucocutaneous and arthritic symptoms **(Mumcu et al , 2007).** HSV type 1 can be detected in saliva, intestinal ulcers, and genital ulcers by polymerase chain reaction in patients with BD compared with healthy controls **(Sohn et al , 1998)**. In addition, a BD-like mouse model was developed by inoculation of mouse earlobes with HSV and demonstrated HSV DNA sequences in cutaneous and gastrointestinal ulcerative lesions. Famciclovir seemed to be effective in improving BD-like symptoms and preventing recurrence in a symptomatic mouse model **(Sohn et al , 2001)**. However, to date, there is no information supporting the role of a single microorganism as the specific etiologic agent. The most generally accepted theory for the role of infectious agents is that microorganism antigens have high homology with human proteins (like heat shock protein (HSP 65), obtained from Mycobacterium, which has high homology with human protein (HSP60) and that cross-reaction leads to immune response **(Ergun et al , 2001).**

2.3 Immunologic theory

Autoimmune reactions in BD are suggested to target primarily blood vessels, especially endothelial cells, causing the clinical presentation of vasculitis Anti-endothelial cell antibodies (AECA) have been described in many vasculitides, including BD and, in some of these diseases, their presence has been linked to the pathogenesis **(Mendoza-Pinto et al , 2010).** identified α-enolase as a target antigen of IgM-type anti-endothelial cell antibodies (AECA) in patients with BD using proteomic techniques. Several mechanisms were proposed in order to explain the action of AECAs in the pathophysiology of inflammatory diseases, including the binding of AECA to endothelial cells resulting in cell activation, which may in turn increase secretions of cytokines. AECAs might also trigger inflammatory processes by complement dependent cytotoxicity and/or antibody-dependent cellular toxicity **(Cho et al , 2012).** T cells are the major lymphocytes implicated in BD pathogenesis. T lymphocytes have an activated phenotype in BD and produce inflammatory cytokines **(Zhou et al , 2012).** The discovery of new T cell subpopulations in the recent years has shed new light on BD pathogenesis. Numerous perturbations in T cell homeostasis have been reported. γδT cells and cytotoxic T cells, Th1 T cells, regulatory T cells (Tregs) and more recently Th17 cells have been implicated in the pathogenesis of BD **(Pineton et al ,2012).** γδ T lymphocytes play a major role in mucosal immunity as the first line of host defence. Evidence of an increased proportion of activated γδ T cells have been reported in BD and seems to play an important role in the pathogenesis of the disease **(Freysdottir et al , 2006).** Culture of γδ T lymphocytes from BD patients proliferates in response to products from microorganisms in oral ulcers **(Bank et al , 2003).** Accumulation of γδ T cells in the sites of inflammation in BD has been reported **(Hamzaoui et al , 1994).**

Natural Killer T (NKT) cells are implicated in the control of autoimmune diseases. They can also regulate immune response through cytokine production or cell/cell contact. Activated NK cells have been reported to be increased in active BD patients **(Yamaguchi et al , 2010)**. IL-8 is produced by T cells and is a major chemokine known to activate leukocytes, it was assumed to represent a link between immune system activation and endothelial alteration in BD. Elevated level of IL8 was reported in serum of BD patients, and in skin lesions and small vessel endothelial cell. IL8 was correlated with disease activity and vascular involvement **(Durmazlar &Ulkar , 2009)** . An increase in Th1 cytokine production has been found in peripheral blood of active BD patients and in lesions of active BD patients (ileal, mucocutaneous, skin) **(Imamura et al , 2005).** Th1 cells infiltrates including TNFα, INFγ, IL8 and IL12 was reported in oral and genital ulcer, and gastrointestinal lesions of BD **(Dalghous et al , 2006).** Recently reported an increase of Th17 cells and a decrease of Tregs in peripheral blood of active BD patients. IL21 is a recently identified cytokine produced by central memory activated CD4+ T cells also able to drive Th17 differentiation but also to modulate Th1 and Tregs cells **(Geri et al , 2011).** IL21 producing CD4+ T cells were dramatically increased in peripheral blood of BD patients and correlated positively with Th17 and negatively with Tregs, IL21 may act upstream of Th17 and Th1 pathways. Th17, a subset of T helper cells, characterized by their production of IL17, has been more recently isolated and is implicated in many autoimmune/inflammatory disorders. IL17 promotes neutrophilmediated inflammatory response **(Direskeneli & Fujita , 2011).** Tregs have a central role in protecting an individual fromautoimmunity and have been widely studied in different autoimmune disorders **(Miyara &Sakaguchi , 2011)** . Activated Tregs were particularly decreased in BD patients. Tregs from BD patients were able to suppress effector cells meaning

that they were functional **(Geri et al , 2011).** Neutrophils are one of the major players of the innate immunity system. Neutrophil abnormalities have been extensively reported in BD. In vivo, the priming state of neutrophil has been reported among BD patients. The role of T cells in the neutrophil activation has been shown in experimental studies. High level of proinflammatory cytokines including IL8, INF γ and TNFα are suggested to be responsible for the prime state of neutrophils **(Pay et al , 2007).** Strikingly, Th17 cells are implicated in the up-regulation of the neutrophil inflammatory response **(Ekinci et al , 2010).** Neutrophil are directly implicated in specific lesions of BD as histopathological analysis of BD lesions showed venous and arterial infiltrates of neutrophils. It has been proposed to classify BD as a neutrophilic vasculitis **(Kobayashi et al , 2000)**. and the concept of the neutrophilic phlebitis was advocated **(Hayasaki et al , 2004).** Endothelial cells have pleiotropic functions which maintain the integrity of the vessel lumen to keep the blood flow intact. Many studies have reported endothelial dysfunction in BD. Endothelium is one of the main targets in BD, and endothelium dysfunction and activation have been clearly established **(Pineton et al , 2012).** Triggering factors such as viruses or bacteria are supposed to participate in the outbreak of BD. T cell homeostasis perturbation, especially Th1 and Th17 expansions and decrease regulation by Tregs are now supposed to be the cornerstone of BD pathogenesis. Inflammatory cytokine such as IL21 are playing a critical role in pathogenesis of BD. Inflammatory cells within BD inflammatory lesions included mostly neutrophils, and cytotoxic cells. Lastly, endothelium dysfunction and activation have been clearly established **(Greso et al. , 2018).**

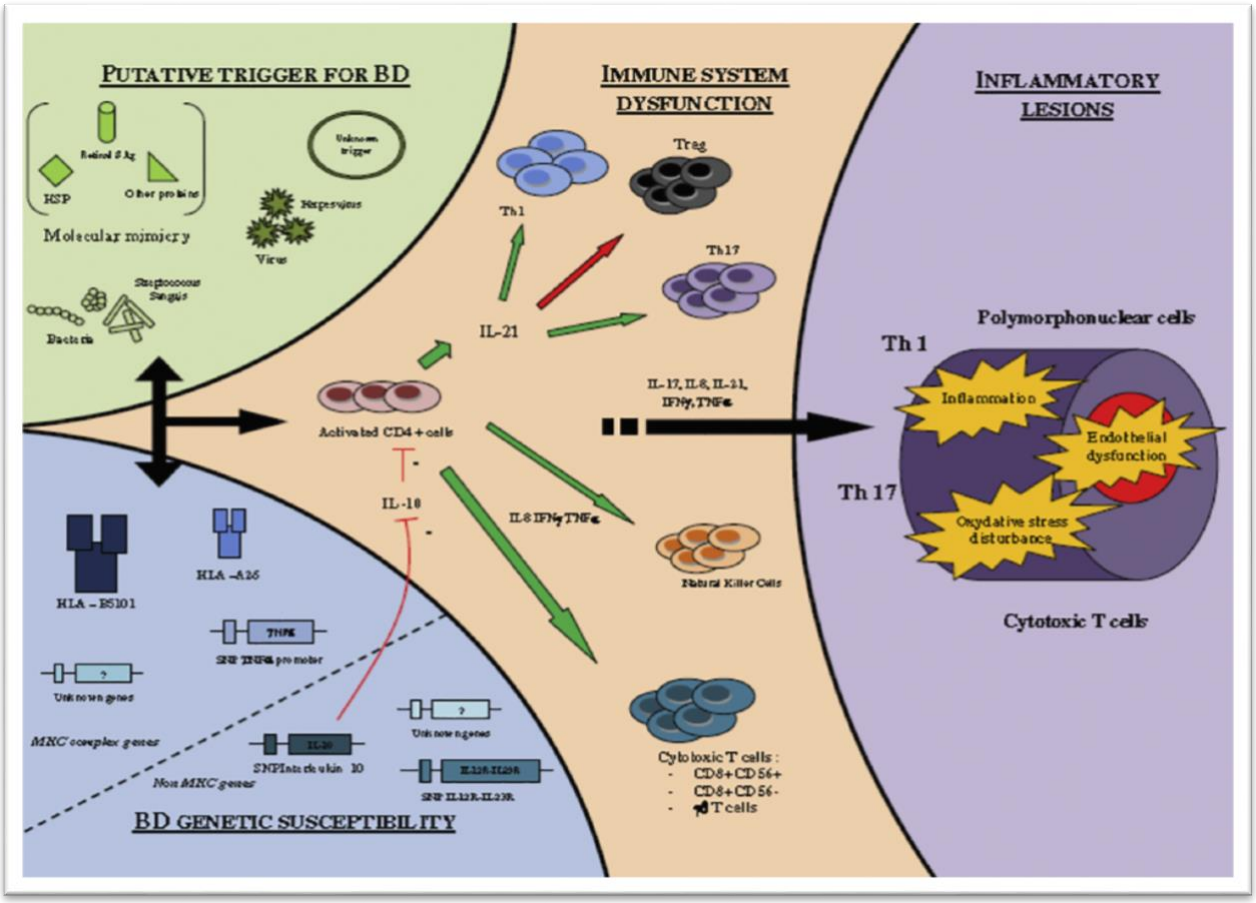

Figure 2 : actual knowledge into behcet disease pathogenesis. (pineton et al. ,2012).

3.Clinical manifestation

Despite being originally described as a dermatological disease, the majo causes of morbidity and mortality result from ocular, major vascular and neurological involvement. (Erdinç et al. , 2004).

3.1 Mucocutaneous lesions

The mucocutaneous lesions constitute the hallmark of BD. Oral aphthae occur in 98% of cases and are mandatory in the international criteria of classification **(Antonio et al. , 2017).** Painful oral ulcers appear in the tongue, pharynx, buccal and labial mucosal membranes. 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. Genital aphthae occur in 60 to 65% of cases and are very suggesting of the diagnosis of BD. They are localized in men on the scrotum and in women on the vulva and vagina where they can be disseminated and painful or totally indolent. They are morphologically similar to the oral ulcers but usually larger and deeper (Fig. 3) **(Saadoun & Wechsler , 2012).** Other skin lesions are Erythema nodosum, Pseudofolliculitis, Papulopustular lesions, Acneiform nodules.

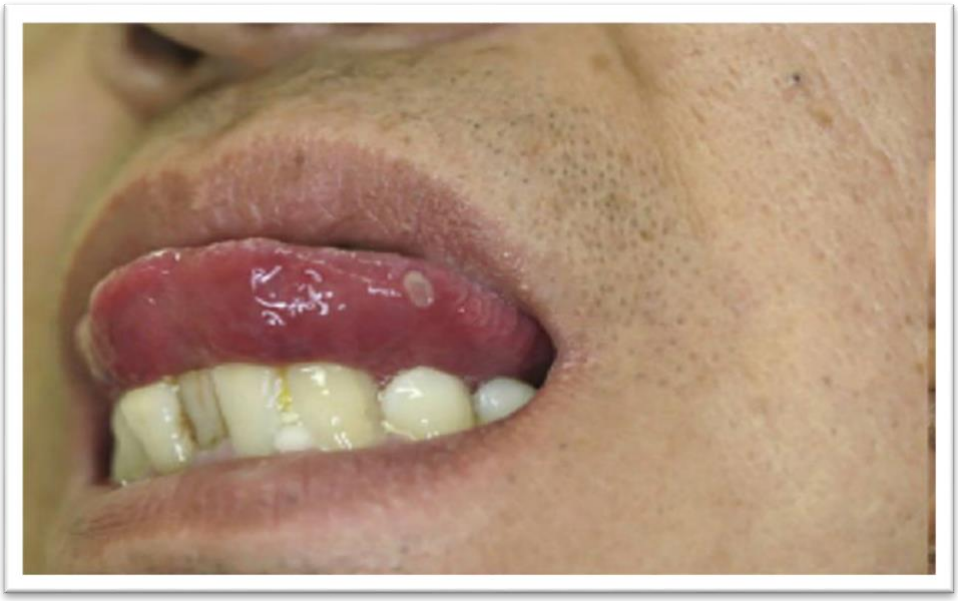

Figure 3 : Oral aphtha. (Kaneko et al. , 2012).

Recurrent aphthous ulcers are seen in almost all patients during the course of BD **(Alpsoy et al. , 2007).** In most cases, oral aphthous lesions are the first manifestation of the disease, preceding the fulfilment of criteria for the diagnosis by 4–8 years **(Ekmekci et al. , 2003).** They appear as circular or oval ulcers with erythematous borders covered with a white–yellow pseudomembrane. Oral aphthae can appear anywhere in 1–3 mm, grouped or scattered oral aphthous lesions appear as superficial ulcerations during an attack. Local trauma by a dental procedure, burn or bite may trigger the aphthous lesions, which may be the equivalent of a pathergy reaction in the oral mucosa. Female patients may have flares during menstruation **(lew et al. ,2008).** Smoking may decrease the frequency of oral aphthous lesions, and cessation of smoking may result in activation of oral lesions**(Soy et al. , 2000).** Recurrent aphthous lesions may be associated with other diseases than BD. These include inflammatory bowel disease, systemic lupus erythematosus, coeliac disease, reactive arthritis, conditions associated with neutropenia (cyclic neutropenia) and haematologic deficiency (vitamin B12, iron, folate). In human immunodeficiency virus infection and acquired immunodeficiency syndrome, large, treatment resistant oral aphthous lesions may develop. Recurrent intraoral HSV infection may clinically resemble the herpetiform aphthous lesions of BD. Tzanck smear or herpes simplex polymerase chain reaction test may aid in differentiating these two conditions. Clinically, aphthous ulcers of BD are indistinguishable from the aphthae observed in recurrent aphthous stomatitis (RAS). Therefore, RAS is the major differential diagnosis of BD oral aphthous lesions. A survey of RAS and BD patients disclosed that major aphthous lesions and involvement of more than two sites are more common in BD than in

RAS**(Oh et al. , 2009).** RAS may be associated with periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA). PFAPA is a recurrent fever syndrome of unknown aetiology with autosomal dominant inheritance and variable penetrance characterized by regular episodes of fever, pharyngitis, oral aphthosis and cervical lymphadenopathy **(Batu , 2019).** Complex aphthosis is a term introduced by (Jorizzo et al.). to describe patients presenting with recurrent oral and genital aphthous ulcers without manifestations of systemic disease **(McCarty et al. , 2003).** The authors suggest using the pathergy test to differentiate BD and complex aphthosis. However, this approach has some disadvantages. In Europe and United States, the prevalence of BD and the positivity of a pathergy reaction are relatively low. On the other hand, in countries with higher BD prevalence.

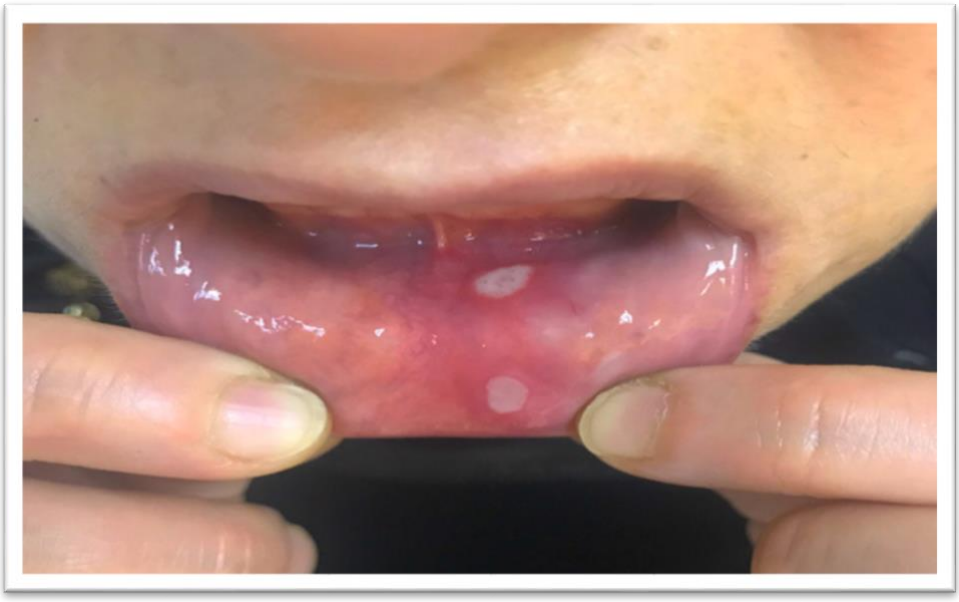

Figure 4 : Multiple minor aphthous lesions located on the buccal mucosa (Vural et al. , 2022).

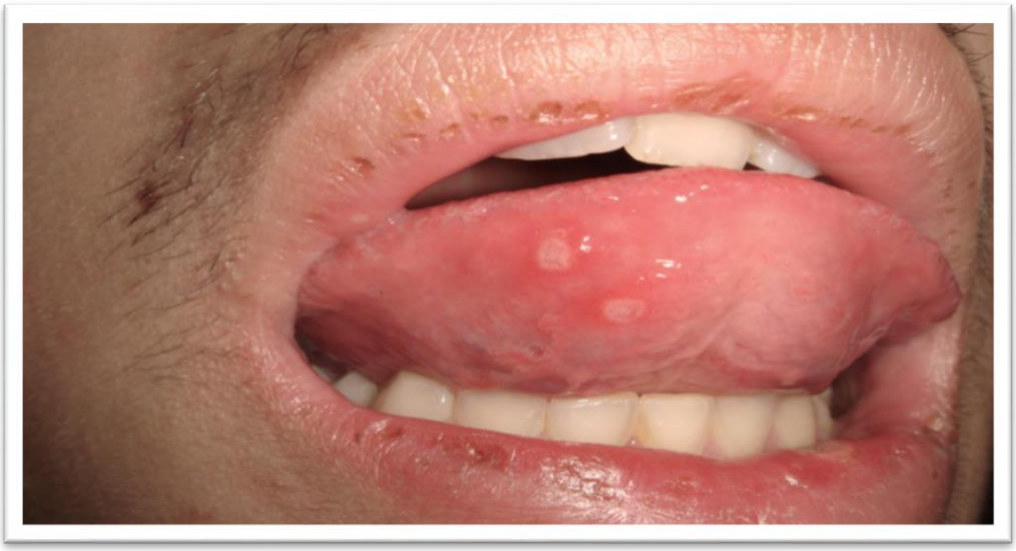

Figure 5 : Minor aphthous ulcers under the tongue. (Vural et al. , 2022).

CUTANEOUS MANIFESTATIONS

3.1.a Papulopustular lesions

Papulopustular lesions or pseudofolliculitis are the most common cutaneous sign in BD, seen in 50%–96% of patients **(vural et al. , 2022).** The most common location for PPLs is the lower extremities, but they can be located anywhere on the body, including the upper extremities, trunk, face or neck (Figure 6). The initial lesion is an erythematous papule that evolves to form a clearly visible pustule with erythematous borders within 24–48 h (Figure 7). The sensitivity and specificity of PPLs are 53%–70% and 76%–92%, respectively**(vural et al. , 2022).** Pathologic examination of PPLs shows karyorrhexis, extravasation of erythrocytes, leukocytoclastic vasculitis with fibrinoid necrosis,

lymphocytic vasculitis or neutrophilic vasculitis. In PPLs with significant perivascular cellular infiltration, activated CD8+ T cells expressing interleukin (IL)-17A were prominently increased **(Vural et al. , 2022).** Lymphocytic vasculitis in BD was proposed to initiate neutrophil recruitment and prominent neutrophil extracellular trap formation**(vural et al. , 2022).** In areas, such as the arms and legs, are more specific for BD **(Boyvat , 2009).**

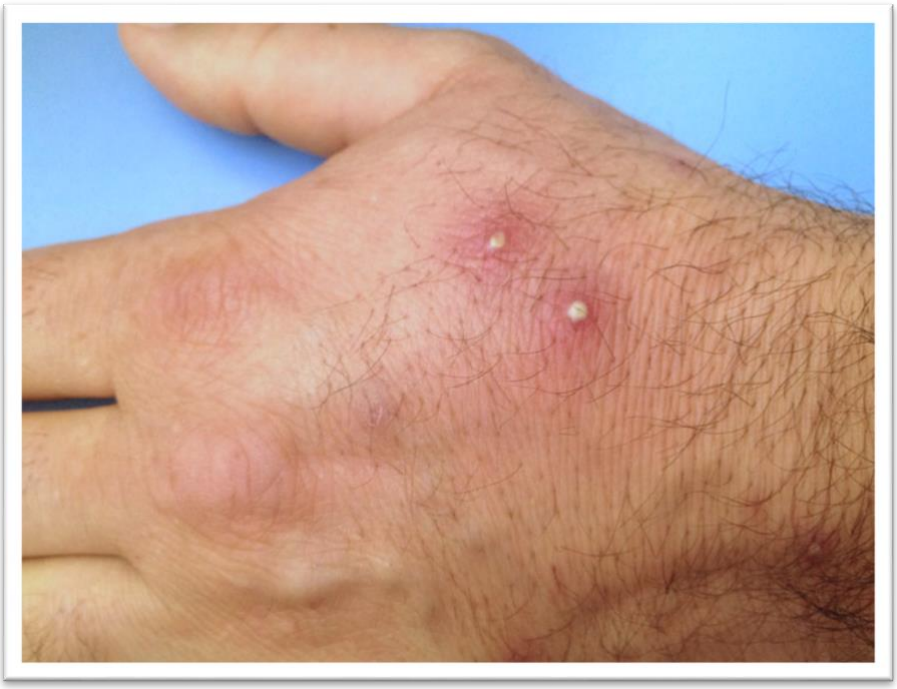

Figure 6 : Papulopustular lesions on hands. (Vural et al. , 2022).

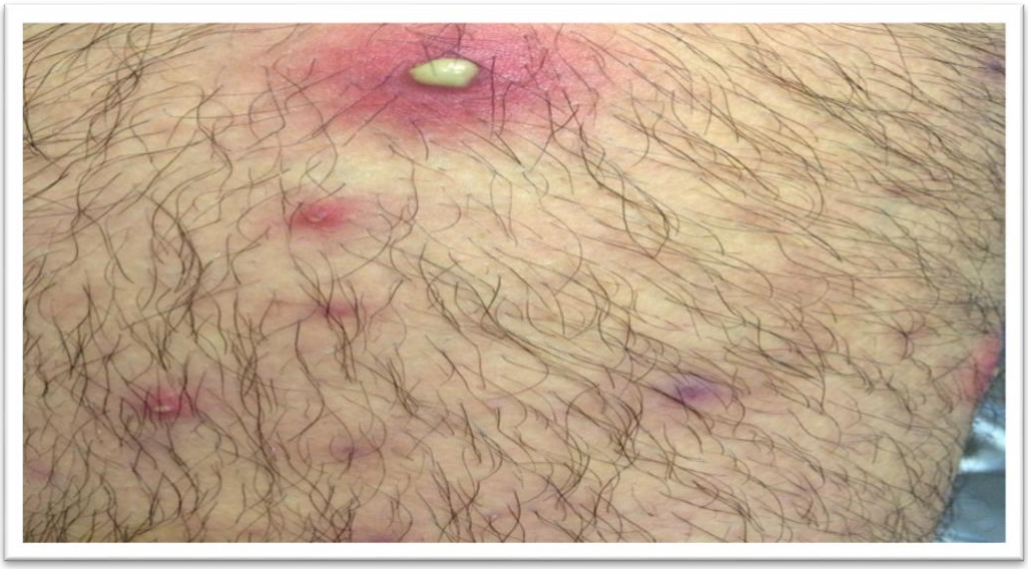

Figure 7: A typical papulopustular lesion with a pustule surrounded by erythema. (Vural et al. , 2022).

3.1.b Erythema nodosum-like lesions

EN-like lesions are present in almost half of BD patients(15%–78%) **(Gurler et al. , 1997)**. They are seen more commonly in females.Usually, EN-like lesions are located on the lower extremities, but they can appear on other areas such as the gluteal region, upper extremities, face and neck (Figure 8). They do not ulcerate and heal within 2–3 weeks without scar formation. Sometimes these lesions may heal with hyperpigmentation. They clinically resemble classical EN. Histopathological examination reveals subcutaneous dense inflammation, either neutrophil-rich or lymphocyte-rich **(Jorizzo et al. , 1995).** Lymphocytic, leukocytoclastic or pustular vasculitis involving arterioles or venules is reported in 40%–100% of the EN-like lesions**(Lehman et al. , 2010).** Histopathologic studies of EN-like lesions have also shown vascular changes resembling polyarteritis nodosa. Nodular vasculitis is another

differential diagnosis; granuloma formation and necrosis are more common in nodular vasculitis than in EN-like lesions of BD **(Demirkesen et al. , 2001).** On the other hand, true EN is characterized by septal panniculitis and lack of vasculitis and vascular changes. The histologic features of EN-like lesions have enough specificity to differentiate them from EN associated with other disease**(Vural , 2022).**

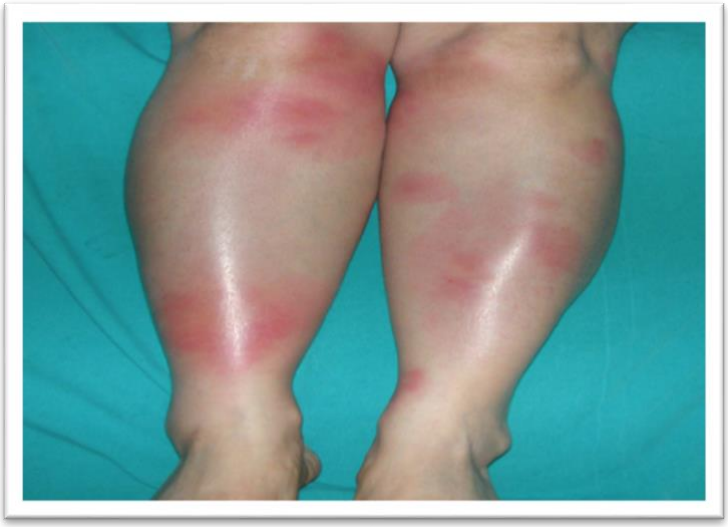

Figure 8 : Multiple erythema nodosum like lesion on the legs.(Vural et al. ,2022).

3.1.c Superficial thrombophlebitis

Superficial thrombophlebitis is seen in 10%–20% of BD patients and has a male predominance. Although it is not strictly a skin finding, superficial thrombophlebitis can be suspected by dermatological examination. Usually, a linear painful erythematous induration following the trace of a superficial vein is seen in the lower extremities. Most commonly, the great saphenous vein is affected. Thrombi within the vein can be felt by palpation. Ultrasound imaging can be useful for diagnosis. Superficial thrombophlebitis is indicative of vasculitis.

3.1.d Sweet syndrome-like findings

Sweet syndrome-like lesions in BD were first reported by Mizoguchi et al. **(Mizoguchi et al. , 1987).** They have been reported in isolated case reports, and patients were treated with systemic steroids **(vural et al. , 2022).** Sweet syndrome-like lesions are single or multiple, erythematous nodules with or without pustules that mainly appear on the face, neck and hands (Figure 10). Two patients have been reported with generalized lesions involving the face, extremities and buttocks **(Karadogan et al. , 2009).** Sweet syndrome-like lesions in BD patients present with fever, elevated acute phase reactants and leukocytosis with high numbers of neutrophils. On pathologic examination, diffuse infiltration of neutrophils, histiocytes and lymphocytes in the periadnexal and perivascular areas together with mild infiltration of histiocytes, lymphocytes and sparse neutrophils between collagen bundles are observed. Histopathology of these lesions is similar to classic Sweet syndrome. True vasculitis may be detected **(Lee & Barnetson , 1996)**

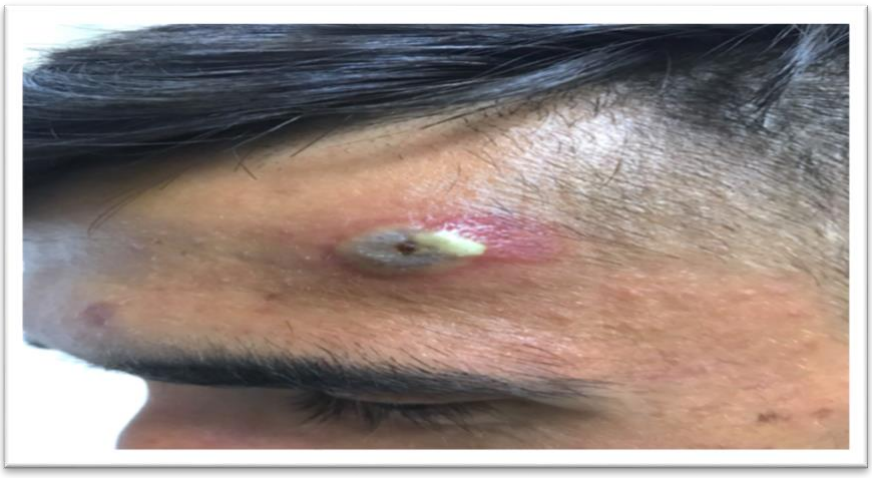

Figure 9 : Sweet syndrome-like lesion on the forehead with erythematous nodule and pustule formation. (Vural et al. , 2022).

3.2 Eye manifestations

Eye involvement occurs in 30–70% of cases of BD and is cause of significant morbidity, about 25% of patients with ocular disease become blind despite treatment, although prognosis is improving with the use of modern immunosuppressant therapy. The typical ocular involvement is a chronic, relapsing bilateral non-granulomatous uveitis that may involve the anterior segment, the posterior segment or both (panuveitis) **(Mendes , et al. , 2009).** A variety of other eye lesions have been found including cataract, glaucoma, posterior segment involvement with vitritis, retinitis, and retinal detachment (Fig. 10).

Figure 10 : Retinography and angiography images of central retinal vein occlusion on the right eye and branch retinal vein occlusion on the left eye. (Mendes , et al. , 2009).

3.3 Vascular manifestations

Vascular manifestations are characterized by involvement of vessels of all sizes, both in the arterial and venous systems and venous disease is more common than arterial involvement. Venous thrombosis occurs in 30% of cases. The arterial involvement is seen in 3 to 5% of cares **(Saadoun et al. , 2012).** The incidence is probably underestimated because an autopsy survey showed that 33% of patients had arterial lesions, most of them had been asymptomatic **(Calamia et al. , 2011).** Cardiac involvement includes pericarditis, myocarditis, endocarditis **(Geri et al. , 2012)**. Aneurysms and/or thrombosis of the coronary arteries are observed complicated by hemorrhage, myocardial infarction and sudden death.

3.4 Articular manifestations

Arthralgia and/or arthritis occur in 45% of cases. They are frequently the presenting feature, long before the other manifestations. The knees and ankles are most involved, although smaller joints may also be affected **(Saadoun & Wechsler , 2012).**

3.5 Neurologic manifestations

They are observed in 20 to 40% of **cases (Akman-Demir et al. , 1999).** Central nervous system involvement in BD included parenchymal and non-parenchymal (i.e. cerebral venous thrombosis or arterial aneurism) lesions **(Wechsler et al. , 2002).** Parenchymal lesions (Neurobehcet's disease) frequently onset with an

attack rather than a mild progressive course. They include headache, meningitis or meningoencephalitis, hemiplegia, or cranial nerve palsies **(Greco et al. , 2012).** Psychiatric symptoms including personality changes may develop.

3.6 Gastrointestinal manifestations

It is difficult to distinguish between BD and inflammatory diseases of the intestine, because of the similarity in intestinal and extra intestinal symptoms. This may explain the discrepancy of frequency ranging from 30% to 1% **(Yurdakul et al. , 1996)** . Gastrointestinal involvement causes nausea, abdominal pain, diarrhea which can be bloody and sometimes can lead to perforation. The ileocecal region is the most commonly affected part of the gastrointestinal tract, but tranverse colon and ascending colon are sometimes involved, as is the esophagus. Histologically, the intestinal ulcers are indistinguishable from Crohn's disease, nevertheless the granuloma formation can be used to rule out BD**(Greco et al. , 2011).**

3.7 Inner ear involvement

The otological features of BD can be divided into hearing loss and disequilibrium. Sudden sensorineural hearing loss was reported in two patients with BD **(Greco et al. , 2011).** In the literature, there are many case reports about the inner ear involvement, and incidence of hearing loss in BD. In these studies, the incidence of HL has been reported as 12–80% **(Elidan et al. , 1991).**

4. Diagnosis

At least two ‘major’ signs of the disease should be present to make the diagnosis. These major signs include aphthous-like ulcerations of the oral mucosa, genital ulcerations, and uveitis **(Helm et al. , 1991).** Other systems reported to be involved through the course of the disease are inner ears with sudden cochlear hearing loss (HL), cardiovascular, pulmonary, gastrointestinal, central nervous system, skin and joints. As there are no pathognomonic clinical or laboratorial findings of BD, several diagnostic criteria have been developed during the years, all having in common the 3 major features of oral ulceration, genital ulceration and eye lesions. In 1985 during the Fourth International Conference on BD, in London, an International Study Group (ISG) for BD was created, in order to create a set of criteria for the diagnosis of BD that could be used in the future. These ISG criteria were published in 1990, considering diagnosis of BD when recurrent oral ulcers plus 2 other features are present, in the absence of other clinical explanations . The pathergy test is the non-specific hyperreactivity of the skin following minor trauma and is a unique feature of BD **(Ozdemir et al. , 2007).** It consists of the intradermal puncture of the skin with a 20-gauge or smaller needle 5 mm obliquely into the patient’s flexor aspect of the avascular forearm skin under sterile conditions and without injecting saline. It is considered positive when an indurated erythematous small papule or pustule forms within 48 h. Positivity of the test varies with geographical location, being positive in more than 60% of Middle Eastern patients, in 15% of Korean patients and in about 5% of Caucasian, which considerably reduces its diagnostic values in populations with low positivity **(Evereklioglu , 2005).** A study demonstrated that surgical cleansing of the skin before the puncture reduced the test positivity **(Fresco et al. , 1993).** Differential diagnosis plays a relevant role in BD. The diagnosis of BD is only supported by

clinical criteria that require the exclusion of other diagnoses based on clinical presentation. Oral ulceration is not specific of BD as it may occur in 30-40% of the general population. In contrast, bipolar ulcerations are more specific of BD. Oral ulcerations may also be associated with hemopathy, HIV, Crohn's disease, lupus, bullous dermatosis or vitamin deficiencies. Sarcoidosis, Crohn's disease, Vogt-Koyanagi Harada and Cogan syndrome**(Greco et al. , 2013)** . must be ruled out in case of ocular involvement. Venous involvement should exclude the antiphospholipid syndrome or thrombophilia. Arterial lesions of BD may mimic Takayasu's arteritis or polychondritis. Neuro-BD is sometimes difficult to distinguish from multiple sclerosis or Susac syndrome **(Greco et al. , 2014)**. Lastly, chronic inflammatory bowel disorders must be ruled out in case of gastrointestinal involvement . When audio-vestibular symptoms are present we must consider differential diagnosis with SSHL **(Fusconi et al. , 2012).**and Meniere's disease .

5. Treatment

Corticosteroids are commonly used to treat clinical manifestations of BD as a monotherapy or in combination with immunosuppressant drugs. Corticosteroids can be used as topical therapy (ocular and mucocutaneous disease), and/or as systemic therapy (oral prednisolone (1 mg/kg/day) or intravenous methylprednisolone pulses (1 g/day for 3 days) **(Evereklioglu , 2005).** When steroids are used, they can be reduced with caution after 4 weeks. Relapses are frequently seen after discontinuation of steroids. Despite successfully decreasing acute inflammation, corticosteroids alone often fail to prevent relapses, so they are frequently used in combination with other medications. Combined treatment is also

used in order to diminish corticosteroid dose **(Evereklioglu , 2005).** Immunosuppressive drugs have been shown to be effective. Due to their delay of action, they are prescribed initially in association with corticosteroids. Azathioprine (2,5 mg/Kg/day) was proved effective in a controlled study **(Yazici et al. , 1990).** Cyclophosphamide orally (2 mg/Kg/day) or intravenously (750 to 1g every 4 weeks) is also used. The efficacy of oral methotrexate (7.5 mg once a week) has also been reported. Cyclosporine A used in combination with corticosteroid has a corticosteroid sparing effect, permitting the use of lower dosages . Colchicine (1-2 mg/day has beneficial effects on the mucocutaneous symptoms**(Davatchi et al. , 2009).** Interferon α is a naturally occurring cytokine that has immunomodulatory properties. It has been shown to reduce the number of circulating γδ-T cells, and to inhibit T cell adhesion to endothelial cells in vitro **(Treusch et al. , 2004).** It was first used in the treatment of BD due to its antiviral activity against herpes simplex virus type 1**(Pipitone et al. , 2006)**. The doses of IFN-a used have ranged from 3 to 9 x10 alla 6 units 3 times a week; nevertheless, the optimum dosage and duration of interferon in the treatment of BD still needs to be determined. Thalidomide has immunomodulatory properties, including diminished TNF production and activity and decreased neutrophil migration **(Shek & lim , 2002).** Thalidomide has reported efficacy in treating patients with mucocutaneous lesions refractory to treatment with colchicine. However, teratogenicity restricts usage of this drug **(Hello et al. , 2010).** Contraceptive measures are mandatory due to severe foetal malformations. usually prescribe antiagregant therapy or anticoagulation in case of vascular involvement. Penicillin has been administered in Turkish BD patients as a prophylactic method to reduce the frequency and duration of mucocutaneous symptoms **(Suzuki , 2004).** The recent progresses in the knowledge of BD pathogenesis pave the way for innovative therapy **(Comarmond et al. , 2014).** In contrast to current non-specific

immunosuppressive agents mainly used empirically, the emergence of biotherapies provides the possibility of interfering with specific pathogenic pathways. Novel targeted biotherapies might be used in the future for BD. Meanwhile, the treatment of BD therapy remains still empirical, but nowadays new insights into BD immunopathogenesis have led to novel therapeutic approaches **(Osman k. , 2012).** Clinical and laboratory observations suggested an important role of TNF-mediated process in the pathogenesis of BD **(Arida et al. , 2011).** Tumor necrosis factor (TNF)-blocking agents such as Infliximab, Etanercept, and Adalimumab have been reported to have some success in patients with BD **(Arida et al. , 2011).** There is enough published experience to suggest that TNF blockade represents an important therapeutic advance for patients with severe disease who are resistant to standard immunosuppressive regimens and for those patients with contraindications or intolerance to these treatments **(Arida et al. , 2011).** Among the anti-tumor necrosis factor (anti-TNF) agents, Infliximab, an anti-TNFα chimeric monoclonal antibodies, has been used in more than 300 cases, mainly for refractory ocular BD and with 89% of improving patients who were resistant to conventional therapies **(Sfikakis et al. , 2004).** Infliximab, was able to suppress in vivo and in vitro γδ T cells expansion, activation and cytotoxic activity **(Accardo-Palumbo et al. , 2010).** This could be an explanation of the infliximab efficacy in BD and that underlined the important role of γδ T cells in BD pathogenesis. The dosing regimen for Infliximab is 5mg/kg IV at weeks 0, 2, 6, and every 8 weeks thereafter **(Benitah et al. , 2011).** Etanercept is administered subcutaneously (SC) in a dose of 25 mg twice a week or 50 mg once a week. Etanercept was found successful in sustaining remission for mucocutaneous findings in significantly more patients than placebo **(Cantarini et al. , 2009).** Adalimumab was administered SC as 40 mg every 15 days with god results **(Arida et al. , 2011).**

6. prognosis

BD has a variable course characterized by relapses and remissions. Prognosis depends on the clinical involvement. Loss of visual acuity and neurological disease are major causes of morbidity and disability. This rare disease, often leads to blindness and fatal systemic involvement **(Cho et al. , 2012).** Prognosis of BD improved in the last decade due to the use of modern immunosuppressant therapy and of a more aggressive treatment strategy **(Kump et al. , 2008).** The mortality rate in adult cases varies with series, the highest was reported in Turkey (9.8%) and is related to large vessel vasculitis causing sudden-death by aneurysm rupture or thrombosis **(Kural et al. , 2003).** Main causes of death include major vessel disease (43.9%) and central nervous system involvement (12.2%). The mortality rate at 1 and 5 years was of 1.2% and 3.3% respectively **(Saadoun &Wechsler ,2012).**

7. Conclusions

BD is a systemic vasculitis, characterized initially by oral aphthous ulcers and then by systemic involvement. As there are no laboratorial findings of BD, the diagnosis is only supported by clinical criteria. Although the etiology of BD is still obscure the close correlation between the genetic internal and triggering external factors is thought to be present in the pathogenesis of BD. T cell homeostasis perturbation, especially Th1 and Th17 expansions are now supposed to be the cornerstone of BD pathogenesis. IL21 may act upstream of Th17 and Th1 pathways and IL21 blockade represents a promising therapeutic target in BD. Further investigation is needed on the various aspects of the etiopathogenesis of BD. The recent progress in the knowledge of BD pathogenesis may pave the way for innovative therapy

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