Behçet’s disease and dentistry: Literature review and clinical case report

Azzouz Youssra and Chbicheb Saliha

Abstract

Behçet’s disease (BD) is a systemic vasculitis whose main signs are: mouth ulcers, genital ulcers and uveitis. BD involves a particular immunogenetic field whose etiopathogenesis remains unknown until our days.

Diagnosis of BD rests on clinical signs also the doctor’s judgment and experience since there’s no pathognomonic sign or specific test for the disease.

In BD the oral manifestation which is recurrent oral aphthous is one of the major diagnostic criteria. In addition to this manifestation, ocular and neurological damages can cause serious sequelae.

The management of BD is multidisciplinary. The dentist plays a key role in contributing greatly to the early diagnosis of the disease since the first and most widespread manifestation is recurrent oral aphthous. He is also responsible of the topical treatment of aphthous stomatitis or he can manage the oral consequences induced by the basic treatment of the disease.

Keywords: Behçet’s disease, recurrent aphthous stomatitis, diagnosis, management of BD patients

1. Introduction

Behçet’s disease (BD) is a multi-systemic vascular disorder characterized by oral and genital ulcers, as well as cutaneous, ocular, arthritic, vascular, central nervous system and gastrointestinal involvement. It usually affects young adults [1].

BD can be described as a complex and multifactorial disease involving interactions of several genes with unclear environmental exposures. There is evidence for the implication of both adaptive and innate immune systems in the disease process [2]. However, the exact etiology and pathogenesis of BD remain unknown. BD shares some clinical and pathophysiologic features with auto inflammatory diseases [3].

This review covers the reciprocal implications that BD and the oral cavity can have by specifying the role of the dentist in the diagnosis and management of this condition. This study of the oral manifestations of BD was illustrated by iconographies of patients followed at the Mohammed V Military Instruction Hospital.

2. Clinical Features

2.1 Oral ulceration

Oral aphthous occur in 98% of cases [4] and are one of the major diagnostic criteria according to the international criteria of classification. [5] Oral aphatous can precede other clinical signs by several years, especially in children [5]. Minor aphthous ulcers are the most common type. Although quite similar to recurrent aphthous stomatitis, oral ulcers in Behçet syndrome could be multiple, more painful and more frequent [6]. They appear in the tongue, pharynx, buccal and labial mucosal membranes (figure 1, 2).
2.2 Genital ulceration
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 [7].

2.3 Skin manifestations
Skin lesions are Erythema nodosum, Pseudofolliculitis (figure 5), Papulopustular lesions, Acneiform nodules.

2.4 Eye manifestations
Eye involvement occurs in 30–70% of cases of BD and is cause of significant morbidity [6]. Uveitis is usually bilateral and remitting. In addition to uveitis, the following are described during BD: conjunctival ulcers, scleritis or episcleritis, inflammatory or ischaemic damage to the optic nerve, orbital myositis, and occlusions of the central retinal veins or arteries [8].

2.5 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 cases [9].

2.6 Articular manifestations
Articular manifestations are sometimes inaugural or very late. They are frequently the presenting feature, long before the other manifestations. Approximately 50% of patients with BD suffer from non-specific, non-erosive inflammatory arthritis [10].

2.7 Neurologic manifestations
They are observed in 20 to 40% of cases. Central nervous system involvement in BD included parenchymal and non-parenchymal. Neurobehçet’s disease frequently onset with an attack rather than a mild progressive course. They include headache, meningitis or meningocerebralitis, hemiplegia, or cranial nerve palsies. Psychiatric symptoms including personality changes may develop [6].

2.8 Gastrointestinal manifestations
Gastrointestinal involvement in Behçet syndrome resembles Crohn’s disease in its presentation, with abdominal pain and diarrhea that may be accompanied by bleeding [11]. The ileocecal region is the most commonly affected, Behçet syndrome usually causes round or oval ulcers most commonly in the terminal ileum [12], but tranverse colon and ascending colon are sometimes involved, as is the esophagus [6].

3. Diagnosis
The dentist is in a suitable position to diagnose BD since he is the only one able to cope with recurrent oral stomatitis which is the first and main manifestation of the disease.
### 3.1 Classification Criteria for Behçet's Disease

The diagnosis of Behçet’s Disease, in the absence of a characteristic biological test, is clinical and upon an expert opinion. However, Classification/Diagnosis (C/D) criteria may be of help. Up to now, there are 17 sets of C/D criteria, from Curth criteria in 1946 to the revised International Criteria for Behçet’s Disease (ICBD) in 2014 [13]. ICBD is the C/D criteria of choice to help the diagnosis of BD.

#### Table 1: A score of ≥ 4 is in favour of the diagnosis [14].

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye manifestations</td>
<td>2</td>
</tr>
<tr>
<td>Genital aphthae</td>
<td>2</td>
</tr>
<tr>
<td>Oral ulceration</td>
<td>2</td>
</tr>
<tr>
<td>Skin manifestations</td>
<td>1</td>
</tr>
<tr>
<td>Neurologic manifestations</td>
<td>1</td>
</tr>
<tr>
<td>Vascular manifestations</td>
<td>1</td>
</tr>
<tr>
<td>SPT</td>
<td>1</td>
</tr>
</tbody>
</table>

### 3.2 Distinction between a simple RAS and a RAS of Behçet’s disease

Through their study I. Krause et al. I studied the expression of RAS in BD patients and the correlation between recurrent major or minor aphthous and systemic expression and severity of the disease. They found that the frequency of major aphthous was higher in patients with BD than in individuals with recurrent idiopathic aphthous [15].

SH. Oh et al. I looked for elements that would allow us to orient ourselves towards BD rather than RAS. The patient with BD presents a lower risk of minor aphthous, and a higher risk of major aphthous. However, the author concludes that there is no criterion for distinguishing between oral ulcers due to BD and those of recurrent oral aphthous. However, a patient with recurrent oral aphthous and presenting additional symptoms, especially joint symptoms, should be followed for the diagnosis of BD [16].

We can therefore conclude that it is difficult if not almost impossible to diagnose BD in the case of isolated oral aphthous.

### 3.3 Diagnostic approach

The diagnosis of BD by the dentist is often a diagnosis of exclusion.

#### 3.3.1 Positive diagnosis

History and clinical examination remain the key to diagnosis. Additional examinations may be prescribed by the dentist in order to rule out a similar pathology to BD.

#### 3.3.1.1 Medical history

The medical examination of the patient will be adapted on a case-by-case. When the patient informs the dentist of the presence of an oral lesion or when he detects one, the medical examination will be more specific [17-18].

- The date of appearance of the first lesion.
- The frequency and duration of the episodes.
- The number of ulcers per episode.
- The form of the ulceration: minor, major, herpetiform.

#### 3.3.1.2 Clinical examination

**3.3.1.2.1 The extra-oral examination**

The dentist will have to call on

- **His sight:** visual search for skin lesions. Faced with visible skin lesions at first, the dentist will ask if other areas of the body are affected [20].

- **Her touch:** palpation of the facial muscles, temporomandibular joints, cervical lymph glands and salivary glands. He will look for lymphadenopathy or painful areas to the touch.

#### 3.3.1.2.2 Intra-oral examination

The dentist will look at all of the oral mucosa as well as the dentition of the patient. Faced with an ulceration, it will look at its single or multiple character, flexible or hard, inflammatory or not, necrotic or not, superinfected or not, as well as its location (s) and size. The recurrent nature of the oral lesion is important. We must rely on the presence of other clinical manifestations as well as on the classification of "The International Criteria for Behçet’s disease" to establish a diagnosis.

#### 3.3.1.3 Additional investigations

The purpose of the additional investigations is to distinguish between the common aphthous without associated pathology and aphthous, symptom of an underlying disease.

#### 3.3.1.3.1 Saliva test

The saliva test is correlated with the following hypothesis: BD is induced by bacteria such as streptococci and in particular Streptococci Sanguis. The patients with BD would have hypersensitivity to streptococci. The saliva test results are correlated with presence of particularly sensitive oral streptococci in people with BD. 90% of patients with BD would have a positive saliva test [21-22].

#### 3.3.1.3.2 Skin pathergy test

The dentist can refer the patient to a dermatologist if BD is suspected. The dermatologist can then perform the SPT. It’s part of various diagnostic classifications of BD. A positive result indicates the immune system is overreacting to a minor injury [23].

#### 3.3.1.3.3 Blood tests

Blood tests allow to check that there is no impairment of kidney function or anemia, disorders that occur frequently in inflammatory diseases. In addition, blood tests show the presence of inflammation, which results in an increase in the number of white blood cells and by increasing the speed of sedimentation which increases only in the event of inflammation [24].

### 3.3.2 Differential diagnosis

#### 3.3.2.1 Oral differential diagnosis

The dentist with information obtained from clinical examination, and if necessary, with the help of complementary investigation, should be able to eliminate differential diagnosis of BD in front of RAS, which can have various origins:

- Induced extrinsic lesions (trauma or caustic, pathomimia)
- Viral infections (herpes, chickenpox, shingles, herpangina, foot-hand-bush syndrome, HIV)
- Bacterial infections (syphilis, chancreoid, ulcerative necrotic gingivo stomatitis)
- Deficiency (vitamin B12 and / or folate)
- Auto-immune (Reiter's syndrome, pemphigus vulgaris, lupus erythematosus disseminated, certain vasculitides, Stevens – Johnson syndrome).
- Cancerous: ulcerated squamous cell carcinoma.
- Medication: captopril, gold salts, nocardanil, niflumic acid, phenindione, phenobarbital, piroxicam, sodium hypochlorite [25-26].

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### Table 2: Differential diagnosis

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Common clinical manifestations with BD</th>
<th>Manifestations or discriminatory examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reiter syndrome</td>
<td>Oral and genital ulcers, synovitis</td>
<td>Urethritis, papular palmoplantaris lesion</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>Erythema nodosum, uveitis, arthralgia</td>
<td>Absence of oral ulcers, pulmonary nodules, lymphadenopathy, granuloma at histology.</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>Oral and anogenital ulcers, Behçet pseudo-entero table</td>
<td>Perianal and digestive fistulas to other organs, pyoderma, granuloma at histology.</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Behçet pseudo-neuro clinical picture.</td>
<td>Absence of any extraneurological sign, lumbar puncture, extensive lesions on MRI of nevral.</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>Oral ulcers, system disease chart</td>
<td>Specific antibodies</td>
</tr>
<tr>
<td>Recurrent herpes</td>
<td>Oral and / or genital ulcerations, possible deterioration of the general condition, fever.</td>
<td>IGM positive herpes serology, virus identification on a samples of mucosa</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Uveitis, joint pain, cutaneous lesions, possible association with Crohn's disease.</td>
<td>Joint radiological signs.</td>
</tr>
<tr>
<td>Neuro-sweet</td>
<td>Skin lesions, bipolar bipolar aphthosis possible, pathergic reaction, neurological manifestations of pseudo -neuro -Behçet episcleritis, conjunctivitis.</td>
<td>Absence of any vasculitis at histology, absence of uveitis, HLAB54 very common.</td>
</tr>
<tr>
<td>Idiopathic aphthosis</td>
<td>Possibly bipolar aphthosis.</td>
<td>Isolated aphthosis.</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Persistent aphthosis, general context (fever, diffuse pain, diarrhea...).</td>
<td>Positive serology for HIV.</td>
</tr>
</tbody>
</table>

### 3.3.3 Confirmation of the disease

In the presence of RAS, the dentist should seek other clinical manifestations. At this point, he is confronted with two scenarios:

- The patient presents one of the manifestations of BD
- The patient responds to epidemiological data from BD (young man, from a Silk Road region). So, exams will be performed to confirm or rule out the diagnosis of BD. These exams include:
  - The SPT.
  - Blood test.
  - Imagery [24].
- The patient presenting no other manifestation of the disease:

  In the absence of other manifestations, the established diagnosis will be RAS. Nevertheless, the patient will be regularly followed by his dentist. He must check in the follow-up if the patient develops other manifestations [29].

### 4. Management of the patient with behçet’s disease in the dental office

#### 4.1 Contact the referring physician (known patient with BD)

The patient with BD benefits from multidisciplinary care because the manifestations affect several organs. The center of this care off is the internist and the general practitioner. Before starting treatment, the dentist should learn about the course of the disease, its clinical manifestations and the treatment of patient [29].

#### 4.2 Precautions taken by the dentist during dental treatment

##### 4.2.1 Management of a patient treated by VKA:

Dental extractions and dental implants can be performed without interrupting VKAs (after checking the INR and verifying a value < 4). For operations and invasive procedures with high risk of bleeding, the discontinuation of VKA with or without relay heparin, depending on the risk of thrombosis for the patient, is recommended. The decision to temporarily discontinue VKA therapy should be taken after consultation with the physician who prescribed the VKA [30].

### 4.2.2 Management of patients on immunosuppressants

Patients with a severe and refractory form of BD are treated with immunosuppressants. The main risk for patients immunocompromised is the risk of infection. The management of these patients must be earlier, ideally before the start of the treatment. Management continues during treatment with regular examinations. Immunosuppression itself is not against any treatment, but the risk of local infectious disease and the risk of spreading oral germs justifies in these patients the prescription of ATB during the oral surgery. An adapted antibiotic prophylaxis must be prescribed during invasive procedures (with invasive risk). Antibiotic prophylaxis is not justified during non-surgical periodontal care and non-invasive procedures [31]. The practitioner must take into account the significant risk of drug interactions before any prescription.

### 4.2.3 Management of patients on anti TNF alpha

Targeting immunosuppressive therapies from biological engineering are widely used today, such as BD. Their links with oral infections is in their ability to inhibit one or more pathways of the adaptive immune response. Taking these new immunosuppressants is an important risk factor for oral infections. Oral hygiene and regular care are recommended. In Conservative care there is no evidence to discontinue anti-TNF alpha. It is recommended to stop anti-TNF alpha and to offer antibiotic prophylaxis in infectious risk treatments (avulsion, abscess drainage, etc.). In implant placement there is no formal indication to stop anti-TNF alpha, while remaining alert to potential infectious risks [32-33].

### 4.2.4 Management of patients on long-term corticosteroids in dentistry

Due to their anti-inflammatory properties, the use of glucocorticoids in the long term may partially mask the signs of an underlying infection which may cause delayed diagnosis and treatment. The risk of infection is established in the case...
of long-term corticosteroid therapy with a greater than 10 mg / d in prednisone equivalent [34]. Below, all treatments are feasible, the same is true in the case of corticosteroid therapy short [35]. For long-term corticosteroid therapy with a dosage> 10 mg / d equivalent prednisone, performing non-invasive and minor bloody invasive procedures does not require antibiotic therapy. However, any act involving bone and / or mucosal scarring requires the implementation of antibiotic prophylaxis 1 hour before the realization of the act followed by curative antibiotic therapy until mucosal healing (7 days minimum) [36].

4.3 Treatment of RAS in the context of Behçet’s disease

4.3.1 Topical treatment

Antimicrobial agents (Listerine mouth rinse, chlorhexidine gel, penicillin G potassium troches, tetracycline suspension, triclosan mouth rinse), sucralate, corticosteroids, Amlexanox and 5-aminosalicylic in OU, and pimecrolimus in GU can be selected as first-line topical treatment choices [37]. Topical treatments such as corticosteroids help to decrease the severity and duration of lesions and can be used without the need of continuous systemic treatment in patients whose recurrences are infrequent and do not cause much discomfort [6-38].

Minocycline, camil thorn distillate, diclofenac, silver nitrate such as IL-1, -2, -6, -12, -17 and -23-blocking agents and monoclonal antibody against CD20 have been increasingly used in recent years in patients with BD refractory to other treatments [37]. Apremilast (a phosphodiesterase 4 inhibitor) was shown to be relatively safe and effective for oral and genital ulcers. IFNβ and etanercept are other alternatives for refractory skin, mucosal and joint lesions [39].

5. Conclusion

Dentist’s role is important in establishing BD diagnosis; they could be the first to detect the disease. Recurrent oral ulcers are a common initial symptom of BD, accompanied by skin and eye lesions. A multidisciplinary approach is required to diagnose and treat the disease.

6. References

16. OH SH, Han EC, Lee JH et Coll. Comparison of the clinical features of recurrent aphthous stomatitis and