HARRISON'S PRINCIPLES OF INTERNAL MEDICINE — 22nd Edition

Behçet Syndrome

Chapter 376 | Part 11: Immune-Mediated, Inflammatory, and Rheumatologic Disorders | Part 11 – Rheumatology & Immunology | DETAILED EDITION

KEY CLINICAL POINTS

1. Behçet syndrome is a systemic vasculitis first described by Hulusi Behçet, a Turkish dermatologist.
2. Oral ulcers are seen in virtually all patients and are commonly the first manifestation.
3. Genital ulcers are the most specific lesions, occurring on the scrotum or labia, and tend to scar.
4. Diagnosis is clinical; International Study Group (ISG) criteria require recurrent oral ulcers plus two of four other manifestations (genital ulcers, skin lesions, eye lesions, or positive pathergy).
5. Pathergy reaction is a nonspecific hyperreactivity of the skin to trauma; a papule or pustule forms in 24–48 h after needle insertion.
6. Up to 50–60% of patients can be positive for HLA B*51, but it is not used as a diagnostic test due to prevalence in ~20% of the normal population.
7. Males frequently have more severe disease and poorer outcomes compared to females.
8. Gastrointestinal involvement is rare in Turkey but more common in Japan and the United States (~30% of patients in the US).
9. Behçet syndrome is not typically associated with autoantibodies, Raynaud's phenomenon, or other autoimmune diseases.
10. Features separating it from autoinflammatory conditions include tendency to abate with time and absence of mutations associated with familial Mediterranean fever.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

• Behçet syndrome is a systemic vasculitis.

• It can present with oral and genital ulcers, skin lesions, uveitis, arthritis, major arterial and venous vessel disease, and gastrointestinal and neurologic manifestations.

• These manifestations can be present in various combinations and sequences over time.

• Patients are most commonly from the Middle East, the Mediterranean region, and the Far East.

• It is relatively rare before the late teens and after age 50.

• Males and females are equally affected; however, males frequently have more severe disease and poorer outcomes.

• Some manifestations may show regional differences; for example, gastrointestinal involvement, rare in Turkey, is more common in Japan and is seen in ~30% of patients in the United States.

1.1 Classification & Variants

• Retrospective patient cohort analyses suggest there may be different clusters of disease presentation.

• Acne lesions are more commonly seen with arthritis.

• Behçet syndrome is associated with enthesitis.

• Each of these clusters may have a different pathogenesis.

2. EPIDEMIOLOGY

• Behçet syndrome is most prevalent in Turkey.

• Prevalence in Turkey is 1 in 250 adults.

• It is relatively rare before the late teens and after age 50.

• Males and females are equally affected.

• Males frequently have more severe disease and poorer outcomes.

• Gastrointestinal involvement is rare in Turkey.

• Gastrointestinal involvement is more common in Japan.

• Gastrointestinal involvement is seen in ~30% of patients in the United States.

3. ETIOLOGY & PATHOPHYSIOLOGY

• The pathogenesis and etiology of Behçet syndrome are unknown.

• Family studies show a possible genetic predisposition.

• Increased inflammation and immunologic mechanisms play a role.

• Both innate and adaptive immune systems may be involved.

• Unlike other autoimmune diseases, Behçet syndrome is not typically associated with autoantibodies.

• It is not typically associated with Raynaud's phenomenon.

• It is not typically associated with Sjögren's syndrome.

• It is not typically associated with thrombocytopenia.

• It is not typically associated with hemolytic anemia.

• It is not typically associated with sun hypersensitivity.

• It is not typically associated with serosal involvement.

• It is not typically associated with an increased risk for other autoimmune diseases.

• On the other hand, features that separate it from autoinflammatory conditions include tendency to abate with time.

• Absence of mutations associated with familial Mediterranean fever (Chap. 381) separates it from autoinflammatory diseases.

• There is neutrophil hyperreactivity; however, it is not clear whether this is primary or secondary to cytokine-directed activation.

• There is also evidence from retrospective patient cohort analyses that there may be different clusters of disease presentation.

3.1 Genetic Factors

- Up to 50–60% of patients, depending on where they are from, can be positive for HLA B*51.
- HLA B*51 is not used as a diagnostic test because it is also found in around 20% of the normal population.

3.2 Immune Mechanisms

- There is neutrophil hyperreactivity.
- It is not clear whether neutrophil hyperreactivity is primary or secondary to cytokine-directed activation.
- Both innate and adaptive immune systems may be involved.

4. CLINICAL FEATURES

- The most common symptoms are associated with mucocutaneous tissues.
- Oral ulcers are seen in virtually all patients and are commonly the first manifestation.
- Commonly, like ordinary canker sores, they are usually multiple.
- They last around 10 days but recur unless treated.
- Only the uncommon, major ulcers tend to scar.
- Beneficial effects of dental and periodontal therapies suggest that decreased oral health is associated with disease severity.
- Genital ulcers are the most specific lesions.
- They most commonly occur on the scrotum or labia.
- They are larger and deeper and take longer to heal than oral ulcers.
- They tend to form scars.
- Acne-like or papulopustular lesions are indistinguishable from acne vulgaris in appearance and pathology.
- They are seen both at the usual acne sites as well as at uncommon sites such as lower extremities.
- Other skin findings are the nodular lesions, which are of two types.
- Erythema nodosum lesions due to panniculitis.
- Superficial vein thromboses.
- Superficial thrombophlebitis often occurs in men and is associated with deep-vein thrombosis.
- It should trigger workup for other vascular involvement, including pulmonary artery aneurysms.

4.1 Oral Ulcers

- Seen in virtually all patients.
- Commonly the first manifestation.
- Usually multiple.
- Last around 10 days.
- Recurrence unless treated.
- Major ulcers tend to scar.
- Decreased oral health is associated with disease severity.

4.2 Genital Ulcers

- Most specific lesions.
- Occur on the scrotum or labia.

- Larger and deeper than oral ulcers.
- Take longer to heal.
- Tend to form scars.

4.3 Skin Lesions

- Acne-like or papulopustular lesions.
- Indistinguishable from acne vulgaris in appearance and pathology.
- Seen at usual acne sites.
- Seen at uncommon sites such as lower extremities.
- Nodular lesions of two types.
- Erythema nodosum lesions due to panniculitis.
- Superficial vein thromboses.

4.4 Vascular Involvement

- Superficial thrombophlebitis often occurs in men.
- Associated with deep-vein thrombosis.
- Should trigger workup for other vascular involvement.
- Includes pulmonary artery aneurysms.

5. DIFFERENTIAL DIAGNOSIS

- Behçet syndrome is diagnosed clinically.
- There are no specific laboratory, imaging, or histologic features that can help in the diagnosis of a patient with suggestive symptoms.
- However, these can be used in ruling out conditions that may mimic Behçet syndrome.
- The diagnosis is based on a combination of clinical features in the setting of ruling out other potential causes.
- Some patients may require months to years to develop the array of symptoms that would lead to a definitive diagnosis.
- A tentative diagnosis may be made well before.

5.1 Mimickers

- Conditions that may mimic Behçet syndrome must be ruled out.
- Specific conditions are not detailed in the provided source text.

6. INVESTIGATIONS & DIAGNOSIS

- Behçet syndrome is diagnosed clinically.
- There are no specific laboratory, imaging, or histologic features that can help in the diagnosis of a patient with suggestive symptoms.
- The most commonly used and best performing diagnostic criteria are the International Study Group (ISG) criteria.
- Sensitivity is ~95%.
- Specificity is ~96%.
- Patients need to have recurrent oral ulcers plus two of the following four clinical manifestations.

• Additional clinical manifestations may involve various organ systems, including the gastrointestinal, vascular, pulmonary, and central nervous systems.

• Up to 50–60% of patients, depending on where they are from, can be positive for HLA B*51.

• It is not used as a diagnostic test because it is also found in around 20% of the normal population.

6.1 International Study Group (ISG) Criteria

• Recurrent oral ulcers: At least 3 times in a 12-month period.

• Recurrent genital ulcers: Usually scarring.

• Skin lesions: Erythema nodosum, pseudofolliculitis, papulopastular or acneiform nodules (postadolescent, not receiving corticosteroids).

• Eye lesions: Anterior or posterior uveitis, cells in vitreous or retinal vasculitis.

• Pathergy: Evaluated in 24–48 h, after dermal insertion of a 20-gauge needle.

Table 1 Table 376-1 International Study Group Criteria for the Diagnosis of Behçet Syndrome

CRITERIA	FREQUENCY	COMMENTS
Oral ulcers	~98%	At least 3 times in a 12-month period
Recurrent genital ulcers	~80%	Usually scarring
Skin lesions	~80%	Erythema nodosum, pseudofolliculitis, papulopastular or acneiform nodules (postadolescent, not receiving corticosteroids)
Eye lesions	~50%	Anterior or posterior uveitis, cells in vitreous or retinal vasculitis
Pathergy	~50%	Evaluated in 24–48 h, after dermal insertion of a 20-gauge needle

6.2 Pathergy Test

• Pathergy reaction is a nonspecific hyperreactivity of the skin to trauma.

• Typically, a papule or pustule forms in 24–48 h after a dermal insertion of a 20-gauge needle.

7. MANAGEMENT & TREATMENT

• Behçet syndrome is diagnosed clinically.

• There are no specific laboratory, imaging, or histologic features that can help in the diagnosis of a patient with suggestive symptoms.

• Specific pharmacologic regimens not detailed in provided source text.

• Beneficial effects of dental and periodontal therapies suggest that decreased oral health is associated with disease severity.

7.1 General Management

• Diagnosis is based on a combination of clinical features in the setting of ruling out other potential causes.

• Some patients may require months to years to develop the array of symptoms that would lead to a definitive diagnosis.

• A tentative diagnosis may be made well before.

8. PROGNOSIS & COMPLICATIONS

- Males frequently have more severe disease and poorer outcomes.
- Some manifestations may show regional differences.
- Gastrointestinal involvement, rare in Turkey, is more common in Japan and is seen in ~30% of patients in the United States.

8.1 Disease Severity

- Males frequently have more severe disease.
- Males frequently have poorer outcomes.

8.2 Regional Variations

- Gastrointestinal involvement is rare in Turkey.
- Gastrointestinal involvement is more common in Japan.
- Gastrointestinal involvement is seen in ~30% of patients in the United States.

9. SPECIAL CONSIDERATIONS

- Some manifestations may show regional differences.
- Gastrointestinal involvement, rare in Turkey, is more common in Japan and is seen in ~30% of patients in the United States.

9.1 Regional Differences

- Gastrointestinal involvement is rare in Turkey.
- Gastrointestinal involvement is more common in Japan.
- Gastrointestinal involvement is seen in ~30% of patients in the United States.

10. KEY PEARLS & CLINICAL TRAPS

- Oral ulcers are seen in virtually all patients and are commonly the first manifestation.
- Genital ulcers are the most specific lesions.
- Pathergy reaction is a nonspecific hyperreactivity of the skin to trauma.
- HLA B*51 is not used as a diagnostic test because it is also found in around 20% of the normal population.
- Behçet syndrome is not typically associated with autoantibodies, Raynaud's phenomenon, Sjögren's syndrome, thrombocytopenia, hemolytic anemia, sun hypersensitivity, serosal involvement, or an increased risk for other autoimmune diseases.
- Features that separate it from autoinflammatory conditions include tendency to abate with time, absence of mutations associated with familial Mediterranean fever.

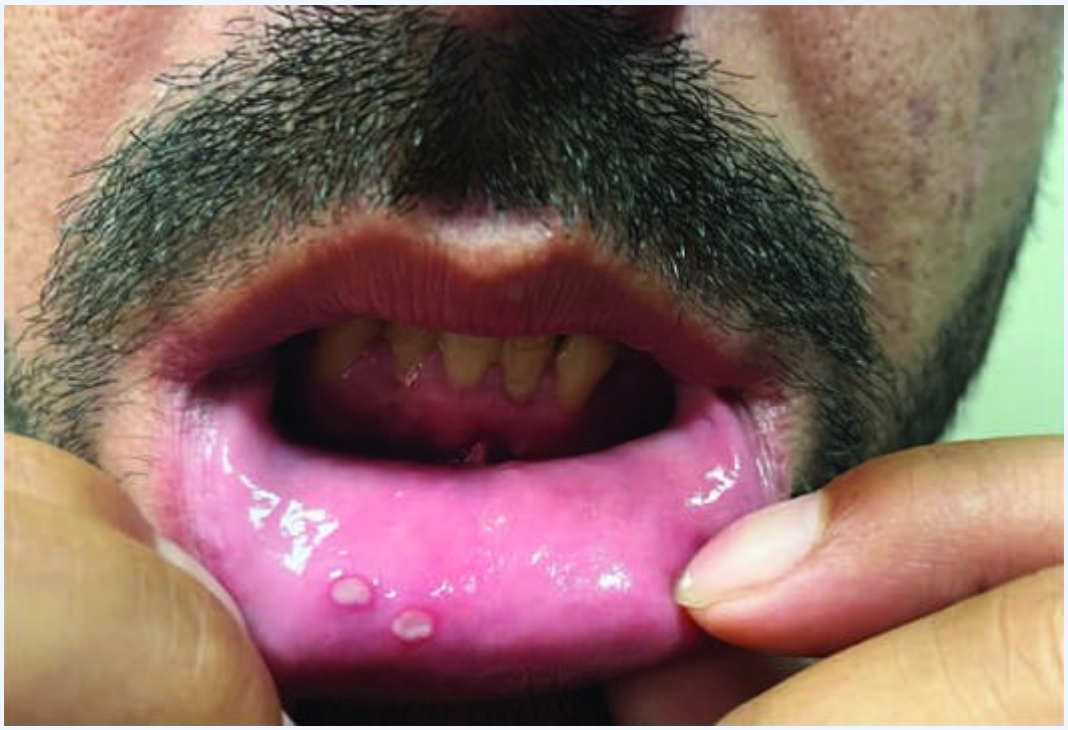
10.1 Diagnostic Pearls

- Oral ulcers are seen in virtually all patients.
- Genital ulcers are the most specific lesions.
- Pathergy reaction is a nonspecific hyperreactivity of the skin to trauma.
- HLA B*51 is not used as a diagnostic test.

10.2 Pathophysiology Pearls

- Behçet syndrome is not typically associated with autoantibodies.
- Features that separate it from autoinflammatory conditions include tendency to abate with time.
- Absence of mutations associated with familial Mediterranean fever.

FIGURES & ILLUSTRATIONS — FROM HARRISON'S



Harrison's 22e · Figure 1

FIGURE 376-1 Clinical findings in Behçet syndrome. A. Behçet oral ulcer. B. Behçet scrotal ulcer. — Clinical findings in Behçet syndrome. A. Behçet oral ulcer.

Harrison's 22e · Figure 2

FIGURE 376-1 Clinical findings in Behçet syndrome. A. Behçet oral ulcer. B. Behçet scrotal ulcer. — Clinical findings in Behçet syndrome. B. Behçet scrotal ulcer.

Harrison's 22e · Figure 3

FIGURE 376-1 Clinical findings in Behçet syndrome. A. Behçet oral ulcer. B. Behçet scrotal ulcer. — Pathergy test reaction site showing papule or pustule formation 24–48 h after dermal insertion of a 20-gauge needle.