Behet Syndrome

Chapter 376 | Part 11: Immune-Mediated, Inflammatory, and Rheumatologic Disorders

KEY CLINICAL POINTS

1. Behçet syndrome is a systemic vasculitis characterized by mucocutaneous involvement.
2. Oral ulcers are nearly universal and often the first clinical manifestation.
3. Genital ulcers are highly specific for Behçet syndrome and tend to scar.
4. Diagnosis is primarily clinical, supported by International Study Group (ISG) criteria.
5. Pathergy test identifies a non-specific skin hyperreactivity to trauma (papule/pustule in 24–48 h).
6. HLA B*51 is common (50–60%) but not diagnostic due to high prevalence in the general population (~20%).
7. Males typically experience more severe disease and poorer outcomes.
8. Regional variations exist, particularly regarding gastrointestinal involvement (higher in Japan/USA than Turkey).
9. Unlike other autoimmune diseases, it lacks associated autoantibodies or Raynaud's phenomenon.
10. Distinguished from autoinflammatory conditions by its tendency to abate over time and lack of specific mutations.

1. DEFINITION & OVERVIEW

- **Definition:** A systemic vasculitis.
- **Clinical Presentation:**
  - Manifestations include oral and genital ulcers, skin lesions, uveitis, arthritis, major arterial/venous disease, and gastrointestinal/neurologic involvement.
  - Symptoms may present in various combinations and sequences over time.
- **Demographics:**
  - Typically 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.
- **Clinical Clusters:**
  - Evidence suggests different clusters of presentation (e.g., acne lesions more commonly associated with arthritis).
  - Associated with enthesitis.
  - Different clusters may suggest distinct underlying pathogenetic mechanisms.

2. EPIDEMIOLOGY

- **Prevalence:**
  - Most prevalent in Turkey (1 in 250 adults).

  - Common in Middle East, Mediterranean, and Far East regions.
- **Gendered Outcomes:**
  - Males frequently experience more severe disease and poorer outcomes.
- **Regional Variations:**
  - Gastrointestinal involvement:

→ Rare in Turkey.

→ More common in Japan.

→ Seen in ~30% of patients in the United States.

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3. ETIOLOGY & PATHOPHYSIOLOGY

3.1 Genetic Factors

- **HLA B*51:**
  - Present in 50–60% of patients (depending on region).
  - Not used as a diagnostic test because it is found in ~20% of the normal population.

3.2 Immune Mechanisms

- **Pathogenesis:**
  - Unknown etiology; involves both innate and adaptive immune systems.
  - Evidence of neutrophil hyperreactivity (status as primary or secondary to cytokine-directed activation is unclear).
- **Distinction from Other Conditions:**
  - Not typically associated with autoantibodies, Raynaud's phenomenon, Sjögren's syndrome, thrombocytopenia, hemolytic anemia, sun hypersensitivity, or serosal involvement.
  - Distinguished from autoinflammatory conditions by:

→ Tendency to abate with time.

→ Absence of mutations associated with familial Mediterranean fever (Chap. 381).

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4. CLINICAL FEATURES

4.1 Oral Ulcers

- **Frequency:** Seen in virtually all patients; often the first manifestation.
- **Characteristics:**
  - Usually multiple.
  - Last ~10 days; recur unless treated.
  - Only major ulcers tend to scar.
- **Clinical Correlation:**
  - Decreased oral health is associated with increased disease severity.

4.2 Genital Ulcers

- **Specificity:** Most specific lesions of the syndrome.
- **Location:** Most commonly on scrotum or labia.

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

4.3 Skin Lesions

- **Acne-like/Papulopustular:**
  - Indistinguishable from acne vulgaris in appearance and pathology.
  - Occur at standard acne sites and unusual sites (e.g., lower extremities).
- **Nodular Lesions:**
  - Erythema nodosum (due to panniculitis).
  - Superficial vein thromboses.
- **Clinical Warning:**
  - Superficial thrombophlebitis in men is associated with deep-vein thrombosis.

→ Should trigger workup for other vascular involvement, including pulmonary artery aneurysms.

4.4 Vascular Involvement

- **Thrombophlebitis:** Often occurs in men; linked to deep-vein thrombosis.
- **Systemic Risk:**

→ Requires investigation of pulmonary artery aneurysms.

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5. DIFFERENTIAL DIAGNOSIS

- **Diagnostic Basis:**
  - Diagnosis is clinical; no specific laboratory, imaging, or histologic features are definitive for diagnosis.
  - Tests are primarily used to rule out mimicking conditions.
- **Clinical Progression:**
  - Some patients may take months to years to develop the full array of symptoms required for a definitive diagnosis.
  - A tentative diagnosis can often be made well before full presentation.

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6. INVESTIGATIONS & DIAGNOSIS

6.1 International Study Group (ISG) Criteria

- **Diagnostic Utility:**
  - Most commonly used and best performing criteria.
  - Sensitivity: ~95%.
  - Specificity: ~96%.
- **Criteria Requirements:**
  - Diagnosis requires recurrent oral ulcers plus 2 of the following 4 clinical manifestations:

1. **Oral ulcers:** ≈98% frequency; must occur at least 3 times in a 12-month period.
2. **Recurrent genital ulcers:** ≈80% frequency; usually scarring.

3. **Skin lesions:** ≈80% frequency; includes erythema nodosum, pseudofolliculitis, papulopustular or acneiform nodules (postadolescent, not receiving corticosteroids).
4. **Eye lesions:** \50\% frequency; anterior or posterior uveitis, cells in vitreous or retinal vasculitis.
5. **Pathergy:** \50\% frequency; evaluated 24–48 h after dermal insertion of a 20-gauge needle.

6.2 Pathergy Test

- **Definition:** Non-specific hyperreactivity of the skin to trauma.
- **Procedure:**

→ Dermal insertion of a 20-gauge needle.

→ Evaluation at 24–48 h.

- **Positive Result:** Formation of a papule or pustule.

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7. MANAGEMENT & TREATMENT

1. **Clinical Diagnosis:**

→ Based on clinical features and ruling out other potential causes.

2. **Supportive Care:**

→ Dental and periodontal therapies (beneficial for oral health; improved oral health correlates with lower disease severity).

3. **Monitoring & Progression:**

→ Long-term observation may be required as symptoms can develop over months or years; tentative diagnosis may be made early.

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8. PROGNOSIS & COMPLICATIONS

- **Gendered Prognosis:**

→ Males frequently have more severe disease and poorer outcomes.

- **Regional Complications:**

→ Gastrointestinal involvement (more common in Japan/USA than Turkey).

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9. SPECIAL CONSIDERATIONS

- **Regional Differences:**
  - Turkey: Gastrointestinal involvement is rare.
  - Japan: Gastrointestinal involvement is more common.
  - United States: Gastrointestinal involvement seen in ~30% of patients.

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10. KEY PEARLS & CLINICAL TRAPS

Diagnostic Pearls

- **Oral Ulcers:** Nearly universal; often the first sign.
- **Genital Ulcers:** Most specific clinical finding.

- **Pathergy Test:** Non-specific skin hyperreactivity to trauma.
- **HLA B*51:** Not a diagnostic test (high prevalence in normal population).

Pathophysiology Pearls

- **Autoimmunity Profile:**

→ NOT associated with autoantibodies, Raynaud's, Sjögren's, thrombocytopenia, hemolytic anemia, or sun hypersensitivity.

- **Distinction from Autoinflammatory:**

→ Behçet tends to abate over time.

→ Absence of mutations associated with familial Mediterranean fever.

REFERENCE TABLES

TABLE 376-1

International Study Group Criteria for the Diagnosis of Behçet Syndrome CRITERIA Oral ulcers Plus 2 out of 4 from...

CRITERIA	FREQUENCY	COMMENTS
Oral ulcers	~98%	At least 3 times in a 12-month period
Recurrent genital ulcers	~80%	Usually scarring
	~80%	
Eye lesions	~50%	Anterior or posterior uveitis, cells in vitreous or retinal vasculitis
	~50%	