Behçet disease

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An uncommon condition with common manifestations

Abstract: *Behçet disease (BD) is a rare yet complicated chronic inflammatory condition related to vasculitis that may present with multiorgan involvement. BD has a number of potential clinical presentations, with painful oral and genital lesions being the most common. Outcomes of BD range from recurring, painful, transient rashes to life-threatening episodes. Primary care NPs are in a key position to develop suspicion for BD based on clinical presentation of combined manifestations. This article uses a case study to explore the diagnosis of BD.*

By Debra Lee, PHCNP, MN

Behçet disease (BD) is a rare form of chronic vasculitis first described by Hippocrates and later named after Hulusi Behçet after he published his case findings in 1937.[1,2] Although BD may present as a singular sign or symptom, it is, by definition, a chronic inflammatory condition related to multisystem vasculitis.[3] Primary care providers (PCPs) may be the first point of contact for patients presenting early on with symptoms of BD. Unfortunately, given the broad differential list related to the symptomatology seen with BD, the condition may go unrecognized for long periods while PCPs treat other suspected diagnoses with similar presentations to BD that are more commonly seen in primary care.

Additionally, although the genetic marker human leukocyte antigen (HLA-B51) can be associated with BD, there is no concrete test available to diagnose BD, making it a particularly challenging condition to identify.[4] It is imperative for PCPs to apply diagnostic reasoning and reevaluate treatment outcomes for optimal patient care.

Clinical presentation

Clinical presentation of BD may include, but is not limited to, recurring painful oral and vaginal lesions, headaches, arthralgia, visual changes, and inner ear dysfunction (see *Rates of common clinical manifestations of BD by system*).[3,5] A single center study showed that oral manifestations are the most common form of presentation followed by others, such as genital, ocular, and articular symptoms.[6] A retrospective monocentric study found that in patients diagnosed with neuro-Behçet disease (NBD), a subset of BD, 45% of the patients first presented with ophthalmologic manifestations, such as papilledema from cerebral venous thrombosis along with third and sixth cranial nerve palsy.[7]

Additionally, nonmucosal skin lesions may be present as along with involvement of the gastrointestinal (GI) system and vascular system.[3,8] With the multisystemic involvement seen in BD, reaching a diagnosis of a collective disease (or syndrome) rather than addressing each presentation as a sole condition can be clinically challenging.

Case study

Ms. O, a 42-year-old female patient of Greek descent, presented to her primary care NP for a 1-week follow-up appointment after a recent trip to the ED. She initially presented to the ED with a flare of recurring painful oral and vaginal lesions. From review of the emergency

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report, viral swabs were collected from the genital lesions. The results came back negative for herpes simplex virus type 2 (HSV-2), or genital herpes. The patient reported that although she did not receive treatment in the ED, the lesions spontaneously resolved over the course of 1 week.

As recommended by the 2013 CARE guidelines for providing comprehensive case study reviews, a timeline of relevant clinical events is presented (see *Timeline of events for the case study patient*).[9]

Although the painful lesions had resolved at time of presentation to her primary care office, Ms. O reported multiple ongoing concerns. She stated that she has had fatigue "for as long as I can remember" and chronic joint pain that she attributed to a history of fibromyalgia. Ms. O also reported worsening blurred vision over the past 2 years, periodic headaches for 2 to 3 years, and decreased hearing over the past year.

Medical history. Verbal account from Ms. O and review of her electronic medical record revealed the following medical history: migraine headaches, seizures, Bell palsy, fibromyalgia, possible systemic lupus erythematosus (SLE), iron deficiency anemia, pernicious anemia, hypothyroidism, and mixed generalized anxiety disorder with depression and possible borderline personality disorder. Ms. O also reported a remote history of Lyme disease causing fatigue and joint pain approximately 5 years ago for which she was taking long-term antibiotics for over the course of a year. It was later confirmed through serology that antibodies for Lyme disease were negative.

Rates of common clinical manifestations of BD by system[3,4]

System	Examples of common clinical manifestations of BD
Ocular	Visual disturbance from uveitis or retinal vasculitis (45%-90%)
Oral	Ulcerative mucosal lesions (95%)
Dermatologic	Pseudofolliculitis and erythema nodosum (40%-90%)
Gastrointestinal	Diarrhea, pain, hemorrhage, or perforation (4%-48%)
Musculoskeletal	Arthralgia and/or joint pain (11.6%-93%)
Vascular	Venous or arterial thrombosis or aneurysm (2.5%-50%)
Neurologic	Headaches, mostly from meningoencephalitis (2.3%-38.5%)
Genitourinary	Genital ulcers (60%-90%)

Over the past 6 years, Ms. O has been followed by a rheumatologist regarding the arthralgia and fatigue. She has also been followed by a neurologist to monitor a history of seizures, previous recurring episodes of unilateral facial neuralgia diagnosed as Bell palsy, and recurring headaches. She reports that she is overdue to see both specialists.

Her list of oral medications includes: daily escitalopram for anxiety and depression, topiramate for seizures, and levothyroxine for hypothyroidism. Additionally, she takes scopolamine for abdominal spasms, oral valacyclovir for recurrent cold sores (HSV-1), and nortriptyline for support with sleep on an as-needed basis. Ms. O also receives vitamin B12 I.M. injections monthly for pernicious anemia. She has no history of allergies to medications but has environmental allergies to dust and mold. Her family history is positive for her father having rheumatoid arthritis (RA) and her paternal aunt having SLE.

Physical exam findings. Physical exam findings at the time of presentation were grossly unremarkable. Vitals signs included: temperature 98.1° F (36.7° C) tympanic, heart rate 76, and BP 118/64 mm Hg. Ms. O's general appearance was that of a female appearing of stated age, appropriately dressed, and rapid speech at times with irregular eye contact.

The eyes, ears, nose, neck, and throat exam was unremarkable including no cervical lymphadenopathy. Chest auscultation revealed bilateral breath sounds with no adventitious sounds. Ms. O's heart sounds were normal with no extra sounds or murmurs. Her abdomen was flat and soft with no organomegaly or palpable masses noted and was nontender on palpation.

Musculoskeletal exam revealed no redness, swelling, or visible deformities over joints to upper and lower limbs. Neurologic exam showed normal cranial nerve testing with no ptosis of the eyelids along with normal upper and lower extremity strength and reflexes. Ms. O's cerebellar testing was normal along with her gait and balance. Dermatologic exam was negative for any visible rash or lesions, including no visible lesions to the oral mucosa.

Diagnostic testing. Diagnostic testing for fatigue, joint pain, and headaches was started in 2013 by her PCP, and Ms. O was referred to the rheumatologist and neurologist for additional testing. Initial labs ordered by the PCP were all within normal range aside from an elevated C-reactive protein (CRP) and a low hemoglobin and ferritin level (see *Serology results from case*

study). Additional labs ordered through the rheumatologist were normal aside from an elevated erythrocyte sedimentation rate (ESR) and CRP level.

Further diagnostic tests over the years included an MRI and a computed tomography scan of the head as well as a lumbar puncture due to the persistent headaches. The MRI results showed white matter lesions of unknown significance. The lumbar puncture revealed mildly elevated protein at 0.73 g/L and +1 leukocytes. After 2 years of workup and recurring symptoms, genetic testing was performed to check for the presence of HLA-B51 (a genetic marker associated with BD), which tested positive.[4,10]

Treatments and interventions. Due to the recurring oral and vaginal lesions, the patient had been treated periodically with oral antiviral medication (valacyclovir) for possible HSV. The painful lesions would resolve after approximately 1 week of treatment; however, as previously noted, the painful lesions resolved spontaneously after 1 week without treatment with the most recent episode.

Ms. O had also been treated for seronegative SLE based on her previous symptoms. Ms. O was given corticosteroids and immunosuppressants using oral prednisone and mycophenolate mofetil (MMF) as directed by her rheumatologist. The use of MMF for SLE is FDA off-label use. Over the course of 2 to 3 years, the follow-up antinuclear antibody (ANA) results suggestive of SLE were repeatedly negative.

Clinically, the patient reported no real improvement with the medications, which were discontinued. From this point forward while presenting to the NP in primary care, the patient continued to experience periodic flares of recurring oral and vaginal lesions, arthralgia, visual changes, and headaches. These symptoms reflect the multisystem involvement of this challenging diagnosis.

Discussion on BD

Epidemiology. BD is most prevalent among populations of Euro-Asian descent from an area historically referred to as the Silk Road region.[11,12] The global prevalence rate of BD is 10.3 per 100,000, a relevant rate within North America given the multiethnic population.[11] Occurrence rates affect both genders equally, although severe outcomes affect males more than females.[11,12] The typical age of onset is within the 30 to 40 years age group, although children under the age of 16 may also be affected and account for approximately 4% to 26% of cases.[11,12]

Timeline of events for the case study patient

Year	Specialists
2014	**Rheumatologist:** Chief complaint (CC): recurring perianal lesions of unknown origin; canker sores; arthralgia. Differential diagnosis: SLE, vasculitis, BD **Neurologist:** CC: unilateral facial weakness. Diagnosis: Bell palsy **Cardiologist:** CC: shortness of breath with chest pain. Diagnosis: pericarditis
2015	**Rheumatologist:** CC: recurring oral ulcers, joint pain Differential diagnosis: SLE versus vasculitis
2016	**Rheumatologist:** CC: worsening arthralgia
2017	**Rheumatologist follow-up:** ANA tests negative and SLE diagnosis excluded Diagnosis: fibromyalgia HLA-B51 genetic test positive **Neurologist:** CC: recurring headaches, poor vision with decreased night vision and blurred vision following exposure to bright lights Tests: Lumbar puncture: mild protein present; MRI of the brain, findings showed white matter lesions of unknown significance Differential diagnosis: multiple sclerosis versus NBD
2018	**Audiologist:** CC: decreased bilateral hearing loss Diagnosis: Sensorineural hearing loss with mild loss to left ear, moderate loss to right ear
2019	**Primary care follow-up:** Recurring oral and genital lesions; HSV-2 swab negative Plan: Referred back to rheumatologist with high index of suspicion for BD due to recurring symptoms and previously positive HLA-B51 genetic marker.

Pathophysiology. Multisystem chronic inflammation from vasculitis is the primary manifestation of BD. Although the exact physiology of BD is unclear, the disease is thought to be from a disruption to the T-cell homeostasis with abnormal neutrophil accumulation, swelling of endothelial cells, and fibrinoid necrosis.[12,13] In vitro studies have shown that neutrophils induce the process of vasculitis through the release of neutrophil extracellular traps.[14] There appears to be both a genetic and environmental cause to the disruption of the immune system, including previous infection from Streptococcus or HSV-1 infections that may trigger the autoimmune events.[8]

Diagnosis. BD is essentially a diagnosis of exclusion.[15] The differential list is vast considering the range of possible diagnoses related to the signs and symptoms presenting from multisystem involvement, making the disease a diagnostic challenge.

Differential diagnosis. The differential diagnosis list for symptoms related to BD is extensive and is related to the clinical multisystemic presentation (see *Differential diagnosis of common presentations of BD with relevant diagnostic workup*). For example, the differential list regarding recurring headaches may include migraines, encephalitis, brain tumors, and NBD.[7,15] Multiple sclerosis may also be considered in a patient with a history of limb neuropathy or facial neuralgia. Differential diagnoses related to the recurring joint pain include SLE, fibromyalgia, Sjögren syndrome, and RA. The recurring oral and genital lesions may include differentials such as HSV-1 and HSV-2, respectively. The oral lesions may also be from transient cold sores with a similar presentation of oral aphthous ulcers.

Diagnostics. The International Criteria for Behçet's Disease can be further used to support the diagnosis of BD.[16] Clinicians familiar with the relevant signs and symptoms can make a clinical diagnosis of BD. Diagnosis is further supported by test results suggestive of BD. As BD is a form of vasculitis, a full vasculitis workup is considered, which may include complete blood cell (CBC) count with peripheral blood smear, ESR, liver function tests, uric acid, streptococcal antibodies, hepatitis B and C testing, HIV, ANA, complement levels (C3, C4), rheumatoid factor (RF), serum electrophoresis and immunofixation, cryoglobulins, and antineutrophil cytoplasmic antibodies.[17]

Relevant diagnostics to rule-out BD. To further evaluate oral and genital lesions, HSV-1 and HSV-2 swabs, respectively, vesicular lesions should be obtained to rule out an HSV infection. If arthralgia are present, inflammatory markers are checked (ESR, ANA, RF) to rule out autoimmune conditions such as RA or SLE. However, a clear link between results of inflammatory markers and diagnosing an inflammatory condition does not always exist. For instance, fibromyalgia is also a diagnosis of exclusion that presents with multiple sites of chronic pain, similar to BD; however, recurring genital and oral lesions are not seen with fibromyalgia as they are with BD. Diagnostic reasoning and clinical suspicion are required to reach an accurate diagnosis.

Relevant diagnostics to rule in BD. Relevant diagnostics to consider include inflammatory markers and vascular histology of arteries and veins to assess for vasculitis, HLA-B51 for genetic testing relevant to BD, and lumbar puncture assessing for elevated protein levels in the cerebrospinal fluid seen in neuro-Behçet.[12,15]

Serology results from case study

Testing by family PCP	Testing by rheumatologist
Hemoglobin: low (99 g/L)	ANA: negative
Ferritin: low (8 mcg/L)	ESR: elevated (59 mm/Hr)
TSH: normal	CRP: normal
T4: normal	RF: negative
ESR: normal	Anti-ds DNA: negative
RF: negative	p-ANCA: negative
CRP: normal	c-ANCA: negative
Uric acid: normal	HLA-B51: positive
B12: normal	Anti-CCP: normal
Creatinine: normal	
AST, ALT: normal	

Key: ALT: alanine aminotransferase, ANA: antinuclear antibody, Anti-ds DNA: anti-double-stranded DNA antibody, AST: aspartate aminotransferase, c-ANCA: cytoplasmic antineutrophil cytoplasmic antibodies, CRP: C-reactive protein, HLA-B51: human leukocyte antigen, p-ANCA: cytoplasmic antineutrophil cytoplasmic antibodies, RF: rheumatoid factor, anti-CCP: anti-cyclic citrullinated peptide, TSH: thyroid-stimulating hormone

Differential diagnosis of common presentations of BD with relevant diagnostic workup[12,15,18,21]

Clinical case presentation	Differential diagnosis	Diagnostic workup
Oral mucosal lesions	HSV-1, aphthous ulcers	Viral swab
Genital mucosal lesions	HSV-2	Viral swab
Cutaneous lesions	Acne, vasculitis, SLE	Punch biopsy
Headaches with facial and limb weakness	Migraine, Bell palsy, multiple sclerosis, brain tumor, stroke	MRI head and spine, CT head, lumbar puncture
Decreased vision	Uveitis, nearsightedness	Full optometry exam
Arthralgia, fatigue	RA, SLE, fibromyalgia, vasculitis	Inflammatory markers including: ANA, ESR, CRP, RF, HLA-B51, anti-CCP. Vasculitis-specific: p-ANCA, c-ANCA

Histopathology results from punch biopsies of cutaneous lesions may confirm vasculitis.[18] Although vasculitis is a broad diagnosis with multiple causes, positive histology results can further alert the PCP to a diagnosis pointing toward BD.

Although not definitive, MRI results on patients with NBD may show single to multiple lesions in the brainstem.[7] Lumbar puncture results tend to show mild-to-moderate elevations in protein and leukocyte levels of the cerebrospinal fluid.[7]

Treatment

Early identification of BD is imperative for best patient outcomes, including prevention of flares and early treatment of painful symptoms. BD is a multisystem disease, and treatment is based on various considerations including the organs involved, age, comorbidities, drug interactions, and severity of BD (see *Treatment options for common manifestations of BD*). Lecesse and colleagues reviewed 37 studies including 21 randomized controlled studies that support the use of colchicine, azathioprine, interferon-alpha, thalidomide, etanercept, and apremilast for clinical manifestations from skin and joint involvement.[19] Treatment goals involve controlling the inflammatory response and decreasing the frequency of recurrences.[20] Treatment may be on an as-needed basis or as an ongoing basis for maintenance treatment.

European League Against Rheumatism (EULAR) recommendations. Updated EULAR guidelines from 2018 provide five guiding principles developed from an international task force of specialists.[21] These principles reinforce the importance of addressing BD management from a multidisciplinary perspective while providing individualized care of this often relapsing and remitting condition. The principles also reflect the seriousness of clinical presentation, particularly when presenting with ocular, vascular, neurologic, and GI involvement, as these are associated with a poor prognosis. Further, 10 recommendations were made that reflect the findings from updated research studies with an emphasis on the role of biologics in managing BD, or Behçet syndrome as the preferred terminology of the task force. Outside of the treatment options discussed from this case study, an updated overview of treatment recommendations for vascular and GI involvement is highlighted, including surgical options in severe cases.

Referral to specialists. BD is typically managed and monitored by a rheumatologist. However, if NBD is suspected or confirmed, a neurologist should be involved. Involvement of further specialists will depend on which body system is affected. For example, optometry, audiology, cardiology, or vascular specialists are

Treatment options for common manifestations of BD[19-21]

System	Recommended treatment options
Mucocutaneous (genital and oral lesions)	**Topical steroids:** • Triamcinolone acetonide cream (0.1%) applied three to four times daily as needed **Topical gastroduodenal cytoprotective agents:** • Sucralfate suspension used four times per day as mouthwash **Topical immunomodulating agents:** • Pimecrolimus (for genital only lesions, FDA off-label use)
Musculoskeletal arthralgia	**Antigout agents:** • Colchicine oral daily divided doses • Glucocorticoids • Prednisone oral dosing that may be tapered over 2 to 3 weeks, or oral daily dose for maintenance therapy **Dosages typically at direction of specialist:** • Immunosuppressants (such as azathioprine) and/or disease-modifying antirheumatic drugs • Tumor necrosis factor (TNF)-alpha inhibitors (infliximab, adalimumab, or etanercept) **Others:** • Methotrexate • Interferon alfa-2a or -2b
Neurologic	Treatment dosages to be determined in consult with specialist **Steroids:** • Glucocorticoids **Immunosuppressants:** • Azathioprine • Mycophenolate • Methotrexate **TNF-alpha inhibitors:** • Infliximab or adalimumab
Ocular	Treatment plan determined in consultation with the ophthalmologist **Treatment options may include:** • Topical corticosteroids and dilating eye drops • Immunosuppressants • High-dose glucocorticoids • TNF-alpha inhibitors

Note: BD is a multisystem disease and treatment is based on current evidence-based recommendations for the organ system involved. The drugs listed in the table do not have specific FDA indications for BD. Consult the manufacturers' product information for complete prescribing information.

consulted as needed. The PCP may remain a point of contact for the patient to review consult reports, medication reviews, and to provide case management. Patients may be overwhelmed with regular lab monitoring related to their condition and their medications. Continuing regular contact with their PCPs allows patients an opportunity to ensure that recommendations from specialists are in place and understood by the patient.

Prognosis. BD is a chronic condition. Symptoms such as recurring painful oral and genital lesions may resolve spontaneously; however, spontaneous resolution can take additional time that, in turn, results in unnecessary patient pain and suffering. In severe conditions, increased rates of BD-associated mortality are seen from neurologic and vascular complications, affecting males more than females.[11] Early identification and management are pivotal to obtain optimal patient outcomes, reduce the duration of painful flares, and preserve vision.

Conclusion

In the presented case study, the patient had multiple specialty groups involved including rheumatology, neurology, immunology testing for allergies, and ophthalmology. Although numerous tests had been conducted, unfortunately, due to the multiple differential diagnoses associated with BD, a clear diagnosis of BD took years. After the NP conducted a review of Ms. O's case, including a thorough review of previous consult notes and tests, communication was established from the NP to both the neurologist and rheumatologist seeking clarification on a possible diagnosis of BD, particularly highlighting the positive HLA-B51 result and the patient's recurring episodes of painful vaginal and oral lesions.

Through this communication, the neurologist supported the suspicion of nonneurologic BD and further asked that the rheumatologist manage Ms. O's case from this point forward. Ms. O was promptly seen by her rheumatologist who agreed with the most likely diagnosis of BD. Ms. O was started on oral MMF for immunosuppression. After 3 months of daily oral MMF 1 g twice daily, Ms. O returned to her rheumatologist for a follow-up appointment. At this time, she was reporting recurring oral mouth lesions and joint pains with no further genital lesions. Her rheumatologist recommended the addition of anti-tumor necrosis factor therapy be initiated, pending the approval of her insurance company. MMF does not have a specific FDA-approved indication for BD nor is MMF recommended through the updated EULAR guidelines presented by Hatemi and colleagues; however, it may be used off-label if clinicians see fit.

Additionally, regular lab monitoring was advised every 2 weeks for three rotations followed by monthly lab checks to monitor CBC count, liver function tests, creatinine, and inflammatory markers. For additional support, the rheumatologist referred the patient onward to a vascular specialist. The patient voiced appreciation for support with case management and was optimistic that the appropriate treatment will provide her with symptom resolution.

Psychosocial impact. Reaching a definitive diagnosis of BD can take time and collaboration between specialists, the PCP, and the patient. Throughout this process, patients are at risk for physical pain and suffering that may also take a toll on their psychosocial well-being.[22,23] The patient from this case study also had a diagnosis of depression that was established before the onset of physical symptoms, which led her to present to her family practice setting for assessment.

It is uncertain whether the depression was exacerbated by her physical symptoms; however, BD is associated with a greater report of fatigue, depression, anxiety, and lower quality of life scores due to poor symptom management, causing pain and decreased function.[22] Clinicians need to be vigilant toward monitoring the mental health status of patients with BD. Counseling and pharmaceutical treatment (if needed) may be considered to optimize overall patient health and ability to best cope with the physical symptoms.

Implications for NP practice. NPs in primary care often see patients of all ages with a wide range of clinical presentations. Although common clinical presentations often lead to common diagnoses that NPs may become familiar with, it is important to remain vigilant with history taking, physical assessments, and diagnostic reasoning. If treatment has failed, patients must be appropriately reevaluated rather than simply retreated. It is crucial that NPs keep a wide lens on the patient as a whole rather than treating singular conditions in order to put clinical puzzle pieces together.

While a number of specialists may be involved in cases such as BD, patients need to rely on their PCPs to be a central meeting point to review the multiple consults and results. NPs are positioned to navigate and advocate for patients as they assist with case management. As always, listening to the patient's concerns is critical.

A complicated case, such as BD, requires critical thinking and communication from all the clinicians involved to track trends in patient symptoms, evaluate labs results, monitor response to treatments tried and, ultimately, reach a diagnosis to optimize patient care. BD can be effectively managed with the appropriate topical or oral medications and is commonly managed with the support of a rheumatologist. NPs may wish to consider continuing education on topics related to arthritic conditions, vasculitis, and advances in pharmacology of immune conditions to stay abreast of topics and differentials related to BD. NP

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