CLINICAL VIGNETTE

Behçet's Disease

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Case Presentation

An 18-year-old female presented for multiple seemingly unrelated complaints. She complained of nausea, diarrhea, sore throat, mouth sores, vaginal discharge, frequent UTIs and rash. She also reported of bouts of abdominal pain, nausea, vomiting and diarrhea. She described her abdominal pain as crampy, associated with chronic bloating, epigastric burning, nausea, vomiting and diarrhea. There was blood and mucus in the diarrhea.

She previously underwent colonoscopy and endoscopy because of family history of ulcerative colitis in her mother. Colonoscopy showed some inflammation and she was started on mesalamine, although she was not diagnosed with ulcerative colitis or Crohn's disease. Mesalamine helped to reduce the severity of her abdominal symptoms but she continued to have epigastric discomfort and diarrhea. She also had negative celiac disease testing. She reported losing weight because she could not eat due to sores in her mouth. The oral ulcers had been present for three months. She had 3-4 "canker sores" at a time usually once every few weeks. The mouth sores were extremely painful and would last 5-10 days and prevented her from eating well. In addition, she felt like she has a perpetual sore throat which seemed more prominent when she had the oral ulcers. Her last episode of oral ulcers was ten days before her initial visit.

Her clinical history included frequent urinary tract and throat infections. She had back-to-back UTIs between her sophomore and junior year of high school. UTIs had improved but then a few months ago, she had recurrence with about 5-6 urinary tract infections during the past 6 months.

She also reported infectious mono and strep throat during the past year and it took her almost 6 months to recover from each episode.

The infections seemed to aggravate her oral sores and conversely when she had sores, she got sick more frequently with headaches, sore throat, swollen glands and rash. The rash was splotchy and bumpy on her forehead, cheeks and thighs. She had pictures of what looked like a papulopustular rash.

Recently, she also reported some itching and burning of the eyes which were visibly swollen and red. This occurred when she was not feeling very well.

In addition, she complained of episodes of burning vaginal pain and discharge. Vaginal pain was worse with sexual intercourse. Sex felt like a "razor" blade and she had blood tinged vaginal discharge. She tested negative for STD, bacterial vaginosis, vaginal yeast infection each time when she had symptoms.

She suffered from depression and was being treated by a psychologist and a psychiatrist. Her depression seemed to correlate with some of these flare-ups. She was on sertraline but still felt "overwhelmed."

Past medical history included two prior hospitalizations during high school for concurrent pleurisy and pancreatitis without gallstones. She also recalled profound fatigue causing her to miss school for about 2 months and sleep 16-17 hours a day. She underwent extensive testing at that time, but no cause was found. She had her first genital ulcer at the age of 10 before she was sexually active. Previous HSV tests were all negative.

Review of symptoms included: longstanding purplish discoloration of the fingers on cold exposure. Chronic chest tightness, which she says was previously misdiagnosed as prolonged QT. Chronic neck pain and ankles stiffness and popping. Frequent intermittent headaches with prior diagnosis of migraine headaches as a child. She does not notice any triggers. She has been diagnosed with B 12 deficiency and has been on B 12 supplements.

Family History

Mother with ulcerative colitis, severe arthritis, and similar symptoms including oral vaginal ulcers and skin rash on her shin that has been undiagnosed for years. Her sister had history of prolonged QT and died from sudden death at the age of twelve.

Physical Exam

BP 113/69, Pulse 72, Temperature 97.5 F, Sat O2:98%, Height 5'6", Weight 103 lb, BMI 16.75
General – alert, thin appearing, in no acute distress
Psych – slight depressed mood.
Eyes – slight conjunctiva injection. No pus in the anterior chamber. Pupils equal and reactive, extraocular eye movements intact.
Mouth - dry and red lips. Erythema on the left side of the throat.

Neck - supple, mild prominent lymph nodes in the anterior cervical chan.
Chest - clear to auscultation, no wheezes, rales or rhonchi, symmetric air movement
Heart - normal rate, regular rhythm, normal S1, S2, no murmurs, rubs, clicks or gallops
Abdomen - soft, nontender, nondistended, no masses or organomegaly, no abdominal bruits, no CVA tenderness, no hernias noted
Musculoskeletal – no joint swelling or tenderness. Full range of motion.
Pelvic - VULVA: vulvar erythema but no ulcer or scarring. VAGINA: erythema of the vaginal wall and a small ulcer on the left side of the vaginal wall. Vaginal discharge: white and creamy.
Skin – acne on forehead. A few popular lesions over her thighs.

Discussion

Behçet syndrome is a rare disease characterized by recurrent oral aphthous ulcers and any of several systemic manifestations including genital aphthae, ocular disease, skin lesions, gastrointestinal disease, neurologic disease, vascular disease, and arthritis. Most clinical manifestations of Behçet syndrome are believed to be due to vasculitis.

Behçet syndrome is more common and often more severe along the ancient silk road, which extends from eastern Asia to the Mediterranean. It is most common in Turkey, while the prevalence is much lower in North America and northern Europe. It typically affects young adults 20 to 40 years of age.

The common clinical feature in patients with Behçet syndrome is the presence of recurrent and usually painful mucocutaneous ulcers.

Oral ulcerations — Most, but not all, patients initially manifest recurrent oral aphthous ulcerations (also known as canker sores), which are grossly and histologically similar to common oral ulcers and recurrent aphthous stomatitis (RAS), but which tend to be more extensive and often multiple. The ulcers are painful and, in severe cases, may limit eating. Outer portions of the lips are not involved.

Healing of oral ulcers is typically spontaneous within one to three weeks with recurrent lesions. However, some patients will have ulcers present continuously. Oral ulcers are typically the first to come and last to leave in the course of the disease.

Urogenital lesions — Genital ulceration, the most specific lesion for Behçet syndrome, occurs in 75 percent or more of patients with Behçet syndrome. The ulcers are similar in appearance to the oral aphthae and are usually painful. Genital ulcers are most commonly found on the scrotum in men and the vulva in women. Recurrence is typically less frequent than with oral ulcerations. Scar formation is frequent for genital lesions. Scrotal scarring secondary to ulcers is rarely, if ever, seen in conditions other than Behçet syndrome. Epididymitis, salpingitis, varicocele, and other genitourinary inflammatory conditions may also occur in patients with this disorder. Urethritis is an unusual feature.

Cutaneous lesions — Cutaneous lesions also occur in over 75 percent of patients with Behçet syndrome. The skin manifestations vary and may include acneiform lesions, papulo-vesiculopustular eruptions, pseudofolliculitis, nodules, erythema nodosum (septal panniculitis), superficial thrombophlebitis, pyoderma gangrenosum-type lesions, erythema multiforme-like lesions, and palpable purpura. Biopsy of erythema nodosum lesions reveals a septal panniculitis, with medium vessel vasculitis in up to half of lesions.

Acneiform lesions may be more common in those with associated arthritis. These lesions consist of papules and pustules that are indistinguishable from ordinary acne and share characteristic microbiologic flora with papulopustular lesions of acne. Pustular skin lesions are often not sterile and may contain *Staphylococcus aureus* and *Prevotella* spp. Nailfold capillary abnormalities, mainly enlarged capillaries, may also be observed in patients with Behçet syndrome.

Ocular disease — Ocular disease occurs in 25 to 75 percent of patients with Behçet syndrome, depending upon the population studied, and in most cases progresses to blindness if not treated. Male patients are more likely to get eye disease, with about 75 to 80 percent developing involvement, and also have worse visual outcomes, even with treatment.

Neurologic disease — Neurologic disease occurs in less than 10 percent of patients with Behçet syndrome in most series. It is observed more frequently in men than women. Neurologic disease is classified as parenchymal or non-parenchymal. Focal parenchymal lesions and complications of vascular thrombosis are the most common abnormalities. Progressive personality change, psychiatric disorders, headache and dementia may develop. Unlike many other systemic vasculitic disorders, peripheral neuropathy is not a common feature of Behçet syndrome.

Non-parenchymal disease includes cerebral venous thrombosis, intracranial hypertension syndrome (pseudotumor cerebri), acute meningeal syndrome, and uncommonly stroke due to arterial thrombosis, dissection, or aneurysm. Cerebral venous thrombosis may present with headache, papilledema, sixth nerve palsy, and an elevated CSF pressure.

Vascular disease — Most clinical manifestations of Behçet syndrome are believed to be due to vasculitis, and Behçet is remarkable for its ability to involve blood vessels of all sizes (small, medium, and large) on both the arterial and venous sides of the circulation.

Vascular involvement is one of the major causes of morbidity and mortality in Behçet syndrome. In particular, pulmonary artery aneurysm carries a mortality of approximately 25 percent, and early recognition is important.

Arterial disease — Arterial disease is most commonly a small vessel vasculitis, but medium and large vessel disease may also develop. Carotid, pulmonary, aortic, iliac, femoral, and popliteal arteries are most commonly involved; and cerebral and renal arteries are rarely involved. Acute myocardial infarction can occur due to coronary artery vasculitis but is uncommon. Atherosclerosis does not appear to occur at an accelerated rate in Behçet syndrome, as has been observed in autoimmune diseases such as systemic lupus erythematosus.

Pulmonary artery aneurysms involving the large proximal branches of the pulmonary arteries are the most common pulmonary vascular lesion in Behçet syndrome and are uncommonly seen in diseases other than Behçet syndrome. Hemoptysis is the most common presenting symptom; cough, dyspnea, fever, and pleuritic pain are other presenting symptoms. A misdiagnosis of pulmonary embolism and subsequent anticoagulation can lead to a poor outcome if the underlying inflammatory large vessel vasculitis is not appreciated. Pulmonary infarction does not commonly occur. Hemoptysis may be the result of pulmonary artery-bronchus fistulae and frequently coexists with venous obstruction elsewhere.

Pulmonary artery thrombosis and aneurysms in association with peripheral thrombophlebitis are known as Hughes-Stovin syndrome, and this syndrome most commonly occurs in Behçet syndrome and may represent a part of the spectrum of manifestations seen in Behçet syndrome.

Venous disease — Venous disease resulting in venous thrombosis is more common than arterial involvement, and is often an early feature of Behçet syndrome. Superior and inferior vena cava occlusion, Budd-Chiari syndrome, dural sinus thrombosis, and other venous obstructive lesions can occur in addition to the more common superficial and deep vein thrombosis. Recurrent thrombosis of the lower extremities may lead to a post-thrombophlebitic syndrome.

Arthritis — A non-erosive, asymmetric, usually non-deforming arthritis occurs in about one-half of patients with Behçet syndrome, particularly during exacerbations. The arthritis most commonly affects the medium and large joints, including the knee, ankle, and wrist. In many patients, the arthritis is intermittent, lasting one to three weeks, though manifestations may be persistent. Fibromyalgia co-occurs in many patients with Behçet syndrome.

Renal disease — Renal involvement in Behçet syndrome is less frequent and often less severe than in other types of vasculitis. Patients with renal disease may have proteinuria, hematuria, or mild renal insufficiency but can progress to renal failure.

Cardiac disease — Symptomatic cardiac disease is uncommon in Behçet syndrome. Abnormalities that can occur include pericarditis, myocarditis, coronary arteritis with or without myocardial infarction, coronary artery aneurysms, atrial septal aneurysm, conduction system disturbances, ventricular arrhythmias, endocarditis, endomyocardial fibrosis, mitral valve prolapse, intracardiac thrombosis, and valvular insufficiency including aortic regurgitation.

Gastrointestinal involvement — Symptoms of intestinal Behçet syndrome include abdominal pain, diarrhea, and bleeding. Gastrointestinal involvement can be difficult to differentiate from inflammatory bowel disease, as other clinical signs and symptoms may also overlap, leading to difficult diagnostic issues. Gastrointestinal ulcerations occur in some patients with Behçet syndrome, and intestinal perforation can occur. Discrete ulcerations can be found throughout the gastrointestinal tract but are most often seen in the terminal ileum, cecum, and ascending colon.

Small intestinal bacterial overgrowth has been described in patients with treated Behçet intestinal disease in endoscopic and radiologic remission, and treatment of bacterial overgrowth may be beneficial for these patients. Oral ulcers that frequently occur in patients with inflammatory bowel disease are indistinguishable from the oral aphthae of Behçet syndrome; thus, inflammatory bowel disease must be considered before making the diagnosis of Behçet syndrome.

Increased rates of iron, vitamin B12, and folate deficiencies have been observed in patients with Behçet syndrome. This may be associated with the presence of serum gastric parietal cell antibodies in patients with Behçet syndrome.

There are no pathognomonic laboratory tests in Behçet syndrome; as a result, the diagnosis is made on the basis of the clinical findings. In the absence of other systemic diseases, we diagnose Behçet syndrome in patients with recurrent oral aphthae (at least three times in one year) plus two of the following clinical features:

- Recurrent genital aphthae
- Eye lesions (including anterior or posterior uveitis, cells in vitreous on slit lamp examination, or retinal vasculitis observed by an ophthalmologist)
- Skin lesions (including erythema nodosum, pseudovasculitis, papulopustular lesions, or acneiform nodules consistent with Behçet syndrome)
- A positive pathergy test. Pathergy refers to an erythematous papular or pustular response to local skin injury. It is defined as a pustule-like lesion or papule that appears 48 hours after skin prick by a 20-gauge needle.[1]

Case Follow Up

Patient was referred to rheumatology who confirmed the diagnosis of Behçet's disease. She started Colchicine 0.6 mg orally twice daily and immediately, her oral and vaginal sores cleared up quickly, bloody diarrhea resolved, and depression improved as well. Furthermore, they have not been recurring as they would before. She is less achy and feels like she can do more without being exhausted. Her rashes have also improved especially acne.

REFERENCES

1. **Smith EL, Yazici Y**. Clinical manifestation and diagnosis in Behçet syndrome. In: *UpToDate*, Post TW, ed. *UpToDate*. Waltham, MA 2020.