International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Navigating Complex Comorbidities: A Case of Behcet's Syndrome with Lumbar Disc Bulging and Cardiovascular Disease

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Abstract: ***This study aims to explore the prevalence, clinical manifestations, prognosis, etiopathogenesis, differential diagnosis, and treatment of Behcet's Disease (BD), a chronic relapsing multisystem disorder. The research problem addresses the geographical and ethnic variations in the prevalence of BD, and the challenges in diagnosis, monitoring, prediction, and treatment personalization. This case study explores the complex management of Behcet's syndrome in a 41-year-old female, complicated by lumbar disc bulging and cardiovascular disease. The patient presented with recurrent oral ulcers, skin lesions, and severe lower back pain, and was managed using hydroxychloroquine and azathioprine to avoid corticosteroid complications. The study highlights the importance of personalized treatment in managing comorbidities, focusing on the benefits of early diagnosis, multimodal drug therapy, and close monitoring. The findings emphasize the need for a tailored therapeutic approach for improved outcomes.***

Keywords: Behcet's disease, lumbar disc bulging, personalized treatment, cardiovascular disease, hydroxychloroquine

1. Definition

Behcet's Disease (BD) also referred to as Behcet's syndrome, is an idiopathic chronic relapsing multisystem disorder characterized by oral and genital aphthosis, skin lesions, and ocular manifestations like recurrent anterior uveitis. Vasculitis due to this syndrome involves blood vessels of all vital organs and different sizes[1]. This inflammatory disorder of unknown etiology can also affect joints, the brain, and the gastrointestinal tract.[2]

2. Prevalence

Behçet's disease (BD) has distinct geographical and ethnic variations. Behçet's syndrome can manifest at any age but it usually peaks in the third decade of life. Globally, prevalence varies; 10.3 per 100,000 people is the pooled prevalence. Nonetheless, there is a noticeable regional variation in this prevalence. Males are more likely to contract the disease, however certain nations report higher prevalence and severity rates among females. Due to factors like migration and increased epidemiological knowledge, the incidence has increased during the past 20 years in non-endemic countries. Behçet's syndrome is notably widespread in the Mediterranean Basin, east Asia, and the Middle East, especially in nations that were once part of the Silk Route [3,4,5]. Turkey has reported the highest prevalence, ranging from 80 to 420 per 100,000. Other Asian countries such as Saudi Arabia, Iran, Korea, China, and Japan show prevalence rates oscillating between 13.5 and 85 per 100,000 [6]. The prevalence in these regions reaches 420 per 100,000 compared to 2 per 100,000 in Western countries [7]. There are only a few reports of Behcet's disease from India. This could be due to the disease being truly uncommon in India, or it could be that cases are either going undiagnosed or are being under-reported [8,9,10].

3. Prognosis

A waxing and waning course marked by exacerbations and remissions is characteristic of Behçet disease. The outlook for young men is typically worse. Moreover, patients with an HLA-B51 allele seem to be at higher risk. The early stages of the disease are often marked by worsening arthralgias and mucocutaneous and ocular lesions. If symptoms arise, they usually appear later and involve the central nervous system and large vessels. Aneurysms, gastrointestinal problems, or neurological symptoms are typically the cause of death in cases where the disease takes a life. Patients who have arterial disease or a high frequency of flare-ups, as well as young men, are most at risk of dying. Eventually, remission occurs for many patients [11].

Etiopathogenesis

According to a genome-wide association study Human Leukocyte Antigen, B51 (HLA-B51) is the strongest genetic/endogenous factor in BD. Between 40% and 80% of patients with BD have HLA-B51[12]. An autoimmune background is suggested by positive responses to immunosuppressive drugs, the presence of autoantigens, and antigen-specific T cells. Episodes of inflammation that appear to be unprovoked may have an autoinflammatory origin. Based on the association with HLA-B51, interactions with epistatic endoplasmic reticulum aminopeptidase 1 (ERAP-1), increased response, and neutrophilic involvement, it shares some characteristics with spondyloarthropathy. On the other hand, infectious agents have been suggested as a BD

development trigger. In genetically predisposed people, a cross-reaction between human proteins and microbial antigens can result in a pathological immune response. The bacteria belonging to the Streptococcus species, including Streptococcus sanguinis and Streptococcus pyogenes, as well as the Herpes simplex virus, have demonstrated the strongest correlation with BD [13,14] Oral microbial flora is thought to have a part in the pathophysiology of BD because the condition typically begins in the oral mucosa and tends to flare up in the oral cavity following dental and surgical procedures.[14]

Clinical Manifestations:

Recurrent mouth ulcers, genital ulcers, and skin lesions that can occur in Behçet's disease include red, tender swellings on the legs called erythema nodosum and more widespread acne-like spots called pseudofolliculitis, arthritis-like symptoms such as pain, stiffness, swelling, warmth, and tenderness. The joints most often affected include the knees, ankles, wrists, and small joints in the hands. Inflammation of the uveal tract is known as uveitis and it can cause symptoms that include: painful red eyes, sensitivity to light, floaters (dots that move across the field of vision), blurred vision, and sudden loss of vision. In some people with Behçet's disease, the skin is particularly sensitive to injury or irritation, known as pathergy. Behçet's disease can cause inflammation of the stomach and bowel, which can lead to symptoms such as feeling and being sick, stomachache, indigestion, loss of appetite diarrhea with bleeding. One of the most common types of blood clot to affect people with Behçet's disease is deep vein thrombosis (DVT), symptoms of DVT include pain, swelling, and tenderness in the legs (usually in the calf), a heavy ache in the affected area, warm skin in the area of the clot, redness of the skin, particularly at the back of the leg below the knee. Inflammation of the blood vessels can cause the walls of blood vessels to weaken and develop an aneurysm. A ruptured aneurysm can lead to internal bleeding and organ dysfunction. Inflammation of the central nervous system (CNS) causes the most serious symptoms associated with Behçet's disease. The symptoms usually develop quickly over the space of a few days and can include: headache, double vision, loss of balance, seizures, partial paralysis on one side of the body, and behavioral or personality changes. Behcet's syndrome can manifest with constitutional symptoms such as fever, fatigue, and malaise. These symptoms are often non-specific and can vary in severity among individuals.[15]

Diagnosis:

The most common classification criteria for the diagnosis are International Criteria for Behçet's Disease (ICBD).

- Ocular lesions (uveitis, retinal vasculitis, chorioretinitis, papillitis)—two points;
- Oral aphthosis of at least three times/year—two points;
- Recurrent genital aphthosis—two points;
- Skin lesions (papulopustular rash, erythema nodosum)—one point;
- CNS lesions (parenchymal CNS involvement, venous sinus thrombosis)—one point;
- Vascular manifestations (venous thromboembolism, superficial thrombophlebitis, arterial thrombosis, aneurysm—especially aortic and pulmonary)—one point;
- The positive pathergy test—one point;
- A patient scoring ≥ 4 points is classified as having BD[12]

Table 1: Differential Diagnosis of Behcet's Syndrome:[16]

Condition	Overlapping clinical features	Important distinguishing feature/test
SLE with or without APS	Oral ulcers, non-erosive arthritis, neurological, vascular, and constitutional manifestations	Autoantibody positivity, low complement C3 and C4 levels
HLA-B27 related disease	Oral ulcers, uveitis, arthritis; GI and skin manifestations	HLA-B27 positivity
Crohn's disease	Oral ulcers, non-erosive arthritis; GI, and skin manifestations	Granulomatous disease, scleritis
Ulcerative colitis	Oral ulcers, non-erosive arthritis, uveitis, GI and skin manifestations	Ascending proctitis/colitis
Coeliac disease	Mouth ulcers, GI manifestations, constitutional symptoms	Coeliac autoantibodies and characteristic histology
Autoinflammatory disease	Orogenital ulcers, skin disease, non-erosive arthritis, neurological and constitutional manifestations	Prominent fevers, childhood-onset, genetic testing
Sarcoid	Oral ulcers, lung disease, erythema nodosum, neurological complications, and skin manifestations	Granulomatous disease on biopsy
SAPHO syndrome	Arthritis, acne, pustular lesions	Osteitis and hyperostosis
MAGIC syndrome	May have all of the features of Behcet's syndrome	chondritis
ANCA vasculitides	Vascular disease, arthritis; constitutional, eye, and skin manifestations	ANCA positivity

4. Treatment

A patient's age, gender, frequency of attacks, severity and duration of involvement, and the organ or organs involved all affect the course of treatment. When treating mucocutaneous lesions, colchicine is a viable first option. Patients who experience recurrent arthritis or have resistant diseases may benefit from taking Azathioprine. Agents such as IFN-α and anti-TNF-α may be utilized in rare but even more severe cases. Initially, acute inflammation in the choroid, optic disc, retina, and retinal vessels must be suppressed and managed when treating ocular BD. It is possible to recommend oral corticosteroid therapy in addition to topical corticosteroids and mydriatics. Azathioprine and/or Cyclosporine should be started in addition to systemic corticosteroids in cases that are not responding or when there is posterior segment involvement. In patients who do not respond well to this treatment or who present with an acute ocular threat that could impair their vision, anti-TNF-α agents or IFN-α should be the next line of therapy to be explored. Depending on the severity of gastrointestinal involvement, different medications are used to treat it [17]. Patients reported symptomatic improvements with hydroxychloroquine treatment, particularly joint pains, fatigue, and rash. Vasculitis relapses were less frequent, with a reduction in corticosteroid doses. Hydroxychloroquine was generally well tolerated.[18] When

treating milder cases, 5-amino salicylate derivatives (such as sulfasalazine or mesalamine) should be used initially; however, in more severe or unresponsive cases, azathioprine should be considered. In the worst circumstances, oral or intravenous high-dose corticosteroids should be considered [17]. Although the disease has been better understood and managed, Behçet's syndrome remains a complex disorder with a higher risk of morbidity due to unmet needs in diagnosis, monitoring, prediction, and treatment personalization that pose challenges to clinical practice.[3]

5. Case Study

Case Presentation: A 41-year-old female, weighing 70 kilograms, obese patient presented with complaints of pain and swelling of the left lower limb, left shoulder, and severe lower back pain for two weeks, and worsened skin itching on the face for 2 days. She was recently diagnosed with Behcet's syndrome (HLA-B51 positive) with previous complaints of recurrent oral ulcers and skin lesions and was prescribed azathioprine 50mg once daily orally. She was prescribed metoprolol 50mg once daily, and sitagliptin phosphate/metformin hydrochloride 50/500mg for hypertension, and Type II diabetes mellitus respectively, Erythrocyte Sensitisation Syndrome, she underwent Percutaneous Coronary Intervention (PCI) in 2023 due to CAD and was given with aspirin 75mg and rosuvastatin 5mg once daily orally for management. She had no known medication allergies but food allergies to tamarind and brinjal where rashes occurred when taken were reported. On physical examination of the cardiovascular system, heart sounds S1 and S2 were heard, bilateral air entry was equal for the respiratory system, soft and non-tender findings per abdomen, and back pain particularly left-sided with a pain score of 7/10 which is severe following numeric pain rating scale.

Investigations: Vitals on arrival include a temperature of 98.2 F, pulse rate of 86 beats/minute, Blood pressure-110/70mm of Hg, respiratory rate of 19 breaths/minute, and SpO_2 – 98% on room air. She weighs 70 kilograms, is 152cm in height, has and BMI is 30.3 kg/m^2 and is considered to be obese. Dietary instructions by the treating consultant include a Diabetic low-salt diet. Hematological Investigations include Haemoglobin-11.7g/dl, MPV-9.2fl, Total leucocyte count-8700 cells/mm^3 in which Neutrophils-48.7%, Lymphoctes-40.1%, Eosinophils-5.3%, Monocytes-5.3%, Basophils-0.6%, Haematocrit-37.9%, RBC-5.2 million cells/ul, MCV-73.5fl, MCH-22.6pg, MCHC-30.8g/dl, RDW-CV-13.8%, platelet count-2,58,000, ESR-10.32mm/1^{st} hour. Urinalysis showed no casts, crystals, proteinuria, glucosuria, pH- 5.5, specific gravity-1.020, and pale yellow-colored urine. Biochemical Investigations like serum creatinine-0.82mg/dl, urea-26mg/dl, uric acid-3.1mg/dl, ALT-19U/L, AST-17U/L, Amylase-69U/L, alkaline phosphate-73U/L, albumin:globulin ratio-1.0, Total bilirubin-0.3mg/dl, serum calcium-8.7mg/dl, serum chloride-105mmol/L, serum magnesium-3.2mmol/L , serum potassium-3.8mmol/L, serum sodium-139mmol/L, vitamin B12- >128pmol/L, vitamin D-35ng/ml, random blood glucose-165mg/dl and HbA1C-6.9% were done. Other investigations including bilateral lower limb venous doppler were done in view of pain and swelling in the left lower limbs resulting in no evidence of DVT, a single tiny deep perforation in the left thigh, Ultrasound abdomen showed grade I fatty liver, and mild right-sided hydroureteronephrosis, bulky uterus with heterogeneous echotexture and loss of endomyometrial junction, 2D-ECHO-normal sized cardiac chambers, valve morphology, no regional wall motion abnormality, normal LV systolic function with EF-60%, no pericardial effusion, MRI L-S spine was done which showed mild compression at L3-L4 and L4-L5 levels. This confirms the diagnosis of lumbar disc bulging.

Diagnosis:
Primary: Behcet's syndrome (HLA-B51 positive)
Secondary: Lumbar disc bulging (L3-L4 and L4-L5), Type II diabetes mellitus, Hypertension, Coronary Artery Disease, and mild right-sided hydroureteronephrosis

Management: The patient was managed conservatively and administered medications like hydroxychloroquine along with azathioprine for the treatment of Behcet's syndrome instead of the usual anti-inflammatory corticosteroid therapy, which may worsen diabetes mellitus condition. Kojic dipalmitate hydroquinone and SPF 55 sunscreen lotion were given for skin protection and itch over the face slowly subsided. Patient was pain-free after administering etoricoxib/thiocolchicoside combination and gabapentin for pain. Metoprolol and rosuvastatin were given for the management of CAD, sitagliptin phosphate/metformin hydrochloride, and pantoprazole for Acid pepsin disease prophylaxis. The condition of the patient improved clinically and strict medication adherence was advised with Hydroxychloroquine 200mg once daily, Azathioprine 50mg once daily for Behcet's disease, metoprolol 50mg once daily for hypertension, nicorandil 5mg twice daily, rosuvastatin/aspirin/clopidogrel combination 20/75/75mg capsule once daily, sitagliptin phosphate/metformin hydrochloride 50/500mg for type II diabetes mellitus, gabapentin/nortriptyline 400/10mg for neuropathic pain, etoricoxib/thiocolchicoside 60/4mg twice daily for pain, pantoprazole 40mg once daily for acid pepsin disease prophylaxis and a calcium supplement as discharge medications.

6. Conclusion

This case study demonstrates the importance of an individualized, multimodal approach to treating patients with Behcet's syndrome, especially those with multiple comorbidities. It underscores the need for early diagnosis, tailored therapeutic strategies, and close monitoring to improve patient outcomes. This case highlights the challenges of managing Behcet's syndrome in patients with complex comorbidities, such as lumbar disc bulging and cardiovascular disease. By employing a personalized treatment approach, using medications like hydroxychloroquine and azathioprine, the patient showed clinical improvement without exacerbating other conditions. The findings underscore the importance of early diagnosis, individualized treatment, and ongoing monitoring in the management of multisystem disorders.

7. Learning Points

1) **Multimodal Approach in Comorbid Conditions:** Treating Behcet's syndrome in patients with diabetes, CAD, and hypertension requires careful drug selection to prevent adverse effects from steroids and anti-inflammatory agents.
2) **Importance of Early Diagnosis and Monitoring:** Timely MRI confirmed lumbar disc bulging, allowing for conservative treatment and pain management, preventing the need for surgical intervention.
3) **DMARDs in Behcet's Syndrome:** Hydroxychloroquine and azathioprine are effective treatment options for Behcet's syndrome, particularly for patients at risk of corticosteroid-related complications.
4) **Personalized Care for Multisystem Diseases:** Careful management of diabetes, hypertension, and CAD with appropriate medications ensured the patient's overall condition improved without exacerbating comorbidities.
5) **Adherence and Follow-up:** Strict medication adherence and lifestyle modifications, including a diabetic low-salt diet, were emphasized to maintain long-term control of the patient's chronic conditions.

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