

A RARE CASE IN BANGLADESH - BEHÇET'S DISEASE

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Abstract:

This was a case of a 21 years old young man presenting with recurrent oral and genital ulcers, multiple nodules over all the four limbs and lower limbs' pain. However, as these were so much painful, it hampered his daily life. We were also in doubt that whether this was really Behçet's disease. We finally could diagnose it which was rare in Bangladesh.

Key words: Behçet's Disease, oral ulcer.

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Introduction:

Behçet's disease (BD) was named in 1937 after the Turkish dermatologist Hulusi Behçet, who first recognized the syndrome in one of his patients in 1924 and reported his research on the disease in 1936.¹ It is the triple-symptom complex of recurrent oral aphthous ulcers, genital ulcers, and uveitis. This disease can affect nearly every system in the body, other conditions such as vasculitis, fibromyalgia, migraines/central nervous system problems, eyesight problems, tachycardia and joint pain and swelling are also commonly linked to Behçet's Disease¹.

Nearly all patients present with some form of painful oral mucocutaneous ulcerations in the form of aphthous ulcers or non-scarring oral lesion.¹ Painful genital ulcerations usually develop around the anus, vulva, or scrotum and cause scarring in 75% of the patients.¹ Additionally, patients may present with erythema nodosum, cutaneous pustular vasculitis, and lesions similar to pyoderma gangrenosum, inflammatory eye disease can develop early in the disease course and lead to permanent vision loss in 20% of cases. Ocular involvement can be in the form of posterior uveitis, anterior uveitis, or retinal vasculitis. Behçet's disease may result in primary or

secondary optic nerve involvement. Papilloedema as a result of dural sinus thrombosis² and atrophy resulting from retinal disease have been characterized as secondary causes of optic nerve atrophy. When these symptoms occur with concurrent mucocutaneous ulcerations, they raise suspicion of acute optic neuropathy. GI manifestations include abdominal pain, nausea, and diarrhea with or without blood, and they often involve the ileocecal valve.¹ Many patients with Behçet's disease often complain about abdominal tenderness, bloating, and generic abdominal discomfort that closely mimics irritable bowel syndrome. Lung involvement is typically in the form of hemoptysis, pleuritis, cough, or fever, and in severe cases can be life threatening if the outlet pulmonary artery develops an aneurysm which ruptures causing severe vascular collapse and death from bleeding in the lungs.¹ Nodules, consolidations, cavities and ground glass lesions are common in patients with pulmonary involvement.³ Pulmonary artery thrombosis may occur. Arthralgia is seen in up to half of patients, and is usually a non-erosive poly or oligoarthritis primarily of the large joints of the lower extremities.¹ CNS involvement most often occurs as a chronic meningoencephalitis. Lesions tend to occur in

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the brainstem, the basal ganglia and deep hemispheric white matter and may resemble those of MS. Brainstem atrophy is seen in chronic cases. Neurological involvements range from aseptic meningitis to vascular thrombosis such as dural sinus thrombosis and organic brain syndrome manifesting with confusion, seizures, and memory loss.¹ They often appear late in the progression of the disease but are associated with a poor prognosis. Pericarditis is a frequent cardiac manifestation.³ Chronic aortic regurgitation due to aortic root disease may also be seen.⁴ The cause is not well-defined, but it is primarily characterized by auto-inflammation of the blood vessels. Although sometimes erroneously referred to as a "diagnosis of exclusion", the diagnosis can sometimes be reached by pathologic examination of the affected areas.

Case Report:

A 21 years old young unmarried muslim male was admitted into the Department of Medicine in Dhaka Medical College Hospital, with the complaints of recurrent oral & genital ulcer since childhood, multiple nodular swelling over all the 4 limbs for 6 months and pain in both lower limbs for 4 years. According to the statement of the patient, he was reasonably well about 14 years back. Then he developed multiple painful oral ulcers as erythematous margin with central white base appearing about 2 monthly. There is also cracking, fissuring, bleeding on touch resulting in deep ulceration. Throat pain & burning was also present when the oral ulceration became aggressive. There were also some boils over the scrotum and painful ulceration over his glans penis similar to oral ulcer and often itchy. As a result, during micturition he felt burning. The scrotum became inflamed and tender. He also complained of high grade fever accompanied by those ulcers associated with chills and rigor, subsided with drugs. There is also headache which is dull & diffuse associated with neck pain. Again, he complained of watering, burning and painful red eyes. Sometimes his vision became blurred. When he was 18 years old, he developed arthritis in the right ankle joint, subsequently the left one.

These were so tender that he could hardly move for 1 month. For that, he took analgesics. Successively, there developed pitting oedema from mid knee to foot of both limbs. He took hot foot bath and the oedema subsided with blackening of the skin. However, for last 5 months, multiple painful nodular swelling of different sizes & shapes, appeared in all the 4 limbs off & on in both flexor and extensor compartments. The nodule was at first soft, then reddish with progressive thickening, hardening and blackening. There was blackish palpable cord like lesion in the medial aspects of both lower limbs, often painful there is ongoing alteration of bowel habit for last 6 months. There was also abdominal cramps, tinismus, heart burn and abdominal bloating. Palpitation and history of gum hypertrophy is also present. He lost 6 kg in last 4 months. He was normotensive, nondiabetic and nonasthmatic.

He was nonsmoker, nonalcoholic, not addicted to drugs, no habit of betel leaf chewing and no history of sexual exposure. He had no significant past medical history. He came from a lower middle class family. All his family members were well, except his mother, who had also recurrent oral ulcer. He maintained hygiene. He had no definite travel history to the abroad and was immunized according to the EPI schedule.

He had no history of jaundice, anorexia, nausea, vomiting, chest discomfort, dyspnoea, hemoptysis, hematemesis, melaena, hematochezia, hematuria, steatorrhea, arthralgia, heel pain, syncope, seizure, psychosis, photophobia, photosensitivity, altered personality, intermittent claudication, rest pain, Raynaud's phenomenon.

On examination, his pulse was 86/min, BP-110/70 mm of Hg, normal temperature, respiratory rate was 16 breaths/min, mild anaemic, non-icteric, non-cyanotic, clubbing and koilonychia, leukonychia and dehydration were absent. Multiple oral ulcers with erythematous margin and central whitening, more in the buccal surfaces and inner part of lips. The tongue is also involved. The eyes were red. Pupil reaction was normal. There was no



Fig. 1: *Clinical manifestations of Behçet's disease.*

cranial nerve palsy. Lymph nodes were not enlarged; neck veins were not engorged and bony tenderness was absent. Multiple erythema nodosum of different size and shape is found over all the limbs, some appears reddish, firm, tender and some are blackish, non-tender and thick. Oedema was absent. The skin of the feet got black and thick. There were two blackish, non-tender cord like lesions over the medial aspects of both lower limbs. All the peripheral pulses are normal. There was folliculitis over the scrotum and a few ulcerations over the glans penis. No organomegaly and cardiorespiratory abnormality was found. Fundoscopic examination reveals no abnormality. Slit lamp examination was also normal. Other systems were quite normal. Pathergy test was negative.

His baseline investigations consisting of a complete blood count showed that WBC count was 9650/mm³; RBC count was 4.36 million/mm³; platelet count was 5,23000/mm³; Hb was 11.1gm/dl, the differential count and red cell indices were within normal limit, peripheral

blood film shows non-specific findings. Urine routine examination was normal except pus cells (2-4/HPF), stool routine examination showed few mucus and starch granules, serum creatinine, random blood sugar, serum electrolytes, chest x-ray, x-ray of right lower limb, ECG were within normal limit. C-Reactive protein was increased (12.0 mg/dl), C-ANCA(<1.00U/L), P-ANCA (1.06 U/L), ANA (12.0 IU/ml), RA titre (10 IU/ml) and anti-phospholipid antibody (<1.00 U/ml), anti-CCP antibody (0.5 U/ml) were found negative. Ultrasonogram of the whole of the abdomen revealed no abnormalities. Venous Biopsy was done from the right forearm on 10/02/2014 and the histopathological examination showed a medium size blood vessel with small amount of smooth muscle in the wall. The lumen contained a thrombus. The wall showed infiltration by many acute and chronic inflammatory cells. No granuloma or microabscess were seen, which was suggestive of thrombophlebitis. Duplex study of both lower limbs on 25/02/2014 reveals diffusely thick

and irregular both long saphanous venous wall (long segment around both knee joints), focal thickening in both long saphanous veins (near opening) and right common femoral vein, mildly thick and irregular wall of both arteria dorsalis pedis with mildly reduced flow velocity. One enlarged lymph node (25 mm × 10 mm) in the right inguinal region. No atherosclerotic plaque or venous thrombus is seen suggestive of vasculitis in both lower limbs. These all gives the clues of Behçet's Disease. Before doing duplex study, we started Mebeverine, Prednisolone (45 mg) & Azathioprine (200 mg) for medication. After dulex study was done, we added tab. Aspirin (75 mg) daily. His skin nodules was started to subside. The colonoscopy report was normal.

Discussion:

Behçet's disease is a rare, multi-system rheumatic disorder of unknown aetiology that causes the vasculitis anywhere in the body. It is presumed to be an autoimmune disease and includes involvement of the mucocutaneous, ocular, cardiovascular, renal, gastrointestinal, pulmonary, vascular, musculoskeletal, urological and central nervous systems. Behçet's disease or Behçet disease sometimes called Behçet's syndrome, Morbus Behçet, Adamantiades syndrome, Oculo-Bucco-Genital Syndrome, Triple Symptom Complex of Behcet, Hulusi-Behcet's Syndrome or Silk Road disease¹. In many patients the activity of this disease diminishes with time. Silk Road countries include those in the Mediterranean basin, Middle East and Far East. Behçet's syndrome is not proven to be contagious².

Criteria for Behçet's disease by American Behçet's Disease Association:⁵

- Mouth sores (oral ulcers) at least three times in 12 months
- Any two of the following:
 - o Recurring genital sores/ulcers
 - o Eye inflammation with loss of vision
 - o Characteristic skin lesions
 - o Positive pathergy (skin prick test)¹

In the Silk Road countries, Behçet's disease is more common in men than in women. However, in Western Europe and the U.S., the trend is

reversed: more women have BD than men. Symptoms typically develop when patients are in their 20s and 30s; however, the disease has been seen in all ages, from infants to the elderly. The incidence is around 1 in 10,000 people in silk road countries and 1 in 20,000 in USA⁶.

The primary mechanism of the damage is an overactive immune system that seems to target the patient's own body. The involvement of a subset of T cells (Th17) seems to be important. The primary cause is not well known. In fact, no one knows yet why the immune system starts to behave this way in Behçet's disease. There does however seem to be a genetic component involved, as first degree relatives of the affected patients are often affected in more than expected proportion for the general population. An association with the GIMAP family of genes on the long arm of chromosome 7 (7q36.1) has been reported. The genes implicated were GIMAP1, GIMAP2 and GIMAP4. A large number of serological studies show a linkage between the disease and HLA-B51. HLA-B51 is more frequently found from the Middle East to South Eastern Siberia, but the incidence of B51 in some studies was 3 fold higher than the normal population. However, B51 tends not to be found in disease when a certain SUMO4 gene variant is involved and symptoms appear to be milder when HLA-B27 is present⁷. At the current time, a similar infectious origin has not yet been confirmed that leads to Behçet's disease, but certain strains of *Streptococcus sanguinis* has been found to have a homologous antigenicity. Vasculitis resulting in occlusion of the vessels supplying the optic nerve may be the cause of acute optic neuropathy and progressive optic atrophy in Behçet's disease⁵. Histological evaluation in a reported case of acute optic neuropathy demonstrated substitution of the axonal portion of the optic nerve with fibrous astrocytes without retinal changes. CNS involvement in Behçet's may lead to intracranial hypertension most commonly due to dural venous sinus thrombosis and subsequent secondary optic atrophy⁷.

Mouth ulcers (aphthus ulcers) are the most common and earliest sign of Behcet disease.

However, before these appear a patient may for a number of years experience a variety of recurrent signs and symptoms that include: sore throats and tonsillitis, muscular and joint pain, malaise, generalised weakness, anorexia, weight loss, headache, fluctuations in body temperature, painful mouth ulcers are usually the first outward sign of Behçet's disease and occur in about 70% of patients. Ulcers can occur anywhere in the mouth including on the tongue and inside the lips and cheeks. They usually last for 1-2 weeks but can remain for as long as 3 weeks. Behçet disease can be difficult to diagnose as signs and symptoms come and go and may not be apparent all at one time. If you have a history of recurrent mouth and genital ulcers, uveitis and skin sores this is suggestive of the condition⁶.

There are no specific tests to confirm the diagnosis, but screening investigations such as blood count, kidney and liver function tests and C-reactive protein may be performed to determine which organs are affected by the condition⁸.

There are many complications in this disease like vasculitis, rupture of aneurysms and thrombosis may all lead to potentially fatal cardiovascular complications. CNS involvement can lead to permanent deficits. Eye involvement may result in blindness⁸.

Behçet's disease can cause male infertility, either as a result of the condition itself or of a side effect of concomitant medication such as colchicine, which is known to lower sperm count.⁹

Management:

Though Behçet's disease is an incurable disease, it is not impossible to control the disease process. The aim of treatment is to prevent long-term damage. The most severe manifestation present in the patient usually determines the choice of treatment. Current treatment is aimed at easing the symptoms, reducing inflammation, and controlling the immune system. High dose corticosteroid therapy (1mg/kg/day oral prednisone) is indicated for severe disease manifestations.⁷

Anti-TNF therapy such as infliximab has shown promise in treating the uveitis associated with the disease.⁸ Anti-TNF agent, Etanercept, may be useful in patients with mainly skin and mucosal symptoms⁹.

Interferon alfa-2a may also be an effective alternative treatment, particularly for the genital and oral ulcers¹⁰ as well as ocular lesions. Azathioprine, when used in combination with interferon alfa-2b also shows promise, and Colchicine can be useful for treating some genital ulcers, erythema nodosum, and arthritis. Thalidomide has also been used due to its immune-modifying effect. Dapsone and rebamipide have been shown, in small studies, to have beneficial results for mucocutaneous lesions¹⁰.

Given its rarity, the optimal treatment for acute optic neuropathy in Behçet's disease has not been established. Early identification and treatment is essential. Response to ciclosporin, periocular triamcinolone, and methylprednisone followed by oral prednisone has been reported although relapses leading to irreversible visual loss may occur even with treatment⁹. Immunosuppressants such as interferon alpha and tumour necrosis factor antagonists may improve though not completely reverse symptoms of ocular Behçet's, which may progress over time despite treatment. When symptoms are limited to the anterior chamber of the eye prognosis is improved. Posterior involvement, particularly optic nerve involvement is a poor prognostic indicator. Secondary optic nerve atrophy is frequently irreversible⁸. Lumbar puncture or surgical treatment may be required to prevent optic atrophy in cases of intracranial hypertension refractory to treatment with immunomodulators and steroids¹⁰.

Conclusion:

People with Behçet's disease usually have a normal life expectancy. It is important to have regular reviews with the doctor. Most people with Behçet's disease can lead productive lives and control symptoms with proper medication, rest, and exercise. There is a very variable course of recurrences and remissions lasting

for years. The majority of new manifestations occur within the first five years after onset of the disease. Prognosis will depend on which systems are involved. Men tend to have a poorer prognosis. Mortality is usually low but death may occur as a result of neurological involvement, vascular disease, bowel perforation, cardiopulmonary disease, or as a complication of immunosuppressive therapy. Many patients go into remission with time. Although treatment of skin-mucosal manifestations, eye disease and pulmonary artery aneurysms has improved significantly in the past couple of decades, the treatment of CNS lesions is still problematic.

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