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Bechet's Disease and its association with Herpes Simplex Virus : Case Report of a rare Multisystem disorder with review of the literature

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ABSTRACT

In the year 1937, A Turkish dermatologist Prof Hulusi Bechet described a syndrome based upon three cases. His first reported case in the year 1924 was a female who presented with recurrent aphthous ulcers of the oral cavity, genital ulcers, erythema nodosum and visual impairment which later lead to blindness. The second patient presented in 1930 with oro-genital ulcerations and scleral injection in the eyes. The third case was reported in the year 1936, a male which similar complaints, scrotal ulcers, loss of vision, scleral injection, fever and myalgia. Professor Hulusi Bechet grouped these clinical findings into a syndrome known as Bechet's syndrome. Bechet's disease may present in several ways, and many patients' oral ulcers are the presenting complaints. Oral ulcers are usually underdiagnosed and often ignored by the patients. Later on, genital ulcers and complications such as Uveitis appear, which cause the patients to seek medical help. This is a rare disorder, but it must be considered as the complications may lead to a permanent impairment of vision. In many cases and studies, Bechet's disease is associated with the Herpes simplex virus. The evidence that we report is also found to have positive antibodies for Herpes simplex virus. Herpes Simplex Virus is a DNA Virus and is a causative agent in various ocular diseases such as conjunctivitis, corneal ulceration, stromal keratitis, scleritis iridocyclitis, Uveitis. On an average HSV Uveitis occurs at the age of 46 years. Herpetic corneal ulceration is a cause of blindness in these patients. Bechet's disease is also associated with Uveitis and has a dreaded complication of blindness. The patient that we report had both oral ulceration, genital ulceration, Uveitis and was found to have HSV antibodies. Management and treatment must reduce relapses.

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INTRODUCTION

This multisystem disorder affects males and females equally. Found in the younger age group with increased severity in males. The diagnosis of Bechet's Syndrome is clinical and based on these diagnostic criteria. Presence of recurrent Oral ulceration plus any two of the following 1) Recurrent Genital Ulceration 2) Ocular lesions 3) Skin lesions 4) Positive pathergy test. The ulcers are usually painful, shallow or deep with a central yellowish or necrotic base, appear singly or in crops and can be located anywhere in the oral cavity. These ulcers resolve without leaving any scar. Genital Ulcers are

less commonly found but more specific, they are painful and do not affect glans penis and urethra but produce scrotal and vulval scars (Harrison *et al.*, 2018).

Skin is involved in 80 percent of patients. It includes erythema nodosum, Acne-like rashes, folliculitis and sometimes vasculitis, sweet Syndrome and pyoderma gangrenosum. Pathergy test is positive. This test is non-specific inflammatory reactivity to scratch or intradermal normal saline injection and is a particular manifestation of Bechet's Syndrome (Harrison *et al.*, 2018).

Uveitis occurs primarily in males and only in 15 percent of patients. Eye involvement with scarring and pan uveitis can lead to blindness and is the most dreaded complication. 50 % percent of cases have arthralgia or arthritis and mainly affects ankles and knees (Harrison *et al.*, 2018).

Arterial involvement occurs in less than 5 percent of patients and may have aortitis, peripheral arterial thrombosis and aneurysm. Neurological involvement is seen in 80 percent of cases and is primarily parenchymal form. Brainstem involvement is seen, and the prognosis is grave. GI involvement may also be present and consists of mucosal ulcerations in the gut, resembling Crohn's disease. Kidneys may also get involved (Harrison *et al.*, 2018).

Life expectancy in these patients is normal and blindness is the most severe complication. Treatment involves Topical Glucocorticoids. In severe cases, Thalidomide 100 mg/day is effective. Recently, Apremilast is found to be effective for oral ulcers. Uveitis and CNS involvement in Bechet's Syndrome requires systemic glucocorticoid therapy 1mg/kg/day, Azathioprine 2-3 mg/kg/day And Cyclosporin 2-5 mg/kg/day (Harrison *et al.*, 2018).

Case Report

We report a case of a female, age 30 years Hindu by religion resident of Bahadurgarh, Haryana, India was admitted with the chief complaints of fever associated with chills and rigors. She complained of ulcerative lesions in the genitals and swelling and tenderness in bilateral ankles and burning micturition.

The detailed history is as follows. The patient was apparently all right a month ago when she developed fever, which was acute on the onset, high grade (102 to 103 F), progressive, continuous, relieved by taking medicine. Fever was associated with chills and rigors, generalized body ache, and headache. Fever was also associated with rash and joint pain.

As per the history given by the patient, 3 to 4

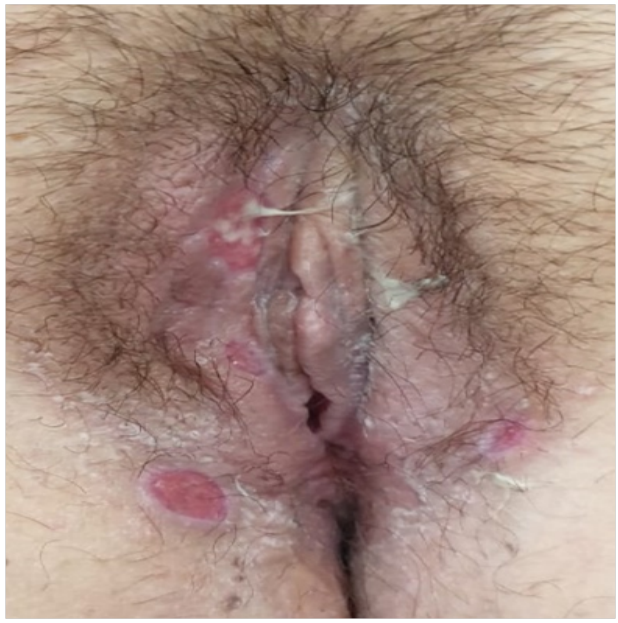

Figure 1: Genital Ulcers

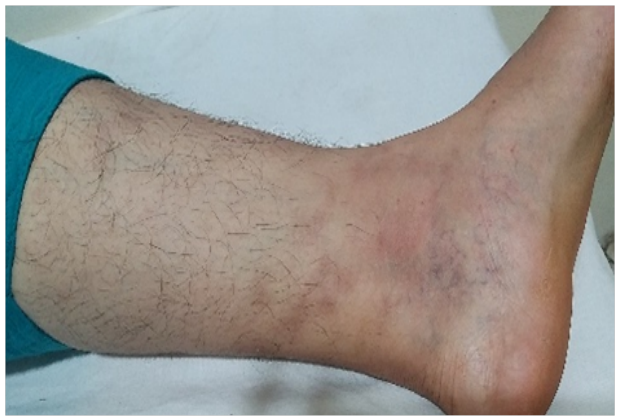

Figure 2: Arthritis

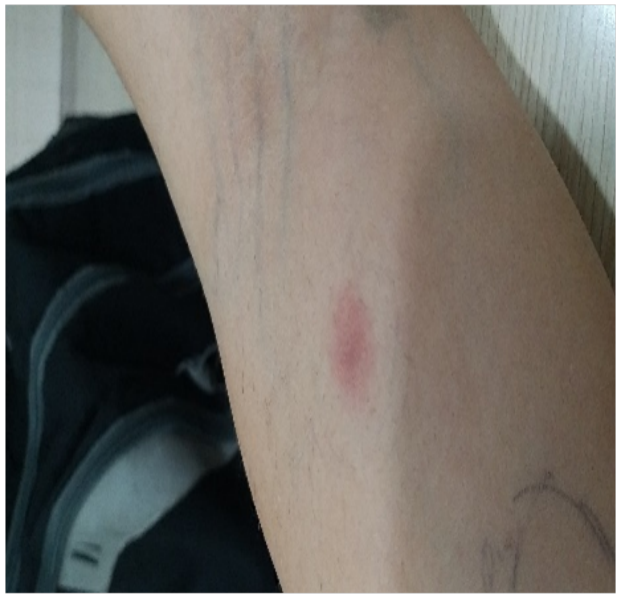

Figure 3: Positive Pathergy test

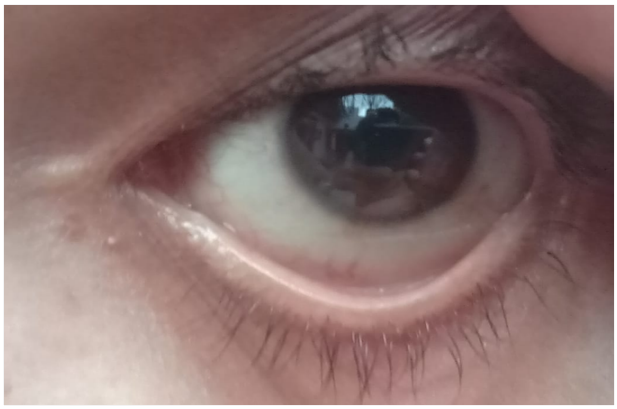

Figure 4: Uveitis

days following the development of fever(the 24^{th} of February), the patient developed irregular bleeding per vagina, which was scanty in amount and followed by the development of ulcerative lesions, painful, round and of varying sizes ranging from 2 cm to 1.5 cm, located in the genital region. The patient also had developed oral ulcers along with the genital ulcers. She has a history of applying betadine to the Genital Ulcers. There was no itching in the genitals and the history of lesions on the lips was also present.

She developed pustular lesion, reddish to purplish in colour, multiple in number located, with mild itching in the inner aspect of the thighs, 2 or 3 in number on the abdomen, 1 or 2 lesions on the right forearm. There was crusting, and scars of the lesion are remaining.

There was a presence of red to purplish coloured purpuric spots, of sizes ranging from 0.5cm to 1.5 cm, non-tender, located on the lower limbs, extending below the level of knees, mainly on the bilateral ankles.

The patient also had a complaint of acute onset (less than six weeks) swelling and tenderness in Bilateral Ankles as shown in Figure 2. The pain and tenderness were present throughout the day. The pain was severe in intensity, and morning stiffness was absent. Joint pain was worsened by activity and during the spike of fever and only mildly improved by medication. Swelling, warmth and redness were present. There was no deformity, but the range of motion was limited. There was no pain or tenderness found in any other small or large joint.

Following the development of painful ulcerations in the genital region she also had profuse vaginal discharge, which was yellowish in colour, copious, foul-smelling which stopped after getting treated from a gynaecologist. There was no complaint of pain in Abdomen, vomiting, loose stools, hematemesis or malena was seen. She did not complaint of cough, throat pain, hemoptysis, or shortness of breath. She had no blurring of vision, neck stiffness, photophobia . or any redness or discharge from the eyes at the time of admission. No history of weight loss/ loss of appetite, blood transfusion or multiple sexual partners was seen.

The patient is working at a bank. She is a vegetarian, Non-smoker, Non-Alcoholic, With Normal Sleep pattern, Normal Bowel, and bladder habits. Menstrual and Obstetric history was normal. She is married and is having four children. No History of Blood transfusions. No history of multiple sexual partners.

No history of DM/HTN/TB/Asthma/Jaundice and significant family history was found.

General and systemic Examination

It revealed that the patient was conscious and oriented. There was no pallor, icterus, cyanosis, clubbing or lymphadenopathy. BP: 100/60 mmHg, PR: 110 Beats/Minute, RR: 18 Times/min. All other respiratory, cardiovascular, CNS and GI examination were normal.

Local Examination: Scar marks of the previous lesion, around 1cm, is size are found on the abdomen, thighs and arm found. Vulva examination shows extensive genital ulcerations with profuse discharge, with the necrotic base which was surrounded by erythema and ranging from 2 cm to 1.5 cm as shown in Figure 1.

There was tenderness present in the Bilateral knees. Erythema was also present on ankles which can be seen in Figure 2.

Investigations

CBC: Hb: 10gm/dl, TLC: 6500/Cmm, DLC: P/L/M/E/B: 74/20/3/3/0

Platelet Count: 3,07,000 RBC Count: 4.64 Million/mm, HCT: 33.9%, MCV:73.1 Fl, MCH:22.4 pg., MCHC: 30.7 g/dl, RDW-CV: 15.4%.

CBC shows Microcytic hypochromic anemia. KFT: S. urea: 37.0 mg/dl, S. Create: 1.1 mg/dl, S. Na+: 136 mmol/L, S. K+ :4.3 mmol/L.

LFT: S. Bilirubin: 0.4mg/dl, S. Bilirubin (Direct): 0.2 mg/dl, Bilirubin (Indirect): 0.2 mg/dl, S. SGPT: 16.0 U/L, SGOT: 19 U/L. RBS: 97mg/dl. LFT and KFT were within normal limits. ESR: 55 mm (on 9/03/2020), 34mm (on 20/3/2020) Typhi Fast IgG/IgM Negative (IgM positive in previous reports). Urine: Culture and sensitivity show no growth after 24 hours of the aerobic incubation period. Urine: Blood: Traces. Leukocyte esterase +++, RBC:2-3, Pus cells: Full Field, Epithelial cells: 8-10 cell/HPF Granular casts seen. ECG: Normal. VDRL, HIV 1 and

2, was negative. G6PD was 12.88 U/g. RA Factor <5 IU/mL, Anti CCP: 1.1U/ml, c-ANCA- 7.50 Units, p-ANCA-10 Units.

Her Ultrasound whole abdomen revealed that the liver was enlarged 18.5 cm in size and echogenicity. Other than hepatomegaly there was no abnormality seen in the USG. Pathergy test was positive as shown in Figure 3. Herpes Virus Simplex 1 and 2 IgG was found to be positive whereas IgM was negative.

Follow Up and Treatment

In view of the above history, investigations and positive pathergy test a diagnosis of Bechet's Syndrome was made. She was treated with Tab Omnacortil 10 mg TDS, Tab Microdox LBX 1-tab BD and Mupirocin for local application. The patient had symptomatic relief and the ulcers started healing. Oral Ulcers almost disappeared and genital ulcers reduced in size and number within a week. Pain in the ankles had also reduced. The patient was discharged from the hospital to take her medication regularly. In the follow up after around 30 days later, she developed redness and burning in the eyes and was found to develop uveitis as shown in Figure 4 She had a relapse as she became non-compliant with medications.

Discussion

In a Case study By Mason Et al., 33 Patients were studied in four years. Out of these 33 Patients, 25 had definite Bechet's disease, and the other nine were suspects. The authors studied the clinical profile of these patients and made some important conclusions. The studies revealed that the out of the 25 definite cases, the most typical initial symptom is seen in 16 patients was Oral Ulcers. They also mentioned that the initial symptoms did not make the patients attend to the hospital and were mostly ignored. This correlates with our case, which also developed Oral Ulcers first that went unnoticed. As per their study, the average age of onset varied between 9 to 43 years for men and 9 to 41 years in women. The average age was calculated to be 21 years for men and 22 years for women. The patient that we report in our study is also a 30-year-old married woman (Harrison *et al.*, 2018).

In this study by Mason et al. it is mentioned that out of 25 confirmed cases, 13 had attended hospital with the major complained of arthritis. Oral Ulcers were mostly not the initial cause of hospital visits. Seven of these patients arrived due to eye lesions, and three had skin lesions. Arthritis was found among 19 patients out of which 11 were males and eight females. Knee was the most affected joint seen in 15 patients. Ankles were involved in 8 patients. Our case also had a chief complain of pain and tenderness in Ankles. Arthritis was an inflammatory type, and pain on movement with swelling of the joints was a prominent symptom. Synovial thickening with warmth was present. Our patient also had pain in movement with, warmth and tenderness present in bilateral knees. Her knees had also started getting affected, but timely intervention reduced the effect on the knees. Mason et al. report that arthritis was not migratory with no joint deformity, and this also correlates with our case. Our patient had no migratory arthritis. Out of the 19 cases reported, 13 patients had a raised ESR, which the range of 24 to 114mm/1hr. The case the report had an ESR of 55 mm/hr. No radiographic changes were found in these patients, and our patient too had a normal Xray. Mason et al. describe that one of the cases had avascular necrosis due to large doses of Corticosteroids given for severe uveitis.

Genital ulceration was seen in 19 cases, i.e., 76 per cent of cases studied (Harrison *et al.*, 2018).

CNS and CVS involvement were seen only in one case each. GI was involved in 6 patients, and six had thrombophlebitis. Our patient reported one or two episodes of redness in the eyes during the spike of fever, but the ophthalmologist's review showed no Uveitis (Harrison *et al.*, 2018).

The differential diagnosis of Rheumatoid or Psoriatic arthritis is excluded by serological tests and also the fact that arthritis in our patient was self-limiting and non-destructive. Rheumatoid arthritis and Psoriatic arthritis are destructive and cause deformity. The differential diagnosis of Ulcerative colitis is also ruled out. Though in Ulcerative colitis the Oral Ulcers are associated with arthritis, there r no relapses. Our patient has had relapses. The differential diagnosis of Reiter's Syndrome affects hands more commonly, whereas our patient had involvement of bilateral ankles. The presence of Genital Ulcers was of great importance in our case for getting a definite diagnosis (Harrison *et al.*, 2018).

Influence of Age on onset and sex has been studied to understand its co-relation with prevalence and severity of clinical manifestations in 297 patients of Bechet's Syndrome by Yazici H et al. They classified patients into Early and late onset. Patients who were less than or equal to 24 years of age were classified as "early-onset" and those who were more than 24 years were classified as "Late-onset". They concluded that clinical manifestations such as arthritis and folliculitis were common in late-onset male group, and erythema nodosum was found to be common in late-onset females. According to this classification, our patient presented in the "Late-onset" as

she is a 30-year-old female and her clinical manifestations included arthritis. They also stated that Eye involvement was more common in Males and a chief indicator of disease severity in the young. As our patient is older, she did not show uveitis. According to this study, in older patients' eyes involvement is significantly low in both sexes. Thrombophlebitis and all other major vascular complications were mainly seen in males. Our patient being a female did not show any complications. To conclude, the age on onset and the sex influences the severity of the disease expression. Male and younger age of onset has more severe clinical manifestations and complications (Yazici *et al.*, 1984).

Marinho KCT et al reported a case study of a 47 years old married female with 5 children who presented with pain in the vagina while sitting and having sex. Her ulcers measure 0.5 to 1.2 cm, with erythematous halo and fibrinolytic bed. The patient had a gynaecological exam and was found to have vaginal discharge and painful ulcerative ulcers. Five months later, the patient had a relapse and developed arthritis also. This is similar to our patient and just like the case reported by Marinho KCT, and the patient responded to corticosteroids in no time. The patient reported had developed eye involvement and lost her visual acuity, reddening and burning of eyes. So, the striking similarities with our patient guided us to counsel our patient and keep regular follow up with the ophthalmologist. Although she has not developed uveitis yet (Marinho *et al.*, 2016).

In another study by Nomura Y et al., the involvement of Herpes Simplex Virus Type 1 with Bechet's disease was studied. Our patient also had a complaint of blistering lesions on the lips which encouraged us to get HSV antibodies checked. The aetiology of Bechet's disease is still unknown. Although viral involvement is not considered to be the likely cause, the presence of HSV 1 has been reported in cases of Bechet's disease. Nomura et al. studied 32 patients with Bechet's disease and 30 healthy volunteers. With the use of a highly sensitive competitive RT-PCR method, HSV-1 specific mRNA was not detected either in peripheral blood leukocytes from any of the patients or volunteers. In contrast, serum levels of IgG anti HSV-1 antibody were higher in patients with Bechet's disease; however, there were 70% sero-positives among the control subjects. The patient that we report in our case was also screened for HSV 1, and the result was found to be positive for HSV 1 and 2 IgG anitbodies (Nomura *et al.*, 1998).

The pathogenesis of Bechet's disease is unknown, but the role of viral infections is long studied. In studies Virus was isolated from the ocular fluid, eye, and brain of patients with BD. As advances happened in virology and immunology, DNA from various types of viruses have been has been isolated in BD patients such as HSV, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, human herpes virus 6 and 7, hepatitis virus, human immunodeficiency virus, and parvovirus B19. BD mouse model were established by Kim DY et al using HSV inoculation to study the pathogenesis of BD. In the study by Kim DY et al. it is stated that HSV plays a potentially very important role in the pathogenesis of BD. In situ DNA-RNA hybridization techniques demonstrated that there is a presence of part of the HSV-1 genome in peripheral blood mononuclear cells of patients with BD. Polymerase chain reaction (PCR) studies have confirmed the presence of a 211-base pair (bp) HSV-1 DNA fragment in the peripheral blood leukocytes of patients with BD and demonstrated significantly greater quantities of HSV-1 DNA in the saliva, intestinal ulcers, and genital ulcers in BD patients than controls. To explore the role of HSV in the pathogenesis of BD, Kim et al developed an HSV-induced Bechet's disease mouse model. After inoculation of the scratched earlobe of 258 ICR mice with HSV type 1, 77 (29.8%) mice exhibited BD like syndrome, defined by the presence of two or more BD symptoms such as skin ulcers (57.1%), eye symptoms (39.0%), partial hair loss(33.8%), genital ulcers(19.5%),bullae(11.7%),arthritis (5.2%); gastrointestinal ulcer (5.2%), and tongue ulcers(3.9%) (Kim *et al.*, 2013).

Studd M et al describe in their research that Serum anti-HSV-1 antibodies were found in a greater proportion of patients with BS ($p < 0.02$) than in healthy controls. However, Biopsy samples taken from oral ulcers did not show any virus-specific DNA in patients with BS (Studd *et al.*, 1991).

A study by Tojo M et al was made to investigate the relationship between herpes viruses and Bechet's disease. They used polymerase chain reaction to detect herpes simplex virus 1 &2, and human herpes virus 6&7 (HHV-7) DNA in samples of lesional tissues from patients with Bechet's disease and other related inflammatory disorders. They examined 11 patients, out of which 3 were male and 8 females who were diagnosed with BD based on the international diagnostic criteria. They also took 7 patients with other related inflammatory disorders, including 3 with Sweet's disease, 3 with Erythema nodusom, and one with phlegmone. PCR was carried out for amplification of HSV-1, HSV-2, HHV-6 and HHV-7 DNA. In their study they concluded that three of the patients with BD had several lesions at the same time. One of 15 BD samples (no. 4) and 1 of 3 EN samples (no. 21) tested positive for both HSV-

1 and HSV-2. The possible BD sample was from a patient with incomplete type of BD and EN-like skin symptom; his oral aphthae sample (no. 5) was, however, negative for both HSV-1 and HSV-2 (Tojo *et al.*, 2003).

Herpes Simplex Virus ,a DNA Virus and is a causative agent in various ocular diseases such as conjunctivitis, blepharitis, dermatitis corneal ulceration, stromal keratitis, endothelitis, retinal necrosis syndrome, scleritis iridocyclitis, uveitis. On an average HSV Uveitis occurs at the age of 46 years. Several studies state that 20 to 60 percent of recurrent HSV disease present as stromal keratitis. Herpetic corneal ulceration is a cause of blindness in these patients. HSV affects corneal stroma by direct stromal invasion, necrotising stromal keratitis, or due to immune reactions to stromal antigens. Stromal keratitis may present as blurred vision, eye pain and HSV related loss of vision (Green and Pavan-Langston, 2006).

A study was done by Roam J et al to evaluate the possible associations between Bechet's disease and infection by type I herpes simplex virus (HSV-1) in Spain. 34 patients with BD and 21 with primary uveitis and 40 controls were studied. It was found that the frequency of evaluable titers of anti-HSV-1 is greater in patients with BD especially those with ocular involvement than in the control series (Sánchez *et al.*, 1992).

CONCLUSIONS

Bechet's Syndrome is a multisystem disorder that is sometimes difficult to diagnose as its common presentation oral ulcers usually go ignored. This disorder itself is rare, but it should be diagnosed appropriately to save the patient from severe complications such as blindness. Further HSV positivity in our case makes it more interesting since it could be related to the aetiology of triggering factors of this Bechet's syndrome. We report this case for its rarity.

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Conflicts of interest

The authors declare that they have no conflict of interest for this study.

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