Successful Treatment of Behcet’s Disease Utilizing Bacterial and Viral Antigens

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Abstract

Objective

To describe the successful therapy of a patient with Behcet’s disease using streptolysin O and other bacterial and viral antigens.

Methods

A 32-year-old man with a 24-year history of Behcet’s disease symptoms not alleviated by several standard treatments (methotrexate, azathioprine, and prednisone) is described. He was given a treatment regime that included antigens from Streptococcus, other bacteria, viruses, and streptolysin O.

Results

After seven months treatment, the patient’s BD symptoms improved dramatically including almost total cessation of mouth and genital ulcers, almost total disappearance of chronic pain, and significant increase in energy levels.

Conclusion

Treatment with antigens from Streptococcus and other common bacteria and streptolysin O may be useful in treating Behcet’s disease.

Keywords: Behcet’s Disease; Chronic Fatigue; Streptolysin; Histamine; Streptococcus antigens

Introduction

Behcet’s disease (BD) is a complex multi-system auto-inflammatory and autoimmune disease involving many organ systems [1, 2]. A majority of BD patients experience mucocutaneous problems such as oral and genital ulcers, papulopustular skin lesions, and erythema-nodosum (EN) like skin lesions [3, 4]. Other common BD manifestations include eye difficulties such as uveitis [3], joint disorders [3], cardiovascular complications [3, 5-7], neurological and neuropsychiatric conditions such as hearing loss, depression and anxiety, cognitive function loss and hemiparesis [3, 8-12], and gastrointestinal problems such as diarrhea, GI pain, bleeding, and ulceration [3, 13, 14]. Other common health problems include chronic fatigue, sexual dysfunction, and significantly lower quality of life [10, 11].
BD is generally diagnosed by the presence of recurrent oral ulcers and two or more of the following features: genital ulcers, skin lesions, eye lesions, and positive pathergy test (pathergy test involves needle puncture) [3, 15]. BD development is believed to be related both to genetics (especially the human leukocyte antigen (HLA)-B51 allele) and possibly microbial factors such as the HSV-virus or Streptococcus [2-4].

BD is usually a lifelong disease that is treated symptomatically [4]. Many BD patients have significant long term morbidity and more systemic treatments are needed to reverse many of the disease processes which cause considerable loss of quality of life.

Methods

We present the case of a 32 year-old man with a 24 year BD symptom history who was successfully treated with bacterial antigens, viral antigens, and streptolysin O.

The antigens used to treat the patient in this case study came from several sources including: Hollister Stier (Spokane, WA, USA) for the histamine, Milkhaus Labs (Providence, RI, USA) for the M2SO, and the remainder from American Type Culture Collection, (Manassas, VA, USA). All of the antigens were diluted with sterile 0.9% NaCl saline solution and were used to challenge the patient intradermally and sublingually. The patient was treated with an allergen extract containing only the reactive antigens.

Results

Case Report

The patient is a 32 year-old male of German/Italian/American Indian descent who has experienced BD symptoms for 24 years. He had a history of many infections including ear infections (frequent between age 1 and 16 years), streptococcal throat infections (age 8 and 12 years), tonsillitis (10, 15, and 20 years), pneumonia (12, 16, and 23 years), and infectious mononucleosis (ages 8, 16 and 24 years).

Between 8 and 32 years, patient often had 8 to 16 concurrent mouth ulcers. By 8 years he had other health problems including chronic fatigue, chronic joint pain, and GI distress. At age 26 had colonoscopy which found multiple ulcer scars. He had a painful kidney stone at age 30 years. Patient worked as a fast food worker, manual laborer, and auto care worker between ages 15 and 27 but was disabled between 27 and 32 with debilitating fatigue. By age 32 years, he had many health problems including chronic fatigue, flu-like feeling with sore throat, muscle and joint aches; frequent mouth, facial, anal and genital (groin, inguinal crease, scrotum) ulcers, frequent skin pustules, intense lower GI pain and constipation, depression and anxiety, insomnia, sensitivity to both heat and cold, burning skin sensations, hair sensitive to touch, and lymphadenopathy. He reported waking up “feeling like being beaten up by a baseball bat”.

At age 22 years he was formally diagnosed with Behcet’s disease as the patient was experiencing oral and genital ulcers and a positive pathergy test. Patient was treated with methotrexate at age 25 and azathioprine at age 28 with no benefit. His medications when initially seen by one of the authors (AL) on 8/24/15 included morphine 60 mg BID, oxycodone 15 mg 1-2 PRN 4 hrs, alprazolam 0.25 mg QPM to sleep, sertraline 50 mg QD, and prednisone 20 mg taper when needed.

Physical exam on 8/27/15 found ulcers on the back of his throat, tongue, palate, ears, groin, scrotum, and inguinal area. Serology tests from 8/27/15 reported high IgG for HSV1 (50.8 IU/ml with 1.0 IU/ml being considered positive) and negative for HSV2 (<0.91 IU/ml). Patient did not receive any anti-viral medication for his HSV1.

Skin allergy testing for bacteria and neurotransmitters indicated the following:

Positive Skin Tests with Wheeling and Provoked Reactions
1. *Streptococcus sanguinis* (caused itchy skin, tingly tongue, warmth in face, scratchy throat).
2. Poly *Staphylococcus* antigens (anxious feelings),
3. *Helicobacter pylori* (warm feeling)
4. Serotonin (sweating)

Negative Tests
1. *Borrelia burgdorfi*
2. *Mycoplasma pneumoniae*
3. *Mycoplasma arthritidis*
4. *Mycobacteria avian paratuberculosis*
5. *Yersinia*
6. *Escherichia coli*
7. α-hemolytic *Streptococcus*
8. Histamine

Stool testing also found high levels of *Citrobacter freundii* and *Klebsiella pneumoniae*.

The patient was prescribed a treatment plan with M2SO (mixture of *Rubeola* antigen, histamine, and oxidized streptolysin...
from *Streptococcus pyogenes*), sublingual antigens from *Streptococcus sanguinis*, poly *Staphylococcus*, *Staphylococcus epidermidis*, and *Helicobacter pylori*. Patient was also treated with nystatin 1 million units day for yeast eradication for one month and nutritional supplements curcumin 400 mg, TID, vitamin D 5,000 IU QD, and fish oil 2 tsp QD. Curcumin, fish oil (rich in omega 3- fats), and vitamin D all have anti-inflammatory and immunomodulating properties that show promise for treating auto-immune disease [16].

He tapered off his opiate consumption which caused some initial withdrawal issues. Seven months after initial treatment, the patient reported that after 24 years, all of his Behcet’s symptoms were under control and he has returned to full-time work and a busy social schedule.

After three months treatment, he reported less frequent mouth ulcers but more frequent groin ulcers. After four months treatment, the patient reported only three ulcers in mouth. After seven months treatment, patient reported that he was experi-encing “very, very few eruptions” and his chronic fatigue and chronic pain had both almost completely resolved. The patient felt strongly that the addition of M2SO antigens were the overt trigger for his symptom improvement. Figures 1 and 2 compare tongue and mouth ulcers before and his treatment at age 32 years.

Figure 1a- Patients Tongue and Mouth- August 2015- Before Treatment.

Figure 1b- Patients tongue before treatment.

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Figure 2. Patients tongue in May 2016 after about nine months treatment.

**Discussion**

This case report describes successful treatment of Behcet’s disease with a combination of bacterial and viral antigens in a 32 year old man with a 24 year history of chronic Behcet’s symptoms refractory to several standard treatments such as methotrexate, azathioprine, and prednisone (patient was not treated with thalidomide, cyclosporine, or tumor necrosis factor). We are not aware of any other published case of Behcet’s being treated with bacterial and viral antigens.

Microorganisms and their antigens may play a critical role in Behcet’s pathogenesis by autoimmune and or autoinflammatory mechanisms [1, 2]. We elected to treat the patient with bacterial and viral antigens because of their known involvement with autoimmunity. Some studies have associated viral and bacterial (especially Streptococcal) infections with significantly higher rates of BD [17]. Infectious agents may operate through a molecular mimicry process in which BD and other...
autoimmune disease could be perpetuated by abnormal immune responses to an autoantigen in the absence of active infection [18]. Such a molecular mimic may be the streptococcal heat shock protein hsp65 which is similar to the human heat shock protein hsp60 and stimulates T-Cell hypersensitivity mediated by IL-12 [19].

Studies have reported that sera from BD patients and cultures of Streptococcus sanguinis stimulate expression of inflammatory markers such as hnRNP A2-B1 and α-enolase in human dermal microvascular endothelial cells [20, 21]. Several human studies have reported that oral cavity concentrations of Streptococcus salivarius, sanguinis, and mutans are significantly elevated in BD patients relative to controls [19, 22, 23]. One study reported significantly higher antibody to Streptococcus sanguinis in 34 Behcet’s disease patients as compared to 29 controls [24]. It is not certain whether the higher levels of some Streptococcus species are causative or reactive to the BD disease process [23].

Elevated titres to the streptococcal hemolytic antigen tox in streptolysin O are often seen in BD patients. One study reported that significantly higher anti-streptolysin O titres were seen in 249 BD patients as compared to 149 patients with aphthous ulcers [25]. Among the BD patients higher anti-streptolysin titers were associated with significantly higher rates of tonsillitis (p = 0.001) and erythema nodosum (p = 0.001) but significantly lower rates of genital ulcers (p = 0.027) [25].

Preliminary research suggest multifunctional streptolysin O antigen therapy may be useful in several ways including promoting wound healing, increasing clinical response to antibiotics, and anti-metastatic effects [26-29]. Tissue explant studies have reported that streptolysin O therapy promotes skin organ culture wound healing and keratinocyte migration and proliferation in vitro [26]. Streptolysin O was also useful for reducing excess collagen formation in murine scleroderma models [27]. Streptolysin O treatment also was found to improve survival time and response to antibiotics in foals with Rhodococcus equi pneumonia [28]. The authors speculated that the streptolysin O may have increased antibiotic penetration into the lungs. Oxidized streptolysin O was also found to significantly inhibit metastasis of human breast cancer cells in vitro [29].

Other autoimmune diseases appear to be related to Streptococcal antigens such as PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcal infection) [30]. An Italian study reported that anti-streptolysin titres were significantly higher in 77 children with PANDAS as compared to 191 controls (Mean IU 705±222 vs. 125±45, p = 0.0001) [30]. This study also reported that significantly higher serum anti-streptolysin levels were seen in PANDAS patients with autoimmune disease, organ specific antibodies, or frequent throat infections (p < 0.0001 for each) [30]. High streptolysin O antibodies have also been associated with tic disorders, with a meta-analysis of 13 papers finding elevated streptolysin O titres significantly more often in tic patients as compared to healthy controls (OR 3.22, 95% CI of 1.51-6.88) and non-psychiatric patients (OR 16.14, 95% CI 8.11-32.11) [31]. Screening for BD with anti-streptolysin titres may be useful.

In addition to the streptolysin, the M2SO complex also contained histamine and rubeola antigens. Some studies have reported significantly higher levels of both mast cells and histamine in Behcet’s skin lesions as compared to unaffected skin [32]. Recent research suggests that histamine may have previously underappreciated roles in immunoregulation and autoimmunity in such diseases as Crohn’s, ulcerative colitis, rheumatoid arthritis, and multiple sclerosis [33]. The relationship between rubeola antigens and Behcet’s disease is not clear; with one study reporting marginally higher anti-IgG measles level in 30 Behcet’s patients compared to 18 controls [17]. However, it is known that the measles virus can inhibit dendritic cells and may play a major role in immunoregulation and autoimmunity [34].

The purpose of a case report is to describe a potential etiology and or treatment of a disease. In summary, this case reported the successful treatment of BD with antigens for streptolysin O and other bacteria/viruses after 24 years of treatment failure with standard treatments like prednisone, methotrexate, and azathioprine. 

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References


5. Demirelli S, Degirmenci H, Inci S, Arisoay S. Cardiac manifestations in Behcet’s disease. Intractable Rare Dis Res. 2015,


