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Behçet's Disease: A Retrospective Study of 30 Cases from China

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Abstract

Background: Behçet's disease is a chronic systemic inflammatory vasculitis with multi-organ involvement. The etiology remains unknown and despite the genetic correlation with HLA-B51, it is thought that certain environmental triggers such as viral and bacterial infections are necessary for the development of this disease. The purpose of this case series is to retrospectively study clinical characteristics of Behçet's disease and analyze the efficacy of a standardized treatment regimen.

Methods: We analyzed 30 patients, aged 20-50 years old, with Behçet's disease in terms of clinical characteristics and treatment outcomes. Patient selection was based on the presence of recurrent oral ulcers plus at least two additional findings, including recurrent genital ulceration, ocular involvement, skin lesions, or positive pathergy test. All patients were placed on a standardized treatment regimen based on individual disease characteristics.

Results: In our study, ocular involvement occurred exclusively in male patients with the disease involving predominantly young to middle aged individuals (20-40 years old). No pathognomonic clinical and laboratory findings were specific to the disease, thus often delaying the diagnosis. Treatment regimens consisted of combination therapy with immunosuppressive and anti-inflammatory medications. Treatment was divided into two phases: management of acute disease and maintenance therapy with all patients achieving clinical remission after completing treatment.

Conclusion: Behçet's disease is a multifactorial disease involving many possible mechanisms, both genetic and environmental. The mainstay of treatment is immunosuppression and anti-inflammatory medication. Our standardized treatment regimen was based on a therapeutic ladder and proved to be effective with all 30 patients in our study.

Keywords: Behçet's disease; Chronic systemic inflammatory; Bacterial infections

Introduction

Behçet's disease was first described in 1937 by a Turkish dermatologist by the name Hulusi Behçet [1]. Behçet formally described two patients with a triad of findings including recurrent oral ulceration, genital ulceration, and hypopyon [1]. Many years after this report, it became known that patients with these findings also had evidence of neurological, vascular, gastrointestinal, and musculoskeletal involvement. Behçet's disease (BD) is a chronic systemic inflammatory vasculitis with multi-organ involvement seen most commonly in the Mediterranean and Far East [2]. Genetic factors play a role in the development of BD, specifically the human leukocyte antigen (HLA)-B51 [3]. Despite this genetic correlation, it is thought that certain environmental triggers such as viral and bacterial infections are necessary for the development of BD. The etiology of the disease remains unknown, but exogenous triggers are thought to play a large role in initiating immune system dysregulation in a genetically susceptible host. The complex interplay between intrinsic and extrinsic factors along with abnormal innate and adaptive immunity contributes to disease expression. Current studies have demonstrated increased levels interleukin (IL)-6 and interferon (IFN)-γ as a result of T-cell stimulation by antigenic peptides of *streptococcus* and *Escherichia coli* strains. Autoimmunity and neutrophil hyper function are also thought to play a significant role in disease development.

The major manifestations of BD include relapsing episodes of oral aphthous ulceration, genital ulceration, ocular involvement, and papulopustular/erythema nodosum-like skin lesions. The cardiovascular, pulmonary, gastrointestinal, neurological, musculoskeletal, renal, and reproductive systems may also be affected during the course of the disease. Because it lacks pathognomonic signs or symptoms as well as specific laboratory findings, the diagnosis of BD is easily overlooked. The International Study Group for Behçet's Disease (ISG) defined new diagnostic criteria [4]. The diagnosis of BD consist of the presence of recurrent oral ulceration plus two of the following features: eye lesions, genital ulceration, positive pathergy test, or skin lesions [4]. This criteria is considerably reliable with a 92% sensitivity and 97% specificity [4]. There are many treatment options for BD, but recurrence remains high and long-term remission is

difficult. Treatment of BD varies widely throughout the literature and is based largely on anecdotal case reports, series, and randomized clinical trials. Pharmacological treatment depends on the severity of the disease and organ involvement. In our study, we have analysed 30 cases of BD in terms of clinical characteristics and treatment outcomes. All patients in our study achieved clinical remission after completing treatment. The follow-up period varied from three months to five years. Treatment of BD was divided into two phases: management of acute disease and maintenance therapy. Although the therapeutic principle was the same for all patients, the dosage and regimen is tailored to meet the needs of the individuals.

Methods

Patients selection was based on international study group criteria for BD established in 1990: recurrent oral ulcers plus at least two of the following findings: recurrent genital ulceration, ocular involvement, skin lesions, or positive pathergy test. A total of 30 patients participated in the study with a male to female ratio of 14:16. Patient ages varied from 20-50 years old with 19 patients under 30 years old (Figures 1-4).

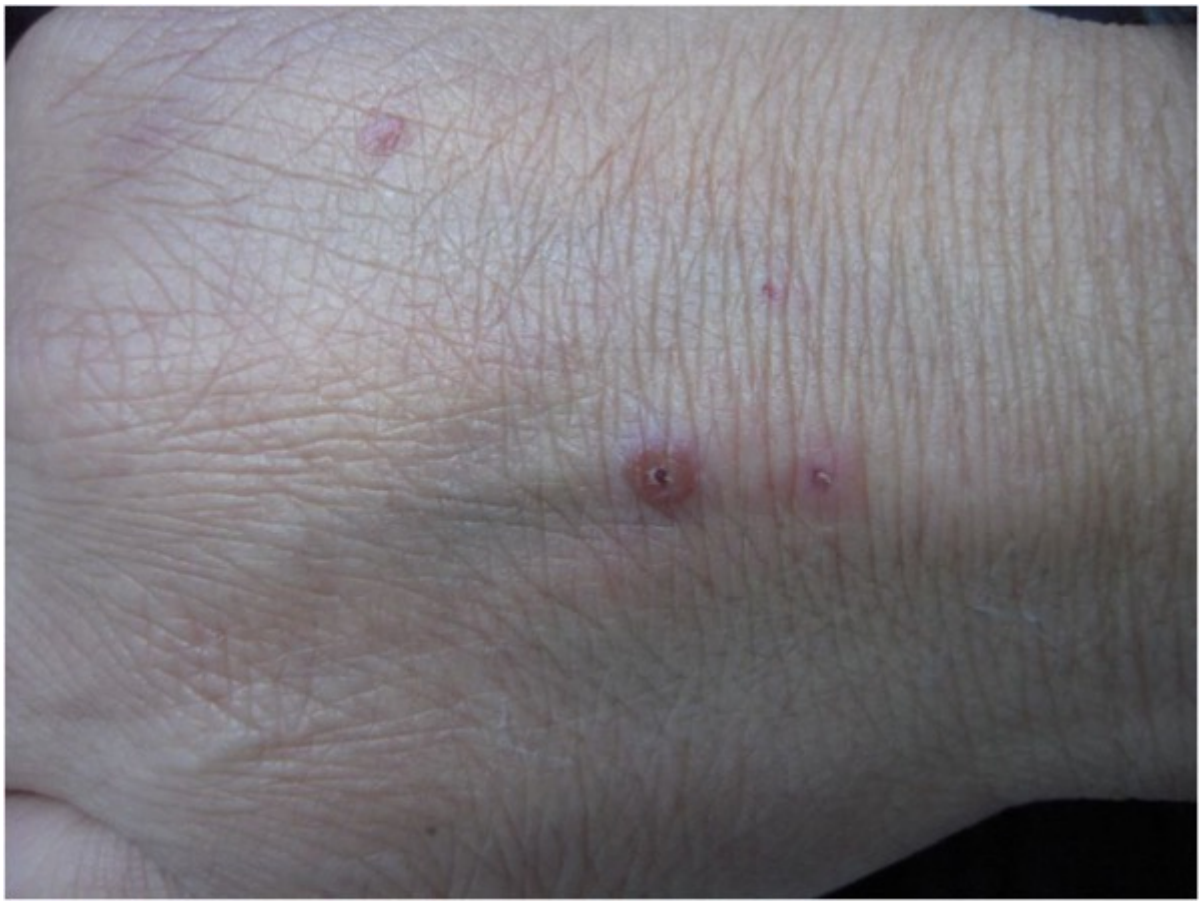

Figure 1: Positive pathergy on the dorsal hand.

The age of disease onset ranged from 19-45 years old. The disease duration prior to presentation to our clinic varied from 2 months to 8 years. All patients in our study had recurrent oral ulceration and skin lesions. Oral ulcers occurred at least three times in a 12-month period. The most common involved sites were the tongue, buccal mucosa, and frenulum. Cutaneous lesions included erythema nodosum (20), acneiform and papulopustular lesions on the trunk and extremities (14), Sweets-like lesions (2), and skin ulcers (1). Eight patients presented with two different types of skin lesions simultaneously. Twenty out of 30 patients had genital ulcers (13 male patients, 7 female patients). In male patients, the scrotum, penis, foreskin, and anus were common sites of involvement. In female patients, the labia majora, labia minora, and anus were more commonly affected. Ocular involvement was noted in seven patients in who all were male. Uveitis was the major finding in these seven men. Two out of seven patients developed blindness in one eye as a result of their ocular disease prior to presentation to our clinic.

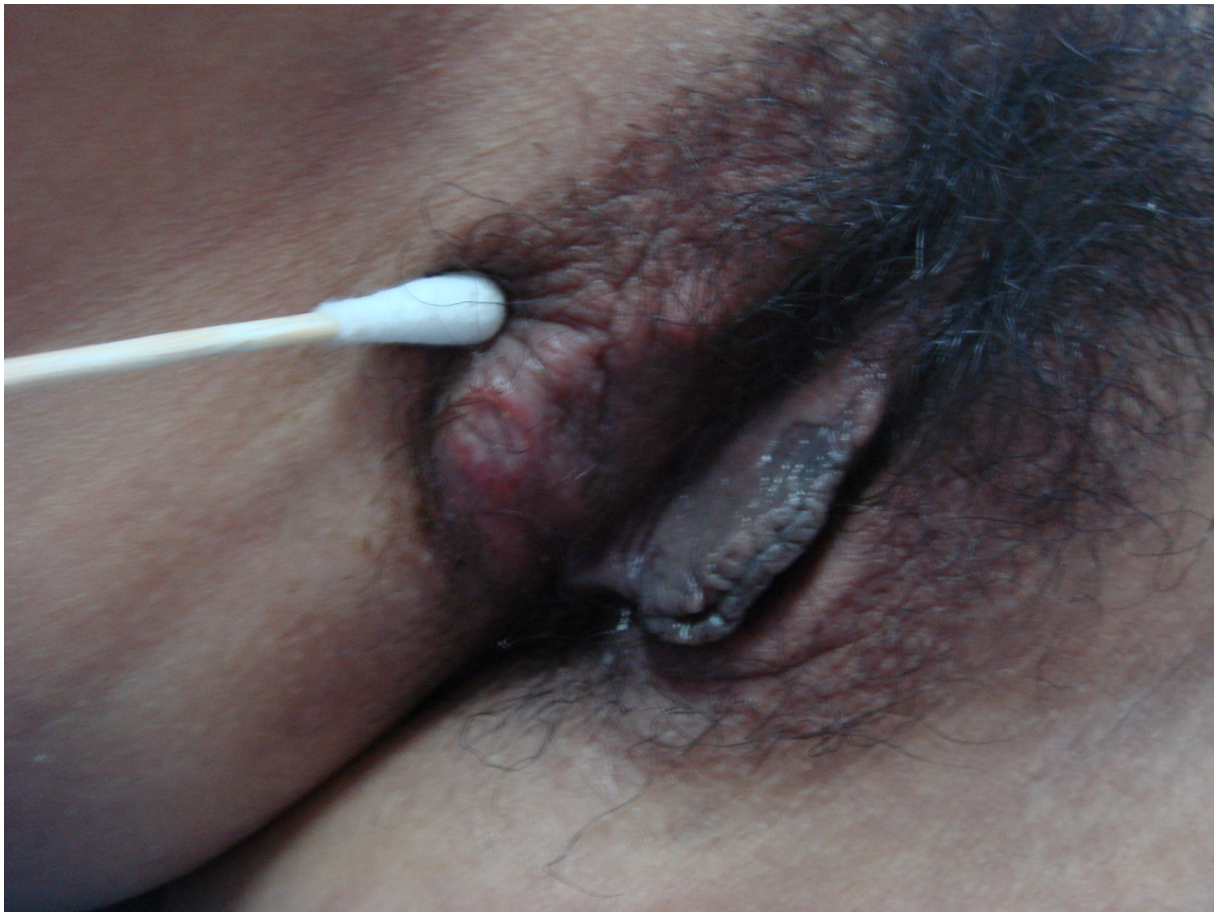

Figure 2: Genital ulceration on right labia majora.

Five patients also had coexisting conjunctivitis in addition to uveitis. Systemic symptoms were present in the acute phase of the disease. Twelve patients had fevers of approximately 38°C, and 18 had joint pain in large joints without deformity. A positive pathergy test was noted in 15 patients (Table 1). The initial presenting symptoms included oral ulcers (11 cases); genital ulcers (4); simultaneous oral and genital ulcers (within one month) (6) and skin lesions (7). Other symptoms ensued within a period of three months to four years. Positive pathergy was demonstrated in 15 patients, but none of the patients had it as the initial presenting sign of the disease. Emotional distress and lack of sleep, excessive physical strain, upper respiratory infection, and the menstrual cycle were reported as exacerbating factors in five, seven, seven, and six cases, respectively. All 30 patients in our study had either normal or negative findings in liver and kidney function tests, chest X-ray, and anti-ENA antibody. There was a mild and transient increase in immunoglobulins in four patients and various degrees of elevation in ESR in 17 patients. Neutrophilia was noted in 19 patients and a left shift occurred in five patients.

ID	Sex	Age	Duration prior to presentation (month)	Skin lesions other than oral ulcers	Pathergy test	Systemic symptoms	Exacerbating factors	Treatment regimen	Maintenance therapy	Follow up period month	Follow up
1	F	38	42	Pustular vasculitis	+	-	Menstrual cycle & physical strain	a	a	9	b
2	F	23	18	Pustular vasculitis	+	Weak	Physical strain	a	a	9	b
3	F	32	6	Pustular vasculitis, Erythema nodosum	-	Joint pain & fever	Menstrual cycle & upper respiratory tract infection	c	b	12	b
4	F	20	12	Pustular vasculitis	+	Joint pain	-	a	a	12	b

5	F	50	60	Pustular vasculitis, genital ulcers	-	Weak	-	a	a, c	60	a
6	M	24	3	Erythema nodosum, genital ulcers, eye disease	-	Joint pain	Physical strain & lack of sleep	e	e	48	a
7	M	38	6	Erythema nodosum, genital ulcer	-	Fever	Upper respiratory tract infection	b	c	25	a
8	M	24	12	Pustular vasculitis, Erythema nodosum, eye disease	+	Joint pain	-	e	e	21	a
9	F	36	12	Pustular vasculitis, Erythema nodosum	+	Joint pain	-	c	a	16	b
10	F	28	8	Pustular vasculitis, Erythema nodosum, genital ulcers	+	Joint pain & fever	Lack of sleep	d	b, c	16	a
11	M	34	24	Genital ulcers, Erythema nodosum,	+	Joint pain & fever	Physical strain	d	a, d	15	a
12	F	28	6	Erythema nodosum, genital ulcers	+	-	Upper respiratory tract infection	b	c, d	17	a
13	F	31	6	Erythema nodosum, genital ulcers	-	Joint pain	Menstrual cycle & upper respiratory tract infection	d	c, a	36	a
14	F	42	20	Erythema nodosum, genital ulcers	-	-	Menstrual cycle & upper respiratory tract infection	b	a	27	a
15	M	31	6	Erythema nodosum, genital ulcers, eye disease	+	Fever	-	e	e	24	a
16	M	29	60	Erythema nodosum, pustular vasculitis, genital ulcers, pyoderma gangrenosum, eye disease	+	Fever	-	e	e	29	a
17	F	23	6	Genital ulcers, Sweets syndrome-like lesion	+	Fever	-	d	b, d	23	a
18	M	34	96	Genital ulcers, Erythema nodosum, eye disease with one blind eye	-	Joint pain	-	e	e	28	a
19	M	23	9	Sweets syndrome-like lesion Genital ulcers	-	Fever	Lack of sleep	d	b, d	24	a
20	M	21	10	Pyoderma gangrenosum Genital ulcers	+	Joint pain	Physical strain	d	b, d	12	a
21	F	34	12	Erythema nodosum Pustular vasculitis	-	Joint pain	Menstrual cycle & physical strain	a	a	24	c
22	F	20	1	Pustular vasculitis	+	Joint pain	-	a	a	27	c
23	F	22	12	Erythema nodosum Genital ulcers	-	-	Menstrual cycle	b	c	50	a
24	M	21	28	Pustular vasculitis Genital ulcers Eye disease	-	Fever	-	e	e	24	a
25	M	25	6	Erythema nodosum Pustular vasculitis	-	Joint pain & fever	Upper respiratory tract infection	b	c	26	a

				Genital ulcers							
26	F	26	2	Erythema nodosum	+	Joint pain	Upper respiratory tract infection	c	d	12	c
27	F	28	4	Erythema nodosum Pustular vasculitis	-	Joint pain & fever	Physical strain & lack of sleep	c	d	12	c
28	M	22	12	Erythema nodosum Genital ulcers	-	Joint pain	Lack of sleep	c	d	6	c
29	M	21	11	Erythema nodosum Eye disease Genital ulcers	-	Joint pain	-	e	e	8	a
30	M	36	4	Pustular vasculitis Genital ulcers	+	Joint pain & fever	-	b	b	12	c

Table 1: Treatment regimena. Tetracycline & Tripterygium glycosides; b. Tetracycline & Tripterygium glycosides & Thalidomide; c. Tetracycline & Tripterygium glycosides & steroids; d. Tetracycline & Tripterygium glycosides & steroids & Thalidomide; e. Tetracycline & Tripterygium glycosides & steroids & Azathioprine; Maintenance therapya. Tripterygium glycosides 20 mg qd; b. Tetracycline 25 mg qd & Tripterygium glycosides 20mg qd; c. Thalidomide 25-50 mg qd; d. Triamcinolone 4 mg qd; e. Azathioprine 25 mg qd & Triamcinolone 4 mg qd; Follow up of patients a. Stable on maintenance therapy; b. In remission one year after stopping therapy; c. Stopped medication in the middle of treatment and the disease recurred one month after treatments stopped - Resuming therapy was effective.

Topical treatment

Ulcers were first cleaned with 1:500 povidone-iodine solution, and either 0.5% nitrofurazone or 1% Chlortetracycline ointment was applied. Nitrofurazone 0.5% ointment was used on pustular or erythematous papular lesions. Oral ulcers were rinsed with 3% borax mouthwash and then covered with dexamethasone bio-adhesive mucosal patch. For recalcitrant oral ulcers, tacrolimus 0.1% ointment was used twice daily.

Systemic pharmacological treatment

Medications used for systemic therapy included tetracycline, tripterygium glycosides, thalidomide, oral corticosteroids and azathrioprine. The dosages used in the acute phase of the disease were: tetracycline 250 mg tid; tripterygium glycosides 20 mg bid to tid; thalidomide 25 mg bid; triamcinolone 8-12 mg qd; azathioprine 50 mg bid. A combination regimen consisting of some or all of these drugs was selected for each patient for individualized treatment.

Tetracycline combined with tripterygium glycosides was used as baseline medications for all patients. Additional drugs may be added according to clinical findings of each patient. Patients with severe oral ulcers were supplemented with thalidomide. Low to intermediate doses of steroids (equivalent to prednisone 15 mg/day -0.5 mg/kg/day) plus azathioprine were added for ocular involvement. If the patients' symptoms did not improve two weeks after starting therapy or if patients had systemic symptoms such as fever or joint pain, a low dose steroid (equivalent to prednisone 10-15 mg/d. Triamcinolone, 8-12 mg once a day was used in our cases) was added to the baseline regimen.

Results

All patients' symptoms were well controlled after four weeks of treatment: ulcers healed, pain was significantly reduced and all skin lesions disappeared, except pyoderma gangrenosum-like ulcers. At this time, the medications were tapered as followed: tripterygium glycosides to 20 mg bid; tetracycline to 250 mg bid; triamcinolone to 8 mg/day. These dosages were kept for another 4 weeks. After 8 weeks of treatment all patients showed complete resolution of their lesions including those who had pyoderma gangrenosum-like ulcers. The dosages were further reduced (tripterygium glycosides 10 mg tid or bid; tetracycline 250 mg/day; triamcinolone 4 mg/day) and continued for another 4 weeks. Treatment was then continued at a maintenance dosage: tripterygium glycosides 10 mg bid; tetracycline 250 mg/day; triamcinolone 4 mg/day. For patients with uveitis and severe oral ulcers, the maintenance strength for azathioprine and thalidomide was 50 mg/day and 25 mg/day, respectively. The steroid taper was slower in patients with eye disease and was divided in 5 scenarios among 30 patients based on each patient's condition (see Table 1).

During treatment, 5 out of 30 patients stopped taking the medication against doctors' advice and the disease relapsed 1-2 weeks after discontinuation. Resuming treatment brought symptoms back under control but, a longer duration of treatment was required to achieve usual efficacy.

One case with a pyoderma gangrenosum-like ulcer responded to treatment slower than other patients: Six weeks after starting the medication compared to an average of four weeks in the treatment groups. In all seven patients with eye involvement, uveitis was stable and well controlled with therapy (2 out of 7 patients had blindness in one eye before commencement of treatment). The following signs/symptoms that responded to systemic therapy more rapidly are listed here in descending order: erythema nodosum, acneiform and papulopustular skin lesions, oral ulcers, Sweets syndrome-like ulcers, genital ulcers, pyoderma gangrenosum, and eye disease. Complete blood count and comprehensive metabolic panel (renal and hepatic function) were regularly checked during treatment. Four patients demonstrated neutropenia. The neutrophil count returned to normal approximately one week after stopping tripterygium glycosides. In three patients, the menstruation period was delayed by one month upon the introduction of tripterygium glycosides. It returned to

normal after decreasing the dosage of tripterygium glycosides. Two patients were found to have abnormal liver function test. The dosage of azathioprine was reduced and glycyrrhizic acid (a cytoprotective and liver function-improving agent) was started. After two weeks, the liver function returned to normal.

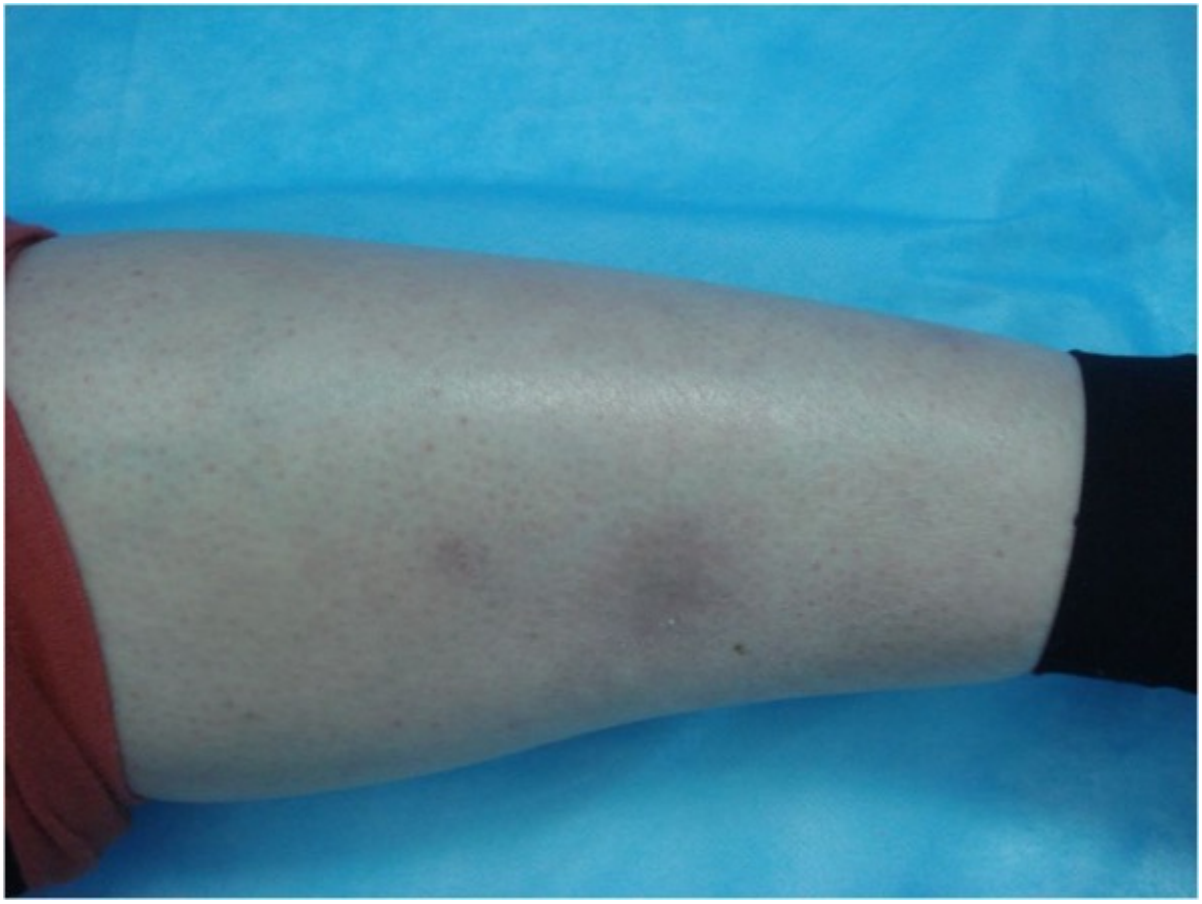

Figure 3: Erythema nodosum of the left anterior leg.

Follow up period varied from three months to five years. Five patients were symptom-free one year after completion of the medication regimen. In these five patients, the duration of maintenance therapy was 9 months (two cases), 12 months (two cases) and 16 months (one case). In six cases, the disease recurred one month after discontinuation of therapy. The symptoms were reduced and controlled after restarting the treatment. The remaining 19 patients were still in maintenance therapy.

Discussion

Behçet's disease (BD) is a rare, chronic and relapsing syndrome of systemic vasculitis involving multiple organ systems with an unknown etiology. In approximately 10% of patients, there is a familial link favoring the role of genetic factors contributing to the disease pathogenesis, in addition to geographic predilection and HLA-B51 positivity [5]. In a meta-analysis of 72 different studies completed by Maldini et al., a strong relationship of HLA-B51 was associated with different clinical manifestations of BD including genital, eye, and skin involvement as well the male gender [6]. The exact pathogenesis remains unknown, but numerous studies demonstrate varying cytokine profiles contributing to the development of specific clinical manifestations. For example, Direskeneli et al. demonstrated a Th1 predominance and Hamzaoui et al. demonstrated a Th17 predominance that seems to play a strong role in the pathogenesis of BD [7,8].

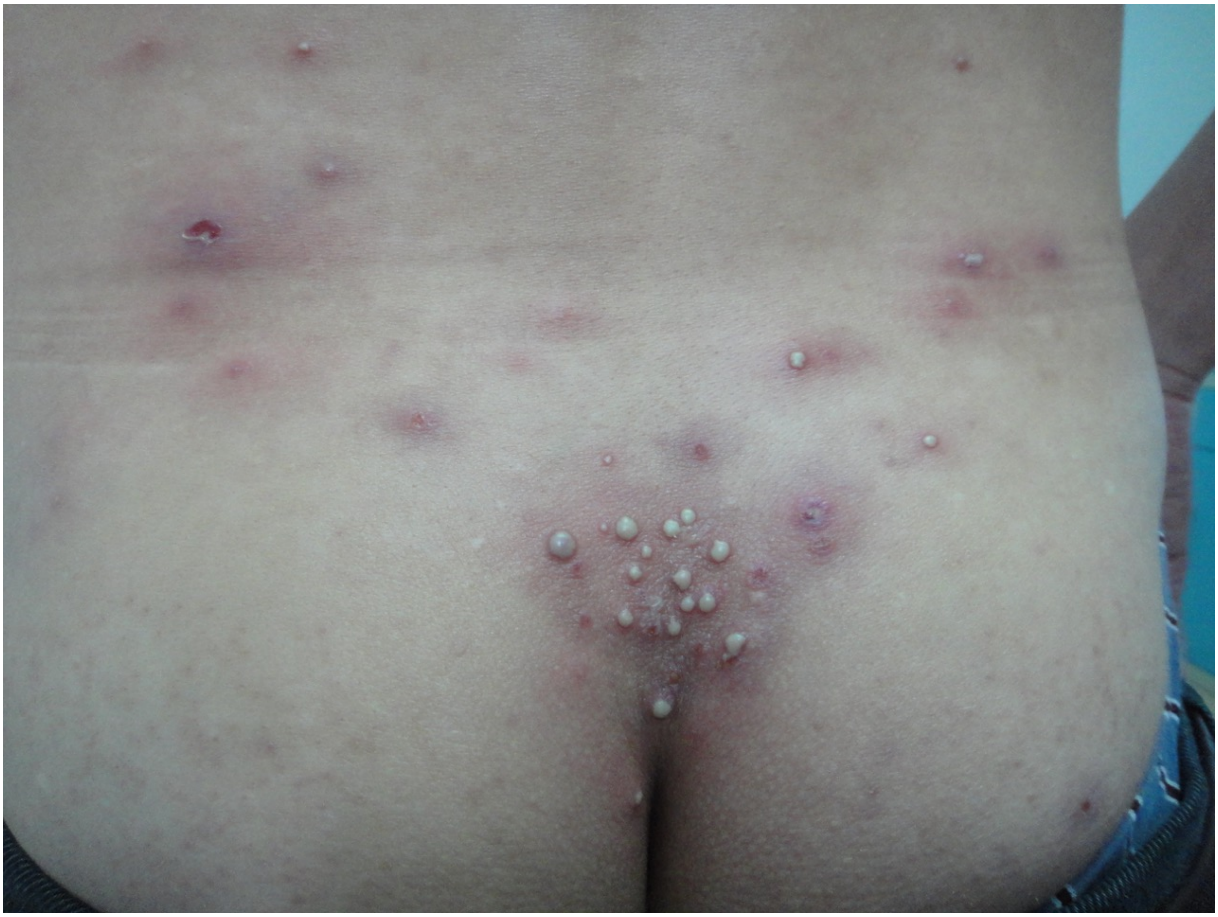

Figure 4: Papulopustular (acneiform) lesions on the lower back and buttocks.

Other studies have demonstrated a reduction of IL-10 production and IL-23R polymorphisms as described by two genome wide association studies [9,10]. IL-10 plays an important role in the down regulation of the innate and adaptive immune system, which leads to a net upregulation of inflammatory cytokines [9,10]. CCR1, STAT4, and KLRC4 have also been reported to play a role in the disease pathogenesis, as described at the 15th International Conference of Behçet's disease. A predominance of Th1 cells over Th17 cells was found to be associated with gastrointestinal involvement [11] as opposed to uveitis [12], which was associated with a predominance of Th17 over Th1 cells. These varying cytokine profiles suggest that BD is not a homogenous entity in itself and may be composed of several cytokine groups that contribute to specific clinical manifestations [13]. Common clinical manifestations of this disease include recurrent oral ulcers, genital ulcers, skin lesions and uveitis. Aphthous stomatitis is the most common clinical manifestation of BD, affecting approximately 97% to 100% of patients [14,15]. Genital ulceration is another key feature of BD, affecting approximately 50% to 85% of patients [14,15] Other cutaneous manifestations of BD include papulopustular eruptions, erythema nodosum, superficial thrombophlebitis, and Sweets syndrome [14-16]. Uveitis is the most common extracutaneous presentation in BD with a prevalence of 70% in young men and up to 30% in older woman, typically beginning in the first several years of disease onset [17,18]. Neurological involvement is estimated to occur in 5% to 10% of patients with a predilection for young men and typically presents within five years of the diagnosis of BD [13]. Vascular involvement typically affects both arteries and veins with an estimated prevalence of 40% as reported in a study from Turkey [17]. Venous thrombosis of the lower extremities has been reported as the most frequent manifestation and usually presents within 2-3 years of the diagnosis of BD [17,19].

Gastrointestinal involvement (nausea, vomiting, diarrhea, and ulcers) is relatively variable among certain regions with the highest prevalence in Japan (nearly 50% of patients with BD) and the lowest prevalence in the Mediterranean [13]. Non-destructive monoarticular/oligoarticular joint involvement occurs in up to 50% of patients with BD and typically resolves within a few weeks of presentation. The most common joints affected include the knee, ankle, wrist, and elbow [20]. Disease severity is based on the amount and extent of organ system involvement.

In our study, the peak incidence of disease occurred during ages of 20-40 with no sex predilection.

This observation is different from what has been reported in the literature: males have a slightly increased frequency than do female patients. The discrepancy noted is likely due to our relatively small sample size. In our series, eye disease exclusively occurred in male patients (all 7 patients with uveitis were men). Genital ulcers also

appeared to preferentially involve male patients as well (among 20 patients who had genital ulcers, 13 were male). Oral ulcers and skin lesions were the most commonly manifested symptoms in our study. Oral ulcers were found to be the most common initial presenting symptom followed by acnei form lesions and erythema nodosum. In our study, no patients had cardiovascular, gastrointestinal or neurological involvement. The reason for such observation is that our hospital is a dermatology specialty clinic and patients with severe disease involving organ systems other than the skin and mucous membranes likely present to a multispecialty hospital.

Behçet's disease is easily missed clinically and its diagnosis is significantly delayed. In this study, the duration from onset to diagnosis ranged from three months to seven years with 14 of 30 patients being diagnosed 1-3 years after onset of their disease. The disease was exacerbated by physical/mental stress, lack of sleep (12 cases), menstrual cycle (6), and upper respiratory system infections (7).

Lab results failed to reveal any specific findings and are not helpful in diagnosing Behçet's disease. Seventeen patients had increased erythrocyte sedimentation rate, four had a mild increase in IgG immunoglobulins, and 19 had neutrophilia. In our study, 63.3% patients demonstrated neutrophilia during acute disease, thus supporting the fact that hyperfunctioning neutrophils play a role in pathogenesis of Behçet's disease.

Conclusion

Behçet's disease is a multifactorial disease involving many possible mechanisms. The mainstay of treatment is immunosuppression and anti-inflammatory medication. Our treatment strategy was based on a therapeutic ladder. The main drugs included in baseline treatment in this series were tripterygium glycosides and tetracycline. Tripterygium glycoside is an immunosuppressive and anti-inflammatory agent. Tetracycline has anti-inflammatory properties and has been found to inhibit neutrophil chemotaxis. Patients with ocular disease or systemic symptoms were placed on systemic steroids and azathioprine. Once the symptoms were controlled, the medication dosages were systematically reduced. Very low dosage regimens of tripterygium glycosides, tetracycline and systemic steroids for relatively long periods of time enabled our patients to achieve and maintain symptomatic remission, in addition to avoiding the significant associated side effects of these medications. Regular hepatic and renal function test and complete blood counts are necessary to monitor side effects of treatment. These tests should be ordered twice a month during the first two months of treatment. This should be followed by once a month for two months and then extended to once every two months for the duration of the treatment.

Our standard treatment regimen proved to be effective for all 30 patients in this study. Initial disease modifying effects and symptom reduction were noted two weeks after initiation of therapy. Resolution of all mucocutaneous lesions, except pyoderma gangrenosum-like ulcers, was achieved by four weeks. The pyoderma gangrenosum-like ulcers healed by eight weeks in those affected. Maintenance therapy was instrumental in preventing disease recurrence. In addition to medical treatment, patients should be instructed to rest well and avoid emotional distress, as these have been shown to possibly exacerbate the disease.

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