Behçet's Syndrome: An Update

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The pathogenic mechanisms in Behçet's syndrome are largely unknown. An autoantigen role for human leukocyte antigen B51 has been proposed. The reasons behind the thrombophilia are also not clear. Endothelial pathology could be the main culprit. The recently proposed association between familial Mediterranean fever and Behçet's syndrome might not be well founded. The long-term prognosis is more guarded among the young and among males. However, the disease burns out in many cases. Clinicians are getting better at management, and have better understanding of the old drugs, such as colchicine, and have new and potent drugs like tumor necrosis factor–alpha inhibitors.

Introduction

The cause of Behçet's syndrome (BS) remains unknown [1,2•]. The main issues are as follows:

1. What are the antigens involved in the immunologic aberrations observed, is there an autoantigen, and what is the meaning of the human leukocyte antigen (HLA) B51 association?
2. What is the mechanism behind the thrombophilia observed in at least one third of the patients?
3. What is the common denominator between the diverse target organs involved?
4. Why do the men have a distinctly more severe disease course?
5. What is the meaning for the peculiar geographic disease distribution?

There surely has been significant progress in understanding and managing this disorder within the past few years. This review is an attempt to mark the highlights of this progress.

Genetics and Pathogenesis

Three decades have passed since the description of the HLA B51 association; however, researchers still do not know its biologic meaning. After extensive work in the major histocompatibility complex region of chromosome 6, it now is clear that the true association is indeed with the HLA B51 [3•]. Also, a new susceptibility locus in the telomere of chromosome 6p has also been recently proposed [4].

Thrombophilia of BS manifests itself as thrombosis in at least one third of patients, and the reason for this is still not clear. An important role for factor V Leiden mutation (the mutation associated with resistance activated protein C) had been proposed by some [5,6], but not by others [7]. Similarly, there have been reports of association with prothrombin gene mutations [8]. A recent and rather comprehensive study from Spain re-examined the causes for thrombophilia in BS [9•]. A group of 38 patients with BS, with and without thrombosis, along with 100 healthy controls were studied for a number of coagulation factors. The important outcomes from this study were that there was not a correlation between being a carrier of factor V Leiden mutation or with prothrombin gene G20210A mutation among patients with BS. Even though thrombin generation and thrombomodulin levels were increased among patients with BS when compared with those among healthy control individuals, their levels did not differ between patients with BS with and without thrombosis.

The authors concluded that soluble thrombotic factors were not pivotal in explaining the thrombophilia in BS. This again throws the ball back to endothelium as the primary site of pathology in BS. However, recent research into the functional changes in the endothelium in BS have been few apart from a controlled study from UK where endothelial dysfunction was shown by a defect in vascular relaxation and, in turn, a function of nitric oxide production [10]. This finding, however, is by no means unique to BS. Another current issue of debate is the association or the role of homocysteine in the vascular pathology of BS. Two recent studies reported increased homocysteine levels [11,12]. However, one of these studies [11] suggested that there was an association of homocystinemia with more thrombotic disease, whereas the other study denied this [12]. Clearly, more work needs to be done.

Autoantibodies are not part of the spectrum of BS. This includes antineutrophil cytoplasmic antibodies (ANCA) [13] and anticardiolipin antibodies [14•]. It is curious that ANCA should be absent even among a group of patients specifically selected for severe vascular disease [14•] in a condition with reported neutrophil hyperactivity and a notable absence of autoimmune phenomenon [1].

Nevertheless two antibodies have recently attracted attention in BS—antibodies to *Saccharomyces cerevisiae* (ASCA) and antibodies to alpha-tropomysin [15,16]. Antibodies to *S. cerevisiae* can be found in up to 70% of patients with Crohn's disease. Specificity is also good, and they are quite useful in the differential diagnosis of Crohn's from ulcerative colitis. Crohn's disease, in turn, shares some features common with BS. Krause *et al.* [15] studied ASCA among 27 patients with BS, 10 patients with systemic lupus erythematosus, 10 with recurrent oral ulcers, and 10 healthy control individuals. Antibodies to *S. cerevisiae* were positive in 13 of 27 (48.1%) patients with BS. Among the control patients, ASCA were positive in patients in each of the three control groups. However, none of the patients in the BS group had gastrointestinal symptoms, and further specificity studies are clearly needed. Also a matter of some concern is the fact that another group, this time from France, did not note an increase in ASCA among patients with BS [16].

The same group from Israel who had studied ASCA also recently reported an increase in immunoglobulin G antibodies to alpha-tropomysin in BS [17]. Immunoglobulin G antibodies were found in four of 15 patients with BS to a 35-kDa band protein, which was eluted from the skin, mucosa, vagina, muscle, and heart tissues from rats. No such antibodies were present in 20 healthy blood donors and 16 patients with recurrent oral ulcers. This antibody was also directed against human tissue, and its tissue specificity turned out to be alpha-tropomysin. When alpha-tropomysin in complete Freund's adjuvant was injected into Lewis rats, it induced a uveitis, some inflammatory skin lesions, and an atrophic arthritis. The authors proposed that these lesions constituted an animal model for BS.

Another important issue in pathogenesis is what perpetuates the chronic inflammation with the accompanying tissue damage in BS. A recent and an attractive hypothesis may shed some light on this for uveitis [18••]. Retinal-S (RS) antigen is a protein found mainly in the retina, which is an immunologically privileged site. It is proposed that tissue destruction, such as that found in uveitis, uncovers an epitope in the RS antigen, making it antigenic. T cell responses against the RS antigen are found in various forms of uveitis, including BS [2•]. It also turns out that this epitope on the RS antigen crossreacts with immunologically conserved region of the Class I HLA B molecules, such as HLA B51 and HLA B27. The theory also suggests that a portion of this Class I molecule also becomes an epitope that triggers an autoimmune response from the $CD4^+$ T cells. Fragments of Class I molecules have been found in the surface of the Class II molecules during antigen presentation [2•]. In brief, in the proposed model, a Class I peptide becomes an autoantigen and elicits a T cell response through its molecular mimicry to another protein, RS antigen (in the author's example), once this second protein becomes antigenic through an initial insult. This attractive hypothesis is a proposal for the continuation of the tissue damage in BS. What initiates the damage is another enigma.

Vasculitis in the Erythema Nodosum Lesions

Behçet's syndrome can present with a variety of dermal manifestations ranging from dermal vasculitis to Sweet syndrome. However, the bulk of dermal manifestations fall into the following categories: 1) the nodular and 2) the acne lesions. The nodular lesions are much like *Erythema nodosum* caused by other sources to the naked eye, but on histology are equally divided between superficial thrombophlebitis and the erythema nodosum–like lesions. Recently, in almost two simultaneous publications [19,20], it was shown that the histology of the second form is rather similar to *E. nodosum* caused by other causes, but, in addition, has elements of vasculitis where a histologic hallmark of the garden-variety *E. nodosum* is the absence of vasculitis.

Association Between Acne Lesions and Arthritis

The acne lesions are mainly of cosmetic concern. They are clinically and histologically indistinguishable from ordinary acne. However, unique to BS, they can also be present at sites uncommon for ordinary acne, such as the face, back, upper torso, arms, and legs.

Recently, the authors and colleagues have shown that the likelihood of arthritis among the patients with acne was significantly high [21•]. This observation obviously brings to mind an analogy to acne-associated reactive arthritis. This association between arthritis and acne still held true in a more recent study when the authors and colleagues prospectively studied target organ associations in 272 consecutive patients using factor analysis [22].

Geographic Differences in Disease Expression: Syndrome or Disease?

An interesting phenomenon in BS is the geographic variation in disease expression. It has long been observed that pathergy reaction was distinctly less frequent among the patients from the north and the west, whereas inflammatory bowel disease, rather common among the patients from the Far East, was infrequent among patients from the Mediterranean basin [23]. Lee *et al.* [24] recently reported in detail the colonoscopic findings among 94 of their patients with bowel disease. Typical colonoscopic findings were single, large, and deep ulcers with distinct borders. This contrasted markedly with the multiple and superficial ulcers that, again recently, were observed among the author's patients with bowel disease [25]. Thus, it seems that the frequency and the type of bowel disease seem to differ among regions. Perhaps this is why some still prefer to call Behçet's a syndrome rather than a disease.

Behçet's Syndrome and Familial Mediterranean Fever

Lately, there has been an interest of the association of BS and familial Mediterranean fever (FMF). After some recent case reports [26], Schwartz *et al.* [27] reported 39 patients with coexisting FMF and BS among a group of patients with FMF. Of those 39 patients, 16 had the complete and 23 had the incomplete form of FMF, casting some doubt on the true strength of this proposal for an association. Table 1 lists the main features of these two conditions that are alike or that differ. As will be noted, the items across "unlike" row are numerous. Although BS and FMF are indigenous for the people of Middle East, BS is common in the Far East only and FMF is almost never seen. Compared with BS, no HLA associations have been described for FMF. Serositis, which is the hallmark of FMF, is most common in BS, whereas the converse is true for eye disease. The rather unique skin mucosa and major vessel disease pathologies of BS are not part of FMF, and the response to treatment also differs. Colchicine has more or less limited usefulness in BS [28••], although it is the treatment of choice for FMF.

The recently described association of pyrin gene (MEFV) mutations in FMF [29] was another reason for some to consider FMF and BS in one bowl, because pyrine is mainly expressed in neutrophils and regulates inflammation. It is suggested that this protein, through a specific domain (PyD), is important in the regulation of the inflammatory process [30••]. Although it is true that the frequency of MEFV mutations are somewhat increased among patients with BS [31], researchers need parallel information about the MEFV mutations in other inflammatory conditions. In fact, a role to MEFV mutations have been ascribed to more severe disease in rheumatoid arthritis [32], secondary amyloidosis in various diseases including BS [33], and multiple sclerosis [34]. In summary, there is little doubt that pyrine is an important molecule in inflammation. However, it is too early to ascribe it a linking function between BS and FMF.

Finally, more recent epidemiologic data were not supportive of the proposed association between BS and FMF. Ben-Chetrit *et al.* [35•] found only two patients with features suggestive of BS among 352 patients with FMF, whereas the same patients represented an overlay of two conditions among their 53 patients with FMF. In one study, none of the 302 patients from Istanbul with BS had any symptoms suggestive of FMF, although none of the 108 patients with FMF fulfilled the International Study Group criteria for BS [36].

Prognosis

Recently, the author and colleagues surveyed the 20-year mortality and morbidity of BS. Four hundred twenty-eight patients (286 men, 142 women) who had registered in a dedicated outpatient clinic between 1978 and 1983 were called back for a re-evaluation during 1999 and 2000 [37••]. Outcome information was available on 387 of 428 (90.2%) patients.

Forty-two patients (9.8%; 39 men, 3 women) had died. Major vessel disease (especially pulmonary artery aneurysms) and neurologic involvement were the main associates of disease-specific mortality. Mortality, as measured by standardized mortality ratios, was specifically increased among the young men, which was the same group with the highest morbidity. The standard mortality ratios tended to decrease significantly with the passage of time. This is unlike what is found in systemic lupus erythematosus or rheumatoid arthritis where mortality is increased with the passage of time. It might be in BS that the disease initiating insult is effective for a limited time or secondary causes of mortality, such as accelerated atherosclerosis, is not part of the clinical spectrum of BS. This survey showed that the frequency of mucocutaneous and articular manifestations also abated with time. Central nervous system involvement and major vessel disease were the exceptions. They could have their onset late (5 to 10 years) during the disease course.

As was very pronounced by the mortality figures, the disease was less severe among the women for almost each disease manifestation. For example, in this series, there were no women with arterial aneurysms.

Management

Even though BS is not yet curable, there is little doubt that has been a substantial progress in drug management [38]. Researchers now not only have new drugs like tumor necrosis factor–alpha blockers, but also know how to use the better drugs, such as colchicine. Many years ago, based on a 6-month study among a limited number of patients, the authors' group had suggested that colchicine had limited usefulness in the management of BS [39••]. In a recent 2-year study, among a greater number of patients, this held true [28••]. This drug, widely used for almost all the manifestations, seems to be good only for arthritis and the erythema nodosum like lesions in each gender with a gender-favoring effect. For example, the drug seemed to benefit genital lesions.

Although it enjoys widespread application, and probably justifiably, double-blind studies of interferon-alpha efficacy on eye disease are still lacking. Its beneficial effects on skin-mucosa disease, however, have recently been published [40]. This was a 3-month double-blind trial of interferon-alpha-2a (6 MU three times per week) against placebo. The duration and the number of oral ulcers decreased, as well as the pain caused these ulcers in those patients who received the active drug. The same was true for the genital ulcers and the papulopustular lesions. There was also a trend for improvement in all the other manifestations, but this did not reach significance presumably because of the insufficient number of patients studied. There was also a resurgence of symptoms once the

Table 1. Features of Behçet's syndrome and familial Mediterranean fever that are "like" and "unlike"

Like features	Unlike features
Fever	Epidemiology
Arthritis orchitis/epididymitis	Human leukocyte antigen association
	Clinical findings (serositis [familial Mediterranean fever], eye disease [Behçet's], skin mucosa disease [Behçet's], and major vessel disease [Behçet's])
	Response to disease

drug was stopped. This is an important study with one drawback. The degree of improvement in various organ systems has not been highlighted in this paper.

Another drug that was recently effective in the skin-mucosa manifestations of BS was dapsone [41]. Investigators from Iraq compared the effect of dapsone at 100 mg per day with placebo in 6-month double-blind, crossover (at 3 months) study among 20 patients with BS. Despite the small numbers (10 in each arm), the dapsone group did better in all skin-mucosa manifestations and arthritis. The acute phase and the pathergy skin test were also dampened. Anemia, seen in one fourth of patients, and headaches, seen in one fifth of patients, were the main side effects observed.

Uncontrolled studies with anti–tumor necrosis factor therapy in BS have shown quite promising results. Sfikakis *et al.* [42] reported a very prompt and dramatic improvement in uveitis of five patients with BS with a single dose (5 mg/kg) of infliximab. Intestinal lesions similarly improved in two patients given infliximab followed by thalidomide [43].

In a short-term, 1-month, double-blind, placebo-controlled study, Melikoglu *et al.* [44] reported that etanercept, at the usual 25-mg twice-weekly dose, was markedly effective in controlling most of the skin-mucosa manifestations and arthritis of BS. The effects were apparent at week 1. However, pathergy test and the cutaneous response to the intradermally injected urate crystals were not effected by etanercept. All patients enrolled in this study had only skin-mucosa disease and the effects of tumor necrosis factor–alpha blockage on the more serious manifestations, such as eye and central nervous system disease, still need to be formally studied.

Conclusions

The pathogenesis of BS remains unknown. The recently proposed association between BS and FMF is an interesting concept that needs more supportive data with emphasis on diseased control individuals. Behçet's syndrome is distinctly more severe among men, and has a disease course severity that abates with the passage of time. Even though the cause is unknown, clinicians are getting better in managing BS. Not only do clinicians know how to use the old drugs like colchicine, there are new and very promising drugs available, such as tumor necrosis factor–alpha blockers.

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