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Dermatologic Manifestation of Behçet's Disease

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Dermatologic lesions in Behçet's disease are regarded as important manifestation for diagnosis. Various kinds of cutaneous lesions appear in patients with Behçet's disease. They present as erythema nodosum-like lesion, papulopustular eruption, erythema multiforme-like lesion, thrombophlebitis, skin ulcer, Sweet's syndrome-like lesion, bullous necrotizing vasculitis, and pyoderma gangrenosum. The hyperreactivity of the skin to any intracutaneous injection or needle prick, which is known as pathergy, is one clinically-unique feature of the disease.

Key Words: Skin lesions, Behçet's disease

Incidence

Various kinds of cutaneous lesions have appeared in 41% to 97% of patients with Behçet's disease (Chajek and Fainaru, 1975; da Cunha *et al.* 1992; Lee, 1992; Gharibdoost *et al.* 1993; Shi and Huang, 1993; Zgradic, 1996; Zouboulis, 1996).

Gharibdoost *et al.* reported that the majority was pseudofoliiculitis in 70% of their cases with skin lesions, erythema nodosum in 23%, and other skin manifestations in 5.5% (Gharibdoost *et al.* 1993). Ghayad reported that in Lebanon, 100 patients seen between 1980 and 1992 showed less frequent skin lesions than those in several other studies (Ghayad and Tohme, 1995).

In a German registry until March 31, 1996, consisting of 130 patients, the frequency of cutaneous manifestations was 73.4% and the positive pathergy test was seen in 53% of patients. Erythema nodosum was the third most common onset symptom (13%) and papules/pustules was the last (2%). Skin lesions of German patients were classified in 5 groups: papule/pustule, erythema nodosum, pyoderma, superficial thrombophlebitis, and ulceration (Zouboulis, 1996). A retrospective clinical review of 25 patients with Behçet's disease in the United States was performed (Mangelsdorf *et al.* 1996), and out of 25 patients, 22 showed cutaneous lesions which consisted of at least one of the following: papulopustular lesions, erythema nodosum-like lesions, or pyoderma gangrenosum-like lesions.

Pediatric patients

The frequencies of cutaneous lesions in pediatric patients with Behçet's disease vary by country. A French study involving 362 pediatric units showed 15 patients with Behçet's disease. Among them, 12 (80%) suffered from skin lesions (Kone-Paut *et al.* 1993).

Kim *et al.* analyzed 40 cases of childhood-onset Behçet's disease. Skin lesions were seen in 29 cases (72.5%)(Kim *et al.* 1994). Papulopustular lesions and erythema nodosum-like eruptions were frequent,

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observed in 69.0% and 58.6% of patients, respectively. Erythema multiforme-like eruptions (10.3%) and thrombophlebitis (6.9%) were rare. Thirty juvenile Behçet's disease patients in Israel showed common skin involvement (93%)(Uziel *et al.* 1996). The pathergy test was positive in 6 out of 30 patients (40%).

In contrast to previous studies, 102 Iranian children with Behçet's disease showed skin lesions in 58% (pseudofolliculitis 52%, erythema nodosum 6%) of patients, which was much less than in adult patients (Shafaie *et al.* 1996).

Benamour *et al.* also reported a low frequency of skin lesions (skin ulcers 16%; erythema nodosum 27%) among 19 juvenile Behçet's disease patients in Morocco (Benamour *et al.* 1996). A recent nationwide retrospective study in Japan showed the frequency of skin lesions among 31 pediatric patients was 55% (Fujikawa and Suemitsu., 1997).

Types and features of dermatologic manifestations

Various cutaneous manifestations can occur in Behçet's disease. Description of cutaneous lesions are also variable. Erythema nodosum-like lesions, subcutaneous thrombophlebitis, folliculitis or acne-like lesions, and cutaneous hypersensitivity or pathergy are listed together as one major criteria (Behçet's Disease Research Committee of Japan, 1974).

The erythema nodosum-like lesions (Fig. 1) were described by the Behçet's Disease Research Committee of Japan as consisting of tender, raised red nodules that appear more commonly on the anterior surface of the legs and slowly resolve within a few weeks without scar formation. These lesions can also occur at other sites, including the face, neck, and buttocks, they may be recurrent, and they may heal with cutaneous hyperpigmentation (O'Duffy *et al.* 1971; Shimizu *et al.* 1979). Shi and Huang reported that some Chinese patients (35.1%) showed right red halos about 1~1.5 cm in width around nodules (Shi and Huang, 1993). They called this feature erythematous halo phenomenon, rarely seen in other diseases with nodules on the lower extremities. The halos subsided two weeks after their occurrence and the nodules disappeared completely from between one-to six month. In Iran, erythema nodosum was defined as not resembling very much the classical erythema nodosum (Chams *et al.* 1993). They also classified similar lesions into different terms, such as small nodules and multiple small subcutaneous nodules.

Subcutaneous thrombophlebitis (Fig. 2) is represented as palpable, painful subcutaneous nodules or string-like hardenings with reddening of the overlying skin (Behçet's Disease Research Committee of Japan, 1974). This may have a migratory tendency developed from the proximal end to the distal end (Shi and Huang, 1993). However, thrombophlebitis is not regarded as the main feature when the International Criteria for Classification of Behçet's Disease is applied (Anonymous, 1990).

Pseudofolliculitis, papulopustular lesions (Fig. 3), or acneiform nodules are listed as one diagnostic criteria (Anonymous, 1990). The terms are very confusing. According to Nazarro (Nazzaro, 1964), the papulopustular skin lesions are the most characteristic of Behçet's disease. The Iran series defines pseudofolliculitis as round and red elevated edema, with a diameter of 10 to 20 mm (Chams *et al.* 1993). The lesion is surmounted in its center by a round and non acuminated pustule. They are situated mainly on the lower limbs, but they can be seen everywhere except on the back and face. Chams *et al.* insisted the lesions are easily differentiated from acne vulgaris (Chams *et al.* 1993). In Chinese patients, folliculitis-like lesions had two types (Shi and Huang, 1993). The first is similar to acne and the second is papulopustules with erythematous halo, which supports diagnosis.

The identification of Sweet's syndrome-like lesion as a symptom of Behçet's disease was first made by Mizoguchi *et al.* (1987). Several supporting reports followed (Mizoguchi *et al.* 1988; Cho *et al.* 1989; Lee *et al.* 1989a; Oguz *et al.* 1992). Behçet's disease and Sweet's syndrome have many similarities. Some patients with Sweet's syndrome had oral aphthae, genital ulcers, erythema nodosum- like eruptions, or iridocyclitis, which are all frequently observed in Behçet's disease. In one study, ten patients with Behçet's disease who had Sweet's syndrome-like skin lesions were presented (Lee *et al.* 1989a). All the patients had already had Behçet's disease for several years, and they had other characteristic manifestations of Behçet's disease,

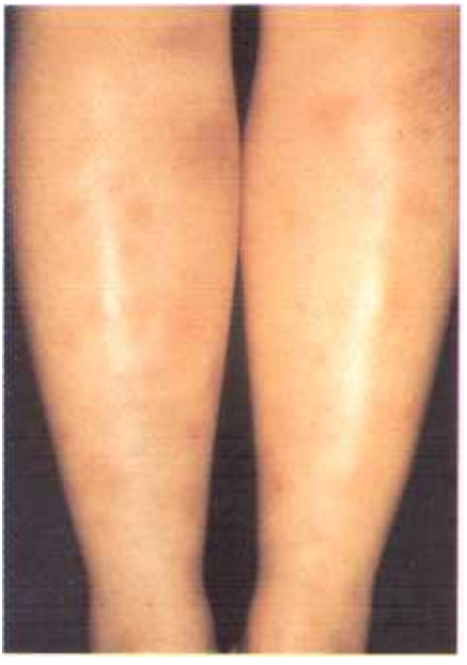

Fig. 1. Erythema-nodosum like lesions on extremities.

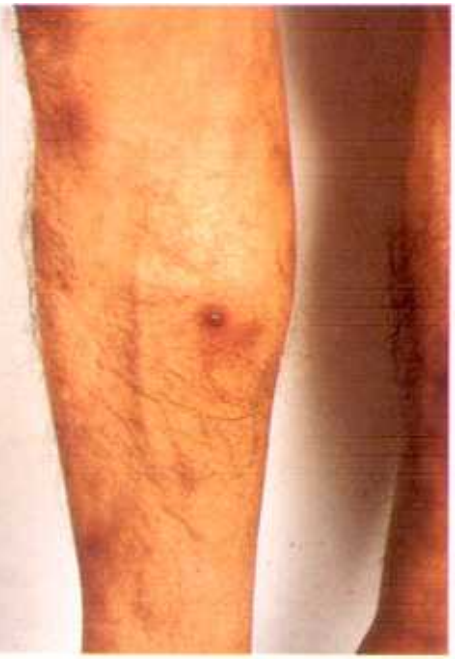

Fig. 3. Papulopustular eruptions.

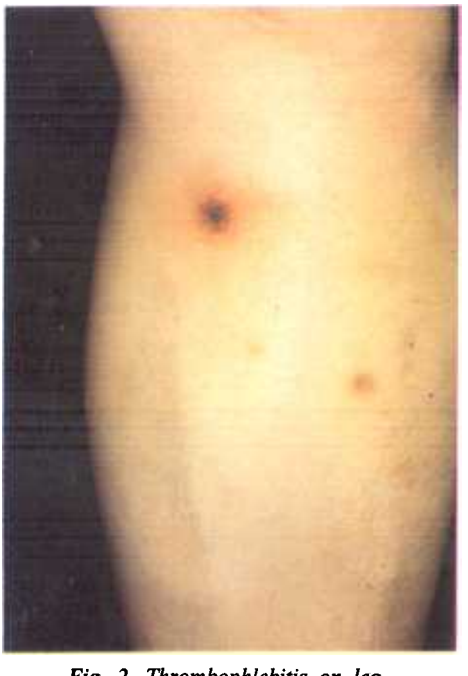

Fig. 2. Thrombophlebitis on leg.

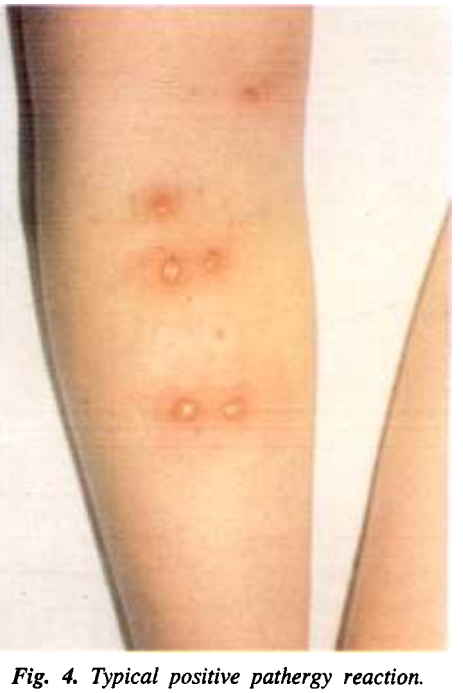

Fig. 4. Typical positive pathergy reaction.

such as oral ulceration, genital ulceration, erythema nodosum, and neurological symptoms. The lesions were located on the face, back and neck. Fever preceded their appearance in 4 cases, 8 complained of severe arthralgia, and a positive pathergy test was shown in 7 patients. Eight had a history of recurrence.

Korean researchers have noted that skin lesions often occur in combination: more than two types of skin lesions occurred in 140 (20.7%) of 677 patients (Lee, 1992). Most frequently combined were erythema nodosum-like lesion and papulopustular eruption, which were found together in 92 patients (65.7%); erythema multiforme-like lesion and papulopustular eruption, found in 13 patients (9.3%); and erythema nodosum-like lesion and erythema multiforme-like lesion, found in 11 patients (7.9%). Other cutaneous lesions occurring in Behçet's disease include nodules, vesicles, ulcerations with or without eschar, furuncles, abscesses, pyodermas, impetigo, cellulitis, erythema multiforme-like lesions, or purpura. Extragenital ulcerations are a different type of skin lesion not defined before (Lee, 1992). These were encountered in 32 of 972 Behçet's patients. The lesions resemble oral aphthae clinically and are recurrent, but heal leaving scar tissue like genital ulcers. These ulcerations are located extragenitally on the breast, legs, axillae, interdigital skin of the foot, inguinal region and on the neck. According to Chams *et al.* (Chams *et al.* 1993), cutaneous aphthosis is the most characteristic and specific lesion of Behçet's disease because it was never observed in other skin diseases. From the analysis of the German Registry, Zouboulis suggested that ulcers mean the end stage of pyoderma (Zouboulis, 1996).

Several rare cases are reported. A case of Behçet's syndrome in an 11-year-old Korean boy who had severe bullous necrotizing vasculitis as a skin manifestation was reported (Lee *et al.* 1989c). Lee *et al.* reported two patients with Behçet's disease and systemic lupus erythematosus(SLE) and the possibility of SLE as part of the symptom complex of Behçet's disease was suggested (Lee *et al.* 1989b; Lee *et al.* 1996). In Japan, a patient was reported with incontinentia pigmenti who developed the clinical picture of intestinal Behçet's disease (Endoh *et al.* 1996). Impaired neutrophil chemotactic activity and an elevated plasma IL-6 level were found. The possibility that there are common immunological abnormalities in the two syndromes was suggested. They agreed with the previous report (Menni *et al.* 1986).

A patient with Behçet's disease who also had pernio-like skin lesions and seronegative arthritis of the small joints was also presented (Yücel *et al.* 1996). Cryoglobulinemia and cryofibrinogenemia were associated with that case.

Pathergy (skin hyperreactivity)

The various clinical manifestations of Behçet's disease are characteristic but not necessarily pathognomonic of the disease. This can cause difficulties in establishing a definitive diagnosis. As well, the often long interval between the first symptom of the disease and the second major manifestations in new target organs (Kim *et al.* 1988; Friedman-Birnbaum *et al.* 1990) can hinder diagnosis. One clinically unique feature of the disease, however, is the hyperreactivity of the skin to any intracutaneous injection or needle prick, which is known as pathergy (Lee, 1992). Pathergy is an outstanding feature of Behçet's disease and has long been used as a diagnostic criteria in guidelines proposed by the Behçet's Disease Research Committee of Japan, especially the revised one of 1987 (Mizushima *et al.* 1988), Dilsen *et al.* in 1985 (Dilsen *et al.* 1985a), the International Study Group for Behçet's disease (ISGBD) in 1990 (Anonymous, 1990) and Davatchi and colleagues (Davatchi *et al.* 1993). The mechanism of the phenomenon remains obscure.

This phenomenon was first described in 1937 by Blobner (Blobner, 1937) and confirmed by many subsequent reports (Jensen, 1941; Jadassohn *et al.* 1961; Katzenellenbogen, 1967; Matsumura *et al.* 1977; Tüzün *et al.* 1979; Jorizzo *et al.* 1985; Wechsler *et al.* 1990). Pathergy, an erythematous induration (Fig. 4) followed by sterile pus at its center can be provoked in patients with Behçet's disease in 12 to 48 hours after cutaneous trauma by needle prick or intradermal injection of normal saline which has been advocated as an adjunct to clinical diagnosis (Haim *et al.* 1976; Altac *et al.* 1982; Jorizzo *et al.* 1985; Mansoori *et al.* 1993). However, other reports have raised questions about

the reliability of the pathergy test (O'Duffy, 1978; Suzuki and Mizuno, 1981; Davies *et al.* 1984). These varying findings may be due to differences in experimental/clinical methods (Suzuki and Mizuno, 1981; Dilsen *et al.* 1993; Fresko *et al.* 1993).

Regarding the relationship of pathergy phenomenon and Behçet's disease manifestations, pathergy may not be predictably correlated with the presence of clinical symptoms, including aphthae, ocular manifestations, erythema nodosum, folliculitis, and thrombophlebitis, or with the results of laboratory tests including leukocytosis and erythrocyte sedimentation rate (Shimizu *et al.* 1979; Suzuki and Mizuno, 1981; Altac *et al.* 1982; Davies *et al.* 1984; Jorizzo *et al.* 1984; Jorizzo *et al.* 1985). By contrast, Chinese patients with this positive reaction were always associated with multiform skin lesions and showed in active state of disease (Shi and Huang, 1993). A prospective study done in Iran showed that the attacks of oral aphthosis were significantly associated with the presence of pathergy (Mansoori *et al.* 1993). On the contrary, when pathergy was negative, patients had more frequent attacks of anterior uveitis. However, verification of the relationship needs a longitudinal study. The degree of positivity of the cutaneous hyperirritability reaction may occasionally correlate with disease activity (Fellner and Kantor, 1964; Nazzaro, 1964; Djawari *et al.* 1981). The pathergy phenomenon in Behçet's disease is waxing and waning, like the majority of other clinical manifestations (Chams *et al.* 1996). Therefore it may be repeated, if necessary, for diagnostic purposes.

On the other hand, the results and interpretations of pathergy tests also vary from region to region: high positivity (84~98%) is found in Mediterranean and Middle Eastern countries (Tüzün *et al.* 1979; Friedman-Birnbaum *et al.* 1990); relatively lower positivity (40~70%) in Far Eastern countries (Shimizu, 1977; Lee, 1992), and significantly lower positivity in Western countries (Davies *et al.* 1984; Scherrer *et al.* 1993). Turkish researchers have contributed remarkably in explaining the high rate of positive pathergy results, using genetic markers in comparative studies of Turkish and British patients (Aral *et al.* 1985). Turkish patients with Behçet's disease have a higher prevalence of pathergy and the HLA-B5 antigen compared to North American and British patients with Behçet's disease, and at least in Turkish patients the absence of these two markers virtually excluded the diagnosis of Behçet's disease. In view of the regional variations in pathergy test results, a positive test can be considered pathognomonic of Behçet's disease in the Mediterranean region. In Far Eastern and Western countries, a positive result should also be considered an important clinical indicator; at the same time, a negative result should not be considered sufficient to rule out a diagnosis of Behçet's disease.

Pathergy is not pathognomonic for Behçet's disease since it may occur in patients with recurrent idiopathic aphthous ulcerations, iridocyclitis, idiopathic erythema nodosum, continuous elevated erythema syndrome, pyoderma gangrenosum, herpes genitalis, rheumatoid arthritis, spondyloarthropathy and chronic myelogenous leukemia (Price, 1969; Haim *et al.* 1976; Shimizu *et al.* 1979; Tüzün *et al.* 1979; Davies *et al.* 1984; Aral *et al.* 1985; Powell *et al.* 1985; Budak-Alpdogan *et al.* 1997; Hamza *et al.* 1997).

Histopathologic findings

There are apparent controversies about the histopathologic findings of Behçet's disease. However, many of the reports indicated that the common underlying pathology is a vasculitis affecting the blood vessels of all sizes including the arteries, arterioles, veins and venules (Lakhanpal *et al.* 1988).

However, vasculitis may not always be demonstrable; rather, Behçet's disease is sometimes included in the category of neutrophilic dermatoses which typically express little morphologic evidence of vasculitis (Haim *et al.* 1976; Hunt and Santa-Cruz, 1989). In addition, two subtypes of leukocytoclastic vasculitis have been described (Kienbaum *et al.* 1993): 1) Lymphocytic vasculitis with predominance of lymphocytes in the perivascular infiltrates which has been interpreted as an own entity by some authors (Lakhanpal *et al.* 1985; Chun *et al.* 1989), 2) Neutrophil vascular reaction or Sweet's-like vasculitis which shows clear predominance of neutrophils and leukocytoclasia but lacks fibrinoid necrosis (Jorizzo *et al.* 1986; Jorizzo *et al.* 1988).

Lehner's group, which has performed much work

in this area, found an early infiltration of mononuclear cells, followed by infiltration of neutrophils (Muller and Lehner, 1982; Arbesfeld and Kurban, 1988; Lakhanpal *et al.* 1988).

In contrast, Jorizzo suggested that the lymphocyte dominance is a feature of older lesions in Behçet's disease and that earlier lesions show varying degrees of leukocytoclastic vasculitis (Jorizzo, 1986). He studied the pathergy lesions and reported leukocytoclastic vasculitis and Sweet's-like vasculitis (neutrophilic vascular reaction) (Jorizzo *et al.* 1985).

Kienbaum *et al.* studied skin biopsy specimens from various mucocutaneous lesions of patients and found the major histopathological finding was leukocytoclastic vasculitis (Kienbaum *et al.* 1993). In a recent Japanese study, 23 specimens with histologically-proven necrotizing vasculitis from 20 of 42 patients with Behçet's disease were investigated (Chen *et al.* 1997). Cutaneous vasculitis in Behçet's disease is predominantly venulitis or phlebitis. Approximately half (48%; 20 of 42) of the patients with cutaneous lesions had either lymphocytic (31%; 13 of 42) or leukocytoclastic vasculitis (17%; 7 of 42).

Thirty Korean patients were studied to determine the histopathologic changes of erythema nodosum-like lesions (Chun *et al.* 1989). Lymphocytic vasculitis was observed in 12 (40%) of the cases, but it was only focal in areas of severe lymphocytic inflammation and was just mild in degree. No diffuse vasculitis was seen. Twelve cases (40%) revealed septal panniculitis, 10 cases (33%) demonstrated lobular panniculitis with moderate-to-marked inflammation and fat-cell necrosis, and 8 cases (27%) showed mild and nonspecific inflammation in the panniculus. Therefore, there is a spectrum of histopathologic changes of erythema nodosum-like lesions in Behçet's disease, similar to that of erythema nodosum secondary to other systemic disorders.

The pathogenesis of the vessel damage in Behçet's disease remains controversial. Some investigators demonstrated immune-complex mediated neutrophilic vasculitis (Gamble *et al.* 1979; Jorizzo *et al.* 1984). To determine the pathogenesis, Japanese researchers performed histological and immunohistochemical studies of these mucocutaneous lesions, an assay of neutrophil activity, and HLA typing (Inoue *et al.* 1994). Dense dermal or subcutaneous infiltrations of polymorphonuclear cells (PMN) without leukocytoclastic vasculitis were found in 28 of 57 lesions. Immunohistochemically, deposits of C3 on the vessels were found in 12 of 31 lesions. Deposits of immunoglobulin were not found, except for one of IgM. C3 deposits and PMN infiltration were significantly related. PMN activity by polarization was enhanced; however, the results did not show a significant relationship with PMN infiltrations of the C3 deposits. The incidence of HLA-B51 was significantly high in Behçet's disease, but no significant relationship was found between HLA-B51 and the results of other examinations. These results suggest that the pathogenesis of Behçet's disease lesions differs from that of collagen diseases and that C3 deposits on the vessels may play an important role in the development of mucocutaneous lesions where PMN have mainly infiltrated.

Mast cells have been implicated in the pathogenesis of Behçet's disease. Mast cell count and histamine determinations were done on the papulopustular and pathergy lesions of 137 patients with Behçet's disease and a control group consisting of 76 patients with acne vulgaris and 45 patients with ankylosing spondylitis (Yurkakul *et al.* 1996). There were no differences in the mast cell or in the histamine content between any of the groups, which was in contrast to the previous finding (Lakhanpal *et al.* 1988).

Mochizuki *et al.* analyzed T lymphocyte-phenotypes infiltrated in cutaneous pustular lesions in Behçet's disease and found that CD4+ T cells were predominant components, although CD8+ T cells were also present in the lesion (Mochizuki *et al.* 1997). In addition, they established T-cell lines from pustular lesions of the 4 patients with a streptococcal antigen, KTH-1. Cell-surface markers, mRNA expressions, and cytokine expressions of these cell lines suggested that the self-reactive T cells play some role in the pathogenesis of Behçet's disease.

Through a series of our electron microscopic studies in erythema nodosum-like lesions, microvascular changes and lymphocyte-mediated fat-cell lysis have been reported (Bang *et al.* 1987; Honma *et al.* 1987). The immunoelectron microscopic study in erythema nodosum-like lesions of Behçet's dis-

ease supported these findings (Bang *et al.* 1993). Bang *et al.* also observed small dermal blood vessels embolized by thrombus at the sites of needle prick reaction as well as erythema nodosum-like lesions in 4 patients with Behçet's disease, by means of electron microscopy (Bang *et al.* 1988).

The histopathological findings of pathergy lesions are dependent on the methodology of induction and time of biopsy (Haim *et al.* 1976; Wong *et al.* 1984; Jorizzo *et al.* 1986). Cutaneous biopsies obtained at 4 hours following the intradermal injection of histamine phosphate may reveal the deposition of immunoreactants or fibrin in the walls of the dermal blood vessels (Jorizzo *et al.* 1984; Jorizzo *et al.* 1985). At 6 hours following the application of needle prick, there may be an inflammatory infiltrate composed mainly of polymorphonuclear leukocytes which may be immune-complex and complement-mediated (Tüzün *et al.* 1980). At 24 hours, one may observe findings consistent with either leukocytoclastic vasculitis or Sweet's-like vasculitis (Jorizzo *et al.* 1985; Jorizzo *et al.* 1986). Direct immunofluorescence of 24-hour-old cutaneous hyperreactivity lesions may reveal IgG, or IgM, C1q, C3, C4, and fibrin in the dermal vessel walls (Reimer *et al.* 1983). The immunohistological findings of the pathergy reaction appeared to indicate a cell- mediated immune response (Gül *et al.* 1993). The expression pattern of adhesion molecules in pathergy reaction suggested a direct epidermal injury as the cause of the cutaneous inflammation. An intense antigen-independent induction phase of cutaneous inflammation might be developed by increased release of cytokines from keratinocytes which might later be amplified by the effect of infiltrating activated mononuclear cells.

REFERENCES

Altac M, Tuzun Y, Yurdakul S, Binyildiz P, Yazici H: The validity of the pathergy test (non-specific skin hyperreactivity) in Behçet's disease: a double-blind study by independent observers. *Acta Derm Venereol (Stockh) 62: 158-159, 1982*

Anonymous: Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet 335: 1078-1080, 1990*

Aral O, Dilsen N, Konice M: *Positive skin pathergy reactivity as a genetic marker of Behçet's disease.* Paper presented at The Fourth International Conference on Behçet's Disease. London, Royal Society of Medicine, *1985, 173-175*

Arbesfeld SJ, Kurban AK: Behçet's disease. New perspectives on an enigmatic syndrome. *J Am Acad Dermatol 19: 767-779, 1988*

Bang D, Honma T, Saito T, Nakagawa S, Ueki H, Lee S: The pathogenesis of vascular changes in erythema nodosum-like lesions of Behçet's syndrome: an electron microscopic study. *Hum Pathol 18: 1172-1179, 1987*

Bang D, Honma T, Saito T, Nakagawa S, Ueki H, Lee S: Ultrastructure of vascular changes in cutaneous manifestations of Behçet's disease. *Acta Derm Venereol (Stockh) 68: 33-40, 1988*

Bang D, Sohn S, Lee S: *The possible role of fat cells in the pathogenesis of erythema nodosum-like lesions of Behçet's disease: an immunoelectron microscopic study.* Paper presented at The Sixth International Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV *1993, 371-374*

Behçet's Disease Research Committee of Japan: Behçet's disease: guide to diagnosis of Behçet's disease. *Jpn J Ophthalmol 18: 291-229, 1974*

Benamour S, Tak-Tak MT, Rafik M, Amraoui A: Juvenile Behçet's disease in Morocco. *Rev Rhum Engl Ed 63: 536, 1996*

Blobner F: Zur rezidivierenden hypopyon-iritis. *Zeitschrift Augenheik 91: 129-139, 1937*

Budak-Alpdogan T, Alpdogan, Demirìay Z, Ergun T, Direskeneli H, Öztürk A, Bayik M, Akoglu T: Positive skin pathergy reaction in patients with chronic myelogenous leukemia. *Rev Rhum Engl Ed 63: 553, 1997*

Chajek T, Fainaru M: Behçet's disease. Report of 41 cases and a review of the literature. *Medicine (Baltimore) 54: 179-196, 1975*

Chams C, Davatchi F, Sharam F, Akbarian M, Gharibdoost F, Nadji A: Longitudinal study of the pathergy phenomenon in Behçet's disease. *Rev Rhum Engl Ed 63: 554, 1996*

Chams C, Mansoori P, Shahram F, Akbarian M, Gharibdoost F, Davatchi F: *Iconography of mucocutaneous lesions of Behçet's disease. Paper presented at The Sixth International Conference on Behçet's Disease Paris,* Elsevier Science Publishers BV, *1993, 359-362*

Chen K-R, Kawahara Y, Miyakawa S, Nishikawa T: Cutaneous vasculitis in Behçet's disease: A clinical and histopathologic study of 20 patients. *J Am Acad Dermatol 36: 689-696, 1997*

Cho KH, Shin KS, Sohn SJ, Choi SJ, Lee YS: Behçet's disease with Sweet's syndrome-like presentation-a report of six cases. *Clin Exp Dermatol 14: 20-24, 1989*

Chun SI, Su WPD, Lee S, Rogers RSIII: Erythema

nodosum-like lesions in Behçet's syndrome: a histopathologic study of 30 cases. *J Cutan Pathol 16: 259-265, 1989*

da Cunha RM, Horta AB, Castro AS: [Behçet's disease. Experience of an internal medicine service from 1982 to 1991]. *Acta Med Port 5: 571-574, 1992*

Davatchi F, Shahram F, Akbarian M, Gharibdoost F, Chams C, Chams H, Mansoori P, Nadji A: *Classification tree for the diagnosis of Behçet's disease.* Paper presented at The Sixth International Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV, *1993, 245-248*

Davies PG, Fordham JN, Kirwan JR, Barnes CG, Dinning WJ: The pathergy test and Behçet's syndrome in Britain. *Ann Rheum Dis 43: 70-73, 1984*

Dilsen N, Konice M, Aral O: *Our diagnostic criteria of Behçet's disease-an overview.* Paper presented at The Fourth International Conference on Behçet's Disease. London, Royal Society of Medicine, *1985a, 177-180*

Dilsen N, Konice M, Aral O, Aykut S: *Standardization and evaluation of the skin pathergy test in Behçet's disease and controls.* Paper presented at The Fourth International Conference on Behçet's Disease. London, Royal Society of Medicine, *1985b, 169-172*

Dilsen N, Konice M, Aral O, Inanc M, Gul A, Ocal L: *Important implications of skin pathergy test in Behçet's disease.* Paper presented at The Sixth International Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV, *1993, 229-233*

Djawari D, Hornstein OP, Schotz J: Enhancement of granulocyte chemotaxis in Behçet's disease. *Arch Dermatol Res 270: 81-88, 1981*

Endoh M, Yokozeki H, Maruyama R, Matsunaga T, Katarama I, Nishioka K: Incontinentia pigmenti and Behçet's disease: A case of impaired neutrophil chemotaxis. *Dermatology 192: 285-287, 1996*

Fellner MJ, Kantor I: Behçet's syndrome: Skin puncture test as guide in therapy. *N Y State J Med 64: 1760-1761, 1964*

Fresko I, Yazici H, Bayramicli M, Yurdakul S, Mat C: Effect of surgical cleaning of the skin on the pathergy phenomenon in Behçet's syndrome. *Ann Rheum Dis 52: 619-620, 1993*

Friedman-Birnbaum R, Bergman R, Aizen E: Sensitivity and specificity of pathergy test results in Israeli patients with Behçet's disease. *Cutis 45: 261-264, 1990*

Fujikawa S, Suemitsu T: Behçet disease in children: a nationwide retrospective survey in Japan. *Acta Paediatr Jpn 39: 285-289, 1997*

Gamble CN, Wiesner KB, Shapiro RF, Boyer WJ: The immune complex pathogenesis of glomerulonephritis and pulmonary vasculitis in Behçet's disease. *Am J Med 66: 1031-1039, 1979*

Gharibdoost F, Davatchi F, Shahram F, Akbarian M, Chams C, Chams H, Mansoori P, Nadji A: *Clinical manifestations of Behçet's disease in Iran analysis of 2176 cases.* Paper presented at at The Sixth International Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV, *1993, 153-158*

Ghayad E, Tohme A: Behçet's disease in Lebanon: report of 100 cases. *J Med Liban 43: 2-7, 1995*

Gül A, Esin S, Dilsen N, Konice M, Wigzell H, Biberfeld P: *Immunohistology of skin pathergy reaction in Behçet's disease.* Paper presented at The Sixth International Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV, *1993, 343-347*

Haim S, Sobel JD, Friedman-Birnbaum R, Lichtig C: Histological and direct immunofluorescence study of cutaneous hyperreactivity in Behçet's disease. *Br J Dermatol 95: 631-636, 1976*

Hamza M, Cheour I, Sammari H: The skin pathergy test in Behçet's disease, connectivite and spondyloarthropathy. *Rev Rhum Engl Ed 63: 553, 1997*

Honma T, Bang D, Saito T, Nakagawa S, Ueki H, Lee S: Ultrastructure of lymphocyte-mediated fat-cell lysis in erythema nodosum-like lesions of Behçet's syndrome. *Arch Dermatol 123: 1650-1654, 1987*

Hunt SJ, Santa-Cruz DJ: Neutrophilic dermatoses. *Semin Dermatol 8: 266-275, 1989*

Inoue C, Itoh R, Kawa Y, Mizoguchi M: Pathogenesis of mucocutaneous lesions in Behçet's disease. *J Dermatol 21: 474-480, 1994*

Jadassohn W, Franceschetti A, Hunziker N: Zur "Behçetin reaction". *Hautarzt 12: 64-65, 1961*

Jensen T: Sur les ulcerations aphteuses de la muqueues de la bouche et de la peau genitale combines avec les symptomes oculaires (syndrome Behçet). *Acta Dermatol Venereol 22: 64-79, 1941*

Jorizzo JL: Behçet's disease. An update based on the 1985 International Conference in London. *Arch Dermatol 122: 556-558, 1986*

Jorizzo JL, Hudson RD, Schmalstieg FC, Daniels JC, Apisarnthanarax P, Henry JC, Gonzalez EB, Ichikawa Y, Cavallo T: Behçet's syndrome: immune regulation, circulating immune complexes, neutrophil migration, and colchicine therapy. *J Am Acad Dermatol 10: 205-214, 1984*

Jorizzo JL, Schmalstieg FC, Solomon ARJ, Cavallo T, Taylor RSIII, Rudloff HB, Schmalstieg EJ, Daniels JC: Thalidomide effects in Behçet's syndrome and pustular vasculitis. *Arch Intern Med 146: 878-881, 1986*

Jorizzo JL, Solomon AR, Cavallo T: Behçet's syndrome. Immunopathologic and histopathologic assessment of pathergy lesions is useful in diagnosis and follow-up. *Arch Pathol Lab Med 109: 747-751, 1985*

Jorizzo JL, Solomon AR, Zanolli MD, Leshin B: Neutrophilic vascular reactions. *J Am Acad Dermatol 19: 983-1005, 1988*

Katzenellenbogen I: *Survey of 22 cases of Behçet's Disease: the significance of specific skin hyperreactivity.* Paper presented at The 13th Congress of International Dermatology. Munich, Springer-Verlag,

1967, 321-324

Kienbaum S, Zouboulis CC, Waibel M, Orfanos CE: *Chemotactic neutrophilic vasculitis: a new histopathological pattern of vasculitis found in mucocutaneous lesions of patients with Adamantiades-Behçet's disease.* Paper presented at The Sixth International Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV, *1993, 337-341*

Kim D-K, Chang SN, Bang D, Lee E-S, Lee S: Clinical analysis of 40 cases of childhood-onset Behçet's disease. *Pediatr Dermatol 11: 95-101, 1994*

Kim HJ, Bang D, Lee SH, Yang DS, Kim DH, Lee KH, Lee S, Kim HB, Hong WP: Behçet's syndrome in Korea: a look at the clinical picture. *Yonsei Med J 29: 72-78, 1988*

Kone-Paut I, Bernard JL: [Behçet disease in children in France]. *Arch Fr Pediatr 50: 561-565, 1993*

Lakhanpal S, O'Duffy JD, Lie JT: Pathology. In Plotkin GR, Calabro JJ, O'Duffy JD, eds. *Behçet's disease: a contemporary synopsis.* Mount Kisco, New York, Futura Pub. Co Inc, *1988, 101-142*

Lakhanpal S, Tani K, Lie JT, Katoh K, Ishigatsubo Y, Ohokubo T: Pathologic features of Behçet's syndrome: a review of Japanese autopsy registry data. *Hum Pathol 16: 790-795, 1985*

Lee E-S, Lee SH, Bang D, Lee S: *Sweet's syndrome-like skin lesions in Behçet's syndrome: an additional cutaneous manifestation.* Paper presented at the The Fifth International Conference on Behçet's Disease. Minnesota, Rochester, Marcel Dekker, Inc, *1989a, 223-227*

Lee S: *Chair's summary; Behçet's disease.* Paper presented at the The 18th World Congress of Dermatology. New York, Parthenon Publishing Company, *1992, 1073-1076*

Lee S, Lee E-S, Bang D, Lee SH, Hong C-S: *Behçet's syndrome and systemic lupus erythematosus: a case analysis.* Paper presented at The Fifth International Conference on Behçet's Disease. Minnesota, Rochester, Marcel Dekker, Inc, *1989b, 243-245*

Lee SH, Chung KY, Lee WS, Lee S: Behçet's syndrome associated with bullous necrotizing vasculitis. *J Am Acad Dermatol 21: 327-330, 1989c*

Lee WS, Kim SJ, Ahn SK: Behçet's disease as a part of the symptom complex of SLE? *J Dermatol 23: 196-199, 1996*

Mangelsdorf HC, White WL, Jorizzo JL: Behçet's disease. *J Am Acad Dermatol 34: 745-750, 1996*

Mansoori P, Chams C, Davatchi F, Shahram F, Akbarian M, Gharibdoost F, Nadji A, Chams H: *Relationship of pathergy phenomenon and Behçet's disease(BD) manifestations.* Paper presented at The Sixth International Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV, *1993, 367-369*

Matsumura N, Matsumura Y, Mizushima Y: *Studies on cutaneous hyperreactivity and leukocyte chemotaxis in Behçet's disease.* Paper presented at The Second International Symposium on Behçet's Disease. Istanbul, Excerpta Medica, Turkey. *1977, 219-223*

Menni S, Piccinno R, Biolchini A, Delle-Piane RM, Bardare M: Incontinentia pigmenti and Behçet's syndrome: An unusual combination. *Acta Derm Venereol(Stockh) 66: 351-354, 1986*

Mizoguchi M, Chikakane K, Goh K, Asahina Y, Masuda K: Acute febrile neutrophilic dermatosis (Sweet's syndrome) in Behçet's disease. *Br J Dermatol 116: 727-734, 1987*

Mizoguchi M, Matsuki K, Mochizuki M, Watanabe R, Ogawa K, Harada S, Hino H, Amagai M, Juji T: Human leukocyte antigen in Sweet's syndrome and its relationship to Behçet's disease. *Arch Dermatol 124: 1069-1073, 1988*

Mizushima Y, Inaba G, Mimura Y, Ono S: [Diagnostic criteria for Behçet's disease in 1987, and guideline for treating Behçet's disease]. *Saishin Igaku 43: 391-393, 1988*

Mochizuki M, Morita E, Yamamoto S, Yamana S: Characteristics of T cell lines established from skin lesions of Behçet's disease. *J Dermatol Sci 15: 9-13, 1997*

Muller W, Lehner T: Quantitative electron microscopy microscopical analysis of leukocyte infiltration in oral ulcers of Behçet's syndrome. *Br J Dermatol 106: 535-544, 1982*

Nazzaro P: *Cutaneous manifestations of Behçet's disease.* Paper presented at the International Symposium on Behçet's Disease. Rome, Karger, *1964, 15-41*

O'Duffy JD: Summary of International Symposium on Behçet's Disease. Istanbul, September 29-30, 1977. *J Rheumatol 5: 229-233, 1978*

O'Duffy JD, Carney JA, Deodhar S: Behçet's disease. Report of 10 cases, 3 with new manifestations. *Ann Intern Med 75: 561-570, 1971*

Oguz O, Serdaroglu S, Tuzun Y, Erdogan N, Yazici H, Savaskan H: Acute febrile neutrophilic dermatosis (Sweet's syndrome) associated with Behçet's disease. *Int J Dermatol 31: 645-646, 1992*

Powell FC, Schroeter AL, Su WPD, Perry HO: Pyoderma gangrenosum: A review of 86 patients. *Q J Med 217: 173-186, 1985*

Price CA: Behçet's syndrome-a distressing, intriguing malady. *J R Coll Gen Pract 18: 38-45, 1969*

Reimer G, Luckner L, Hornstein OP: Direct immunofluorescence in recurrent aphthous ulcers and Behçet's disease. *Dermatologica 167: 293-298, 1983*

Scherrer MA, Vitral N, Bambirra E, Orefice F: *Histologic and clinical study of pathergy in Behçet's disease in Brazil.* Paper presented at The Sixth International Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV, *1993, 363-366*

Shafaie N, Shahram F, Nadji A, Davatchi F, Akbarian M, Gharibdoost F, Jamshidi A: Iran's aspects of Behçet's disease in children, the 1996 survey. *Rev Rhum Engl Ed 63: 535, 1996*

Shi H-L, Huang Z-J: *Study on cutaneous lesions in Behçet's disease and meanings of relative laboratory parameters.* Paper presented at The Sixth Inter-

national Conference on Behçet's Disease. Paris, Elsevier Science Publishers BV, *1993, 325-330*

Shimizu T: *Clinicopathological studies on Behçet's disease.* Paper presented at the The Second International Symposium on Behçet's Disease. Istanbul, Excerpta Medica, *1977, 9-43*

Shimizu T, Ehrlich GE, Inaba G, Hayashi K: Behçet disease (Behçet syndrome). *Semin Arthritis Rheum 8: 223-260, 1979*

Suzuki K, Mizuno N: *Intracutaneous test with physiological saline in Behçet's disease.* Paper presented at The Third International Conference on Behçet's Disease. Tokyo, University of Tokyo Press, *1981, 333-342*

Tüzün Y, Altac M, Yazici H, Basoz A, Yurdakul S, Pazarli H, Yalcin B, Muftuoglu A: Nonspecific skin hyperreactivity in Behçet's disease. *Haematologica 65: 395-398, 1980*

Tüzün Y, Yazici H, Pazarli H, Yalcin B, Yurdakul S, Muftuoglu A: The usefulness of the nonspecific skin hyperreactivity (the pathergy test) in Behçet's disease in Turkey. *Acta Derm Venereol (Stockh) 59: 77-79, 1979*

Uziel Y, Padeh S, Brik R, Barash J, Mukamel M, Harel L, Press J, Tauber Z, Rakover Y, Wolach B: Juvenile Behçet's in Israel. *Rev Rhum Engl Ed 63: 535, 1996*

Wechsler J, Wechsler B, Revuz J, Godeau P: Skin hyperreactivity response (pathergy) in Behçet's disease: usefulness of direct immunofluorescence [letter; comment]. *J Am Acad Dermatol 23: 329-330, 1990*

Wong RC, Ellis CN, Diaz LA: Behçet's disease. *Int J Dermatol 23: 25-32, 1984*

Yurkakul S, Mat C, Tüzün Y, Tüzüner N, Uygun N, Hekim N, Küsem V, Tüzün B, Hamuryudan V, Özyazgan Y, Yazici H: Histochemical examination of papulopustular manifestations of Behçet's disease. *Rev Rhum Engl Ed 63: 553, 1996*

Yücel A, Özbek S, Boga H, Acar MA, Aksungur VL, Memisoglu HR: Pernio-like skin lesions in a patient with Behçet's disease. *Rev Rhum Engl Ed 63: 554, 1996*

Zgradic I: [Behçet's disease-clinical picture and treatment]. *Med Pregl 49: 233-236, 1996*

Zouboulis CC: [Adamantiades-Behçet's disease in Germany: Historical review and current knowledge]. *H+G 71: 491-501, 1996*