

Behçet's Disease - A Rheumatologic Perspective

Soo Kon Lee and Jisoo Lee

Behçet's disease is recognized as a multisystemic disease with various organ involvement including skin, mucous membrane, eyes, joints, veins, arteries, gastrointestinal tract, meninges, and brain. In this review, Behçet's disease has been approached from two rheumatologic perspectives- as an intermittent and periodic arthritic syndrome and as a vasculitic syndrome. Association with seronegative spondyloarthropathy and other autoimmune diseases will also be discussed.

Key Words: Behçet's disease, arthritis, vasculitis, autoimmune association

Since the original description of Hulusi Behçet, a triple syndrome of oral and genital ulceration and iritis in 1937 (Behçet, 1937), other systemic manifestations of Behçet's disease have been continuously identified. Behçet's disease is now recognized as a multisystemic disease with various organ involvements including skin, mucous membrane, eyes, joints, veins, arteries, gastrointestinal tract, meninges, and brain. Although Behçet's disease has been the subject of numerous excellent reviews in various medical fields, few have viewed this disease from a rheumatologic perspective. The purpose of this article is to provide update on Behçet's disease from a rheumatologic viewpoint. In this review, Behçet's disease will be discussed in two perspectives, as an intermittent and periodic arthritic syndrome and as a vasculitic syndrome. Association with seronegative spondyloarthropathy and other autoimmune diseases will also be discussed.

INTERMITTENT AND PERIODIC ARTHRITIS

Reimann grouped a number of recurring disorders of unknown etiology under the name of "periodic disease" with the suggestion that their periodicity might derive from a common etiology (Reimann, 1951). Among Reimann's periodic diseases are several of the recurring arthropathies including Behçet's disease, familial Mediterranean fever, intermittent hydrarthrosis, and palindromic rheumatism. As we begin to understand the pathogenesis of these diseases, we know that they do not share a common etiology or even common pathogenetic mechanisms. Nevertheless, grouping these disorders together stimulates the search for the cause of these diseases of unknown etiology. Approaching Behçet's disease as intermittent and periodic arthritis is advantageous from two perspectives. First, it provides easier diagnosis formulation in rheumatologic care, where most patients complain of musculoskeletal problems. Second, periodicity may provide an important clue to understanding the pathogenesis of the disease.

Articular symptoms

The joint may be the target organ in a wide variety of systemic diseases. Behçet's disease is no exception. Although arthritis has not been included

Received November 10, 1997
Division of Rheumatology, Department of Internal
Medicine, Yonsei University College of Medicine, Seoul,
Korea

Address reprint request to Dr. S.K. Lee, Department
of Internal Medicine, Yonsei University College of Me-
dicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel:
82-2-361-5430, Fax: 82-2-393-6884

in any international study group criteria of Behçet's disease, arthritis is one of the most frequent manifestations following oral and genital ulcers, which about half of all patients will experience (Zizic and Stevens, 1975). In prospective studies, the incidence of arthritis ranges from 40 to 70% (Yurdakul *et al.* 1983; Kim *et al.* 1997). Despite distinct associated systemic manifestations and characteristic arthritis patterns, arthritis of Behçet's disease has been often erroneously diagnosed as rheumatoid arthritis or some other arthritis syndrome. Arthritic symptoms have usually been described as intermittent, non-erosive, oligoarticular arthritis; usually symmetric when not monoarticular (Yurdakul *et al.* 1983). Small and large joints and tendon entheses can be involved (Caporn *et al.* 1983; Kim *et al.* 1995). The most frequent sites of involvement have been knees, ankles, wrists, and elbows (Yurdakul *et al.* 1983; Kim *et al.* 1993). Arthritis has been found present at the time of diagnosis in about 70% of patients (Kim *et al.* 1997) and 9% of patients have had arthritis only as an initial manifestation (Chamberlain, 1977).

Arthritis of Behçet's disease is usually non-erosive. But Behçet's disease with erosive arthritis has been reported continuously in a small proportion of patients. (Mason and Barnes, 1969; Vernon-Roberts *et al.* 1978; Shimizu *et al.* 1979; Caporn *et al.* 1983; Yurdakul *et al.* 1983; Kim *et al.* 1997). Erosive changes have been noted more frequently in axial joints and entheses than in peripheral joints. These have included erosions of the sacroiliac joint, calcanei, metatarsophalangeal joints, interphalangeal joints of feet, manubriosternal joint, temporomandibular joint, hip joint, wrist and intercarpal joints. When erosive changes on the small joints of the hands and feet are involved, the radiologic appearances are indistinguishable from rheumatoid arthritis (Jawad and Goodwill, 1986). However, despite erosive changes in some patients, crippling arthritis is very rare (Kim *et al.* 1997).

Laboratory features are generally non-specific. As in any inflammatory condition, arthritic attacks tend to be associated with leukocytosis, an accelerated erythrocyte sedimentation rate, and an elevated C-reactive protein (Yurdakul *et al.* 1983; Kim *et al.* 1997). There were nevertheless patients with a normal ESR during periods of active arthritis,

suggesting no definite correlation of acute phase reactants and disease activity. Serum rheumatoid factor and antinuclear antibody are usually negative with a normal serum complement level (O'Duffy *et al.* 1971; Kim *et al.* 1993). Synovial fluid resembles those of rheumatoid arthritis; inflammatory with a predominance of polymorphonuclear leukocytes (Zizic and Stevens, 1975). Common pathologic findings of synovial biopsy are hyperemia, edema and cellular infiltration (Zizic and Stevens, 1975; Shimizu *et al.* 1979). Some researchers report similarities in synovial pathology with rheumatoid arthritis showing fibrinoid necrosis, cellular proliferation and lymphoid follicle (Yurdakul *et al.* 1983; Kim *et al.* 1997), but others have demonstrated chronic mild inflammation with fibrosis and granulation tissue (Gibson *et al.* 1981) and histologic findings of lymphocytic vasculitis as seen in erythema nodosum (Kim *et al.* 1993). Immunohistochemical studies revealed IgM or IgG deposition on the wall of synovial veins (Shimizu *et al.* 1979; Gibson *et al.* 1981), suggesting humoral factors involved in the pathogenesis. A wide spectrum of pathologic features suggests that these may reflect the severity and duration, as much as the nature, of arthritis. Comparing synovial biopsy specimens with other intermittent and periodic arthritides may provide clues to understanding the immunopathogenesis of arthritis in Behçet's disease.

Periodicity and therapy

The clinical course of arthritis in Behçet's disease is dominated by periodicity as seen in other clinical manifestations. Patterns of periodicity vary in different clinical symptoms. It can be divided into 4 patterns; relapsing, remittent, remittent-progressive, or progressive. Arthritis shows a relapsing pattern with the majority of attacks lasting 2 months or less, although in about 20% a more protracted episode may occur (Yurdakul *et al.* 1983). Oral and genital ulcers and skin eruptions also show a relapsing pattern with periods of inactivity. Eye symptoms, nervous system symptoms, and vascular symptoms tend to be remittent and when they become chronic, they take on a remittent-progressive or progressive pattern. Attacks are frequent in the early course of the disease and a slowing of attacks occurs after 3-7

years (Shimizu *et al.* 1979). The flaring up of joint disease coincides with an eruption of stomatitis (Livneh *et al.* 1996), but associations with other clinical manifestation are not definite.

Infectious, psychological, nutritional, immunologic, genetic and other factors have been implicated in the pathogenesis of periodicity. In hereditary periodic fever syndrome, genetic factors are most important in determining disease susceptibility and are probably associated with the intermittent nature of the disease. In Behçet's disease, however, an autoimmune basis for the periodicity has been implicated which is supported by the presence of circulating immune complexes (Valesini *et al.* 1981) and antibodies to endothelial cells (Aydintug *et al.* 1993), as well as by findings suggestive of abnormal cell-mediated immunity (Sakane *et al.* 1982).

Since the course of arthritis is episodic and unpredictable, evaluation of treatment is difficult. Nonsteroidal antiinflammatory drugs (NSAIDs) and colchicine are widely used but their effect is uncertain, since many arthritic attacks spontaneously resolve without any therapy. Yurdakul *et al.* reported that uncontrolled experience with NSAIDs is of no benefit (Yurdakul *et al.* 1983). A double-blind controlled experience with colchicine indicates that this drug may improve arthralgia but not arthritis (Aktulga *et al.* 1980). Perhaps the best way to manage episodic arthritis is by waiting and giving reassurance. But in protracted episodes, more aggressive management is necessary, as in rheumatoid arthritis, although the therapeutic effect should be confirmed through controlled studies.

VASCULITIC SYNDROME

Behçet's disease is a multisystemic disease of unknown cause but vasculitis has been implicated as an important factor. Vasculitis has been demonstrated in mucosal lesions, gastrointestinal tract, the central nervous system, and occasionally large vessels. Many rheumatologists classify Behçet's disease in the vasculitis category (Valente *et al.* 1997). The evidence that vasculitis is the key feature of the disease is supported by microscopic findings of immune-mediated occlusive vasculitis at most sites

of Behçet's disease and by the presence of anti-endothelial antibodies (Cervera *et al.* 1994).

The evidence of vasculitis is found in various clinical findings. Although subcutaneous micro-abscesses found in acute lesions are usually non-vasculitic, and although perivascular lymphocytic infiltrates in erythema nodosum lesions may be interpreted as perivasculitis, frank vasculitis is encountered in subcutaneous venules and arterioles and in genital ulcers (O'Duffy *et al.* 1971; Shimizu *et al.* 1979). Infiltrates are mostly T lymphocytes and the epidermis becomes necrotic and sloughs off (Lehner, 1977). Enucleated eyes of patients blinded by retinal disease reveal vasculitis of arteries and veins and vasculitis may best correlate with the loss of vision (Shimizu *et al.* 1979). In major venous occlusions, the pathogenesis underlying the occlusion is generally understood as vasculitis of veins with superimposed thrombosis, since these thromboses are not prevented by anticoagulant therapy. Vasculitis has been described as a cause in over half of the arterial lesions in one large series (Lakhanpal *et al.* 1985). In the gastrointestinal tract, a resected area of bowel has shown vasculitis (Baba *et al.* 1976).

Clinical features with documented evidence of vasculitis are often associated with poor prognosis. As in necrotizing vasculitides, if untreated or inadequately treated, survival time is shortened. And patients with active vasculitis are at increased risk for complications and recurrence after any type of vascular surgery (Le Thi Huong *et al.* 1995). Behçet's disease with evidence of vasculitis is subject of aggressive immunosuppressive therapy. Corticosteroid alone is usually not sufficient. The addition of cytotoxic agents such as azathioprine, chlorambucil, or cyclophosphamide or cytokine inhibitors such as cyclosporine-A can improve prognosis. Although there is only one controlled trial demonstrating the therapeutic effect of immunosuppressive agents, many uncontrolled experiences showing the effect of immunosuppressive drugs are being published (Nussenblatt *et al.* 1985; Shahram *et al.* 1993; Le Thi Huong *et al.* 1995). In most serious manifestations of Behçet's disease, vasculitis is a key feature of the disease. Aggressive therapy including immunosuppressive agents is needed to control the progression of the disease.

AUTOIMMUNE ASSOCIATIONS

Behçet's disease can be associated with other autoimmune disorders. The most popularly described association is with seronegative spondyloarthropathies. There are case reports of myositis (Lingenfeller *et al.* 1992) and systemic lupus erythematosus (Lee *et al.* 1991) occurring with Behçet's disease. Moreover, occasional patients develop an overlap between Behçet's disease and relapsing polychondritis, which has been designated MAGIC (mouth and genital ulcers with inflamed cartilage) (Firestein *et al.* 1985). Autoimmune associations in Behçet's disease lead to 2 important questions. Is the temporal relationship between these disorders diagnostically important? And do these associations have implications regarding pathogenesis?

Behçet's disease in association with other autoimmune disorders has always given rise to much controversy. The main reason for such debate is due to overlapping clinical manifestations between Behçet's disease and other associated autoimmune disorders. There are conflicting reports as to whether sacroiliitis is an extended feature of Behçet's disease or is a feature of ankylosing spondylitis overlap. Incidence of sacroiliitis and ankylosing spondylitis varies among different authors. Dilsen *et al.* found 33 patients (10%) with AS and 112 (34%) with sacroiliitis among 331 Turkish patients with Behçet's disease (Dilsen *et al.* 1986). HLA B5 and B27 occurred with significantly higher frequency in both AS and Behçet's syndrome. Caporn *et al.* in Britain reported erosive sacroiliitis in 7 (50%) of 14 patients (Caporn *et al.* 1983). However, no association of Behçet's syndrome with sacroiliitis or AS was found in Japanese (Shimizu *et al.* 1979) or in North American patients (O'Duffy *et al.* 1985) with Behçet's disease. In Turkey, Yazici *et al.* found only 1 patient with AS among 184 patients with Behçet's disease (Yazici *et al.* 1981). Behçet's disease seems to share several features with other seronegative spondyloarthropathies. However, in other seronegative spondyloarthropathies there is an increased incidence of HLA B27 positivity. This association was not found consistently in previous reports. Validity of the diagnosis was raised by Yazici *et al.* (1987) by demonstrating great inter- and intra-

observer variation in observing sacroiliitis while Olivieri *et al.* (1990) performed CT scans and found a high false-positive rate in plain pelvis X-ray. Recently, a controlled study of sacroiliitis in Behçet's disease revealed no evidence of an increased prevalence of sacroiliitis in Behçet's disease (Chamberlain and Robertson, 1993). There remains insufficient evidence at this time to view sacroiliitis as extended features of Behçet's disease or as an overlap with ankylosing spondylitis.

Finding common pathogenetic mechanisms between Behçet's disease and autoimmune diseases may be more important in understanding these disorders than the diagnostic debate. In a case report by Lee *et al.* a patient started out with Behçet's disease with classic symptoms and the clinical manifestation evolved into of SLE (Lee *et al.* 1991). In this case, after corticosteroid treatment, the SLE symptoms remarkably improved but typical Behçet's disease manifestations recurred. Interchangeable features of two diseases suggested a common autoimmune mechanism. In MAGIC syndrome, common clinical manifestations between Behçet's disease and relapsing chondritis were divided into specific, less specific, and relatively nonspecific findings. Through such analysis, common pathogenesis has been postulated as an autoimmunity to components of cartilage other than type II collagen, such as proteoglycans or elastic tissue (Firestein *et al.* 1985).

CONCLUSION

The clinical spectrum of Behçet's disease is expanding and affecting various fields of medicine. Rheumatologists meet patients with Behçet's disease ranging from a mild disease with non-specific musculoskeletal complaints to a serious life-threatening disease with multiple organ failure. We have described two major approaches to Behçet's disease in current rheumatology practice- as an arthritic syndrome and as vasculitis. Arthritis belongs to an intermittent and periodic arthritic syndrome which is mostly non-deforming, non-erosive arthritis. Although many questions as to whether periodicity may have implications regarding the pathogenesis of the disease remain to be answered, an autoimmune basis

for periodicity is being suggested. Periodicity makes evaluation of the treatment difficult. The best way to approach episodic events may be palliative management and reassurance. Vasculitis is a more aggressive manifestation of the disease that may sometimes lead to mortality. Aggressive immunosuppressive therapy is needed to control the disease progression.

The specific immunopathogenetic mechanism in Behçet's disease is still poorly understood. Association with other autoimmune diseases might provide some clues to the pathogenetic mechanism. Further case collection is needed until a common pathogenetic mechanism is elucidated.

Treatment is still empiric and palliative. A wide range of antiinflammatory drugs, immunosuppressive agents, and immunostimulant drugs are being used alone or in combination, but the effectiveness of any specific therapy is still elusive. Until a specific therapeutic target is identified, any strategy to treat Behçet's disease should be based on an identifiable pathology of the manifested symptoms.

REFERENCES

- Aktulga E, Altac M, Muftuoglu A, Ozyazgan Y, Pazarli H, Tuzun Y, Yalcin B, Yazici H, Yurdakul S: A double blind study of colchicine in Behçet's disease. *Hematologica (Pavia)* 65: 399-402, 1980
- Aydintug AO, Tokgoz G, D'Cruz DP, Gurler A, Cervera R, Duzgun N, Atmaca LS, Khamashta MA, Hughes GR: Antibodies to endothelial cells in patients with Behçet's disease. *Clin Immunol Immunopathol* 67: 157-162, 1993
- Baba S, Maruta M, Ando K, Teramoto T, Endo I: Intestinal Behçet's Disease: Report of five cases. *Dis Colon Rectum* 19: 428-440, 1976
- Behçet H: ber rezidivierende, aphthöse, durch ein Virus verursachte Geschwüre am Mund, am Auge und an den Genitalien. *Dermatol Wochenschr* 109: 1152-1157, 1937
- Caporn N, Higgs ER, Dieppe PA, Watt I: Arthritis in Behçet's syndrome. *Br J Radiol* 56: 87-91, 1983
- Cervera R, Navarro M, Lopez-Soto A, Cid M, Font J, Esparza J, Reverter J, Monteagudo J, Ingelmo M, Urbano-Marquez A: Antibodies to endothelial cells in Behçet's disease: Cell-binding heterogeneity and association with clinical activity. *Ann Rheum Dis* 53: 265-267, 1994
- Chamberlain MA: Behçet's syndrome in 32 patients in Yorkshire. *Ann Rheum Dis* 36: 492-499, 1977
- Chamberlain MA, Robertson RJH: A controlled study of sacroiliitis in Behçet's disease. *Br J Rheumatol* 32: 693-698, 1993
- Dilsen N, Konice M, Aral O: Why Behçet's disease should be accepted as a seronegative arthritis. In Lehner T, Barnes CG, eds. *Recent advances in Behçet's disease. International Congress and Symposium series No. 103.* London/ New York, Royal Society of Medical Services, 1986, 281-284
- Firestein GS, Gruber HE, Weisman MH, Zvaifler NJ, Barber J, O'Duffy JD: Mouth and genital ulcers with inflamed cartilage: MAGIC syndrome. *Am J Med* 79:65-72, 1985
- Gibson T, Laurent R, Highton J, Wilton M, Dyson M, Millis R: Synovial histopathology of Behçet's syndrome. *Ann Rheum Dis* 40: 376-381, 1981
- Jawad ASM, Goodwill CJ: Behçet's disease with erosive arthritis. *Ann Rheum Dis* 45: 961-962, 1986
- Kim HA, Choi KW, Song YW: Arthropathy in Behçet's disease. *Scand J Rheumatol* 26: 125-129, 1997
- Kim HS, Lee J, Lee CH, Song JH, Bang DS, Lee SK: Heel pain in Behçet's disease. *J Korean Rheum Assoc* 2: 151-156, 1995
- Kim NH, Yang IH, Kim SM, Bang DS: Behçet's arthritis. *J Korean Orthop Assoc* 28: 1890-1897, 1993
- Lakhanpal S, Tani K, Lie JT: Pathologic features of Behçet's syndrome. A review of Japanese autopsy registry data. *Hum Pathol* 16: 790-795, 1985
- Le Thi Huong D, Wechsler B, Papo T, Piette JC, Bletry O, Godeau P: Arterial lesions in Behçet's disease. A study in 25 patients. *J Rheumatol* 22: 2103-2113, 1995
- Lee SN, Lee ES, Bang D, Lee SH, Hong CS: Behçet's syndrome and systemic lupus erythematosus; A case analysis. In O'Duffy JD, Kokmen E, eds. *Behçet's disease. Basic and clinical aspect.* New York, Marcel Dekker, Inc, 1991, 243-245
- Lehner T: Progress report: oral ulceration in Behçet's syndrome. *Gut* 18: 491-511, 1977
- Lingenfelser T, Duerk H, Stevens A, Grossman T, Knorr M, Saal JG: Generalized myositis in Behçet's disease: treatment with cyclosporine. *Ann Intern Med* 116: 651-653, 1992
- Livneh A, Zaks N, Katz J, Langevitz P, Shemer J, Pras M: Increased prevalence of joint manifestations in patients with recurrent aphthous stomatitis (RAS). *Clin Exp Rheum* 14: 407-412, 1996
- Mason RM, Barnes CG: Behçet's syndrome with arthritis. *Ann Rheum Dis* 28: 95-103, 1969
- Nussenblatt RB, Palestine AG, Chan CC, Mochizuki M, Yancey K: Effectiveness of cyclosporin therapy for Behçet's disease. *Arthritis Rheum* 28: 671-679, 1985
- O'Duffy JD, Carney JA, Deodhar S: Behçet's disease: Report of ten cases, three with new manifestations. *Ann Intern Med* 75: 561-570, 1971
- O'Duffy JD: Behçet's disease. In Kelley WN, Harris ED, Ruddy S, Sledge CB, eds. *Textbook of*

- Rheumatology, 2nd ed. Philadelphia, WB Saunders, 1985, 1174-1178
- Olivieri I, Gernignani G, Carmerini E, Serueria R, Paseo G: Computed tomography of the sacroiliac joints in four patients with Behçet's syndrome- confirmation of sacroiliitis. *Br J Rheumatol* 29: 264-267, 1990
- Reimann HA: Periodic disease. *Medicine (Baltimore)* 30: 219-245, 1951
- Sakane T, Kotani H, Takada S, Tsunematsu T: Functional aberration of T cell subsets in patients with Behçet's disease. *Arthritis Rheum* 25: 1343-1351, 1982
- Shahram F, Davatchi F, Chams H, Akbarian M, Gharibdoost F: Low dose pulse cyclophosphamide (LDP) in ophthalmologic lesions of Behçet's disease. In Godeau P, Wechsler B, eds. Behçet's disease. Proceedings of 6th international conference on Behçet's disease. Amsterdam, Elsevier, 1993, 683-686
- Shimizu T, Ehrlich GE, Hayashi K: Behçet's Disease. *Semin Arthritis Rheum* 8: 223-260, 1979
- Valente RM, Hall S, O'Duffy JD, Conn DL: Behçet's disease. In Kelley WN, Harris NED Jr, Ruddy S, Sledge CD, eds. Textbook of rheumatology, 5th ed. Philadelphia, WB Saunders Company, 1997, 1114-1116
- Valesini G, Picardo M, Pastore R, Pirette P, Serafini U: Circulating immune complexes in Behçet's syndrome: purification, characterization, and cross reactivity. *Clin Exp Immunol* 44: 522-527, 1981
- Vernon-Roberts B, Barnes CG, Revell PA: Synovial pathology in Behçet's syndrome. *Ann Rheum Dis* 37: 139-145, 1978
- Yazici H, Turunc M, Ozdogan H, Yurdakul S, Akinci A, Barnes CG: Observer variation in grading sacroiliac radiographs might be a cause of 'sacroiliitis' reported in certain disease states. *Ann Rheum Dis* 46:139-145, 1987
- Yazici H, Tuzlaci M, Yurdakul S: A controlled survey of sacroiliitis in Behçet's disease. *Ann Rheum Dis* 40: 558-559, 1981
- Yurdakul S, Yazini H, Tuzun Y, Pazarli H, Yalcin B, Altac M, Ozyazgan Y, Tuzuner N, Muftuoglu A: The arthritis of Behçet's disease: a prospective study. *Ann Rheum Dis* 42: 505-115, 1983
- Zizic TM, Stevens MB: The arthropathy of Behçet's disease. *Johns Hopkins Med J* 164: 51-56, 1975