

## Behçet's Disease: The First Mongolian Case in Literature Showing HLA B51, MICA Gene Type \*5/\*6

Yae Lee Chung<sup>1</sup>, Dongsik Bang<sup>1</sup>, Eun-So Lee<sup>2</sup>, Sungnack Lee<sup>2</sup>, Jee Won Mok<sup>3</sup>, and Kyung Sook Park<sup>3</sup>

<sup>1</sup>Department of Dermatology, Yonsei University College of Medicine, Seoul, Korea;

<sup>2</sup>Department of Dermatology, Ajou University School of Medicine, Suwon, Korea;

<sup>3</sup>Department of Biology, Sungshin Women's University, Seoul, Korea.

Behçet's disease is a chronic multi-systemic disease of unknown origin that includes mucocutaneous, ocular, cardiac, vascular, renal, gastrointestinal, neurologic and cutaneous involvement. The disease is spread throughout the world, but it is most prevalent in the eastern Mediterranean region-along the Silk Road-, and in Japan, China, and Korea. Recently, we treated a Mongolian patient who had complete-type Behçet's disease. As far as we know, this case is the first report of a Mongolian with Behçet's disease in the English literature. HLA typing in this patient revealed A2, A24;B51, B35; Cw4, Cw7; DR9, DR11. Study of the MICA genotype showed \*5, \*6 positive. Our data provided adequate evidence, from an epidemiological aspect, to support the belief that Behçet's disease is most prevalent along the old Silk Road.

**Key Words:** Behçet's disease, mongolian, HLA B51, MICA genotype

### INTRODUCTION

It is well known that Behçet's disease has a peculiar geographical distribution. It has been shown that Behçet's disease frequently occurs not only in two distant areas,- Japan and the Mediterranean countries-, but also in other populations between these areas.<sup>1-3</sup> However, there have been very few reports of Behçet's disease from Central Asia. Since this area lies between East and West Asia, where this disease is frequently seen, more

patients are likely to be present there.<sup>1</sup> Here, we report the first case of complete-type Behçet's disease in a Mongolian.

### CASE REPORT

A 20-year-old Mongolian male patient visited the Behçet's disease Speciality Clinic of Severance Hospital, Yonsei University College of Medicine in September 1997 with multiple ulceration on both legs and arms.

The patient had suffered from multiple minor oral aphthous ulcers and genital ulcers during the previous year. In most orogenital lesions, the sites of involvement are the buccal mucosa, tongue, lips, and scrotum. After a promonitoring stage, skin lesions evolved from small (less than 1 cm), painful, well-circumscribed erythematous lesions to sharply marginated, painful ulcers. Skin lesions progressed to 3 × 5 cm-sized necrotic ulcers with a purulent base and an indeterminate purple to red margin with a halo of surrounding erythema (Fig. 1). The patient also stated that he had acneiform eruptions and erythema nodosum-like skin lesions. A skin pathergy test performed on this patient showed a negative result.

On diagnosis as incomplete-type Behçet's disease, we began treatment with colchicine, systemic steroid, and NSAID. The patient visited our hospital regularly and took medicine continuously. However, Behçet's disease symptoms occasionally recurred in spite of the medication.

On August 17, 1998, one year after his first visit to our hospital, the patient suddenly complained

Received April 2, 2003

Accepted June 9, 2003

Reprint address: requests to Dr. Dongsik Bang, Department of Dermatology, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-361-5720, Fax: 82-2-393-9157, E-mail: dbang@yuunc.yonsei.ac.kr

of blurred vision. He received an ocular examination by an ophthalmologist and was diagnosed with uveitis.

Laboratory findings, including complete blood count, urinalysis, liver function test, chemistry, ANA, ANCA, anticardiolipin antibody, RF (Rheu-



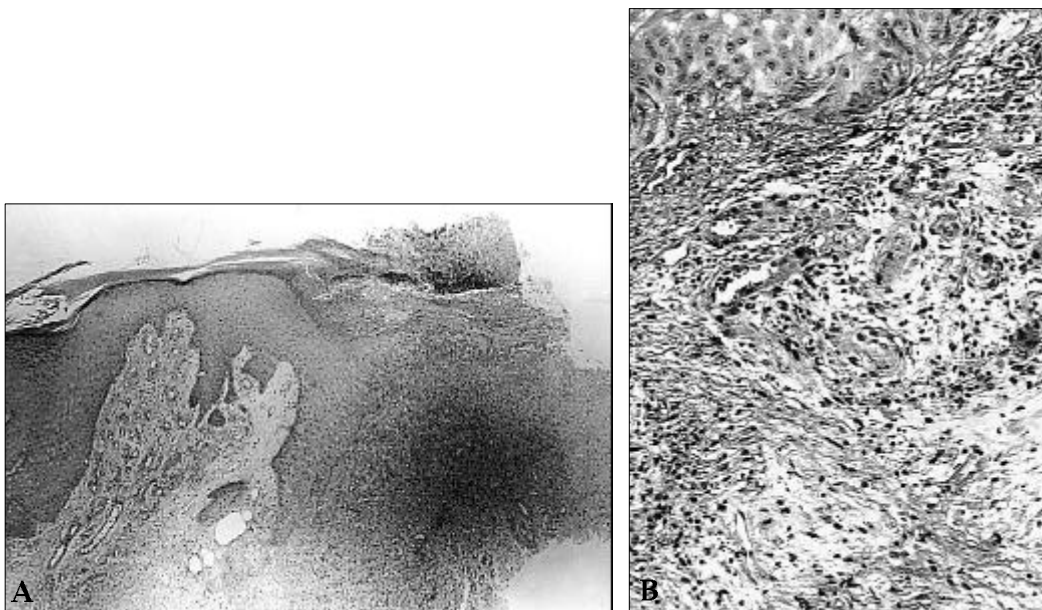
**Fig. 1.** 3 × 5 cm-sized necrotic ulcer with a purulent base and an indeterminate purple to red margin with a halo of surrounding erythema on the left lower leg.

matoid factor), and chest radiography showed either normal or negative results. HLA typing by microcytotoxicity assay revealed A2, A24; B51, B35; CW4, CW7; DR9, DR11. Moreover, MICA \*5, \*6 genotype was shown. Histopathology of the skin biopsy specimen obtained from the lower leg suggested pyoderma gangrenosum (Fig. 2). We diagnosed him with Behçet's disease following international criteria for Behçet's disease.<sup>4</sup> Based on clinical findings, he was diagnosed with complete-type Behçet's disease under Shimizu's classification.<sup>5</sup> Although cyclosporine and systemic steroids are currently being administered, his visual acuity continues to deteriorate.

## DISCUSSION

Behçet's disease was first described in 1937 by the Turkish dermatologist Hulusi Behçet as a complex symptom of recurrent oral ulcers, genital ulcers, and uveitis.<sup>5</sup> Now we have defined complete-type Behçet's disease as having skin lesions in addition to the original three symptoms.<sup>2</sup>

Additional clinical manifestations include the pathergy phenomenon, which shows the induction of a cutaneous pustular neutrophilic vascular reaction after intradermal trauma, arthritis, throm-



**Fig. 2.** Histologic examination of a pyoderma gangrenosum (hematoxylin-eosin stain), showing epidermal ulceration, necrosis, and a mixed inflammatory cell infiltration with focal neutrophilic vasculitis (× 40 A, × 400 B).

bophlebitis, erythema nodosum-like cutaneous lesions, which may represent subcutaneous variants of the pathergy lesions, and neurologic signs and symptoms ranging from benign intracranial hypertension to a condition resembling multiple sclerosis.<sup>6</sup> Unfortunately, there is no pathognomic laboratory test for identification nor specific diagnostic features of Behçet's disease. Therefore, diagnosis must be based on clinical criteria. Diagnosis is also complicated by a tendency toward new clinical features, which occurs years after the onset of the disease.<sup>7,8</sup>

Epidemiologic findings suggest that both genetic and environmental factors contribute to the development of the disease. Gene susceptible to the disease have been studied on a large scale, as in the recent surveys of patients with Behçet's disease in Japan and Great Britain. In addition, a strong association with both HLA B51 and HLA DRw52 has been reported.<sup>6,9,10</sup> The prevalence of the HLA B51 allele is high among patients with Behçet's disease who live in areas along the old Silk Road (up to 81% of Asian patients have the allele) but not among Caucasian patients who live in Western countries (13%). In Japan, the incidence of HLA-B51 is significantly higher among patients with Behçet's disease than among those without the disease (55% vs 10 to 15%). The relative risk of the disease among carriers of HLA B51 compared with noncarriers is 6.7 in Japan, whereas it is only 1.3 in the United States.<sup>11</sup> The allele affects the severity of the disease, since it is more common among patients with posterior uveitis or progressive central nervous system disease than among those with milder disease. In our Mongolian patient, HLA typing also revealed that HLA B51 was positive. Recently, it was reported that the MICA gene, located 47 Kb centromeric of HLA B, has a stronger association with Behçet's disease.<sup>10,12</sup> Furthermore, the microsatellite allele, consisting of 6 repetitions of GCT/AGC (MICA \*6 allele), was present at a significantly higher frequency in the Behçet's disease patient group than in the control group, and a significant fraction of B51 negative patients were in position for this MICA \*6 allele.<sup>10</sup> In Korea, patients with Behçet's disease had a higher frequency of the MICA \*6, \*6 compared to healthy controls (23.0% vs 6.8%,  $p < 0.001$ , R.R=4.1), and patients with

complete type Behçet's disease possessing the MICA \*6 allele were as high as 75.4%. Moreover, MICA \*6, allele rather than HLA-B51, was strongly associated with Korean patients with Behçet's disease, since the MICA \*6 allele is a useful susceptibility marker of Behçet's disease, especially in HLA-B51 negative subjects.<sup>13</sup> However, in our patient, it was the MICA \*5, \*6 heterozygous type.

Although Behçet's disease is spread throughout the world, its incidence is known to be high in Eastern Mediterranean areas and East Asia, especially Korea, Japan and China.<sup>1,6,14</sup> Patients with the disease have been reported in countries around the Mediterranean, such as Turkey, Italy, Greece, and Lebanon, and in Europe, including England and Germany.<sup>8</sup>

This disease seem to occur most frequently between latitudes 30° and 45° N in Asian and Eurasian populations. This area coincides with the old Silk Road, and Behçet's disease has been called the 'Silk Road Disease'.<sup>15</sup> The disease is much less common in Northern Europe, and the United States.<sup>7</sup>

Since the first report on Behçet's disease in Korea was published in 1961,<sup>16</sup> the number of patients with Behçet's disease in Korea has been increasing.<sup>13</sup>

However, there have been very few reports of Behçet's disease from Central Asia. Since this area lies between East and West Asia, where this disease is frequently seen, more patients are likely to be reported in the region. It may be possible that the clinical features of the disease have not been fully understood among the physicians in this area.<sup>1</sup>

We described a Mongolian man with complete-type Behçet's disease, who suffered from oral, genital aphthous ulcers, typical skin manifestations and uveitis. This case is the first report of a Mongolian with Behçet's disease in the English literature.

## REFERENCES

1. Ohno S. Behçet's disease in the world. In: Lehner T, Barnes CG, editors. Recent advances in Behçet's disease, London: Royal Society of Medicine Services; 1986. p.181-6.
2. Agata T, Nakae K, Maede K. The epidemiological

- features and trends of Behçet's disease in Japan from 1972 to 1985. In: Lehner T, Barnes CG, editors. Recent advances in Behçet's disease, London:Royal Society of Medicine Services; 1986. p.187-8.
3. Behçet's H. Über rezidivierende, aphthöse durch ein virus verursachte Geschwüre am Mund, am Auge, und an den Genitalen. *Dermatologische Wochenschrift* 1937;105:1152-7.
  4. International Study group for Behçet's disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990;335:1078-80.
  5. Shimizu T, Erlich GE, Inaba G, Hayashi K. Behçet's disease. *Semin Arthritis Rheum* 1979;8:223-60.
  6. Zouboulis CC. Epidemiology of Amantidaes-Behçet's disease. *Ann Med Interne* 1999;150:488-98.
  7. Lee S. Diagnostic criteria of Behçet's disease: Problem and suggestion. *Yonsei Med J* 1997;38:365-9.
  8. Lee ES, Bang D, Lee S. Dermatological manifestation of Behçet's disease. *Yonsei Med J* 1997;38:380-9.
  9. Mizuki N, Inoko H, Mizuki N, Sugimura K, Nishimura K, Nakamura S, et al. Human leukocyte antigen serologic and DNA typing of Behçet's disease and its primary association of B51. *Invest Ophthalmol Vis Sci* 1992;33:3332-40.
  10. Mizuki N, Inoko H, Ohno S. Molecular Genetics (HLA) of Behçet's disease. *Yonsei Med J* 1997;38:333-49.
  11. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. *N Engl J Med* 1999;21:1284-91.
  12. Kimura T, Goto K, Yabuki K, Mizuki N, Tamiya G, Sato M, et al. Microsatellite polymorphism within the MICB gene among Japanese patients with Behçet's disease. *Hum Immunol* 1998;59:500-2.
  13. Park S-H, Park K-S, Seo Y-I, Min DJ, Kim MU, Kim TG, et al. Association of MICA polymorphism with HLA- B51 and disease severity in Korean patients with Behçet's disease. *J Korean Med Sci* 2002;17:166-70.
  14. Bang D, Yoon KH, Chung HG, Choi EH, Lee E-S, Lee S, et al. Epidemiological and clinical features of Behçet's disease in Korea. *Yonsei Med J* 1997;38:428-36.
  15. Chapoutot-Remadi M. Major trade routes and the Silk Road: Behçet's disease, *Proceeding of the Seventh International Conference on Behçet's disease held at Tunis; 1996. p.22-6.*
  16. Joo CR. Two cases of Behçet's syndrome. *J Cathol Med College* 1961;5:393-400.