A Family with Cases of Adult Onset Still's Disease and Psoriatic Arthritis

Hiroyuki Maeda, Futoshi Konishi, Keiko Hiyama, Shinichi Ishioka and Michio Yamakido

Abstract

Adult onset Still's disease is recognized as an adult variant of the systemic form of juvenile rheumatoid arthritis, whose disease-predisposition is still debated. On the other hand, the association between HLA subtypes and several groups of seronegative arthritis including psoriatic arthritis has been well documented. This report describes a family where adult onset Still's disease in a young man and psoriatic arthritis in his father were seen. Both patients were HLA-B39-positive, which was likely playing important pathogenic roles in the latter case. Clinical and immunological aspects of HLA-B39-related inflammatory diseases are also discussed.

Key words: HLA-B27, HLA-B39, methotrexate, arthritogenic

Case Reports

Patient 1

A 21-year-old man visited a physician in August 1996 because of sudden left ankle joint pain. Under the diagnosis of tendinitis, he was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) with some success. During the next few months, he developed sore throat, arthralgia in wrists, knees, and cervical spine, and spiking fever up to 40°C which lasted for a month. Further, he noticed blunt vision in his right eye, and was referred to our hospital.

At presentation, red eye, painless swelling of cervical lymph nodes, and hepatosplenomegaly were noticed. Painful swelling of joints was seen in bilateral knees and ankles. No rash was observed. Laboratory investigations showed the following: white blood cells 13,800/mm³, neutrophil population 75%, red blood cells 474×10⁴/mm³, hemoglobin 12.9 g/dl, platelet 43.8×10⁴/mm³, the erythrocyte sedimentation rate (ESR; Westergren) 75 mm/hour, C-reactive protein 12.5 mg/dl, ferritin 487.9 ng/ml (normal range: 11.8–128.0 ng/ml), alanine aminotransferase (ALT) 34 units/liter, aspartate aminotransferase (AST) 104 units/liter, negative autoantibodies including rheumatoid factor (RF), antinuclear antibody (ANA), and antineutrophil cytoplasmic antibody, CH50 56 units/ml. No particular findings were observed in chest radiography and joint radiographies. Serological typing of HLA class I and II revealed HLA-B39, HLA-Cw4, and HLA-DR8 were positive (Table 1).

After admission, NSAIDs were continued for a while, in vain. Infectious diseases including Epstein-Bar, hepatitis B and C virus infection, and syphilis were excluded serologically. Despite the absence of rheumatoid rash, he was diagnosed as AOSD based on systemic symptoms and laboratory findings. Serological typing of HLA class I and II revealed HLA-B39, HLA-Cw4, and HLA-DR8 were positive (Table 1).

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Table 1. HLA-class I and II Antigen Analysis

<table>
<thead>
<tr>
<th>Locus</th>
<th>Patient 1</th>
<th>Patient 2</th>
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<tr>
<td>A</td>
<td>A2, A24</td>
<td>A2, A24</td>
</tr>
<tr>
<td>B</td>
<td>B39, B62</td>
<td>B39, B61</td>
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<tr>
<td>C</td>
<td>CW4, CW7</td>
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<td>DR</td>
<td>DR8, DR9</td>
<td>DR8, DR11</td>
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Laboratory findings including white blood cells 8,800/mm³ and C-reactive protein < 0.3 mg/dl was also attained.

**Patient 2**

The father of patient 1 was 42 years old, who had been diagnosed as having psoriasis vulgaris since 1994 and received topical therapy for the skin lesions and NSAIDs for back pain. In December 1996, he visited our hospital because of exacerbation of the back pain.

Well-defined plaques on hip and extremities and arthralgia in cervical, thoracic, and the lumbar spine were present. The laboratory investigations showed the following: white blood cells 10,300/mm³, neutrophil population 71.9%, red blood cells 503×10⁴/mm³, hemoglobin 14.7 g/dl, platelet 30.6×10⁴/mm³, the ESR 57 mm/hour, C-reactive protein 3.4 mg/dl, ALT 21 units/liter, AST 23 units/liter, negative autoantibodies including RF and ANA, CH₅₀ 56 units/ml. Radiography revealed bilateral erosive sacroiliitis without apparent findings of spondylitis (Fig. 1). With the information of his son’s having HLA-B39, HLA-class I and II analysis was conducted (Table 1).

Since several NSAIDs including indomethacin and diclofenac sodium had worsened the skin lesions without apparent improvement in his back pain, and based on the fact that HLA-B39 was a predictor of a refractory disease in PsA (3), oral methotrexate at 5 mg/week was started. In 8 weeks, the back pain had apparently improved without any significant adverse effects. The skin lesion showed some improvement at the same time.

**Discussion**

While the prevalence of arthritis in the general population is estimated at 2 to 3 percent, it varies from 7 to 42 percent in psoriatic patients (6). It has been shown that joint destruction and disability are not rare among patients with PsA, especially in those with HLA-B27 or HLA-B39 (2, 3, 7, 8). In such cases, to avoid irreversible damage and disability, treatment using immunosuppressants should be started earlier than has been generally done, in patient 2.

AOSD is often characterized by the appearance of salmon-colored rashes that are evanescent and become more prominent when patients are febrile (9, 10). Although typical rash was not observed in patient 1, other clinical and laboratory findings were quite consistent with AOSD. Since rashes are known to be absent in a few patients with AOSD (9, 10), AOSD should be a reasonable diagnosis. AOSD has been recognized as a syndrome resembling the systemic form of JRA, whereas the association of HLA-B27 or B39 has been reported in the pauciarticular-onset form (4) which may partly represent a group of juvenile spondyloarthropathies resembling adult AS. Reportedly, HLA-B27 is not overrepresented in patients with AOSD (5) and the association between HLA-B39 and AOSD has not been described so far. Thus, AOSD should be classified as a disease entity distinct from HLA-B27 or B39-related diseases despite a common characteristic of negative test for RF. HLA-Cw4 was positive in patient 1, which has been reported to be increased in the AOSD population (11).

The reported disease-spectrum (PsA, AS and pauciarticular form JRA) is similar between HLA-B27 and HLA-B39-related diseases (1-4), suggesting the presence of common inflammatory mechanisms distinct from the pathogenesis of RA. An attractive hypothesis is the ‘arthritogenic peptide model theory’ where peptides from bacteria homologous to endogenous self peptides presented by HLA-B27, including those derived from HLA-B27 itself, could elicit an autoimmune T-cell response upon infection (12-16). HLA-B39 share Glu at position 45 and Cys at position 67 with HLA-B27, which constitute the peptide-anchoring B pocket of the peptide-binding groove, possessing similar peptide-ligand motifs (17, 18). Further, binding cross-specificity of synthesized peptides to HLA-B27 and B39 has been reported recently (19).
The disease entity and clinical features were different between the inflammatory diseases observed in the two patients although they shared a common biological background, 'arthritogenic' HLA-B39 antigen. Investigating such rare family cases may be useful to elucidate the predisposition of inflammatory disease with unknown etiology.

References