Histocompatibility Antigens and Polymyalgia Rheumatica in a Japanese Patient with Insulin-dependent Diabetes Mellitus

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A 30-year-old Japanese female developed insulin-dependent diabetes mellitus (IDDM). She later complained of muscle pains at the age of 37. Erythrocyte sedimentation rate and C-reactive protein were abnormal, with negative antinuclear antibody and rheumatoid factor tests. The diagnosis of polymyalgia rheumatica (PMR) was made. She had HLA phenotypes including A2 and without DR4, consistent with common types of Japanese PMR. Her DNA typing included DQB1*0303 which is positively associated with Japanese IDDM. It seems likely that she suffered from these diseases at a young age on the basis of having the HLA-susceptibility to both PMR and IDDM.

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Key words: susceptibility, age, haplotype, DNA typing

Introduction

Polymyalgia rheumatica chiefly affects elderly individuals and its prevalence seems to be very low in Japanese as compared with Caucasians (1, 2). Recently, however, more Japanese patients have been reported probably because of the increase in the elderly population and an upsurge in the concern of this disease (3, 4).

We report here a patient with insulin-dependent diabetes mellitus (IDDM) who developed polymyalgia rheumatica at the age of 37. Her histocompatibility antigen (human leukocyte antigens: HLA) phenotypes and DNA typing were analyzed and the relationship between polymyalgia rheumatica, IDDM and HLA typing is discussed with a review of literature.

Case Report

A 37-year-old woman was admitted to our hospital in December 1994 because of general malaise. In March 1988 (at the age of 30), she suddenly noticed thirst, polyuria and general malaise. Her serum glucose concentration rose to 786 mg/dl. She was diagnosed as having diabetes mellitus and insulin was prescribed. She was well under the controlled insulin treatment until June 1994, when she again complained of severe general malaise. Physical examination at the time of admission revealed a thin woman of 144 cm in height and 33 kg in weight. She was neurologically intact and her vital signs were normal. Routine laboratory examinations were normal, including complete blood count, serum electrolytes, urea nitrogen, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations. C-reactive protein (CRP) was less than 0.3 mg/dl and tests for rheumatoid factor (RAT) were negative. Fasting blood sugar was between 279 and 314 mg/dl, and the daily profile was 163 mg/dl (minimum) and 431 mg/dl (maximum) when 22 units of recombinant human insulin (Penfil 30R; Novo, Japan) was injected subcutaneously twice a day in divided doses. Hemoglobin (Hb)A1 was 16% (normal: 4.8–7.2). Urinary excretion of c-peptide was 18 ug/day. The diagnosis of IDDM was confirmed, and her insulin dose was increased.

In January 1995, she suddenly complained of muscle pains in the proximal legs and neck. She suffered from general malaise with morning stiffness for a few hours. The erythrocyte sedimentation rate (ESR) was accelerated to 51 mm/hour and CRP became positive (4 mg/dl). A slight fever (the peak in the day was about 37.5°C) developed. Autoantibodies including anti-single stranded DNA-, anti-double stranded DNA-, anti-ribonucleoprotein-, anti-5m-, anti-Sjögren's syndrome-A-, anti-Sjögren's syndrome-B-, anti-scleroderma-70-, anti-thyroglobulin-, anti-thyroxineoxidase-, and anti-thyrotropin receptor-antibodies, and RAT were all negative. Total leukocyte count, and...
serum immunoglobulins, creatine phosphokinase, AST, ALT and lactic dehydrogenase concentrations were normal. Complement increased; C3 being 133 mg/dl (normal; 51-71), C4, 67 (normal; 16-28) and CH50, 85.5 (normal; 28-40). The muscle biopsy specimen showed no vasculitis, or other inflammatory changes or muscle atrophy. Fundus oculi showed no diabetic retinopathy or ischemic changes. No relief was noted with indomethacin or other non-steroid anti-inflammatory drugs (NSAID) for about two months. After prednisolone of 20 mg/day was started, the symptoms subsided and CRP became negative by April 1995. Thus, the diagnosis of polymyalgia rheumatica was made. The prednisolone treatment did not significantly deteriorate the control of her blood glucose as measured by HbA1 levels.

**HLA analysis**

HLA phenotypes were determined by complement dependent-microleukocyte toxicity. The DNA typing was determined by polymerase chain reaction in combination with restriction fragment length polymorphism analysis. The results of HLA phenotypes and DNA typing are summarized in Table 1 with those reported from other Japanese patients with polymyalgia rheumatica complicated by diabetes mellitus whose HLA were documented in the literature. Her HLA phenotypes included A2 without DR4. DNA typing of DQB1 showed DQB1*3030 and *0402.

**Discussion**

Two characteristics features in this patient are: 1) the early onset age of polymyalgia rheumatica and 2) complication of IDDM.

Polymyalgia rheumatica chiefly affects elderly patients. A set of diagnostic criteria of this disease is as follows: 1) >50 years of age, 2) aching and morning stiffness in at least two of the following areas: neck, shoulder girdle and pelvic girdle, 3) ESR >40 mm in 1 hour, 4) duration of symptoms for 1 month and 5) no other disease present (5). An additional criterion suggested by some is the response to relatively small (20 mg or less per day) doses of corticosteroid. Most patients are over age 60. However, Dailey and McCarty pointed out that it can begin at 40, presenting three younger cases with this syndrome (6) as proof. Tamaoki surveyed 262 Japanese patients with polymyalgia rheumatica and the mean age of the patients was 66.1 ± 2.6 years old (7). He showed that about 4% were under 40, consistent with the results of Dailey and McCarty (6). The youngest patient with this disease reported in the Japanese literature seems to be a 24-year-old pregnant woman who had HLA of A26 and DR4 (8).

In the present case, dermatomyositis was denied by normal muscle enzyme and normal muscle biopsy. Fibromyalgia usually affects younger individuals, however, it is unlikely in this case because of the elevated ESR, the constant pain with active joint movement and distinct morning stiffness. Rheumatoid arthritis was also unlikely because of her negative RAT, lack of the more characteristic distal joint involvement and unresponsiveness to NSAID. Thus, her signs and symptoms were consistent with the set of diagnostic criteria when one considers that polymyalgia rheumatica can begin before age 40.

The present patient developed IDDM at the age of 30, followed by polymyalgia rheumatica at the age of 37. The increased association of HLA-A10 and polymyalgia rheumatica in Caucasians is reported (9-11). In contrast, in Japanese patients, an increased association with A26 (1) or A2 (7) has been reported. Cw3 is commonly increased in both Caucasians and Japanese, while DR4 is increased in Caucasians and decreased in Japanese patients (1, 10-14). These results suggest that the immunopathological processes leading to the disease may differ in the two ethnic groups (1). To our best knowledge, the present patient is the first case with polymyalgia rheumatica complicated by IDDM who underwent HLA analysis. She had HLA-A2, which is one of the common types in Japanese patients and did not have HLA-DR4 which negatively associates with Japanese polymyalgia.

**Table 1. HLA Phenotypes and DNA Typing in the Present Case and in Other Reported Japanese Patients with Polymyalgia Rheumatica and Diabetes Mellitus (DM)**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>HLA Phenotype</th>
<th>DNA Typing</th>
<th>Type of DM</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>M</td>
<td>DR1, DR4</td>
<td>ND</td>
<td>NIDDM</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>A24, Bw59, Bw60, Cw1, Cw3, DR3, DRw8</td>
<td>ND</td>
<td>NIDDM</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>M</td>
<td>DR1, DR2</td>
<td>DRB1<em>0804 DRB1</em>0901 DQB1*0402</td>
<td>NIDDM</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>F</td>
<td>A2, A31, B55, B70, Cw1, DR8, DR9, DQ3, DQ4</td>
<td>DPB1<em>0201 DPB1</em>0402</td>
<td>IDDM</td>
<td>present case</td>
</tr>
</tbody>
</table>

ND: not done, NIDDM: non-insulin-dependent diabetes mellitus, IDDM: insulin-dependent diabetes mellitus.
rheumatica patients (1). Since there has been no report to date regarding DNA typing in Japanese patients with polymyalgia rheumatica, the common association between the types and the disease remains unclear at this time.

In IDDM, the increased association with DR4 is common in both Caucasians and Japanese. However, DR9 is positively associated with IDDM in Japanese, but not in Caucasians (15, 16). Moreover, the HLA-DR9 haplotype in Japanese IDDM patients is associated with DQA1*0301 and DQB1*0303 (17). The HLA haplotype of the present patient included DR9 and had the typing of DQB1*0303. Therefore, it is likely that she had the susceptibility to develop IDDM and that she suffered from polymyalgia rheumatica and IDDM at an early age on the basis of having the HLA susceptibility to both diseases.

Patients with polymyalgia rheumatica may reveal glucose intolerance (18). It is due to the lowered insulin sensitivity followed by insulin resistance depending on the presence of chronic inflammation. In fact, in most Japanese cases with non-insulin-dependent diabetes mellitus (NIDDM) (19, 20), steroid therapy improves their blood glucose control. In the present study, the control of the blood glucose was not significantly affected by steroid treatment. Thus, steroid therapy is not contraindicated in this disease combination in spite of the presence of NIDDM or IDDM.

References