Takayasu’s Arteritis Associated with Ulcerative Colitis; Genetic Factors in this Association

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Both ulcerative colitis and Takayasu’s arteritis are thought to be organ-specific immune-mediated inflammatory diseases. We present the rare case of a 23-year-old woman with a 4-year history of ulcerative colitis who developed Takayasu’s arteritis one month after giving birth. She was found to carry the human leukocyte antigens (HLA)-B52 and DR2, which were previously noted to be associated with these inflammatory conditions in the Japanese population. The pathogenic relevance of this haplotype to the concomitant development of these two conditions is discussed.

Key words: human leukocyte antigens (HLA)-B52, HLA-DR2

Introduction

Takayasu’s arteritis, a chronic inflammatory disease that primarily affects large elastic arteries such as the aorta and its major branches, is rare in North America and Europe but not uncommon in Japan and Southeast Asia. Females younger than 40 years old are predominantly affected. Although the etiology remains unclear, many case reports and studies have indicated that immunological abnormalities may be involved in the pathogenesis of this form of vasculitis. The occurrence of Takayasu’s arteritis in twins suggests that the disease also has a genetic basis (1). Human leukocyte antigens (HLA)-A24, B52, Dw12, and DR2 have been associated with Takayasu’s arteritis in Japanese patients (2-4).

Case Report

A 19-year-old Japanese woman was admitted to Mitoyo General Hospital in June 1989 for the evaluation of persistent abdominal pain and diarrhea characterized by excretion of blood and mucous. Colonoscopic examination showed hemorrhagic friable edema, ulceration, and coarse granularity from the rectum to the hepatic flexure of the colon (Fig. 1). Biopsy study of the sigmoid colon showed infiltration of inflammatory cells composed of lymphocytes and neutrophils, goblet cell depletion, and crypt abscess (Fig. 2). These findings suggested a diagnosis of ulcerative colitis. The patient responded well to treatment with corticosteroids and sulfasalazine, and the condition was later controlled with sulfasalazine administration alone. Treatment was discontinued in October 1992 because of pregnancy. The patient remained well until June 1993, when she developed fever and anemia one month after delivering a baby. Since the fever did not improve with antibiotics and nonsteroidal anti-inflammatory drugs, she was readmitted to the hospital.

On admission, she was moderately pale. Her body temperature was 38.4°C. Pulses were easily palpated in the extremities. Blood pressure on both arms was 100/70 mmHg. Tenderness was localized in the left sternocleidomastoid area, where vascular bruit was audible. No abnormalities of the optic fundi were observed in ophthalmological examination. Laboratory inves-
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Figure 1. Endoscopic view of the sigmoid colon showed hemorrhagic friable edematous mucosa, ulceration, and coarse granularity.

Figure 2. A) A biopsy specimen obtained from the sigmoid colon revealed granulation tissue with a dense infiltrate of lymphocytes (HE stain, x10). B) The mucosa showed goblet cell depletion and crypt abscess (HE stain, x50).

Investigations showed an erythrocyte sedimentation rate of 167 mm/1st h (normal range 4–20), a serum C-reactive protein 12.3 mg/dl (<2.5), white blood cell count 11.2 × 10^3/μl (3.5–9.8), hemoglobin 8.6 g/dl (11.3–15.2), hematocrit 28.5% (33–45), and platelet count 695 × 10^3/μl (130–370). Prothrombin time and active partial thromboplastin time were normal, but the serum fibrinogen level was increased to 957 mg/dl (180–360). Fasting serum levels of glucose and cholesterol were normal. Serum protein electrophoresis revealed polyclonal hypergamma globulinemia, with IgG of 2,540 mg/dl (800–1,800), IgA of 352 mg/dl (130–290), and IgM of 280 mg/dl (110–180). The serum complement level was increased to 61.4 CH_50 U/ml (30–40), with C3 of 104.0 mg/dl (68–120) and C4 of 34.3 mg/dl (20–50). Anti-nuclear antibody was weakly positive with a speckled pattern. Anti-DNA antibody and rheumatoid factor were not detected, and the serological test for syphilis was negative. HLA typing analysis demonstrated the presence of antigens A24, B51, B52, DR12, and DR2. Urinalysis was normal, but stool occult blood was positive. Chest X-ray examination on admission showed protrusion of the aortic arch and a winding of the descending aorta, suggestive of progressive vascular damage over the course of one year (Fig. 3). Angiography revealed stenosis of the left common carotid artery and spindle-shaped segmental dilatation of the aortic arch, left subclavian artery, and descending artery (Fig. 4). The pulmonary artery, renal artery, and coronary artery were not
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Figure 3. Chest X-ray on admission (A) showed protrusion of the aortic arch (arrow) and winding of the descending aorta (arrowhead), compared with X-ray taken one year ago (B).

Figure 4. Aortic angiography showed spindle-shaped segmental dilatation of the aortic arch and left subclavian artery (arrows) and stenosis of the left common carotid artery (arrowhead).

involved, and there was no aortic regurgitation. The diagnosis of Takayasu’s arteritis was made by the angiographic abnormalities. The activity of the ulcerative colitis was assessed as mild based on the colonoscopic appearance of the colonic mucosa, which was characterized by loss of mucosal vascularity and diffuse redness and edema.

We instituted the administration of 30 mg/day of prednisolone, which immediately reduced the fever. However, the inflammatory response persisted, as determined by high serum C-reactive protein levels. The dose of prednisolone was increased to 40 mg/day for two weeks. The patient has since been clinically well on a decreased dose of prednisolone.

Discussion

Takayasu’s arteritis is a rare form of vasculitis that involves the aorta and its proximal branches. Histological changes are characterized by a granulomatous panarteritis with a patchy inflammatory infiltrate of lymphocytes, plasma cells, macrophages, and giant cells, resulting in ischemia of the internal organs triggered by a narrowing of the arteries. The etiology is unclear. However, both humoral and cell-mediated immunity have been implicated in the pathogenesis. A genetic predisposition to this condition, probably linked to the immune response, is also suggested by studies on HLA analysis (2-4).

Takayasu’s arteritis affects young females in Asia and Central America, but is rarely encountered in North America and Europe. Its occurrence is rare even in Japan, with a frequency of 0.04% based on estimates derived from general autopsy cases (8). Ulcerative colitis, however, is commonly seen in the white population of North America and Europe. This inflammatory bowel disease is uncommon in Japan, with an incidence of 0.36/100,000/yr and a prevalence of 7.85/100,000/yr (6). Thus, one would expect these two diseases to rarely occur concomitantly, but in a literature research, we found that 32 such cases have been reported to date (5-18). They occurred predomi-
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Table 1. Review of 9 Published Cases of Takayasu’s Arteritis Associated with Ulcerative Colitis Who Underwent HLA Analysis

<table>
<thead>
<tr>
<th>Case</th>
<th>Author</th>
<th>Age **</th>
<th>Sex</th>
<th>Preceding disease &amp; duration (years)</th>
<th>HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Miwa, et al (5) (1979)</td>
<td>23</td>
<td>F</td>
<td>TA 2 years</td>
<td>A2, A9, B5, B13, Cw3</td>
</tr>
<tr>
<td>3</td>
<td>Achar, et al (16) (1986)</td>
<td>35</td>
<td>F</td>
<td>UC 1 year</td>
<td>A11, B5, B7, DR2, DR4</td>
</tr>
<tr>
<td>9</td>
<td>Present case</td>
<td>23</td>
<td>F</td>
<td>UC 4 years</td>
<td>A24, B51, B52, DR2, DR12</td>
</tr>
</tbody>
</table>


The present patient had a 4-year history of ulcerative colitis when she developed Takayasu’s arteritis just one month after giving birth. The presence of ulcerative colitis as an antecedent condition in 21 of the 32 cases described above, suggests that some bacterial or viral invasion through the intestinal mucosa may be involved in the pathogenesis of this form of vasculitis. Intriguingly, ankylosing spondylitis, which is considered to be a form of enteropathic arthritis, is strongly linked to infection with gram-negative bacteria (19). In addition, the maternal immune response usually shows a reduced cell-mediated immunity during pregnancy. Thus, pregnant women are more susceptible to infection. Patients with rheumatoid arthritis often experience a reduction in symptoms partly because of suppressed cell-mediated immunity, but the symptoms worsen, and arthralgia develops in some, after delivery. Thus, Takayasu’s arteritis may have been a complication of pregnancy-induced immune response changes in our patient.

The pathogenic relevance of HLA-B52 and DR2 to concomitant Takayasu’s arteritis and ulcerative colitis must be clarified; further study is needed to determine other genetic factors and environmental agents that contribute to its pathogenesis.

**References**