Abstract

A 15-year-old Japanese man was referred for evaluation of heart failure. Conventional heart failure therapy had little effect, and severe left ventricular dysfunction as well as elevated erythrocyte sedimentation rate persisted. Magnetic resonance angiography showed aortic dilatation with wall thickening characteristic of Takayasu’s arteritis. An endomyocardial biopsy specimen revealed infiltration of natural killer cells and γδ T lymphocytes, which play major roles in vascular injury of Takayasu’s arteritis. Prednisolone administration provided great benefits to cardiac function. These findings suggest that autoimmune cytotoxic mechanisms similar to those in vasa vasorum may contribute to cardiac impairment in Takayasu’s arteritis.

(Takayasu Myocarditis Mediated by Cytotoxic T Lymphocytes: Norifumi Takeda, Toshiyuki Takahashi, Yoshinori Seko, Koji Maemura, Hideki Nakasone, Kei Sakamoto, Yasunobu Hirata and Ryozo NagaI)

Introduction

Takayasu arteritis is a form of vasculitis that affects the aorta and its main branches as well as pulmonary arteries (1). We have previously reported that natural killer cells and γδ T lymphocytes mediate its cytotoxic autoimmunity by secreting cytotoxic factor perforin (2). On the other hand, cardiac impairment is generally regarded as a consequence of hypertension, pulmonary vascular involvement, coronary artery disease and aortic regurgitation (1, 3) in this disease. However, there has been a speculation that both myocardial and arterial involvement have a similar pathological background in some patients, race or regions (4–7), while the underlying mechanisms have not been fully elucidated.

Here, we describe a 15-year-old man with both Takayasu arteritis and myocarditis. His myocarditis seemed to be caused by the activated T cells, and several molecules, which are related to these cells, including perforin, human leukocyte antigen (HLA) classes I and II, and intercellular adhesion molecule-1 (ICAM-1) were expressed in the myocardium. Prednisolone administration, in conjunction with conventional heart failure therapy, dramatically restored his left ventricular (LV) systolic function. These findings suggest that cytotoxic mechanisms similar to those in vasa vasorum may also contribute to cardiac involvement in certain patients with Takayasu arteritis.

Case Report

A 15-year-old man with short stature (body length 143.2 cm) was admitted to our hospital, complaining of peripheral edema and exertional dyspnea for the past 11 months. His face remained childlike and his secondary sex characteristics had been absent. The pulse rate was 104 beats/min and the blood pressure taken in the right and left arm were 86/62 and 98/58 mmHg, respectively. A chest X-ray revealed cardiomegaly with a cardiothoracic ratio of 72% and a generalized decrease in translucency over the right lung field. An electrocardiogram showed sinus tachycardia (100 beats/min) with prominent mitral P wave in the lead V1.

Laboratory studies revealed hyponatremia (134 mEq/l) and anemia (hemoglobin 11.4 g/dl), which had been noted by a school physician since he was 12 years old. The erythrocyte sedimentation rate (ESR) was 72 mm/hour, and C-reactive protein (CRP) level was 4.1 mg/dl. Plasma levels of neurohumoral factors were as follows: atrial natriuretic peptide (ANP) 539 pg/ml, brain natriuretic peptide (BNP) 1,100 pg/ml, and norepinephrine 512 pg/ml.

Echocardiography demonstrated marked dilatation and generalized hypokinesis of the left ventricle. LV end-diastolic/end-systolic diameters (Dd/Ds) and ejection fraction were 64/55 mm and 0.29, respectively. No significant valvular lesions were detected. Cardiac catheterization revealed no significant stenoses of the coronary arteries, though there were...
accessory blood vessels from the right coronary artery to the right lower lobe of the lung. Blood pressure measured in the ascending aorta was 98/56 mmHg. Magnetic resonance angiography showed no stenotic lesions around the aortic arch, however revealed an occlusion of the right pulmonary artery, dilatation of the descending thoracic and abdominal aorta, and narrowing of the bilateral renal arteries (Fig. 1). LV endomyocardial biopsy specimen showed mild infiltration of mononuclear cells and severe myocyte necrosis on hematoxylin and eosin-stained sections. As demonstrated on immunohistochemically-stained sections (Fig. 2), these infiltrating cells turned out to consist of CD16+ natural killer cells and T cell receptor (TCR) γ+δ T lymphocytes. Perforin was clearly expressed in these cells (Fig. 3). Immunohistochemical study of the cardiac myocytes was also positive for HLA classes I and II, and ICAM-1.

On endocrinological examination, his body height was less than 3 SD below the mean value of Japanese boys with the same chronological age (Fig. 4). His height-age curve depicted a downward trend from the normal one since he was 10 years old. His bone age was also delayed, but it was consistent with his height age. Plasma follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone values were extremely low and insulin-like growth factor 1 (IGF-1) level (129 ng/ml) was also suppressed for puberty. On X-ray films of the skull, the sella turcica was normal in shape and size, and a magnetic resonance imaging scan of the brain revealed a normal appearance of the hypothalamus and pituitary gland. In contrast, growth hormone responses to growth hormone-releasing factor (GRF) 100 µg or arginine 0.5 g/kg administration were kept normal. LH and FSH responses to LH-releasing hormone (LHRH) 100 µg stimulation after LHRH priming were partially restored. Chromosomal study of his lymphocytes showed a normal 46XY karyotype. His delayed growth and sexual maturation were interpreted as functional hypothalamic hypopituitarism. Histocompatibility testing was positive for HLA-B52 antigen.

Based on the above findings, he was diagnosed as having Takayasu arteritis and related myocarditis in association with functional hypothalamic hypopituitarism. Neurohumoral blockade using angiotensin-converting enzyme (ACE) inhibition and β-blocker improved his symptoms from New York Heart Association (NYHA) class IV to II, and plasma BNP level was decreased to 199 pg/ml. In contrast, LV systolic dysfunction and increased levels of ESR and CRP persisted. Thus, oral administration of prednisolone was started at 20 mg (0.6 mg/kg)/day and gradually decreased by 2.5 mg/day every other week. Two months after steroid treatment, his cardiac symptom markedly improved and echocardiograms showed increases in LV ejection fraction 0.54 and decreases in LV diameters (Dd/Ds 52/38 cm). The cardiothoracic ratio decreased to 52% and the BNP levels were lowered within normal ranges. He was discharged from our hospital in a maintenance dose of prednisolone of 10 mg daily. Subsequently the steroid was tapered by 2.5 mg every other month, and a dose of 5 mg was maintained over 12 months. Repeat evaluation of periaortic inflammation by radiologic imaging has not been performed, because of his worsening allergy to contrast medium before steroid therapy. Eighteen months after administration, his ambulant clinical
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Discussion

Heart failure is complicated with Takayasu arteritis generally as a consequence of systemic arterial involvement, hypertension, and pulmonary vascular involvement (1). In some cases, coronary artery disease and aortic regurgitation can be precipitating causes (3). The presence of HLA Bw52 antigen has been attributed to LV dysfunction in this disease (8), but possible immunological processes affecting LV function have not been established.

We have previously shown that natural killer cells and γδ T lymphocyte-mediated autoimmunity may play major roles in vascular cell injury of Takayasu arteritis by releasing the cytotoxic factor, perforin (2). In the present case, there was no associated hypertension, valvular lesion, or coronary artery involvement to account for his LV dysfunction. The infiltrating lymphocytes were predominantly perforin-secreting γδ T lymphocytes, and the immunosuppressive therapy in conjunction with conventional heart failure therapy dramatically restored LV systolic dysfunction. These findings suggest that cytotoxic mechanisms similar to those found in vasa vasorum may also cause cardiac involvement in certain patients with Takayasu arteritis.

Combination of inflammatory myocarditis and Takayasu...
arteritis does not seem to be uncommon in certain races or regions. Earlier studies have reported that a lymphocytic infiltration consistent with myocarditis was present in approximately 50% of the Indian cases (4–7). Breinholt et al (9) demonstrated increases in HLA-DR on cardiac endothelium and immune complex deposition in the walls of small myocardial vessels, suggesting that a vasculitic process might involve the myocardium in Takayasu arteritis. We have shown that HLA classes I and II, and ICAM-I were present on the ventricular myocytes of the present case. These findings strongly suggest that immunological processes play a significant role in his myocarditis. On the other hand, in consideration of the age of the patients susceptible to heart failure (that is, less than 20 years old) (5), active cardiac inflammation may primarily be attributable to LV dysfunction in Takayasu arteritis.

Immunosuppressive therapy may be useful for myocardial involvement of Takayasu arteritis. Talwar et al (4) reported that combined therapy of prednisolone (1 mg/kg) and cyclophosphamide (2 mg/kg) over 12 weeks improved not only clinical and hemodynamic states, but also myocardial morphology of patients with Takayasu myocarditis. The infiltrating lymphocytes were predominantly T suppressor cells and repeated endomyocardial biopsies after the treatment showed healed myocarditis. LV ejection fraction improved from 33% to 49%. These data might also suggest that Takayasu myocarditis is the result of cytotoxicity. In the present case, we have not obtained his consent for repeated

Figure 3. Double immunostaining by enzyme antibody methods for PFP (blue color, by alkaline phosphatase) and surface markers CD8, CD16, or TCR \( \gamma \delta \) (brown color, by horseradish peroxidase). Note that PFP was clearly expressed by infiltrating CTLs (CD8+), NK cells (CD16+), and \( \gamma \delta \) T-cells (TCR \( \gamma \delta + \)) \((\times 400)\).

Figure 4. Height-age curve depicted a downward trend from the normal curve since he was 10 years old, as an unusual feature of a young man with both Takayasu arteritis and myocarditis.
endomyocardial biopsy.

Chronic systemic disorders could have resulted in his short stature and delayed sexual maturation. To our best knowledge, the association of Takayasu arteritis, understructure and sexual infantilism has not yet been reported. The differential diagnosis of this case is inflammatory hypophysitis, which is associated with recent pregnancy and underlying autoimmunity. Lymphocytic hypophysitis is a chronic inflammatory process that should respond to corticosteroid treatment. However, both a lack of response to steroids and a recurrence of symptoms during steroid treatment have been reported (10). In addition, Leung et al (11) reported a case of primary hypophysitis with bilateral internal carotid artery occlusion secondary to inflammatory involvement of the cavernous sinuses and arteritis. In the present case, corticotrophic and thyrotrophic function was normal, which are mainly involved in lymphocytic hypophysitis, and we had not measured antipituitary antibodies, which were detected in as many as 40% of the cases. Radiographic studies and hormonal pharmacological provocative tests have attributed his unusual features to functional hypothalamic hypopituitarism. Treatment of prednisolone provided continuous benefits for his symptoms and cardiac condition, but his growth and sexual development has not yet recovered over 18 months. Further evaluation will be needed for clarifying the relationship between Takayasu myocarditis and hypopituitarism.

Here, we reported a case of Takayasu arteritis, complicated with myocarditis with infiltration of predominantly perforin-secreting \( \gamma \delta \) T lymphocytes. In Takayasu arteritis, immunological cytotoxic processes may play major roles in the genesis of LV dysfunction in some patients, similar to those in vascular cell injury. If stenotic or dilative lesions of aorta and its main branches are detected especially in young patients with heart failure, the possibility of Takayasu’s arteritis should be considered. Steroid therapy may dramatically improve the cardiac function and the prognosis of such patients.

References