Case Report

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A case of ankylosing spondylitis with concurrent Takayasu arteritis

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Abstract

We herein report a case involving a 56-year-old man who had experienced neck and lower back pain since the age of 23 years. Ankylosing spondylitis (AS) was diagnosed at 41 years of age, and treatment with sulfasalazine was initiated. At 44 years of age, the patient developed respiratory distress on exertion and chest pain. Aortic regurgitation (AR) was diagnosed via echocardiography, and the patient presented to our hospital for close examination and treatment. Coronary computed tomography angiography revealed no lesions in the coronary artery; however, magnetic resonance angiography revealed stenotic lesions in the left common carotid artery and left subclavian artery. Based on the findings of a physical examination, fundus examination, and blood tests, the patient was diagnosed with AS with concurrent Takayasu arteritis (TA). Upon administration of steroids to alleviate inflammation caused by an autoimmune mechanism, the patient's chest symptoms and inflammatory findings improved. AR was treated with aortic valve replacement and prosthetic blood vessel replacement, after which the patient progressed well. Intraoperative aortic biopsy revealed findings pathologically consistent with TA. Although AS with concurrent AR is well described, AS with concurrent TA, as in the present case, is rare.

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Introduction

Ankylosing spondylitis (AS) is a common form of spondyloarthritis (SpA) that causes chronic inflammation of the spine and sacroiliac joint. Patients with AS clinically present with pain and a limited range of motion at these sites, often leading to reduced activities of daily living. AS shows a strong correlation with human leucocyte antigen (HLA) B-27. Moreover, the prevalence of HLA-B27 carriers is high among white Americans, and approximately 1.8% of white Americans develop AS; in Northern Europe, this prevalence is even higher.[1–3] In Japan, however, the prevalence of HLA-B27 carriers is approximately 0.4%, and the prevalence of AS is only 0.48 per 100,000 individuals.[4,5] This disease commonly develops in men younger than 40 years of age, and onset in elderly individuals is rare. Clinically, inflammatory symptoms primarily affect the sacroiliac joint, and the initial symptom is often lower back pain that is relieved by exercise. Disease progression is characterized by repeated remission and exacerbation. In addition, AS can present with spine lesions, skin lesions (e.g., enthesitis and psoriasis), intestinal lesions (e.g., Crohn's disease and ulcerative colitis), and cardiac complications [e.g., aortic regurgitation (AR) and mitral regurgitation (MR)].[5] However, systemic vasculitis concurrent with AS is rare.[6,7] We herein report an extremely rare case of AS with concurrent Takayasu arteritis (TA). This case is being reported to add to the existing literature because the coexistence of the two diseases is relatively rare.

Case report

A 56-year-old man had experienced lower back pain one to two times per year since the age of 23 years. At 28 years of age, he began to experience neck pain, for which he received acupuncture and moxibustion treatment as well as massages. However, from around 34 years of age, his symptoms, including the lower back pain, gradually became exacerbated. Upon experiencing limited anteflexion and rotation of the torso and cervical spine, he presented to a local clinic. Despite a follow-up observation with nonsteroidal anti-inflammatory drugs, his symptoms progressed and he was diagnosed with AS based on the findings of plain radiography and magnetic resonance imaging (MRI) of the spine performed at 41 years of age. Treatment with sulfasalazine and etanercept was initiated; however, it was discontinued within only 2 months because of the development of systemic urticaria and acute colitis.

At 44 years of age, the patient developed respiratory distress upon exertion and chest pain attacks, and close examination by echocardiography and cardiac catheterization revealed AR. Although the AR required prosthetic blood vessel replacement, there were findings that could not be explained only by AS with concurrent AR (e.g., a difference in blood pressures in the right and left arms). Therefore, the

patient presented to our hospital, where he was admitted for the purpose of undergoing close examination of AR complicated with AS and surgery for treatment of cardiovascular disease.

At the time of admission, the patient's height was 154.5 cm and weight was 42.4 kg. A significant difference was observed in the blood pressures in his right and left arms: 150/30 mmHg in the right arm and 110/68 mmHg in the left arm. Upon chest auscultation, diastolic murmurs characteristic of AR were heard.

Blood testing revealed a leukocyte count of 7,000/μL (neutrophils: 70.2%, monocytes: 4.1%, lymphocytes: 23.4%, eosinophils: 2.0%, and basophils: 0.3%), C-reactive protein (CRP) level of 5.7 mg/dL, and erythrocyte sedimentation rate of 91 mm/h; testing for anti-nuclear antibodies by indirect immunofluorescence was negative. Furthermore, the brain natriuretic peptide level was high (417.0 pg/mL; reference range, 0.0–18.4 pg/mL). The patient tested positive for HLA-A2, B46, and B61 but negative for HLA-B27, B52, and B67. Furthermore, eye examination revealed a history of uveitis in the right eye, and bilateral funduscopy revealed dilatation and tortuosity of the retinal veins, which were thought to involve vasculitis.

Figure 1 shows the plain radiographs of the lumbar and cervical spine. Bone erosion and osteosclerosis were observed surrounding the sacroiliac joint, and findings suggestive of vertebral body squaring and ossification of the spinal ligament were seen on the lumbar and cervical spine radiograph; these findings were consistent with AS. Furthermore, while the electrocardiogram showed a sinus rhythm, there were findings suggestive of left ventricular hypertrophy and left atrial loading. Echocardiography revealed an ejection fraction of 0.35–0.40; severe AR and first-degree MR were observed with dilatation of the left ventricle and ascending aorta. No significant stenosis of the coronary artery was observed on coronary three-dimensional computed tomographic angiography (3D-CTA);

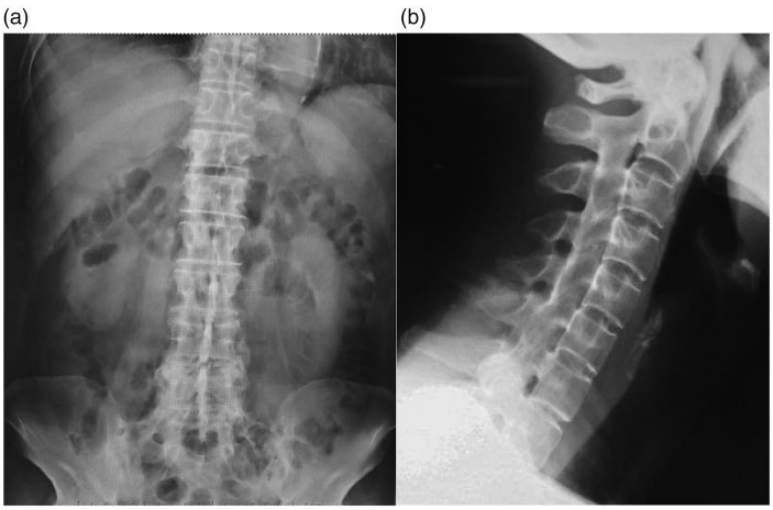

Figure 1. Plain radiographs of the cervical and lumbar spine. (a) Bone erosion and osteosclerosis are observed surrounding the sacroiliac joint. (b) Squaring of the vertebral bodies and ossification of the ligamentum flavum are observed on the radiographs of the lumbar and cervical spine.

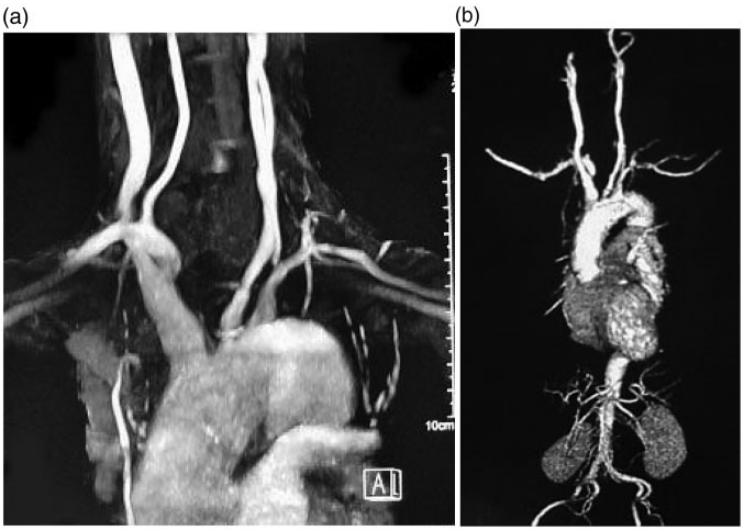

Figure 2. Imaging findings. (a) Chest magnetic resonance angiogram. Stenosis of the left subclavian artery and left-side common carotid artery is observed. (b) Contrast-enhanced three-dimensional computed tomography angiogram extending from the chest to the pelvis. Stenosis of the left subclavian artery and left-side common carotid artery is observed; however, there are no abnormalities in the main peripheral vessels branching from the descending aorta.

however, magnetic resonance angiography (MRA) of the chest revealed stenosis of the left subclavian artery and left-side common carotid artery (Figure 2(a)). Furthermore, 3D-CTA of the chest and pelvis revealed no abnormal findings in the branching vessels peripheral to the thoracic aorta (e.g., renal artery); however, the common carotid and left subclavian artery findings were consistent with the MRI findings (Figure 2(b)), which led to strong suspicion for the presence of TA. Furthermore, no intracranial abnormal findings were observed on cranial MRI and MRA.

These test results and clinical findings satisfied the clinical and radiographic criteria of the Modified New York Criteria for AS proposed by van der Linden et al.[8] in 1984 as well as the diagnostic criteria for TA recommended by the American College of Rheumatology in 1990 (i.e., difference in blood pressures of the left and right arms, difference in brachial pulses of the left and right arms, and stenosis of the left subclavian artery).[9] Therefore, the patient was thought to have AS with concurrent TA.

The AR was severe, and dilatation of the ascending aorta with a maximum diameter of 45 mm was observed; thus, aortic valve replacement and prosthetic blood vessel replacement of the ascending artery were considered appropriate. However, based on the results of various tests, it was highly likely that the elevated CRP level and erythrocyte sedimentation rate contributed to the AS and TA; the active vasculitis in the aorta was deemed to have an unfavorable effect on the postoperative progress. Therefore, 30 mg/day of prednisolone was initiated 44 days prior to performing surgery primarily to treat the TA. On day 14 of treatment, the CRP level normalized, and when the dose was reduced to 15 mg, the Bentall procedure and hemiarch replacement were performed for annuloaortic ectasia. The intraoperative aortic biopsy sample was stained with

hematoxylin–eosin and elastica van Gieson and was analyzed at high- and low-power fields for pathological examination (Figure 3(a)–(d)). Hematoxylin–eosin staining revealed hypertrophy of the aortic tunica adventitia, destruction and necrosis of the elastic fibers indicating lymphocyte invasion in the tunica media, and hypertrophy in the intima. Elastica van Gieson staining revealed giant cell invasion at the site of severe inflammation, which was consistent with the findings for TA.

The postoperative course was uneventful, and the patient was discharged on postoperative day 14. Thereafter, treatment continued with prednisolone, methotrexate, and warfarin potassium, and the patient's condition remained stable.

Discussion

AS exhibits a strong correlation with HLA-B27. Moreover, in Japan, AS is considered to be an extremely rare disease because there are few HLA-B27 carriers.[4,5] TA was first reported in 1908 by Mikito Takayasu, a Japanese ophthalmologist. A recent study revealed that the risk of TA is associated with the presence of HLA-B52. While TA is highly prevalent in Japan and other Asian countries, as well as the Middle East, its prevalence tends to be low in North America, excluding Mexico.[10,11] This disease is often seen in women and is characterized by chronic inflammation of the aorta and its primary branching vessels, with ischemic symptoms

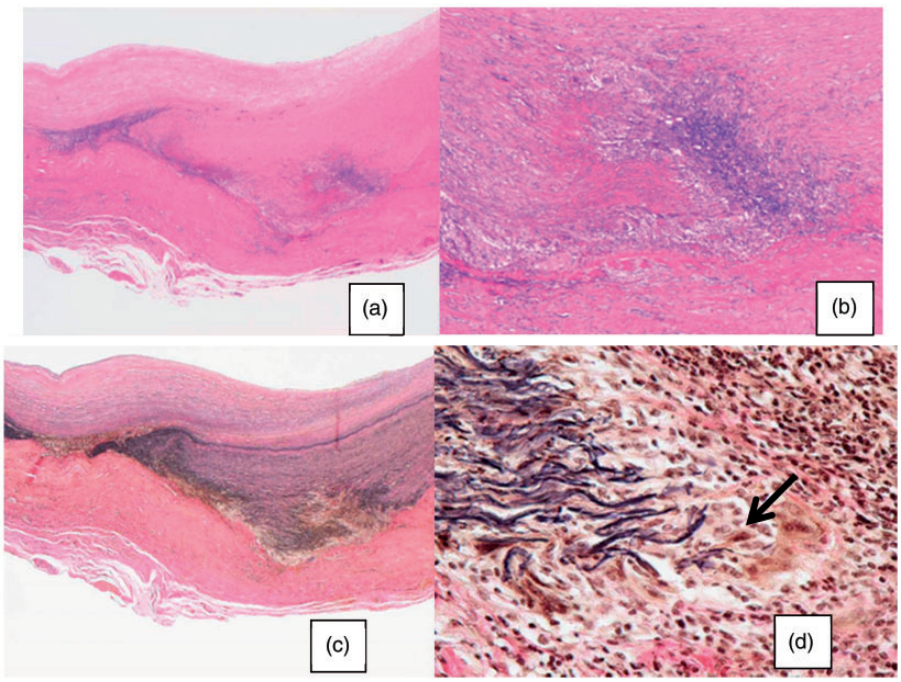

Figure 3. Aortic biopsy. (a) Hematoxylin–eosin staining (low-power field) reveals hypertrophy of the aortic tunica adventitia, destruction and necrosis of the elastic fibers in the tunica media, and hypertrophy in the intima. (b) Hematoxylin–eosin staining (high-power field) reveals abundant lymphocyte invasion in the tunica media. (c) Elastica van Gieson staining (low-power field) reveals destruction of the elastic fibers in the tunica media. (d) Elastica van Gieson staining (high-power field) reveals giant cell invasion (arrow).

in blood vessel-dominant regions.[10] Autoimmune mechanisms may greatly contribute to the onset of TA, similar to that observed in AS; thus, the administration of steroids and biological preparations (e.g., tocilizumab) is expected to be effective.[12]

However, surgical treatment (e.g., prosthetic valve replacement and prosthetic blood vessel replacement) is performed for patients in whom early treatment intervention is difficult, those with severe vasculitis refractory to internal therapy, those exhibiting markedly impaired blood flow, and those who develop valvular disease (e.g., the present case).[13,14] In patients with AS, lesions are found in the spine, sacroiliac joint, and ligaments; however, lesions are also sometimes found in the cardiovascular system. Moreover, various complications have been reported, such as atrioventricular conduction disturbance, cardiomyopathy, myocardial infarction, and valvular disease.[6,7] In some patients, concurrent MR and AR developed as a result of inflammation caused by valvular disease, particularly in the mitral and aortic valves, and these patients underwent surgical procedures.[6,7] However, from a pathological perspective, TA is a form of vasculitis that progresses from the tunica adventitia to the intima and is characterized by hypertrophy of the tunica media and invasion of lymphocytes (i.e., T cells). Histologically, TA is considered to be different from the cardiovascular lesions caused by AS.[15–17]

In the present case, intraoperative biopsy of the aorta revealed that the patient's condition could not be clinically or pathologically explained by AS alone; thus, concurrent TA was considered the most valid explanation. In Japan, TA is commonly observed in women, whereas AS is common among men. Based on the prevalence and male:female ratio, the concurrence of both diseases is considered extremely rare; however, although limited, there have been some reported cases of the coexistence of both diseases.[18,19] In a French study by Rivière et al.,[19] of 14 patients with concurrent TA and SpA including AS and psoriatic arthritis, 11 patients with AS were Caucasians, 10 of whom were women. Moreover, SpA preceded TA in 13 patients and the age at onset was 43.5 years, which was older than the general age of onset. Furthermore, HLA-B27 was tested in 12 patients, 9 of whom had negative results. These findings confirm that AS is particularly common in patients with concurrent SpA and TA, and unlike the general population with AS, the incidence of TA is high. Therefore, it is highly likely that in patients with these concurrent conditions, onset is not incidental but is caused by some underlying factor.[16]

In the present case, the patient experienced low back pain when he was relatively young (in his 20s); however, the onset of AS preceded that of TA, and the fact that HLA-B27 was not detected is partially consistent with the characteristics reported by Rivière et al.[19] Furthermore, in patients who develop TA during the course of AS, a sudden increase in the CRP level is observed; the present case also proceeded in a similar manner. In a study focused on serum cytokine levels, the IL-23 level was higher in patients with AS than in healthy individuals.[20] Furthermore, Sherlock et al.[21] reported that RORγt+/CD3+/CD4−/CD8− cells with IL-23 receptors are involved at the site of attachment where AS inflammation appears. Moreover, it is possible that IL-17 and IL-22 produced by T cells activated by IL-23 play a major role in bone resorption and new bone formation. In a genome-wide association study, Davidson et al.[22] found that STAT3 and TNFRSF1A were overexpressed in the Th17 pathway and reported the importance of signal transducer and activator of transcription 3 and the activation of IL-23 in patients with AS.

As mentioned above, concurrent TA commonly develops in HLA-B52 carriers. Terao et al.[23] conducted a genome-wide association study in Japan and included 167 individuals with TA and 663 healthy controls. In addition to the known HLA-B region on chromosome 6, they reported that TA is related to a single-nucleotide polymorphism of the IL12B region on chromosome 5 and the MLX region on chromosome 17. Furthermore, a single-nucleotide polymorphism of the IL12B region was found to be associated with the incidence and severity of concurrent AR as well as the CRP level. The authors noted that this polymorphism plays a major role in the onset and progression of TA and interacts with HLA-B52.

IL12B has been found to encode IL-12/23p40 proteins, and IL-12 forms a heterodimer sharing the IL-23 and p40 subunits. It plays an important role in T-cell differentiation into Th1 and Th17. Therefore, AS and TA exhibit several differences in terms of clinical symptoms; however, it is considered highly likely that IL-23 and IL-17 greatly contribute to the pathogenesis of both diseases. Furthermore, IL-12/23p40-targeting ustekinumab is effective for treating TA and AS.[24] These findings suggest that the presence of immunological characteristics is common to both diseases.

While AS and TA show specific correlations with HLA, the relationship between HLA and concurrent cases remains unclear. However, characteristic findings, including cytokine abnormalities, are shared in both diseases. Although relatively rare, in patients in whom both diseases coexist, AS most commonly precedes TA and the age at TA onset is somewhat advanced. In their investigation of 23 concurrent cases of SpA, including AP and TA, Mielnik et al.[25] determined that most patients were male (male:female ratio, 14:9), 8 of 17 patients (47%) who underwent testing were positive for HLA-B27, and concomitant inflammatory bowel disease was diagnosed in 2 patients (8.7%). In 22 of the 23 patients, SpA preceded TA (mean duration, 6 years), and a glucocorticoid was administered to all patients except one in whom tumor necrosis factor blockers were administered before TA onset.

Notably, our patient shared several characteristics with the patients mentioned above. Our patient was administered etanercept for 2 months to treat AS before the detection of concurrent TA. However, because this was a very short duration, we consider it unlikely that it significantly affected our patient's clinical course. Because both diseases are currently stable, we have no plans to administer anti-tumor necrosis factor therapy.

In the present case, HLA-B27 and HLA-B52 were not detected in association with either disease, and although etanercept was administered to treat AS for less time, steroids and immunosuppressants that could affect the clinical progression of TA were not administered. Although we cannot rule out the possibility that treatment for AS can inhibit the onset of TA, the coexistence of the two diseases is extremely interesting, and further examinations of their relationship are required.

To conclude, we experienced a case of TA concurrence during the course of AS. Prednisolone and methotrexate were effective, and after undergoing aortic valve replacement and prosthetic blood vessel replacement of the ascending aorta for AR associated with annular dilatation, the patient's progress was good.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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