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Case Report

Concurrent Sarcoidosis and Takayasu's Arteritis: Case Report and Review of the Literature

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A 26-year-old woman was admitted to our hospital with fever, dry cough and elevated serum CRP. Chest CT scans revealed mediastinal and bihilar lymphadenopathy, and sarcoidosis was clinically diagnosed based on additional findings. The walls of the aorta and other arteries were thickened and HLA typing was positive for HLA-B52, suggesting Takayasu's arteritis. Corticosteroid clearly improved the symptoms and the patient has remained free of recurrence since therapy was discontinued. We report the rare case of concurrent sarcoidosis and TA and review the literature.

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Introduction

Systemic vasculitis is a rare complication of sarcoidosis (1), which is a systemic granulomatous disease of unknown etiology that mostly affects the lungs, lymph nodes, eyes and skin (2).

Because sarcoidosis most frequently involves the lung, the most common presenting symptoms include cough, dyspnea and chest pain (1). Other features of sarcoidosis include fatigue, malaise, weight loss and fever (1), although high-grade fever is not usually associated with sarcoidosis, except for Lofgren syndrome or some severe types.

Takayasu's arteritis (TA) is a chronic vasculitis of unknown etiology with an estimated occurrence of 150 new patients per year in Japan (3). It causes thickening of the walls of the aorta and its primary branches via inflammatory processes. Common systemic symptoms during the early phase of TA include fatigue, weight loss and fever, whereas vascular symptoms are rare at presentation (4).

Here, we describe a patient with sarcoidosis accompanied by large vessel involvement due to TA. This case emphasizes the importance of considering other co-existent diseases including systemic vascular disease in patients with sarcoidosis, especially when presenting with atypical symptoms such as high-grade fever.

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Case report

A 26-year-old Japanese woman presented at a clinic June 2006 with low-grade fever, light-headedness and ear fullness. A common cold was initially diagnosed, but her condition gradually worsened and her body temperature increased to 39 ℃. When she attended another clinic two weeks later , CRP was positive (4.4 mg/dL) without leukocytosis, but the origin was unknown. She was subsequently admitted to our hospital for further evaluation on July 4th of the same year with dry cough, nausea and abdominal pain.

Her medical history included surgical resection of a fibroadenoma of the left breast (in the year 2000) and a right ovarian cyst two years later, and surgery and postoperative chemotherapy for a left ovarian immature teratoma during 2005. The patient neither smoked nor consumed alcohol.

A physical examination revealed a body temperature of 39.2 ℃, blood pressure of 96/60 mmHg and a regular pulse of 70 beats per min. Superficial lymph adenopathy was absent. Lung and heart auscultation was normal. The results of abdominal, neurological and skin examinations were normal. An otorhinolaryngologic evaluation suggested a patulous Eustachian tube in the right ear, but no focus of fever. A gynecological assessment showed no abnormalities except post-operative traces.

Laboratory tests upon admission (Table 1) revealed mild anemia (Hb 10.5 g/dL), mild liver dysfunction, an increased

Table 1. Results of laboratory tests.

ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; Anti-dsDNA Ab, anti-double strand DNA antibody; Anti-Jo-1 Ab, anti-Jo-1 antibody; Anti-LKM-1 Ab, anti-liver/kidney microsome type 1 antibody; Anti-RNP Ab, anti-ribonucleoprotein antibody; Anti-Sm Ab, anti-smooth muscle antibody; Anti-Scl-70 Ab, anti-scleroderma-70 antibody Anti- SS-A Ab, anti-SS-A antibody; Anti-SS-B Ab, anti-SS-B antibody; ESR, erythrocyte sedimentation rate; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic autoantibody; PR3-ANCA, proteinase 3 anti-neutrophil cytoplasmic autoantibody; PA, particle agglutination test; RF, rheumatoid factor; sIL-2R, soluble IL-2 receptor; STS, serological test for syphilis; TPHA, Treponema pallidum hemagglutination assay.

Blood cell count

WBC	6400	/μL
Neu	69	%
Lym	22	%
Eos	1	%
Bas	1	%
Mon	8	%
RBC	378	$\times 10^4/\mu L$
Hb	10.5	g/dL
Ht	33.3	%
Plt	45.0	$\times 10^4/\mu L$
ESR	35.3	mm/H

Blood chemistry

TP	8.6	g/dL
γ-globulin	2.3	g/dL
T.Bil	0.6	mg/dL
AST	44	IU/L
ALT	20	IU/L
LDH	144	IU/L
ALP	210	IU/L
γ-GTP	37	IU/L
Amylase	162	IU/L
T.Cho	110	mg/dL
TG	61	mg/dL
Glucose	112	mg/dL
BUN	9	mg/dL
Cr	0.6	mg/dL

Serology

IgG	1870	mg/dL
IgA	486	mg/dL
IgM	114	mg/dL
CRP	10.94	mg/dL
sIL-2R	796	U/mL
ACE	17.1	U/L
Lysozyme	8.4	μg/mL

Infection

HBsAg	0.1	IU/mL
HCV-Ab	0.2	
Anti-HTLV-1 Ab	0.1	-fold
TPHA	-	
STS	-	

Mycoplasma Ab (PA)

On admission	320	-fold
Hospital day 23	80	-fold

Urinalysis

Protein	-
Glucose	-
Blood	-
Ketone	-

Immunological tests

RF	< 9.5	IU/mL
ANA	< 20	-fold
CH50	67.3	U/mL
Anti-dsDNA Ab	0.8	IU/mL
Anti-Sm Ab	1.1	index
Anti-RNP Ab	1.3	index
Anti-SS-A Ab	0.4	index
Anti-SS-B Ab	2.5	index
Anti-Scl-70 Ab	3.7	U/mL
Anti-cardiolipin Ab	0.7	-fold
Anti-Jo-1 Ab	-	
MPO-ANCA	< 10	EU
PR3-ANCA	< 10	EU

BALF

Total cell count	1.7	$\times 10^5$/mL
Macrophage	65.2	%
Lymphocyte	32.1	%
Neutrophil	2.6	%
Eosinophil	0.1	%
CD4/CD8	12.94	

erythrocyte sedimentation rate (ESR) (35.3 mm/h) and elevated CRP (10.94 mg/dL), γ-globulin (26.2%, 1.7 g/dL), IgG (1870 mg/dL), CH50 (67.3 U/mL) and soluble interleukin-2 receptor (sIL-2R) (796 U/mL). Serum angiotensin converting enzyme (ACE) and lysozyme levels were within normal limits. Rheumatoid factor (RA) and ANA (anti-nuclear antibody) were negative. The *Mycoplasma pneumoniae* antibody titer was positive (1:320) and became negative (1:80) on hospital day 23 without antibiotics, which suggested *Mycoplasma pneumoniae* infection within the past year.

Chest X-rays acquired upon admission revealed upper mediastinal and bilateral hilar enlargement (Fig. 1A). Chest contrast enhanced computed tomography (CECT) showed mediastinal and bilateral hilar lymphadenopathy accompanied by small nodules in both lung fields (Fig. 1B, C), as well as wall thickening of the aorta (arch, descending and upper part of abdominal aorta) and of the proximal part of the left common and left subclavian arteries (Fig. 2A, B).

Abdominal CECT showed mild hepatosplenomegaly and wall thickening of the proximal part of the superior mesenteric artery (SMA) indicating arteritis (Fig. 3A). The vascular status of the abdomen was further evaluated using gadolinium-enhanced magnetic resonance imaging (Gd-MRI), which showed wall thickening of the proximal part of the SMA with slight enhancement (Fig. 3B), and wall irregularities of the aorta and proximal part of the right renal artery.

Bronchofiberscopy revealed a submucosal network formation of capillary vessels in the bronchi. Analysis of bronchoalveolar lavage fluid revealed a normal total cell count (1.72×10^5/mL) with a high proportion of lymphocytes (32.1%) and a high CD4/CD8 ratio (12.94) (Table 1). Abnormalities such as alveolitis or granuloma were absent in transbronchial lung biopsy specimens and the tuberculin skin reaction was negative. [67]Gallium scintigraphy showed intense isotope uptake in the mediastinum, the bilateral hilum of the lung (lambda sign) and the lacrimal, parotid and submandibular glands (panda sign). The accumulation to the aortic wall was not detectable (Fig. 4). An ophthalmologic assessment revealed optic neuritis. No cardiac disorders were identified by electrocardiography (ECG), Holter ECG and ultrasonic cardiography (UCG).

Although non-caseating epithelioid granulomas were undetectable, sarcoidosis was clinically diagnosed based on the findings of bilateral lymphadenopathy, small nodules in both lung fields, a negative tuberculin skin reaction, the panda/lambda sign on gallium scans, the bronchial submucosal network, lymphocytosis, a significant increase in the CD4/CD8 ratio in BAL fluid and optic neuritis.

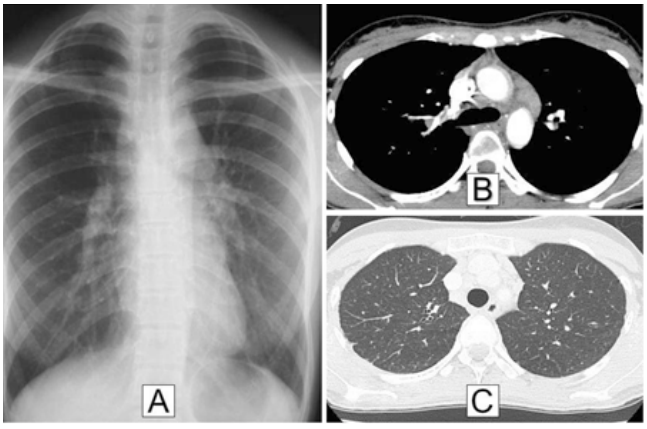

Figure 1. Chest X-ray upon admission shows upper mediastinal and bilateral hilar enlargement (Fig. 1A). Chest computed tomography (CT) shows mediastinal and bilateral hilar lymphadenopathy accompanied by small nodules in both lung fields (Fig. 1B, C).

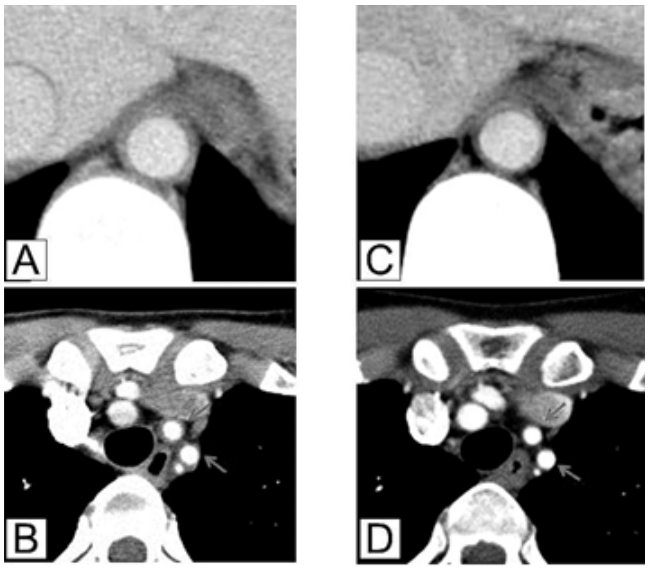

Figure 2. Chest contrast-enhanced computed tomography (CECT) upon admission shows wall thickening of the descending aorta (A) and of the proximal part of left common and left subclavian arteries (B, arrows), Improvement of vascular lesions is obvious after steroid therapy (C, D, arrows).

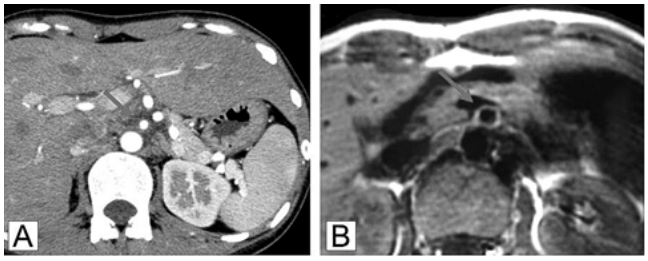

Figure 3. Abdominal CECT shows mild hepatosplenomegaly and wall thickening of the proximal part of superior mesenteric artery (SMA) indicating arteritis (A, arrow). Gadolinium-enhanced magnetic resonance image (Gd-MRI) of abdomen shows wall thickening of proximal part of SMA with slight enhancement (B, arrow).

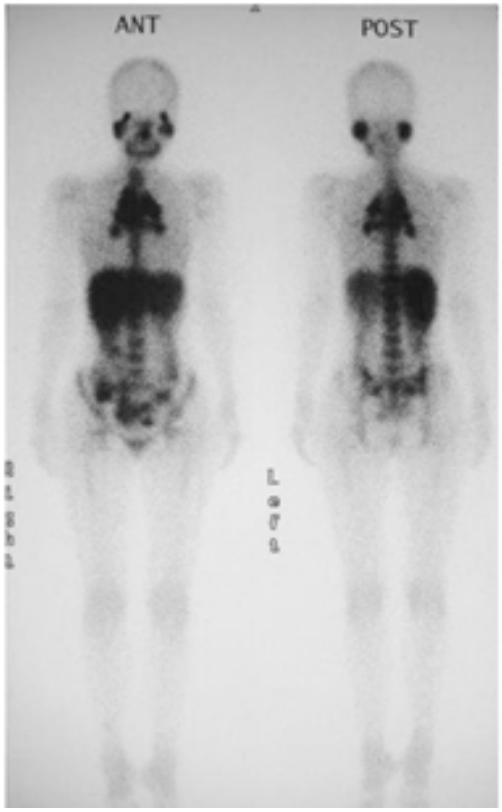

Figure 4. ^{67}Gallium scintigraphy shows intense isotope uptake in mediastinum, bilateral hilum of lung (lambda sign), lacrimal, parotid and submandibular glands (panda sign). The accumulation to the aortic wall was not detectable.

Human leukocyte antigen (HLA) typing using the polymerase chain reaction and a reverse sequence-specific oligonucleotide (PCR-RSSO) was positive for HLA-A1, A24, B37, B52, DR10 and DR15. HLA-B52 is generally considered disease-specific for TA. Moreover, the age of the patient at the time of diagnosis was typical for TA (< 40 years). Additionally, there were no findings suggesting other vasculitis such as systemic lupus erythematosus (SLE), Behçet's disease, Crohn's disease, ankylosing spondylitis, Buerger's disease or temporal arteritis. Hense we diagnosed sarcoidosis accompanied by large vessel involvement due to TA.

Prednisolone (40 mg/day) was started on hospital day 29 to treat the eye lesions and continuous high fever, with a subsequent reduction in these symptoms. Within one week of treatment, the fever, abdominal pain and cough disappeared and the serum CRP level returned to normal. Chest CT two weeks after induction of prednisolone revealed improvements in the pulmonary lesions. Steroid administration for a total of one year was performed. Chest CECT one year later showed marked improvement in the vascular lesions (Fig. 2C, D). The patient has remained free of recurrence despite discontinuance of steroid therapy.

Discussion

Sarcoidosis can affect many organ systems, but large vessel involvement is not a recognised feature of the disease (2). To our knowledge, about a dozen patients with concurrent sarcoidosis and TA have been described in the English literature (2, 5-11). Sarcoidosis generally preceded TA in these patients and the time lag between the two diseases being diagnosed was several years for most of them. About half of these patients had uveitis and a generally good response to steroid therapy. Serological findings of the HLA haplotype of patients with both sarcoidosis and TA have not been described in detail.

The association between the two disorders is rare but not apparently incidental because of their common features. Reports describing Crohn's disease (5, 11, 12), and other granulomatous disorders (13) accompanied by TA further support the notion of a common basis between granulomatous disorders and TA.

The pathogenesis of both sarcoidosis and TA is poorly understood, but it might be the consequence of a chronic immunological response associated with a genetic susceptibility and specific infectious or environmental factors. HLA-B52 has been associated with TA, mainly among the Japanese population (14). On the other hand, the various clinical manifestations of sarcoidosis have been associated with antigens of the major histocompatibility complex. One report from Japan describes significantly increased frequencies of HLA-A1, HLA-Bw46, HLA-Cx46, HLA-DRw8, HLA-DRw9 and HLA-DRw52 in patients with sarcoidosis compared with control individuals (15). Sarcoidosis has been positively associated with HLA-A1, -B8 and -DR3 in patients from the Czech Republic and Italy (16), and HLA-DR15 has been associated with some uveitis entities including sarcoidosis (17). Our patient carried the disease-susceptibility genes HLA-A1, -B52 and -DR15, which might have played some roles in the concurrent sarcoidosis and TA.

In conclusion, we described a female patient with sarcoidosis accompanied by large vessel involvement due to TA. The patient had a high-grade fever that is an uncommon feature of sarcoidosis, she responded well to corticosteroid therapy and both the sarcoidosis and the TA improved. The etiology of these two conditions remains unknown, but the simultaneous occurrence of them does not seem coincidental. Further studies of the attribution of genes in such patients are needed to clarify this mechanism and to identify the etiology of both disorders.

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