Cardiac Sarcoidosis Concomitant with Large-vessel Aortitis Detected by $^{18}$F-fluorodeoxyglucose Positron Emission Tomography

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Abstract:
We herein report a case of concurrent cardiac sarcoidosis and large-vessel aortitis detected by $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) and followed up during immunosuppressive therapy. After high-dose prednisolone administration (1 mg/kg), serial FDG-PET showed that almost all of the abnormal FDG uptake in the heart and extracardiac region, including the abdominal to bilateral iliac arteries, had been disappeared. During the tapering of prednisolone, additive methotrexate therapy was needed to treat the recurrence of cardiac sarcoidosis. FDG-PET is a useful tool for detecting cardiac sarcoidosis concomitant with large-vessel aortitis and monitoring the effectiveness of immunosuppressive therapy.

Key words: cardiac sarcoidosis, aortitis, FDG-PET, prednisolone, methotrexate

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Introduction
Positron emission tomography (PET) is an operator-independent, noninvasive metabolic imaging modality based on the regional distribution of the glucose analogue $^{18}$F-fluorodeoxyglucose (FDG). FDG-PET is a sensitive and specific imaging tool for large-vessel vasculitis (1, 2) and increases the overall diagnostic accuracy in cardiac sarcoidosis (3). Sarcoidosis is a multisystem granulomatous disease of undetermined etiology, involving the lung, heart, liver, spleen, eye, parotid gland, or other organs and tissues (4). To our knowledge, this is the first report of concurrent cardiac sarcoidosis and large-vessel aortitis detected by FDG-PET. The initial high-dose prednisolone treatment markedly diminished the abnormal FDG uptake in both the heart and extracardiac lesions, including the large vessels.

Case Report
A 62-year-old Japanese woman presented to the hospital with shortness of breath and bradycardia. She had a 13-year history of systemic lupus erythematosus and had been treated with a maintenance dose of 5 mg prednisolone. She also had a 5-year history of lung sarcoidosis diagnosed by a trans-bronchial lung biopsy. Electrical cardiography showed advanced atrio-ventricular block, with a heart rate of 44 beat/min. Chest radiography showed bilateral hilar lymphadenopathy, cardiomegaly and mild lung congestion. Echocardiography revealed a depressed left ventricle (LV) systolic function, with an ejection fraction (EF) of 47% and basal thinning of the intraventricular septum. Cardiac sarcoidosis was diagnosed according to the diagnostic guidelines proposed by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (4). The laboratory data were as follows: white blood cell count, 7,100/μL; hemoglobin, 13.2 g/dL; platelet, 18.4×10⁴/μL; erythrocyte sedimentation rate, 26 mm/h; C-reactive protein, 0.35 mg/dL; lysozyme, 6.7 U/L (reference range, 0-10.2 mg/dL); angiotensin-converting enzyme, 14.4 U/L (reference range, 8.3-21.4 mg/dL); soluble interleukin-2 receptor, 510 U/mL (reference range, 272-582 U/mL); serum amyloid A (SAA), 24.4 μg/dL (normal ≤ 1 mg/L).
After one year of immunosuppressive therapy with prednisolone and methotrexate, FDG-PET showed no abnormal FDG uptake in the heart (yellow arrow). References 8 μg/dL; and immunoglobulin 4 (IgG4), 26.9 mg/dL (reference range, 4.5-117 mg/dL). Tests for proteinase 3 antineutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-specific ANCA were negative. The plasma brain natriuretic peptide (BNP) level was elevated at 321.5 pg/mL (normal <18.4 pg/mL).

After elective permanent pacemaker implantation with a REPLY 200 DR pacemaker (Japan Lifeline Co., Ltd. Tokyo, Japan), FDG-PET/computed tomography (CT) was performed with 18-h fasting with a low-carbohydrate diet to reduce the physiological LV FDG uptake (5). FDG-PET showed the accumulation of a high-FDG signal in both the heart and infra-renal abdominal aorta to the bilateral iliac arteries (Fig. 1A). Contrast-enhanced CT showed wall thickening and slight narrowing of the aortic lumen at the same lesion along with the FDG accumulation (Fig. 1C).

The patient was started on high-dose oral prednisolone (1 mg/kg/day, 65 mg/day), which was slowly tapered. Two months later, at a tapered dose of 30 mg prednisolone, serial FDG-PET showed that almost all of the abnormal FDG uptake had been abolished, especially in the extracardiac lesion (Fig. 1B). The findings of enhanced CT also improved si-

Figure 1. FDG-PET and contrast-enhanced CT angiography before (A, C) and after (B, D) steroid therapy. A: FDG-PET image (three-dimensional maximum intensity projection) depicted the focal FDG accumulation in the basal anteroseptal to the lateral wall of the left ventricle (yellow arrow). The extracardiac FDG uptake was also evident along the large vessels from the infra-renal aorta to the bilateral iliac arteries (white arrow) as well as in the hilar and mediastinal lymph nodes and the small nodular lesions of the bilateral upper lobe. B: After tapering prednisolone from 65 mg/day to 30 mg/day over 8 weeks, the abnormal accumulation of FDG was markedly diminished in both the heart (yellow arrow) and extracardiac lesions including large vessels (white arrow). C: Contrast-enhanced CT of the sagittal section of distal abdominal aorta just above the bifurcation, showing the vessel wall thickening and slight narrowing of the aortic lumen (white arrow). D: Contrast-enhanced CT showed recovery of the wall thickness and lumen narrowing compared with (C) (white arrow).

Figure 2. FDG-PET before (A) and after (B) additional methotrexate therapy. A: Follow-up FDG-PET at the tapering dose of 15 mg prednisolone indicated a slightly increased FDG uptake in the basal anteroseptal wall of the left ventricle (yellow arrow), suggesting reactivation of cardiac sarcoidosis. B: After one year of immunosuppressive therapy with prednisolone and methotrexate, FDG-PET showed no abnormal FDG uptake in the heart (yellow arrow). References
multaneously (Fig. 1D). Six months later at a tapered dose of 15 mg prednisolone, FDG-PET revealed the mild re-accumulation of a focal FDG signal in the heart but not within the large vessels (Fig. 2A). The CRP and ESR had decreased to normal levels after starting the steroid therapy, but the levels of the serum inflammation marker SAA (6) had gradually increased from 9.1 to 12.6 μg/dL (normal <8 μg/dL). The BNP level had also risen again from 94.0 to 234.6 pg/mL. Given these results, recurrence of cardiac sarcoidosis was suspected, and additive methotrexate (MTX) therapy at 6 mg/week was started (7). One year after immunosuppressive therapy, at a prednisolone dose of 8 mg/day and MTX dose of 8 mg/week, FDG-PET showed no abnormal FDG uptake in the heart as seen in the previous session (Fig. 2B). The table clearly shows the effect of PSL and additional MTX treatment on the LV function (EF and LV dimensions) and serum biomarkers (SAA and BNP) over the year of follow-up. Additional MTX reduced the serum level of SAA and BNP again and improved the LV function. The level of SAA normalized, while the BNP decreased, however, it was still above the normal range.

**Discussion**

FDG-PET may have potential application for imaging inflammatory cardiovascular diseases, including cardiac sarcoidosis, large-vessel arteritis and atherosclerosis (8). Granulomatous aortitis in sarcoid patients, also known as “sarcoid aortitis” (9), is a rare manifestation of sarcoidosis. Several previous reports have presented cases of large-vessel vasculitis in sarcoidosis patients (9-11); however, no cases have been documented by FDG-PET. When large vessels are involved in sarcoidosis, sarcoi vasculitis may mimic other types of vasculitis, including Takayasu arteritis, which preferentially affects young women with an average age of less than 40 years old. The patient’s age of 62 years at the time of diagnosis was atypical for Takayasu arteritis. Although histology of a biopsy specimen was not available in the present case, we may reasonably assume that this large-vessel vasculitis was not Takayasu arteritis, but rather “sarcoid aortitis”. Weiler et al. (10) reported that sarcoidosis generally precedes aortitis syndrome, and the time lag between the diagnosis of sarcoidosis and that of aortitis syndrome is several years in most patients in concurrent cases of sarcoidosis and aortitis syndrome. The five-year time lag in our case is comparable to their findings. IgG4-related disease (IgG4-RD) is a systemic inflammatory and sclerosing disease characterized by the elevation of the serum IgG4 levels and IgG-4-positive plasmacyte infiltration in tissues, including the cardiovascular system and especially the abdominal aorta (12). We believe that IgG4-RD was not involved in the present case, as the laboratory examinations showed that the serum IgG4 level was not elevated (at 26.9 mg/dL) at baseline, and serial FDG-PET/CT did not reveal any extravascular involvement typical of IgG4-RD, such as the pancreas, lacrimal and/or salivary glands, retroperitoneum, or bile duct.

Physicians should therefore be aware that cardiac sarcoidosis and asymptomatic large-vessel aortitis can coexist. High-dose prednisolone was initially effective in treating both lesions but additive MTX was needed to treat the recurrence of cardiac sarcoidosis during the tapering of prednisolone. FDG-PET is a useful tool for detecting cardiac sarcoidosis concomitant with large-vessel aortitis and can also be used to monitor the effectiveness of such treatment.

**The authors state that they have no Conflict of Interest (COI).**

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