—Case Reports—

Bone Marrow Sarcoidosis with Pancytopenia and Renal Failure Presenting as Fever of Unknown Origin: The Pivotal Role of 18F-FDG PET/CT in Lesion Detection

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We describe a case of fever of unknown origin (FUO), renal failure, and pancytopenia. Initially, lymph proliferative disorder was suspected; therefore, bone marrow biopsy and 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) were performed. Bronchoscopy and lung biopsy were performed because of abnormal FDG uptake in both lung fields. Imaging data and laboratory and histological results confirmed sarcoidosis with bone marrow invasion. The patient was discharged after favorable response to corticosteroid therapy. Sarcoidosis may present as FUO without typical specific presentations in the skin or lungs. Combined 18F-FDP PET/CT helped identify the biopsy site and confirmed the sarcoidosis diagnosis. (J Nippon Med Sch 2021; 88: 145–148)

Key words: sarcoidosis, fever of unknown origin, 18F-FDG PET/CT scan, lung biopsy, bone marrow sarcoidosis

Introduction

Sarcoidosis is a chronic idiopathic inflammatory disease that primarily affects the lungs and skin but can occur in other organs[1]. Clinical presentation varies in relation to the organ affected, and one third of patients present with nonspecific constitutional complaints, including fever, fatigue, malaise, and weight loss[2,3]. Moreover, sarcoidosis is a rare but important cause of fever of unknown origin (FUO)[4]. Because a sarcoidosis diagnosis is established by demonstrating non-caseating granulomas in lesions, it is crucial to identify the affected organ for biopsy. However, in some patients without obvious organ-specific manifestations, diagnosis is exceedingly difficult.

Recently, 18F-fluorodeoxyglucose with positron emission tomography (18F-FDG PET) has gained attention as an auxiliary diagnostic method for cancer and inflammatory diseases, including sarcoidosis. Furthermore, the fusion of 18F-FDG PET with computed tomography (CT) (18F-FDG PET/CT) was found to improve diagnostic accuracy and cancer staging[5]. As reported previously, 18F-FDG PET/CT-guided biopsy of soft tissues increases the probability of identifying sarcoidosis as the main cause of FUO[6–8]. In this case report, we describe a patient with FUO, pancytopenia, and renal failure who was incidentally diagnosed with bone marrow sarcoidosis by using 18F-FDG PET/CT.

Case Report

A 51-year-old man presented with FUO and a history of dilated cardiomyopathy, type 2 diabetes, complete atrioventricular (AV) block, and hyperthyroidism. A pacemaker was implanted for complete AV block 10 years previously. During the previous 10 years, he had several episodes of heart failure due to dilated cardiomyopathy. Cardiac biopsy was performed but the results were not definitive. Although his HbA1c was 10% to 12% during

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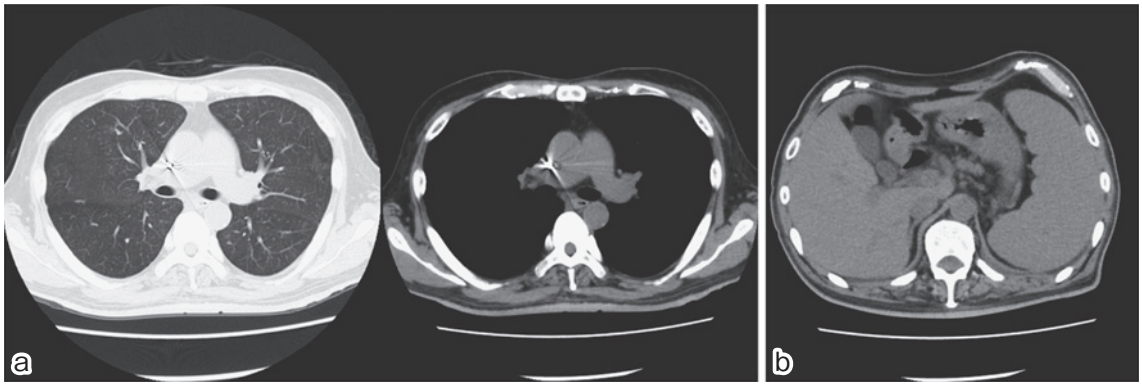

Fig. 1
a Chest computed tomography (CT) scan showing no abnormalities in the lung or mediastinum.
b An abdominal CT showing splenomegaly.

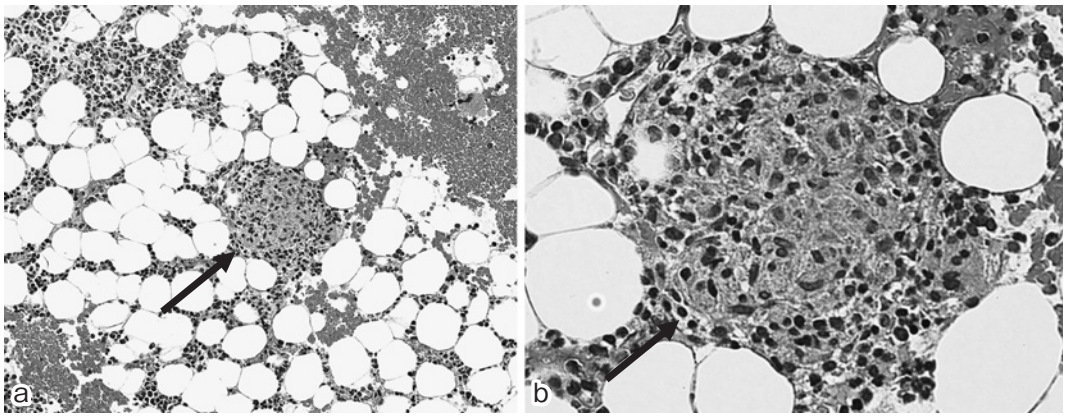

Fig. 2 Histological findings of bone marrow biopsy at low magnification (50×, a) and high magnification (400×, b). Granulomas were present in hypocellular bone marrow. The arrow indicates the same site.

2007-2010, recent hospital visits were more regular and his diabetes was well controlled (HbA1c, 6% to 7%).

He experienced sudden fever, joint pain, night sweats, nausea, and fatigue, which started 2 weeks before visiting our hospital. He was administered 400 mg of acetaminophen 3 times a day until hospitalization, but fever persisted. At presentation, his body temperature was 38.5°C and O_2 saturation at rest and in room air was 97%. Blood pressure was 76/42 because of dehydration due to fever. Physical examination revealed no abnormalities. A complete blood count revealed pancytopenia, with a white blood cell count of 2×10^9/L (2,000 cells/mm^3), a hemoglobin of 8.1 g/dL, and a platelet count of 67×10^9/L. Blood chemistry revealed aspartate aminotransferase, 41 U/L; alkaline phosphatase, 389 U/L; γ-glutamyl transpeptidase, 91 U/L; blood urea nitrogen, 47 mg/dL; creatinine, 4.05 mg/dL; and C-reactive protein (CRP), 0.92 mg/dL. A chest radiograph showed no abnormalities, and a CT scan of the neck, chest, abdomen, and pelvic region showed no significant findings, such as mediastinal or hilar lymphadenopathy, except for splenomegaly (**Fig. 1**). Thus, malignancy-related fever was deemed unlikely. Because 2 blood culture sets were negative, with minor CRP elevations and no elevation of β-D-glucan, infection was also unlikely to be the cause of fever. An additional blood test showed that soluble interleukin-2 receptor (sIL2-R) was 3,890 U/mL (normal, 145-496 U/mL) and that collagen-related markers such as anti-double-stranded DNA, anti-single-stranded DNA, anti-ribonucleoprotein antibody, anti-ss-A Ab, anti-ss-B Ab, rheumatoid factor, MPO-ANCA, PR3-ANCA, and anti-CCP were all within their normal ranges. Fever, night sweats, splenomegaly, pancytopenia, and sIL2-R elevation suggested the possibility of lymphoproliferative disorder in a differential diagnosis. Bone marrow aspiration and bone marrow biopsy showed a non-caseating granulomatous lesion (**Fig. 2**). Nevertheless, stains for acid-fast bacilli and fungi did not yield a definitive diag-

nosis. This, along with an increase in angiotensin-converting enzyme (ACE) level to 37.2 U/L (normal, 8.3-21.4 U/L), indicated a probable diagnosis of sarcoidosis. 18F-FDG PET/CT detected increased metabolic activity in the lower lobes of the lungs (**Fig. 3**), and the patient was hospitalized for bronchoscopy and transbronchial lung biopsy (TBLB). TBLB from the right lower lobe showed a non-caseating granulomatous lesion (**Fig. 4**), and bronchoalveolar lavage yielded a high number of lymphocytes. Taken together, the findings confirmed a diagnosis of sarcoidosis with bone marrow invasion.

The patient was started on prednisolone 30 mg/day (0.5 mg/kg/day). He was responsive to corticosteroid therapy. Fever resolved within 3 days and pancytopenia improved within 14 days. Blood urea nitrogen and creatinine returned to their previous ranges at 1 month after prednisolone initiation. The patient was hospitalized for 1 month, including the lung biopsy. He was continued on 30 mg/day of prednisolone after discharge, and the dose was tapered by 5 mg every 4 weeks at regular monthly follow-ups. ACE level normalized and was maintained with prednisolone 7.5 mg/day, and fever completely resolved. The patient gave his informed consent for publication of this report.

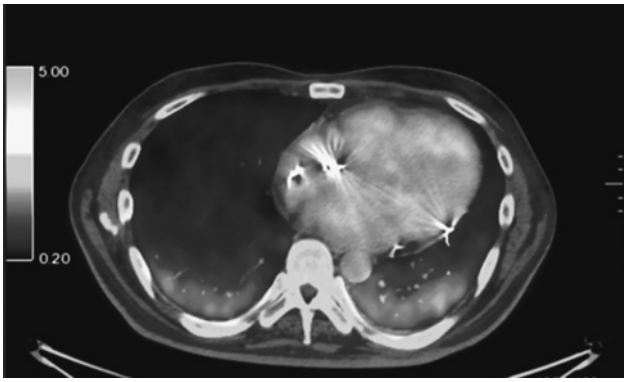

Fig. 3 A fusion image of 18F-fluorodeoxyglucose (FDG) with positron emission tomography/computed tomography in the lower lung showing increased uptake of FDG in the dorsal area bilaterally.

Discussion

Although a case report described bone marrow sarcoidosis with lung involvement in Japanese patients[8], this is the first report of bone marrow sarcoidosis in a patient with no apparent abnormality on an initial chest radiograph or CT scan. Patients with sarcoidosis may present with nonspecific systemic symptoms such as malaise, lethargy, night sweats, and FUO[2,3,9,10]. Fever, weight loss, fatigue, and malaise are the presenting symptoms in 25% of sarcoidosis cases[11]. Although FUO is a relatively rare cause of sarcoidosis[4], it should be included in the differential diagnosis because it responds well to corticosteroids. Our patient had fever, acute renal failure, and pancytopenia but no respiratory problems such as dry cough, dyspnea, or nonspecific chest pain. Additionally, initial assessment by chest radiography and CT scan revealed no abnormality suggestive of pulmonary sarcoidosis.

Bone marrow biopsy may be performed to investigate FUO, and incidental findings of bone marrow granuloma are rare. Differential diagnosis of bone marrow granuloma should include malignancy, infection, drugs for treatment of other diseases, and sarcoidosis[12]. The incidence of granulomatous lesions in bone marrow was 0.6% in a series of 9,641 bone marrow biopsies, of which 21% were related to sarcoidosis[13]. Although sarcoidosis is one of the most frequent causes of bone marrow granuloma, isolated extrapulmonary involvement was noted is

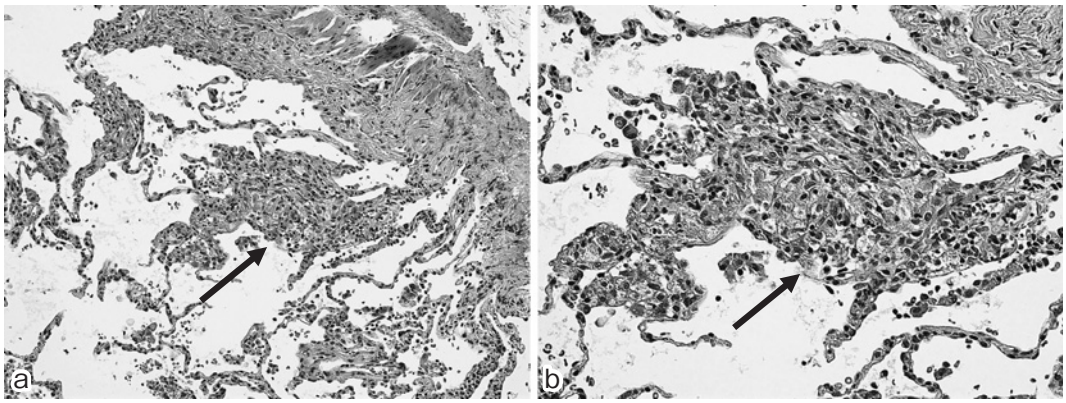

Fig. 4 Histological findings of lung biopsy at low magnification (50×, a) and high magnification (400×, b). The arrow indicates non-necrotizing granulomas, which confirmed the diagnosis of sarcoidosis.

fewer than 5% of cases[12]. Because bone marrow sarcoidosis is not generally accompanied by hematological abnormality[14], bone marrow biopsy is unlikely. Therefore, bone marrow sarcoidosis may be underdiagnosed[14].

Our patient had a history of dilated cardiomyopathy, complete AV block, and pacemaker implantation 10 years previously. Sarcoidosis may have been related to these cardiac problems. Although no histological evidence of sarcoidosis was identified by myocardial biopsy, cardiac involvement might have been missed because its diagnostic yield is reportedly 20% to 50%[15]. Thus, this case exemplifies the challenge of diagnosing isolated cardiac sarcoidosis.

Conclusion

In this report, we presented a rare case of sarcoidosis presenting as FUO with bone marrow granuloma. Despite the absence of abnormal findings on initial chest radiography and CT, 18F-FDG PET/CT led to lung biopsy, which culminated in a final diagnosis of sarcoidosis. Thus, clinicians should consider performing 18F-FDG PET/CT-guided biopsy whenever FUO is suspected as a cause of sarcoidosis.

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Conflict of Interest: None.

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