INTERNAL MEDICINE

□ CASE REPORT □

Disseminated *Mycobacterium tuberculosis* Infection Masquerading as Metastasis after Heavy Ion Radiotherapy for Prostate Cancer

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Abstract

Fluorodeoxyglucose (FDG)-positron emission tomography with computed tomography (FDG-PET/CT) is useful in disease monitoring of malignancies after therapy, while an FDG uptake may also be present in benign diseases. We herein demonstrate a case of disseminated *Mycobacterium tuberculosis* mimicking systemic metastasis of prostate cancer. This case highlights that clinicians should consider *Mycobacterium tuberculosis* in patients with prostate cancer who demonstrate multifocal FDG uptakes masquerading as metastasis, even when the chest photographs reveal a normal appearance and a sputum examination demonstrates negative results. An invasive surgical biopsy may be required and a pathological analysis would be critical in the diagnosis of *Mycobacterium tuberculosis*.

Key words: *Mycobacterium tuberculosis*, FDG-PET/CT, prostate carcinoma, metastasis

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Introduction

Mycobacterium tuberculosis involving any site may produce systemic symptoms. The frequency of a fever ranges from 37-80% and loss of appetite, weight loss, weakness, night sweats, and malaise are also common, although there are some asymptomatic patients as well. The main difficulty with extrapulmonary specimens is that they yield very few bacilli and consequently are associated with a low sensitivity on acid-fast bacillus (AFB) smears and cultures. If the analysis for tuberculosis is negative in the sputum, gastric secretion and urine, then sampling by a surgical biopsy or needle aspiration are mandatory for the diagnosis. Fluorodeoxyglucose (FDG)-positron emission tomography with computed tomography (PET/CT) is useful for diagnosing and staging primary tumors, detecting locally recurrent and/or metastatic disease, assessing the extent of metabolically active castrate-resistant disease, monitoring treatment responses and in prognosticating. On the other hand, its contribution to the diagnosis of a fever of unknown origin, inflammatory conditions and occult infections is increasingly reported. Thus, physicians should pay careful attention to the assessment of an intense FDG accumulation at the time of diagnosis or during the course of treatment. We herein demonstrate a case of disseminated *Mycobacterium tuberculosis* mimicking systemic metastasis during the treatment course after heavy ion radiotherapy for prostate cancer.

Case Report

A 71-year-old man was referred to our institution to investigate FDG-PET/CT results with multifocal 18-fluorodeoxyglucose (18F-FDG) uptakes. He was diagnosed with prostate cancer (T2aN0M0) and treated with bicalutamide, a non-steroidal androgen receptor inhibitor, for 12 months with sequential heavy ion radiotherapy. Two months after radiotherapy, FDG-PET/CT demonstrated multifocal in-

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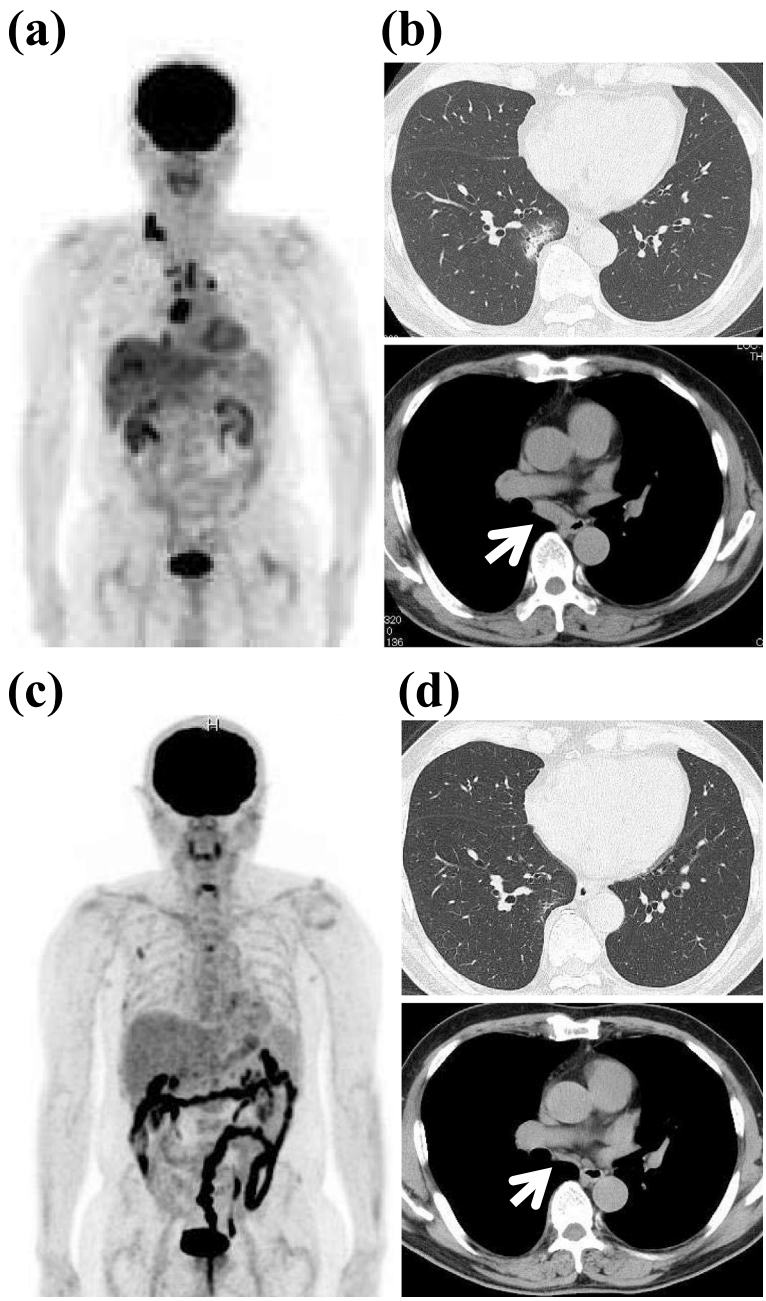

Figure 1. **(a) FDG-PET/CT showed multifocal uptake lesions of supraclavicular and mediastinal lymphadenopathies, right lobe of the liver, right lower lobe of the lung, third right rib, fourth lumbar vertebra and prostate (supraclavicular lymph node: maximum standardized uptake value (mSUV) 9.85, supramediastinal lymph node: mSUV 4.73, paraaortic lymph node: mSUV 6.31, subcarinal lymph node: mSUV 12.31, right lobe of liver: mSUV 6.23, right lower field of the lung: mSUV 4.54, third right rib: mSUV 2.04, the fourth lumbar vertebra: mSUV 2.64, and prostate: mSUV 7.2). (b) Conventional CT showed infiltrations on S7 and subcarinal lymph node swelling (arrow). (c) Follow-up FDG-PET/CT one year after antibiotic treatment showed an improvement in the multifocal intensity lesions, confirming the efficiency of antituberculosis therapy. (d) Follow-up CT showed an improvement in the lung fields and subcarinal lymphadenopathy (arrow).**

tense FDG accumulations in supraclavicular and mediastinum lymphadenopathies, the liver, lung, rib and vertebral columns (Fig. 1a). He had a slight visual disturbance due to glaucoma and was an ex-smoker. Regarding his family history, his mother and grandmother had suffered from tuberculosis although the patient had not been previously diagnosed with tuberculosis.

On a physical examination, he was afebrile, with a regular pulse of 64 beats/min and blood pressure of 103/63 mmHg. A complete blood count (CBC) showed a leukocyte count of 4,960/μL with 45.9 % neutrophils and 28.5% lymphocytes (normal range: 20-44%). A blood chemistry analysis showed

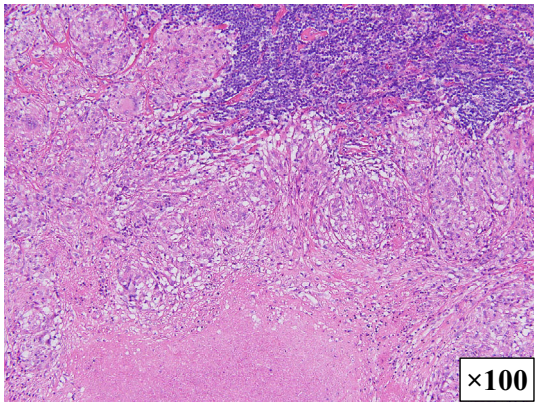

Figure 2. Hematoxylin and Eosin staining specimens. The supraclavicular lymph node biopsy showed granulomatous inflammation with caseous necrosis and multinucleated giant cells. Magnification: 100×.

an aspartate aminotransferase (AST) level of 15.3 IU/L (normal range: 13-33 IU/L), alanine aminotransferase (ALT) level of 15.1 IU/L (normal range: 8-42 IU/L), lactate dehydrogenase (LDH) level of 213 IU/L (normal range: 124- 222 IU/L), albumin level of 3.9 g/dL (normal range: 3.0-4.9 mg/dL), C-reactive protein (CRP) level of 0.05 mg/dL (normal range: <0.25 mg/dL), ACE level of 16.3 U/L (normal range: 7-25 U/L), lysozyme level of 7.4 μg/mL (normal range: 5-10 μg/mL) and sIL-2R level of 529 U/mL (normal range: 127-582 U/mL). Prostate-specific antigen (PSA) decreased to 0.02 ng/mL (normal range: <4.0 ng/mL) although it was 12.78 ng/mL before starting treatment for prostate cancer. A sputum examination demonstrated negative results from an AFB smear and polymerase chain reaction (PCR) for *Mycobacterium* species, while an interferon-gamma release assay (IGRA) showed a positive result and a purified protein derivative (PPD) skin test was strongly positive.

A chest radiograph showed no abnormalities. Chest CT showed infiltrations on S1 and S7 and multiple lymphadenopathies of the right supraclavicular, para-aortic and mediastinum lymph nodes (Fig. 1b). At this time, the differential diagnosis included metastasis of prostate cancer or other type of malignancy, sarcoidosis, tuberculosis and malignant lymphoma. The specimens obtained from a transbronchial lung biopsy (TBLB) pathologically showed non-caseous epithelioid granulomas and *Mycobacterium* was not detected by the AFB smear, culture or PCR. Additionally, a bronchoalveolar lavage fluid (BALF) analysis demonstrated a mild increase in the lymphocyte profile (28.3%) and an increase in the CD4/8 ratio (7.69). The specimens obtained from endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) showed non-caseous epithelioid granulomas and the AFB smear and PCR for *Mycobacterium tuberculosis* were negative. At this time, sarcoidosis was suspected, however, the patient's PSA level was normal and the PPD skin test and IGRA were both positive. These findings allowed us to rule out any other diagnosis, such as a sarcoid-like reaction due to a malignancy or mycobacterial infection, thus a surgical supraclavicular lymph node biopsy was subsequently performed. The biopsy specimen showed granulomatous inflammation with caseous necrosis and multinucleated giant cells, which was consistent with a mycobacterial infection and no evidence of malignancy (Fig. 2). Consequently, the patient was diagnosed with disseminated *Mycobacterium tuberculosis* infection.

The patient was initially started on isoniazid 300 mg daily, rifampicin 600 mg daily, ethambutol 750 mg daily and pyrazinamide 1,500 mg daily for two months, followed by isoniazid 300 mg daily and rifampicin 600 mg daily for seven months. Follow-up CT showed an improvement in the pulmonary infiltrations and lymphadenopathies and FDG-PET/CT showed a significantly decreased intensity of the multifocal lesions detected prior to treatment (Fig. 1c and d).

Discussion

The incidence rate of prostate carcinoma is 11.4% and it is the fourth most prevalent cancer in Japanese men (1). According to the analysis of an autopsy series, lymph nodes, bones, lung and liver are the most frequent metastatic sites of prostate carcinoma (2). FDG-PET/CT provides fused images that demonstrate the complementary roles of functional and anatomic assessments in the diagnosis of carcinoma recurrence through the precise localization of suspected 18F-FDG foci and their characterization as malignant or benign. However, FDG is not a cancer-specific agent, and false positive findings in benign disease have been reported. Infectious diseases (e.g., mycobacterial, fungal, and bacterial infection), sarcoidosis, radiation pneumonitis and postoperative surgical conditions have shown intense uptakes on PET scans. We herein demonstrated a case of multifocal intense 18F-FDG accumulations related to tuberculosis mimicking recurrent prostate cancer after heavy ion radiotherapy.

The serum level of PSA is useful for monitoring the disease activity of prostate carcinoma despite its limited sensitivity (PSA levels might be undetectable or low in some cases of disseminated disease) and specificity (high levels are occasionally associated with benign disease). FDG-PET/CT has shown the ability to assess disease progression along all known routes of prostate cancer recurrence, although the likelihood of tumor detection may be related to the PSA level (3). Tuberculoma is one of the most well-known diseases that show an intense FDG uptake. Active granulomatous processes have been reported to accumulate FDG, in which active inflammatory cells have markedly increased glycolysis and the hexose monophosphate shunt is stimulated by phagocytosis, which increases approximately 20-30 times the baseline values, leading to a high FDG uptake (4). However, the uptake rates of 18F-FDG and 11C-choline may be useful for differentiation. The uptake of 11C-choline is linked to an increase in cell membrane synthesis and tumor cell proliferation. If the lesion size measures greater than 1.5 cm, then the SUV of 18F-FDG is very high and

that of 11C-choline is relatively high in lung cancer, while the former is relative high and the latter is low in tuberculosis. If the lesion size measures less than 1.5 cm, then the difference is not as apparent (5). This procedure may help to differentiate tuberculous granuloma from lung cancer, however, a prospective study is necessary.

Tuberculosis should be considered in the differential diagnosis when a patient has positive results for the IGRA and PPD skin test and a history of previous tuberculosis contact. In the present case, the specimens obtained by TBLB and TBNA demonstrated epithelioid granuloma, however, the AFB smear, culture and PCR analysis showed negative results. Consequently, the surgical cervical lymph node biopsy specimens demonstrated granulomatous inflammation with caseous necrosis and multinucleated giant cells consistent with a mycobacterial infection, although the AFB smear, culture and PCR analysis at this time were also negative. The diagnosis of tuberculosis involving the lymph nodes or sinus tract is based on three or more of the following criteria: (i) cervical mass or draining sinus; (ii) skin sensitivity to purified protein derivative S (PPD-S); (iii) compatible histopathological appearance of biopsied tissue, usual caseous granuloma; (iv) demonstration of AFB on biopsy specimens; (v) growth of *Mycobacterium tuberculosis* from the biopsy specimen or aspirated pus, and (vi) a definite response to specific antituberculosis chemotherapy (6). The present case demonstrated at least four out of six criteria described above, thus fulfilled the diagnose criteria of tuberculous cervical lymphangitis. The diagnosis of extrapulmonary tuberculosis is difficult due to very few bacilli cultured from the specimens; the lack of adequate sample amounts or volumes; the apportioning of the sample for various diagnosis tests, such as histology/cytology, a biochemical analysis, microbiology and PCR; and the presence of inhibitors that undermine the performance of nucleic acid amplification-based techniques that are universally applicable for all types of extrapulmonary samples (7). Thus, the pathological analysis is crucial for the diagnosis of extrapulmonary tuberculosis.

The incidence of late gastrointestinal and genitourinary morbidities has been shown to be due to adverse reactions of heavy ion radiotherapy for prostate cancer, while that of *Mycobacterium tuberculosis* infection has not yet been elucidated. Classically, pulmonary tuberculosis can be divided into a primary and a post-primary pattern, each presenting with characteristic radiological features. On radiology, primary tuberculosis manifests as four main entities, parenchymal disease, lymphadenopathy, pleural effusion and miliary disease, while post-primary tuberculosis manifests as parenchymal disease, airway involvement, and pleural effusion. The distinguishing features of post-primary tuberculosis include a predilection of the upper lobes, the absence of lymphadenopathy and cavitation (4, 8). Therefore the present case may be recognized as primary tuberculosis according to the radiographic findings. Primary tuberculosis may progress, thereby causing disseminated tuberculosis, especially in very young patients or immunosuppressed individuals. Radiation therapy has been shown to alter the immune system by changing the number, balance and interaction of immune cells, which are essential for protection against tuberculosis. Although, a previous case report showed reactive tuberculosis following local radiation therapy for prostate cancer (9), to the best of our knowledge, the present case is the first case report to demonstrate *Mycobacterium tuberculosis* following local heavy ion therapy for prostate cancer. In order to discuss the relationship between the incidence of *Mycobacterium tuberculosis* infection and heavy ion radiotherapy, a further accumulation of cases treated with heavy ion radiotherapy is necessary.

In the present case we had to rule out sarcoidosis because of the presence of non-caseous granuloma in the specimens obtained from TBLB and EBUS-TBNA and an increase in lymphocyte profile and CD4/8 ratio. A meta-analysis indicated that almost 30% of all patients with sarcoidosis demonstrated the presence of mycobacterial nucleic acids within the lesions (10). In addition, Chen et al. identified a specific *Mycobacterium* protein, the catalase-peroxidase protein (mKatG) in 55% of sarcoidosis tissues using a proteomic approach, mKatG may show a T-cell response which leads to formation of granulomas (11). The non-caseous granulomatous lesions in the present case may represent a sarcoid-like reaction due to the *Mycobacterium* antigens. Because it is very rare that tuberculosis and sarcoidosis occur concomitantly (12-14) and the IGRA and PPD skin test demonstrated positive results in the present case, explanation for why the AFB smear, culture and PCR for *Mycobacterium tuberculosis* were negative may be due to the fact that the bacilli were either small in number or absent in the specimens. As a result, mycobacterial involvement in sarcoid pathogenesis remains controversial.

We conducted a search using the PubMed database and 11 cases with *Mycobacterium tuberculosis* masquerading as metastasis or recurrence of malignancy revealed by multifocal FDG uptakes on FDG-PET/CT were identified, including the present case (15-21). There was no information regarding the source of primary carcinoma or the period between the onset and diagnosis of malignancy. The incidence of tuberculosis was not related to whether any type of chemotherapy was administered. Interestingly, an intense FDG uptake in the lung fields was found in only one case, whereas the uptake in lymph nodes tended to be more frequently observed (Table). Considering that most of the cases were diagnosed with extrapulmonary tuberculosis, an analysis of a standard sputum examination may not be helpful for the diagnosis of tuberculosis. Sunnetcioglu et al reported that the main diagnostic modalities for pulmonary tuberculosis were a sputum/smear analysis (72.7%), clinical-radiological data (21.7%) and a biopsy (6.1%), while a biopsy (71.5%), a sputum/fluid analysis (18.5%) and clinical-radiological data (4.9%) were used to confirm extrapulmonary tuberculosis (22). To clarify suspected recurrence or metastasis of malignancy, invasive surgical biopsies and pathological examinations are required in the diagnosis of intense FDG uptake

Table. Characteristics of Patients Diagnosed with *Mycobacterium tuberculosis* Mimicking Recurrence of Metastasis of Malignancy on FDG-PET/CT.

Age	Gender	Primary carcinoma	Duration after malignancy diagnosis	Diagnostic approach	During chemotherapy (yes, no)	PET positive lesion	SUVmax	Reference
52	F	Cervical cancer	8 weeks	Mediastinal lymph node biopsy	no	Mediastinal lymph node	5.5	15
49	F	Lymphoma	3 weeks	Mediastinal lymph node biopsy	yes	Cervical, Supraclavicular, Retropharyngeal, Mediastinal lymph node	5.2	15
47	F	Breast cancer	72 weeks	Excisional lymph node biopsy	yes	Supraclavicular, Cervical lymph node	16.0	16
56	F	Colon cancer	32 weeks	Axillary and mediastinal lymph node biopsy	yes	Axillary, Supraclavicular, Mediastinal, hilar lymph node Abdominal wall related to surgical intervention	24.0	16
58	F	Lymphoma	48 weeks	Supraclavicular and axillary lymph node biopsy	no	Axillary, Supraclavicular lymph node	20.0	16
17	M	Thyroid cancer	24 weeks	Fine needle aspiration cytology	no	Supraclavicular lymph node	8.96	17
65	M	Lymphoma	20 weeks	Prostatectomy and orchiectomy	yes	Prostate Testicle	6.4	18
67	M	Lung cancer	41 weeks	Video assisted thoracoscopic surgery	no	Lung	6.1	19
15	M	Ewing's sarcoma	6 weeks	Fine needle aspiration biopsy	no	Liver	14.6	20
49	M	Anal canal cancer	44 weeks	Lapaloscopic lymph node biopsy	no	Hepatic hilum lymph node	4.48	21
71	**M**	**Prostate cancer**	**14 weeks**	**Cervical lymph node biopsy**	**no**	**Supraclavicular, Mediastinal lymph node, lung, liver, bone**	**12.31**	**Present case**

lesions on FDG-PET/CT.

In conclusion, we should keep *Mycobacterium tuberculosis* infection in mind in the differential diagnosis, except in the case of recurrence and/or metastasis, when an elevated FDG uptake on FDG-PET/CT is demonstrated in patients with prostate cancer at the diagnosis and/or follow-up period. A sputum examination may not necessarily be helpful in the diagnosis, however, histopathological examinations are critical; thus, invasive surgical biopsies may be required.

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

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