Case report

Atypical sarcoid reaction mimicking recurrence on F-18 FDG PET/CT in a patient with breast malignancy✩

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ABSTRACT

Malignancy may lead to sarcoidosis, which is referred to as sarcoid reaction. This reaction is believed to be a host immune response to the release of soluble antigens from cancer cells. Studies have shown strong 2'-deoxy-2'-[F-18]fluoro-D-glucose (F-18 FDG) uptake in sarcoid reaction and in true sarcoidosis. Therefore, in patients with malignancy, sarcoid reactions can mimic metastasis or recurrence on F-18 FDG positron emission tomography/computed tomography (PET/CT). Herein, we report the case of a 58-year-old woman with a history of left breast cancer whose FDG PET/CT evaluated at 3 months after adjuvant chemotherapy presented hypermetabolic lymphadenopathy in the right supraclavicular and right mediastinal areas. We interpreted these as metastases because the involved lymph nodes were intensely hypermetabolic and appeared newly. Pathologic evaluation of the excised lymph node revealed noncaseating chronic granulomas without malignant cells, indicating a sarcoid reaction. After appropriate steroid therapy, both the size and metabolic activity of the lymphadenopathy substantially decreased. Most sarcoid reactions present as bilateral hilar and peribronchial lymphadenopathies. Our patient presents an atypical example that a sarcoid reaction can also present in a unilateral pattern, making its diagnosis challenging.

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Introduction

Sarcoidosis is an idiopathic systemic disorder characterized by epithelioid cell granuloma without caseation. Although it mostly manifests mediastinal lymphadenopathy, lung parenchymal involvement, and skin or ocular symptoms, the clinical manifestations vary with the involved organ [1]. Sarcoidosis has also been observed in patients with malignancy, and numerous studies have reported an association between sarcoidosis and malignancy [2–9]. Such tumor-related, noncaseating granulomas have been termed ‘sarcoid reactions’, which are not indicative of systemic sarcoidosis [2]. Sarcoid reactions are believed to be immune responses to soluble antigenic factors released by the tumor cells [3].

2′-deoxy-2′-[F-18]fluoro-D-glucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) imaging is widely accepted in oncologic diagnosis. Although sarcoid reactions are uncommon, discriminating them from malignancies is challenging because sarcoidosis is a highly FDG-avid disease process. Herein, we report an atypical pattern of sarcoid reaction in FDG PET/CT images of a patient with breast malignancy.

Case report

A 58-year-old woman had a history of left breast cancer (pT1aN0) that was treated 40 months earlier using total mastectomy, followed by 6 cycles of chemotherapy with cytoxan, methotrexate, and fluorouracil. FDG PET/CT imaging was performed 3 months after the completion of chemotherapy, and it revealed hypermetabolic lymphadenopathy (SUVmax, 11.5) in the right supraclavicular, right mediastinal, and right perihilar areas (Fig. 1A). We interpreted those as metastases because the involved sites were intensely hypermetabolic, and did not appear on preoperative CT examination. Fine-needle aspiration cytology of the right supraclavicular lymph node suggested chronic granulomatous lymphadenitis. The patient had refused excisional biopsy; hence, empirical anti-tuberculosis treatment was started. FDG PET/CT imaging repeated 1 year later showed that hypermetabolic lymphadenopathy (SUVmax, 14.4) was aggravated and involved the bilateral supraclavicular, bilateral mediastinal, and intraperitoneal areas (Fig. 1B). Subsequently, an excisional biopsy of the supraclavicular lymph node was performed. The pathologic evaluation revealed noncaseating chronic granulomas composed of epithelioid histiocytes without necrosis. No evidence of malignant cells was seen (Figs. 2A and B). PCR tests for *Mycobacterium tuberculosis* and *nontuberculous Mycobacteria* were negative, and a special stain for acid-fast bacillus was also negative. The serum angiotensin-converting enzyme level was slightly elevated (76.4 IU/L). These findings suggested that the granulomas were because of a sarcoid reaction associated with breast cancer. After appropriate steroid therapy, follow-up FDG PET/CT imaging revealed that both the size and metabolic activity of lymphadenopathy markedly decreased (Fig. 1C).

Discussion

Sarcoid reactions are noncaseating granulomatous reactions in patients with malignancy and are not indicative of systemic sarcoidosis [2]. These reactions have been described in patients with various malignancies; their reported incidence is 4.4% among patients with carcinoma, 13.8% among those with Hodgkin disease, and 7.3% among patients with non-Hodgkin lymphomas [2].

Although the etiology of sarcoid reactions is not yet fully elucidated, they are speculated to be secondary reactions to a T-cell mediated host response to soluble antigenic tumor factors likely originating from the tumor cells or released because of tumor necrosis [2–4]. Thus, some reports have described the association between sarcoid reaction and good prognosis with the inhibition of tumor growth by the immune reaction in patients with a malignancy [5,6]. In our case, the reaction was detected after chemotherapy, and the involved sites were the right supraclavicular and right mediastinal lymph nodes, which were not parts of the regional lymph nodes. A plausible explanation is that causative antigens shed from the dead tumor cells owing to chemotherapy could have induced the host’s immune response, resulting in the formation of the noncaseating granulomas. However, the reason why sarcoid reactions did not occur in the regional lymph node, which is the most common site, remains unclear.

The recent increase in the use of FDG PET/CT imaging has resulted in increased detection of sarcoid reactions [7–13]. Chowdhury, et al. reviewed 2048 patients with solid-organ malignancies and reported the prevalence of FDG PET/CT-detected sarcoid reactions to be 1.1% [13]. As sarcoidosis has high FDG-avidity, all previous studies have shown a high FDG uptake. As such, differentiating a sarcoid reaction occurring during treatment from the progression of malignancy could be challenging. In our patient, only the right side of the supraclavicular and mediastinal lymph nodes showed a high FDG uptake. Given this unusual finding for sarcoidosis and aggravating lesions, we suspected a recurrence of malignancy.

The maximum standardized uptake value (SUVmax) on FDG PET/CT imaging has been used in clinical practice to discriminate between malignant and benign lesions. However, Chowdhury et al. reported that SUVmax varies over a wide range for sarcoid reactions; therefore, SUVmax may not yield
sufficient discriminatory value [13]. $SUV_{\text{max}}$ varied widely in our case too (5.7-14.4). Furthermore, in our case, hypermetabolic lymphadenopathy was observed only in the right side of the supraclavicular, mediastinum, and perihilar areas initially, whereas the primary malignancy was located in the contralateral breast. In addition, the breast malignancy was early-stage malignancy (T1a), and no lymph node metastasis was seen on pathologic evaluation. Mediastinal and perihilar lymph nodes metastasis, without the involvement of regional lymph node, is uncommon in breast cancer, particularly if the lesions are not seen on the pretreatment FDG PET/CT and the patient is in complete remission.

Nevertheless, because the imaging findings of a sarcoid reaction can overlap considerably with those of a malignancy, pathologic evaluation is critical for a definite diagnosis. Aide et al. noted that FDG uptake was decreased in sarcoidosis immediately after steroid therapy; therefore, short-term steroid therapy could help differentiate between sarcoid reaction and malignancies [14]. However, this method is not recommended in case of lymphoma because steroid therapy could decrease FDG uptake in both sarcoid reactions and lymphoma [14]. The onset of sarcoid reaction has been reported vary. It may occur during chemotherapy or a prolonged duration after treatment completion. One study reported its onset was 9-86 months after the initiation of therapy, and 44% of patients had recurring or persistent malignancy at the same time [15]. Another study found that sarcoid reaction developed from 6-70 months after complete remission from malignancies [16].

In conclusion, a sarcoid reaction can mimic the recurrence of malignancy on FDG PET/CT images. Although the occurrence of a sarcoid reaction after therapy is rare, it is possible and hence should be considered. Furthermore, when interpreting FDG PET/CT images, awareness of the variable distribution pattern of sarcoid reactions is crucial. Clinical

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Fig. 1 – F-18 FDG PET/CT images of the patient (A) Intense hypermetabolic lymphadenopathy in the right supraclavicular, right mediastinal, and right perihilar areas can be seen, suggesting metastasis. (B) The follow-up FDG PET/CT performed after the completion of anti-tuberculosis treatment showed aggravated lesions. (C) Both metabolic activity and the size of the lymphadenopathy substantially decreased after appropriate steroid treatment.

Fig. 2 – Pathologic findings of the excised lymph node. (A) Multiple confluent granulomas, replacing nearly the entire lymph node, with a cuff of small lymphocytes, can be seen (H-E, x 100). (B) Granulomas are composed of epithelioid histiocytes and are surrounded by small reactive lymphocytes. Caseating necrosis is absent (H-E, x 400).
information such as malignancy location, stage, and disease status, should be considered to differentiate sarcoid reactions from malignancy.

**Author contributions**

Conceptualization, Investigation, Resources, and Writing - original draft: Jeong YJ, Han YH. Data curation, Software, and Writing - review & editing: Lim ST, Jeong HJ. Formal analysis: Han YH, Lee SY. Methodology, Validation, and Visualization: Park HS, Lee SY. Supervision: Han YH. Approval of final manuscript: all authors.

**Patient consent**

Informed consent for publication of clinical data was obtained from the patient.

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2021.09.032.

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