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ORIGINAL ARTICLE

Hilar and mediastinal sarcoid-like reaction after the treatment of malignant tumors: imaging features and natural course on ^{18}F-FDG-PET/CT

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Abstract

Purpose This study aimed to assess the imaging features and natural course of hilar and mediastinal sarcoid-like reaction on ^{18}F-fluorodeoxyglucose (FDG) PET/CT after the treatment of malignancies.

Methods Sixteen patients with the appearance of sarcoid-like reaction seen on ^{18}F-FDG-PET/CT after treatment were included. Hilar and mediastinal lymph node metastases were pathologically or clinically ruled out. Posttreatment ^{18}F-FDG-PET/CT imaging features were assessed.

Results The maximum standardized uptake values of sarcoid-like reaction were 3.8–13.6 (mean 6.8). FDG uptake of hilar nodes was symmetrical in 12 (75%) patients and asymmetrical in 4 (25%). The time interval between the initiation of therapy and appearance of sarcoid-like reaction was 9–86 months (median 27.1 months). Among 14 patients who underwent further follow-up using ^{18}F-FDG-PET/CT, sarcoid-like reaction regressed in 11 (79%) patients and did not regress in 3 (21%) patients. The time interval between the appearance of sarcoid-like reaction and its regression was 3–80 months (median, 8.5 months).

Conclusion After the treatment of malignancies, benign sarcoid-like reaction was rarely observed during follow-up. Although sarcoid-like reaction appeared a long time after the treatment of malignancies, it frequently and spontaneously regressed in a relatively short period of time.

Keywords PET · Sarcoid-like reaction · Sarcoidosis · Malignancy

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown origin, which is characterized by the presence of noncaseating epithelioid-cell granulomas. It commonly affects young- and middle-aged adults and frequently presents with bilateral hilar and mediastinal lymphadenopathy, pulmonary infiltration, ocular involvement, and skin lesions. The liver, spleen, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved. The incidence of sarcoidosis is dependent on genetic and environmental factors, with the highest prevalence among Northern Europeans and African–Americans. The diagnostic criteria of sarcoidosis include the presence of clinicoradiological findings suggestive of sarcoidosis, histological evidence of noncaseating epithelioid-cell granulomas, and exclusion of other diseases with similar granulomatous reactions, such as infections or malignancies.

To date, the presence of noncaseating granulomas in local lymph nodes or organs of patients with malignancies has been well described [1–13]. This local reaction, known as "sarcoid-like reaction", could occur in patients with a history of hematological malignancies or solid cancers. The term "sarcoid-like reaction" is also used to describe cases with radiological and histological features similar to classic thoracic sarcoidosis (i.e., mediastinal and symmetrical hilar lymphadenopathy) developed during extrathoracic malignancy, without clinical manifestations [2, 4, 9].

There are previous reports of sarcoidosis occurring after malignancies [5, 7, 8, 10]. Moreover, chest CT [2, 9] and ^{18}F-fluorodeoxyglucose (FDG) PET/CT [4, 5] imaging features of sarcoid-like reaction associated with malignancies

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have been described in several radiological studies. However, to the best of our knowledge, no study has investigated the natural course of sarcoid-like reaction seen on ^{18}F-FDG-PET/CT during follow-up after the treatment of malignancies. Therefore, in the present study, we aimed to assess the imaging features and natural course of hilar and mediastinal sarcoid-like reaction seen on ^{18}F-FDG-PET/CT after the treatment of malignancies.

Materials and methods

Patients

The present study was approved by the human research committee of the institutional review board of our hospital, and complied with the guidelines of the Health Insurance Portability and Accountability Act of 1996. The requirement for informed consent was waived due to the retrospective nature of this study. In the present study, sarcoid-like reaction seen on ^{18}F-FDG-PET/CT was defined as abnormal FDG uptake in the hilar and mediastinal nodes. Patients with hilar and mediastinal lymph node metastases were carefully ruled out. Patients with primary sarcoidosis or sarcoid-like reaction seen on ^{18}F-FDG-PET/CT and/or hilar and mediastinal lymphadenopathy seen on chest CT before the treatment of malignancies were excluded. Medical chart systems of two institutions were electronically searched to select patients with sarcoid-like reaction seen on ^{18}F-FDG-PET/CT after the treatment of malignancies during February 2008–May 2018. In total, 16 patients with no prior history or evidence of sarcoidosis before the treatment of malignances were included in the study. Diagnosis was confirmed using histopathological data in 4 patients and clinicoradiological records in the remaining 12 patients. Pretreatment evaluation was performed using ^{18}F-FDG-PET/CT in 13 patients and chest CT in 3 patients.

^{18}F-FDG-PET/CT

Among these 16 patients, whole-body PET/CT imaging from the skull to mid-thigh was performed. PET/CT scanner with 16-row multidetector CT (Biograph Sensation 16; Siemens Medical Solutions, Malvern, PA, USA) was used for 6 patients and PET/CT scanner with single-detector row CT (Eminence SOPHIA; Shimadzu, Kyoto, Japan) was used for the remaining 10 patients. Briefly, after at least 4 h of fasting, patients received an intravenous injection of ^{18}F-FDG (185 MBq). Blood glucose levels were checked in all patients before FDG injection, and no patient had a blood glucose level greater than 150 mg/dL. Approximately, 60 min after FDG injection, CT and subsequent whole-body PET were performed.

Transverse images were reconstructed with 2 mm section thickness and no overlap. Oral or intravenous contrast agent was not used for CT. PET had an axial view of 16.2 cm per bed position with an intersectional gap of 3.75 mm in one bed position, which necessitated data acquisition in six or seven bed positions. Axial PET images were obtained using an imaging matrix of 256 × 256 and a field of view of 50 × 50 cm.

Imaging assessment

Two radiologists with 19 and 15 years of post-training experience in nuclear medicine imaging individually reviewed all the ^{18}F-FDG-PET/CT images, and any disagreements were resolved by consensus.

Reviewers qualitatively evaluated the presence or absence of sarcoid-like reaction seen on ^{18}F-FDG-PET/CT. If the presence of sarcoid-like reaction after the treatment of malignancies was confirmed, the reviewers determined the maximum standardized uptake value (SUV_{max}) of the hilar and mediastinal lymph nodes within the regions of interest (ROIs). FDG uptake of hilar nodes was qualitatively classified into symmetrical or asymmetrical. In addition, the reviewers recorded non-tumoral FDG uptake location in extrathoracic sites. In patients who underwent follow-up using ^{18}F-FDG-PET/CT, the reviewers qualitatively determined whether the sarcoid-like reaction seen on ^{18}F-FDG-PET/CT regressed. If regression was confirmed during follow-up, the reviewers determined the SUV_{max} of the hilar and mediastinal lymph nodes within ROIs.

Results

Patients

Patient characteristics are summarized in Table 1. Sarcoid-like reaction seen on ^{18}F-FDG-PET/CT appeared after the treatment of malignancies in 16 patients (average age, 71.3 years; age range, 53–82 years; 10 men and 6 women) with different underlying malignancies treated by various methods. Clinical stage of malignancies at the time of diagnosis was I in 3 patients, II in 3 patients, III in 3 patients, and IV in 7 patients. Tumor persistence or recurrence after initial treatment was observed in 7 (44%) of 16 patients. Corticosteroid was administered as the initial chemotherapy in 4 patients and for the treatment of sarcoid-like reaction in 1. Among the 16 patients, ^{18}F-FDG-PET/CT was performed 95 times during follow-up period after initial therapy, and the time interval of ^{18}F-FDG-PET/CT examinations ranged from 2 to 86 months (median, 9.8 months). For the 14 patients who underwent further follow-up after appearance of sarcoid-like reaction using ^{18}F-FDG-PET/CT, the final

Table 1 Patient characteristics

Number of patients	16
Age (year)	
Mean	71
Range	53–82
Gender	
Male	10
Female	6
Types of malignancies	
Lymphoma	3
Prostate	2
Uterine cervix	2
Colon	1
Rectum	1
Stomach	1
Bladder	1
Ovary	1
Breast	1
Bile duct	1
Thymus	1
Extramammary Paget	1
Clinical stage of malignancies	
I	3
II	3
III	3
IV	7
Treatment methods	
S and C	4
C and R	3
S	2
C	2
S, C, and R	1
S, R, and H	1
S and R	1
S and H	1
C and H	1

S surgery, *C* chemotherapy, *R* radiotherapy, *H* hormonal therapy

follow-up period was 7–112 months (median 29.8 months; mean 37.6 months).

Imaging features

Table 2 summarizes the imaging findings of sarcoid-like reaction on ^{18}F-FDG-PET/CT. SUV_{max} of sarcoid-like reaction at the time of appearance was 3.8–13.6 (mean 6.8). FDG uptake of hilar nodes was symmetrical in 12 (75%) and asymmetrical in 4 (25%) patients. The time interval between the initiation of therapy for malignancies and appearance of sarcoid-like reaction was 9–86 months (median, 27.1 months). Non-tumoral FDG uptake in extrathoracic sites was observed in 10/16 (63%) patients, and their observed locations were supraclavicular region ($n=7$), regions surrounding the pancreas ($n=5$), spleen ($n=2$), hepatic hilum ($n=2$), and para-aortic ($n=1$). Among the 14 patients who underwent further follow-up using ^{18}F-FDG-PET/CT, sarcoid-like reaction regressed in 11 (79%) patients (Figs. 1, 2) and did not regress in 3 (21%) patients (Fig. 3). Among the 11 patients with regression, tumor persistence or recurrence after initial therapy was observed in 6/11 (55%) patients, and the SUV_{max} of sarcoid-like reaction at the time of regression was 2.8–4.8 (mean, 3.5). The time interval between the appearance of sarcoid-like reaction and its regression was 3–80 months (median, 8.5 months). Among the 3 patients without regression, FDG uptake worsened in 2 patients and was stable in 1.

Table 2 Imaging findings of SLR on ^{18}F-FDG-PET/CT

SUV_{max} of SLR at the time of appearance	
Mean	6.8
Range	3.8–13.6
FDG uptake of hilar nodes	
Symmetrical	12 (75)
Asymmetrical	4 (25)
Time interval between the initiation of therapy and appearance of SLR (months)	
Median	27.1
Range	9–86
Non-tumoral FDG uptake in extrathoracic sites	
Yes	10 (63)
No	6 (37)
Regression of SLR ($n=14$)	
Yes	11 (79)
No	3 (21)
SUV_{max} of SLR at the time of regression ($n=11$)	
Mean	3.5
Range	2.8–4.8
Time interval between the appearance and regression of SLR (months) ($n=11$)	
Median	8.5
Range	3–80

Data are numbers of patients, and numbers in parentheses are frequencies expressed as percentages

SLR sarcoid-like reaction

The results of treatment evaluation of initial therapy were complete response or partial response in 3/3 (100%) patients without regression of sarcoid-like reaction, whereas those were complete response or partial response in 6/11 (55%) patients with regression and stable disease or progressive disease in 5/11 (45%). The 5-year survival rate was 100% in all patients with or without regression of sarcoid-like reaction.

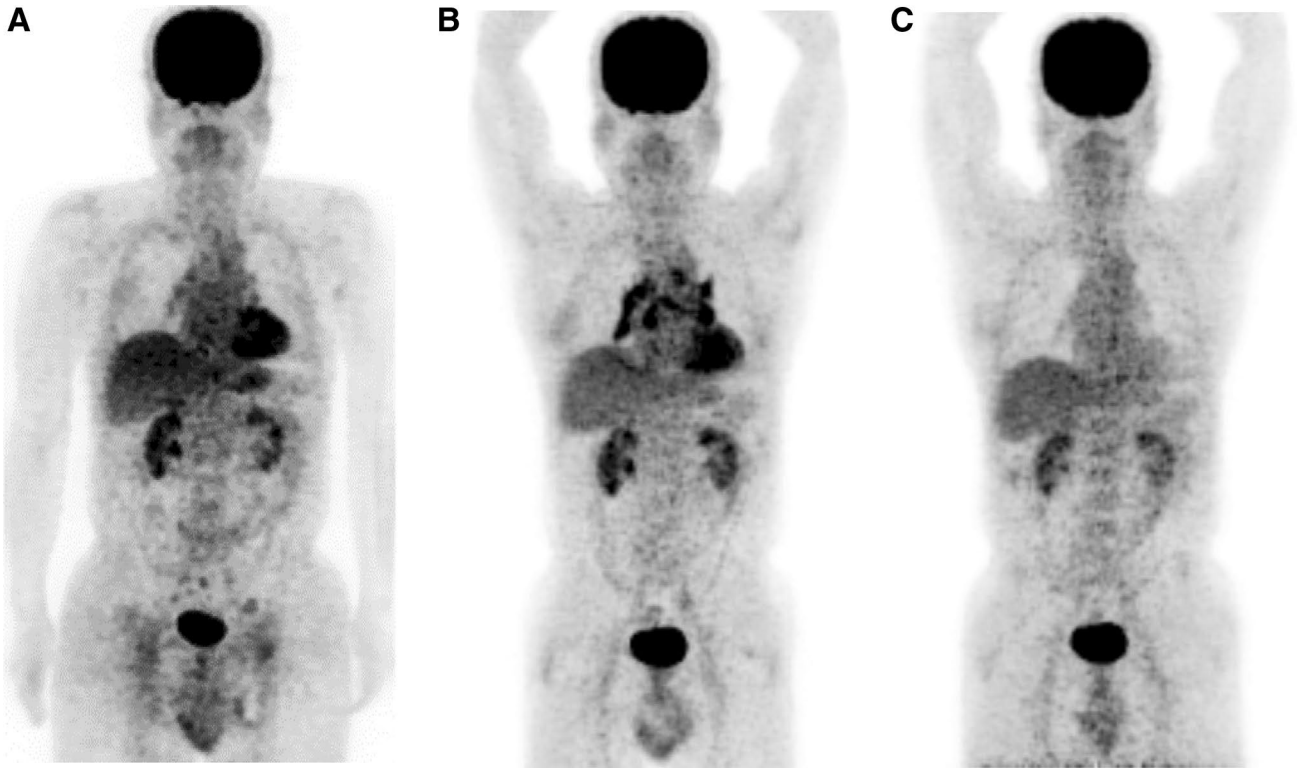

Fig. 1 A 68-year-old man with extramammary Paget disease. **a** Maximum intensity projection image of ^{18}F-FDG PET/CT before treatment shows no abnormal FDG uptake in the hilum and mediastinum. **b** Symmetrical FDG uptake in the hilum and mediastinum appears 24 months after the initiation of therapy (SUV_{max}, 8.4). **c** FDG uptake in the hilum and mediastinum disappears 6 months after the appearance of sarcoid-like reaction (SUV_{max}, 3.1)

Discussion

Because ^{18}F-FDG-PET/CT can detect inflammation throughout the body with high sensibility, it gained a central role in sarcoidosis management as it could suggest diagnosis in certain clinical contexts, guide biopsy, evaluate the extent of the disease, help assess the prognosis, and monitor immunosuppressive therapy [14]. ^{18}F-FDG accumulation in macrophages and $CD4^+$ T lymphocytes could explain the in vivo imaging of this granulomatous process [15]. ^{18}F-FDG-PET/CT could also identify the biopsy location to obtain histological evidence for diagnosis [16]. ^{18}F-FDG-PET/CT is an useful technique for the detection of active inflammatory sites in patients with chronic sarcoidosis and provides data about the extent of active disease, which could influence the decision to change therapy [17]. ^{18}F-FDG-PET/CT usefulness in sarcoidosis management has been well established.

The association between sarcoidosis and malignant tumors has been discussed in many studies [1, 3, 6–8, 10–13]. Patients with respiratory sarcoidosis were 11 times more likely to develop malignant lymphoma and 3 times more likely to develop lung cancer [11]. The diagnosis of B-cell lymphoma was reported several years after the diagnosis of chronic sarcoidosis, whereas the diagnosis of breast or cervical cancer was evenly distributed before, around, and after the time of diagnosis of sarcoidosis [6]. Because patients with sarcoidosis were at a considerably increased risk of cancer, particularly lung cancer, malignant lymphomas, and cancer in other organs, chronic inflammation is a putative mediator of this risk [13]. Similarly, the incidence of sarcoidosis was 175 times higher in patients with lymphoma and 38 times higher in those with breast cancer than the general population [10]. In the present study, various types of malignancies were observed as underlying malignancies of sarcoid-like reaction.

Sarcoid-like reaction is caused by antigenic factors derived from the tumor cells, eliciting an immunological hypersensitivity reaction leading to epithelioid-cell granuloma formation [18]. Sarcoid-like reaction may be a marker of an immunologically mediated antitumor response of macrophages activated by T lymphocytes, and there is evidence that patients with Hodgkin's disease and sarcoid-like reaction had better prognosis [18]. However, sarcoid-like reaction was clinically and radiologically indistinguishable from idiopathic sarcoidosis [10].

Chest CT [2, 9] and ^{18}F-FDG PET/CT [4, 5] imaging features of sarcoid-like reaction associated with malignancies have been described in several radiological studies.

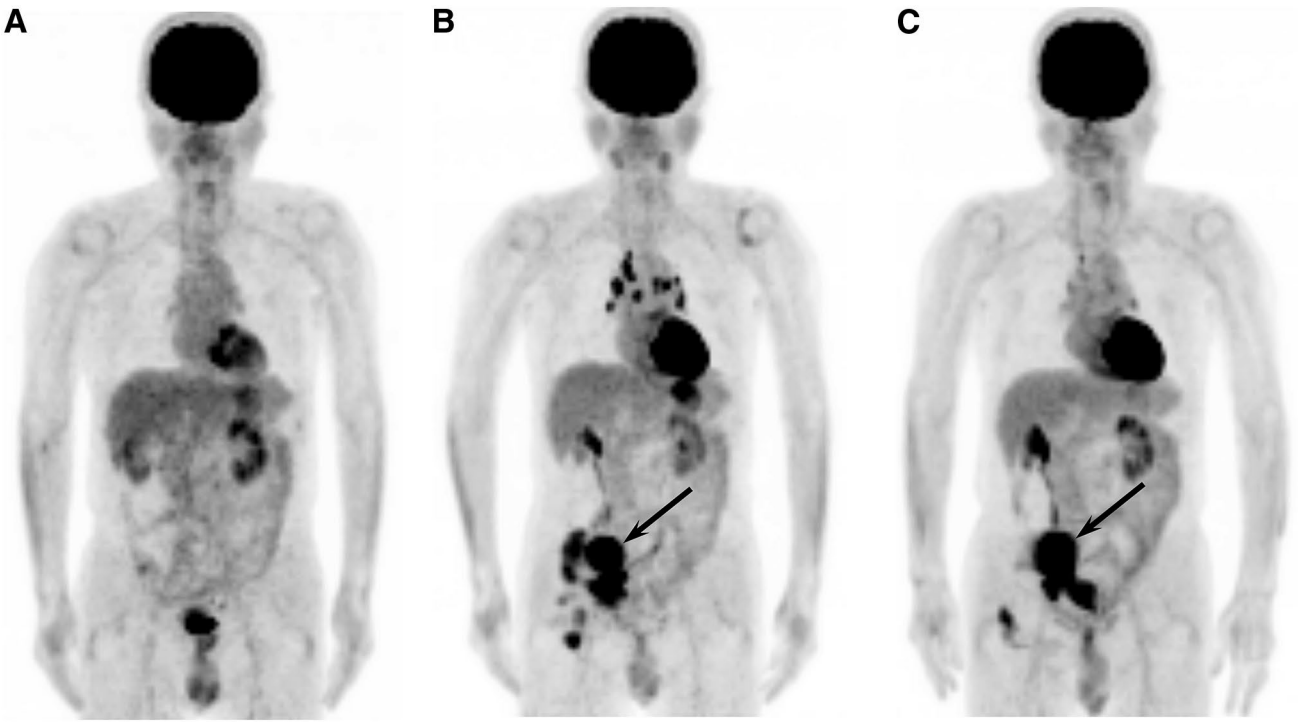

Fig. 2 A 67-year-old man with bladder cancer. **a** Maximum intensity projection image of ^{18}F-FDG PET/CT before treatment shows no abnormal FDG uptake in the hilum and mediastinum. **b** Symmetrical FDG uptake in the hilum and mediastinum appears 16 months after the initiation of therapy (SUV_{max}, 13.6). FDG uptake of ileal conduit is observed in the lower right abdomen (arrow). **c** FDG uptake in the hilum and mediastinum disappears 11 months after the appearance of sarcoid-like reaction (SUV_{max}, 3.3). FDG uptake of ileal conduit is observed in the lower right abdomen (arrow)

Chest CT images demonstrated hilar lymph node enlargement or parenchymal lung disease; however, no distinctive radiographic pattern was observed to distinguish systemic sarcoidosis from sarcoid-like reaction [2]. According to another report, lymphadenopathy, small nodules, and ultrafine nodules with confluence, mimicking GGO, were observed on CT, and these CT imaging findings were frequently resolved during follow-up [9]. In one study, ^{18}F-FDG-PET/CT imaging suspected sarcoid-like reaction in 1.1% patients with cancer and the diagnosis was confirmed in 0.6% patients [4]. In previous studies, symmetrical hilar FDG uptake was observed in 4/4 (100%) patients [5] and 11/13 (85%) patients [4], which is similar to the results of our study [12/16 (75%) patients]. In a previous study, the mean SUV_{max} of hilar and mediastinal nodal uptake was 7.3 (range 3.1–13.6) [4], which is similar to the result of our study [mean 6.8; range (3.8–13.6)]. In another study, non-tumoral FDG uptake in extrathoracic sites was observed in 6/13 (46%) patients, which is similar to the result of our study [10/16 (63%) patients]. Although the natural course of sarcoid-like reaction seen on ^{18}F-FDG-PET/CT has not been reported yet, the present study demonstrated regression of abnormal FDG uptake in 3/14 (79%) patients.

In a previous study, the median time interval between the diagnosis of cancer and that of sarcoidosis was 49 months (range, 7–248 months), with 57% of patients being diagnosed with sarcoidosis within 5 years following the diagnosis of malignancy [10]. In our study, the median time interval between the initiation of therapy for malignancies and appearance of sarcoid-like reaction was 27 months (range, 7–86 months), and 81% patients were diagnosed with sarcoid-like reaction within 5 years following the initial therapy. Although the time interval between the appearance of sarcoid-like reaction and its regression has not been previously reported, the present study demonstrated that the median time interval between the appearance of sarcoid-like reaction and its regression was 9 months (range, 3–80 months). Sarcoid-like reaction spontaneously regressed in a relatively short period of time.

The development of sarcoid-like reaction during induction chemotherapy for lung cancer has been reported as false positive FDG accumulation [19, 20]. Compared to these previous reports, the time interval between the initiation of therapy for malignancies and appearance of sarcoid-like reaction in our study (median, 27 months) was too long. Because the patients who underwent treatment evaluation using ^{18}F-FDG-PET/CT during induction therapy were not

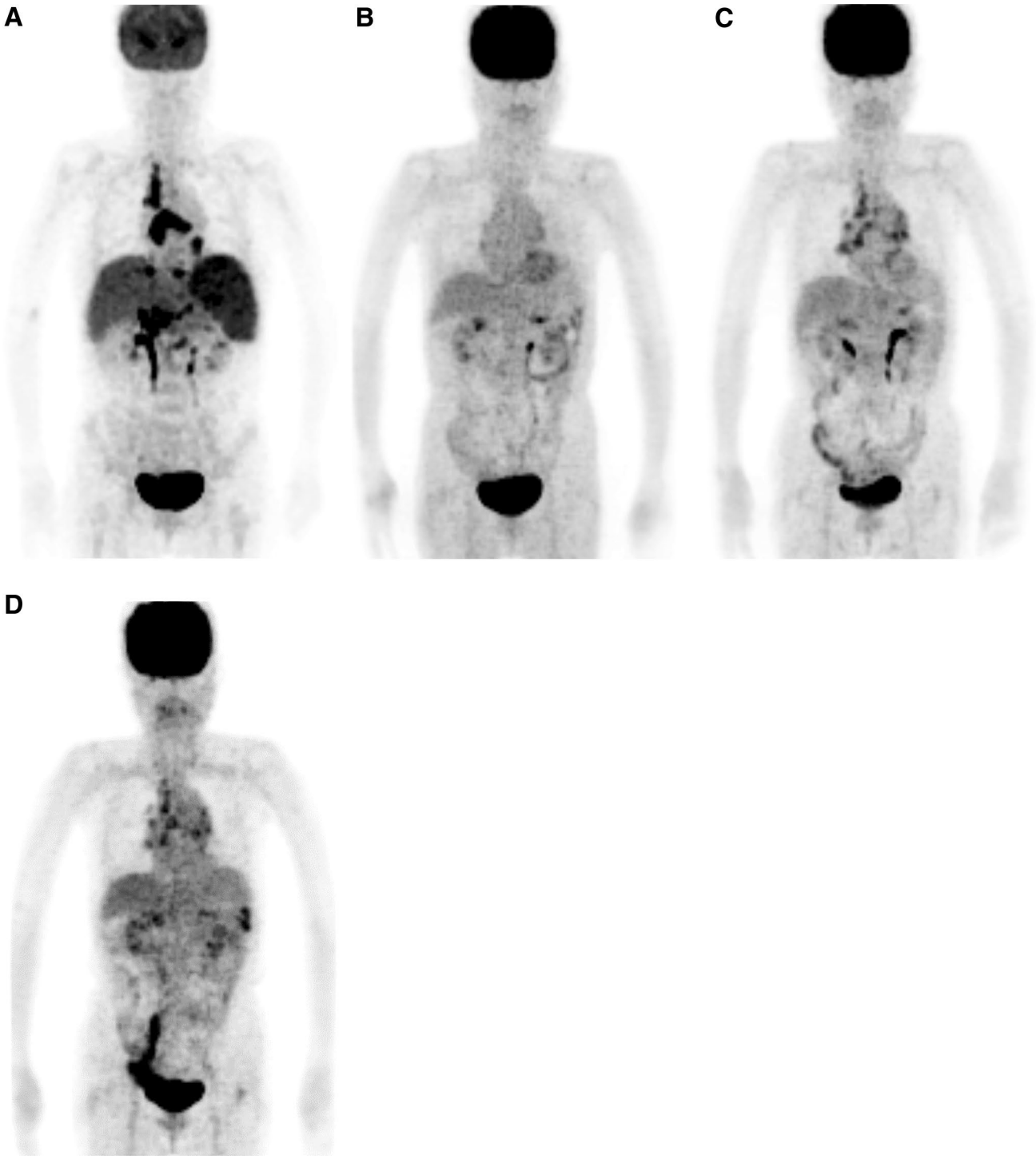

Fig. 3 An 83-year-old woman with malignant lymphoma. **a** Maximum intensity projection image of ^{18}F-FDG PET/CT before treatment shows abnormal FDG uptake suggestive of lymphomatous involvement in the hilum, mediastinum, and abdomen. **b** Abnormal FDG uptake completely disappears after chemotherapy for lymphoma. **c** Symmetrical FDG uptake in the hilum and mediastinum appears 13 months after the initiation of therapy (SUV_{max}, 3.8). **d** FDG uptake in the hilum and mediastinum remains 7 months after the appearance of sarcoid-like reaction (SUV_{max}, 4.2)

included in our study due to the retrospective nature, the present study could not reveal the true timing of the appearance of sarcoid-like reaction, especially after a short period of the initiation therapy. However, in this study, sarcoid-like reaction was certainly identified after a long time of the initiation therapy. The mechanism of sarcoid-like reaction

is still unclear but one probable mechanism is interaction of host and tumor cells. One of the main pathogenetic mechanisms underlying cancer cachexia is a complex interaction between the host and the tumor [21]. Because cachexia is often seen in end-stage cancer, cachexia may be associated with late-onset sarcoid-like reaction.

This study had several limitations. First, the cohort size was relatively small because the study was conducted in two institutions. Second, histopathological diagnosis was obtained from only in 4/16 patients, because pathological confirmation of mediastinal lymph node was difficult owing to its deep location. However, we believe that careful, long-term follow-up could rule out nodal metastasis. Third, the intervals of follow-up ^{18}F-FDG-PET/CT examinations were irregular due to the retrospective nature of this study. Fourth, we only assessed the imaging features and natural course of hilar and mediastinal sarcoid-like reaction and not those at atypical locations.

In conclusion, sarcoid-like reaction was rarely observed during follow-up after the treatment of malignancies, and thus, the differentiation from hilar and mediastinal lymph node metastases was important. Radiologists should recognize the occurrence of sarcoid-like reaction after the treatment of malignancies. Although sarcoid-like reaction appeared a long duration after the treatment of malignancies, it frequently and spontaneously regressed in a relatively short period of time, regardless of the treatment effect of the underlying malignancy. If sarcoid-like reaction was suspected from imaging findings, overzealous treatment could be avoided.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement The authors declare that they preserve ethical standards.

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