

Characterizing POEMS Syndrome with ^{18}F -FDG PET/CT

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POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein elevation, and skin changes) syndrome is a rare paraneoplastic syndrome caused by an underlying plasma cell disorder. The patients usually present with multisystemic involvement. Thus, we performed a study to investigate the role of ^{18}F -FDG PET/CT in characterizing POEMS syndrome. **Methods:** Ninety-one untreated patients with proven or suspected POEMS syndrome were recruited to undergo ^{18}F -FDG PET/CT. Features of bone lesions, lymphadenopathy, hepatomegaly or splenomegaly, bone marrow, and serous cavity effusion were examined, and 15 patients were followed up with PET/CT scans 3 mo after therapy. **Results:** Of the 90 patients diagnosed with POEMS syndrome, there were 140 ^{18}F -FDG-avid bone lesions. These lesions were frequently found in the pelvis, and most showed mixed characteristics. Four patients showed enlarged and ^{18}F -FDG-avid lymph nodes. Sixty-five patients had hepatomegaly or splenomegaly. Some of them had hypermetabolic spleen and bone marrow. Forty-six patients had serous cavity effusion. Five male patients had gynecomastia. Three months after therapy, ^{18}F -FDG-avid bone lesions showed decreased metabolism. **Conclusion:** ^{18}F -FDG PET/CT is a useful tool for the evaluation of patients with suspected POEMS syndrome. ^{18}F -FDG PET/CT may contribute to the diagnosis, evaluation, and follow-up of patients with POEMS syndrome by providing systematic findings of bone lesions, lymphadenopathy, liver or spleen involvement, serous cavity effusion, and the metabolic status of the lesions.

Key Words: FDG; PET; POEMS syndrome

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POEMS syndrome is a rare paraneoplastic syndrome caused by an underlying plasma cell disorder. The patients usually present with hallmark signs of Polyneuropathy, Organomegaly, Endocrinopathy, M protein elevation, and Skin changes. POEMS syndrome is still not well understood, and evaluation of this disease remains challenging (1). The imaging modalities for the evaluation of POEMS syndrome include radiographic skeletal survey, technetium scintigraphy, and CT and focus on the skeletal lesions (2,3). Compared with CT, the sensitivity of the radiographic skeletal

survey and technetium scintigraphy is unsatisfactory (3). MR imaging has been used to evaluate patients with POEMS syndrome and can also be used to evaluate the sciatic nerve (4). However, the availability of and time required for whole-body MR imaging limits its application. Alberti and Montoriol et al. reported several cases of POEMS syndrome evaluated by ^{18}F -FDG PET/CT, which manifested as ^{18}F -FDG-avid bone lesions (5,6). ^{18}F -FDG PET/CT facilitates the diagnosis and follow-up of several hematologic diseases, including lymphoma and multiple myeloma (7–10). Considering the multisystemic involvement of POEMS syndrome, the extraskeletal manifestation on PET/CT is still unclear and of interest to researchers. Thus, we recruited a cohort of POEMS syndrome patients and investigated the role of ^{18}F -FDG PET/CT in characterizing POEMS syndrome.

MATERIALS AND METHODS

Patients

From January 2013 to December 2014, 91 patients (34 women, 57 men; mean age \pm SD, 49.09 \pm 10.93 y) with proven or suspected POEMS syndrome were recruited at Peking Union Medical College Hospital to undergo ^{18}F -FDG PET/CT. Among them, 90 patients were finally diagnosed as having POEMS syndrome according to the 2007 Mayo Clinic Criteria (11). Fifteen patients underwent additional PET/CT scans 3 mo after treatment, and serum vascular endothelial growth factor (VEGF) levels were also evaluated. Biopsy revealed that 1 patient with suspected POEMS syndrome actually had amyloidosis. The institutional review board of Peking Union Medical College Hospital approved this study. All subjects provided written informed consent.

^{18}F -FDG PET/CT Study

^{18}F -FDG PET/CT scans were acquired after the patient had fasted for 4 h and 60–90 min after intravenous administration of ^{18}F -FDG (3.70–5.55 MBq/kg of body weight). The blood glucose level, measured just before tracer administration, was less than 120 mg/dL for all patients. ^{18}F -FDG PET/CT images were obtained using a combined PET/CT Biograph (Siemens Co.). All scans were acquired in 3-dimensional mode. The emission scan was obtained in the craniocaudal direction, from the top of the skull to the middle thigh (2 min/each bed position).

Focal bone lesions were defined as focal areas of increased ^{18}F -FDG uptake visible on at least 2 contiguous PET slices and corresponding to CT abnormalities not attributable to benign bone pathologies. Their maximum standardized uptake value (SUV_{max}), which was normalized for body weight, number, location, and density, was recorded. Lesions with a maximal diameter 0.5 cm or greater on CT were recorded as abnormal. The SUV_{max} of liver, spleen, and lymphadenopathies were measured. The lymphadenopathy included enlarged or hypermetabolic lymph nodes. Enlarged lymph nodes were defined as those with the short diameter of 1 cm or more. The SUV_{max} of bone marrow (BM) was measured by placing a region of interest over axial sections (at least 15 mm

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in diameter) of L5. If there was a bone lesion in L5, the SUV_{max} of L4 was measured, and so on. Hypermetabolism of BM was defined as uptake greater than that observed in the mediastinum.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 22.0; IBM SPSS Inc.). All data were expressed as mean \pm SD. Differences between groups were analyzed using the Student *t* test, nonparametric analysis, and χ^2 test. A probability value of 0.05 was considered statistically significant.

RESULTS

Characterization of POEMS Syndrome

Bone Lesions. The skeletal manifestation on ^{18}F -FDG PET/CT for the patients with POEMS syndrome varied, presenting as both solitary and multiple hypermetabolic bone lesions. The total number of ^{18}F -FDG-avid bone lesions was 140. The lesions were frequently found in the pelvis (55), followed by the thoracic vertebrae (30), ribs (19), and lumbar vertebrae (14). Bone lesions were also commonly seen in the appendicular skeleton of the upper extremities (14), including the scapula, clavicles, and sternum, but less frequently in the proximal of extremities (5) and cervical vertebrae (3). The appearance of these ^{18}F -FDG-avid bone lesions on CT also varied. Most of the lesions showed mixed characteristics (65/140), with decreased frequency showing purely sclerotic (50/140) and lytic (25/140) changes. Although lesions with purely lytic changes were not the most commonly seen, they could be combined with the expanded contour of the bone cavity and present with higher ^{18}F -FDG uptake; the SUV_{max} for lytic changes was much higher than that for sclerotic changes (the lytic lesions, SUV_{max} 10.36 ± 11.73 ; the mixed lesions, SUV_{max} 7.52 ± 9.19 ; the sclerotic lesions, SUV_{max} 4.51 ± 1.57 ; $P = 0.00$). Because there was a little variation in acquisition time, we further analyzed the ratio of SUV_{max} and BM (SUV_{max}/BM) for every ^{18}F -FDG-avid bone lesion as well as the acquisition time among the 3 groups of ^{18}F -FDG-avid bone lesions. The SUV_{max}/BM of lytic bone lesions (SUV_{max}/BM 4.53 ± 4.59) was still much higher than those of the mixed (SUV_{max}/BM 2.63 ± 1.54) and sclerotic lesions (SUV_{max}/BM 1.39 ± 0.76 , $P = 0.00$). The differences in acquisition time for the lytic (range, 1–1.5 h; 1.21 ± 0.14 h), mixed (range, 0.98–1.5 h; 1.24 ± 0.18 h), and sclerotic (range, 1–1.5 h; 1.26 ± 0.17 h) bone lesions were not statistically significant ($P = 0.44$). Representative ^{18}F -FDG-avid bone lesions are shown in Figure 1.

Patients with either solitary (17/39) or multiple (22/39) ^{18}F -FDG-avid lesions also showed normometabolic bone changes. All of the normometabolic bone lesions were sclerotic and well defined, some of which were smaller than 1 cm in diameter and extremely diffuse.

Lymphadenopathy. Four patients showed enlarged and ^{18}F -FDG-avid lymph nodes, located in cervical, axillary, retroperitoneal, and inguinal regions (Fig. 1A). The retroperitoneal lymphadenopathy was most prominent, with the SUV_{max} ranging from 1.0 to 10.0 and the maximum short diameter reaching to 2.7 cm. Only 1 patient showed agglomerated lymph nodes, which were located in the retroperitoneal area. Two of these 4 patients underwent lymph node biopsy, which led to a diagnosis of Castleman disease. One of them was mixed type and the other was hyaline-vascular type. The other 2 patients with lymph node involvement on PET/CT did not undergo lymph node biopsy.

Hepatomegaly or Splenomegaly. Enlargement of the liver or spleen on CT was another prominent feature. Thirty-six patients had hepatomegaly or splenomegaly. Another 29 patients presented

with both liver and spleen enlargement. Only 25 patients had neither hepatomegaly nor splenomegaly. The enlargement was usually slight or moderate; however, the enlargement of the liver or spleen was not correlated with the spleen metabolism. The SUV_{max} of the spleen in the patients with liver or spleen enlargement (65) was 2.04 ± 0.38 , and that in the patients without liver or spleen enlargement (25) was 1.91 ± 0.37 . This difference was not statistically significant ($P = 0.12$). Twenty-five patients showed higher SUV_{max} of the spleen than that of the liver. The distribution was homogeneous, and no focal ^{18}F -FDG-avid lesion was found in the spleen of these 25 patients.

BM. Fifty-nine patients showed hypermetabolism of the central BM. The remaining patients (31) exhibited normal ^{18}F -FDG activity of the BM. The hypermetabolic BM exhibited a homogeneous distribution. No focal uptake was found, and there was no ^{18}F -FDG activity in the peripheral BM. The percentage of plasma cells in BM smears was 2.27 ± 2.61 for patients with hypermetabolic BM and 2.02 ± 1.68 for patients with normal BM. The difference between the 2 groups was not statistically significant ($P = 0.86$).

Serous Cavity Effusion. Serous cavity effusion was commonly seen, especially multiple-cavity effusion. Forty-six patients had serous cavity effusion, and multiple cavities were involved in 77.2% (34/44) of these patients. Thoracic effusion (38) was most commonly seen, followed by pelvic (26), pericardial (24), and abdominal (24) effusion. Thoracic effusion was usually bilateral. Fourteen patients had percutaneous edema. None of the serous cavity effusions was ^{18}F -FDG-avid, except for 2 patients with pelvic effusion who showed a slight distribution of ^{18}F -FDG activity.

Others. Five male patients had gynecomastia, which can be visualized on CT images, but none showed elevated ^{18}F -FDG uptake.

A patient with hepatosplenomegaly, but without typical bone lesions, serous cavity effusion, or lymphadenopathy on ^{18}F -FDG PET/CT images, was finally diagnosed as having amyloidosis after tongue biopsy.

Follow-up of Patients with POEMS Syndrome

Fifteen patients were followed up with PET/CT 3 mo after baseline evaluation and after autologous peripheral blood stem cell transplantation (2 patients received lenalidomide therapy). Nine of these patients had ^{18}F -FDG-avid bone lesions before treatment, and all showed decreased metabolism after therapy; however, the CT appearance of the lesions did not change (Fig. 2). The decrease in SUV_{max} and the VEGF response are listed in Table 1. The decrease in SUV_{max} in these 9 patients was in accordance with the decrease in serum VEGF. However, the degree of ^{18}F -FDG decrease did not reflect whether it was a complete or partial response. There was no change in the metabolism of non- ^{18}F -FDG-avid sclerotic lesions and their appearance on CT after treatment.

DISCUSSION

POEMS syndrome, also known as Takatsuki syndrome or osteosclerotic myeloma, is a rare paraneoplastic syndrome resulting from an underlying plasma cell disorder. Diagnosis of POEMS syndrome is made on the basis of a composite of clinical and laboratory features, which suggests a multisystemic disorder (1,11). Among the diagnostic criteria, sclerotic bone lesions, organomegaly, and extravascular volume overload may be detected by imaging modalities. As a whole-body scan modality, ^{18}F -FDG PET/CT has great advantages for evaluating many systemic diseases, especially hematologic diseases, such as lymphoma and multiple myeloma (7–10,12), that involve multiple systems. Here, according to

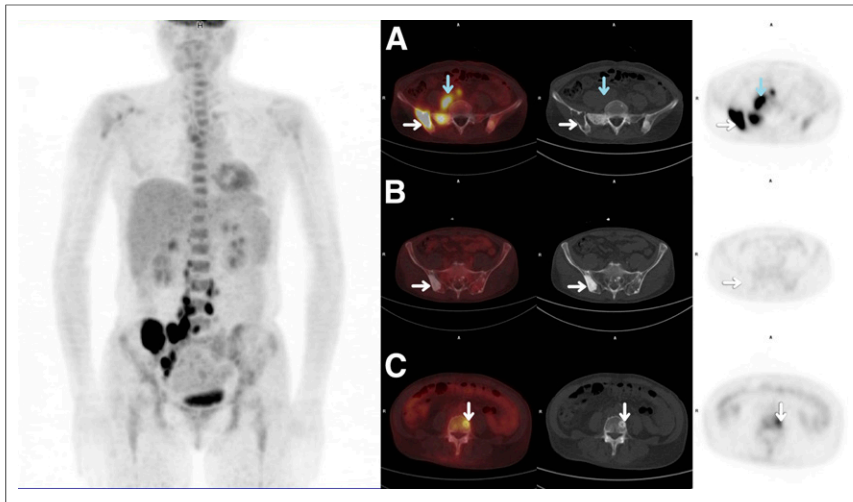


FIGURE 1. (A) Bone lesions with different nature. (White arrow) Lytic lesion of right ilium (SUV_{mean} , 7.1; SUV_{max} , 11.9) and (blue arrow) ^{18}F -FDG-avid lymph nodes in retroperitoneal area. (B) Osteosclerosis of right ilium (SUV_{mean} , 1.5 and SUV_{max} , 1.8). (C) Mixed density of vertebra (SUV_{mean} , 4.1 and SUV_{max} , 6.0). SUV_{mean} = mean standardized uptake value.

our research, ^{18}F -FDG PET/CT can visualize many important features of POEMS syndrome, especially the bone lesions.

Bone lesions are hallmarks of POEMS syndrome and occurred in 95% of cases in a cohort in the United States (11) and 27%–46% in Chinese cohorts (11,13–15). In our study, 74.7% of the patients had bone lesions, which contributed to detection of a greater number of tiny skeletal abnormalities on CT, compared with the traditional radiographic skeletal survey—43.3% of all the patients had ^{18}F -FDG-avid bone lesions. In our research, ^{18}F -FDG uptake was more prominent in lesions with lytic content, which is concordant with the assumption that the pathologic characterization of the bone lesions may be the diffuse infiltration of light chain-restricted plasma cells (1), considering the mechanism of ^{18}F -FDG uptake from the tumor cells. The bone lesions on CT without ^{18}F -FDG uptake may be due to the inactive stage of these lesions or partial-volume effect, especially for the lesions smaller than 1 cm. Another assumption is that some of these lesions are

secondary reaction from cytokines, such as VEGF or interleukin, but not the direct infiltration of plasma cells. The predilection of having more mixed or sclerotic features on CT imaging is different from the manifestation of multiple myeloma and bone metastasis, which contributes to the differential diagnosis. The distribution of ^{18}F -FDG-avid bone lesions on PET/CT was consistent with other studies using CT or radiographic skeletal survey (3,16). Except for its role in aiding in the biopsy of bone lesions (5), the role of ^{18}F -FDG PET/CT in prediction and prognosis is still unclear. We repeated PET/CT scans in several patients 3 mo after therapy. The ^{18}F -FDG activity of bone lesions decreased before the change in CT manifestation, which agrees with the results from research by Glazebrook et al. (3). They reported that the change in CT manifestation showed a lag of 41 mo. Moreover, ^{18}F -FDG avidity decreased along with serum VEGF, indicating a complete or partial response, suggesting ^{18}F -FDG PET/CT may have a role in the early evaluation of disease severity. However, there was no difference in the degree of the decrease in SUV_{max} between patients with complete and partial response in our study. The small sample size and short duration of the follow-up limits further analysis. In addition, parameters other than the decrease in SUV_{max} may need to be studied in the future, such as the total lesion glycolysis index and metabolic tumor burden.

Other features apparent on ^{18}F -FDG PET/CT were hypermetabolic spleen and BM. Some patients also presented with enlarged liver or spleen, which is commonly seen in several diseases, such as hematologic, immunologic, and infectious diseases. There was no difference in the percentage of plasma cells in BM between the 2 groups with and without hypermetabolic BM. This indicates that the cause of hypermetabolism of BM may not be the infiltration of plasma cells directly but just the reactive manifestation of an activated hematologic system. Unlike multiple myeloma, two thirds of patients with POEMS syndrome have clonal plasma cells in their BM, which is less than 5% on average (1). Thus, even if there is focal infiltration of plasma cells in BM, the focal ^{18}F -FDG activity seen on PET/CT could be tiny and sparse.

Usually lymphadenopathy, especially Castleman disease, is another hallmark of POEMS syndrome (17). However, only 4 of 90 patients in our cohort showed abnormal (hypermetabolic or enlarged) lymph nodes on PET/CT. Reportedly, lymph nodes diagnosed as Castleman disease were the most multicentric of the hyaline vascular type (18). The biopsy results from 1 patient in our study showed hyaline-vascular type. Thus, when there is a composite of ^{18}F -FDG PET/CT features with bone lesions, lymphadenopathy, liver, or spleen enlargement and hypermetabolic spleen and BM, the differential diagnosis should include POEMS

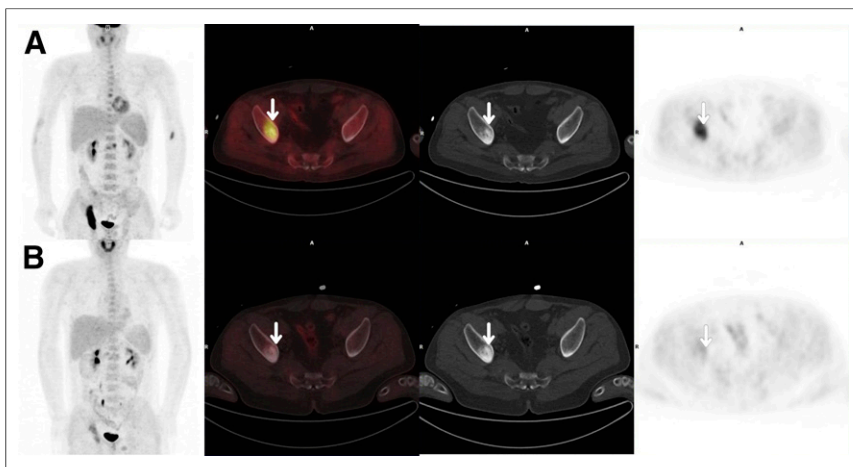


FIGURE 2. ^{18}F -FDG-avid bone lesion (arrow) in pelvis of 1 patient (A) with SUV_{mean} of 3.3 and SUV_{max} of 3.5. (B) Bone lesion (arrow) in pelvis showed decreased ^{18}F -FDG activity (SUV_{mean} , 1.8; SUV_{max} , 2.1) 3 mo later after autologous stem cell transplantation whereas CT manifestation did not change.

TABLE 1
Follow-up of 9 Patients with ¹⁸F-FDG–Avid Bone Lesions 3 Months After Therapy

Patient no.	Decrease in SUV _{max} (%) [*]	VEGF response [†]
1	88.3	CR
2	66.4	CR
3	59.0	PR
4	70.9	CR
5	78.7	CR
6	81.5	CR
7	50.3	CR
8	70.2	PR
9	97.3	CR

^{*}Decrease in SUV_{max} (%) was calculated using average percentage of decrease for every ¹⁸F-FDG–avid lesion in 1 person.

[†]VEGF response; CR, normalized VEGF (<600 pg/mL); PR, VEGF improved by at least 50%.

CR = complete response; PR = partial response.

syndrome. However, the predominantly sclerotic change in bone lesions will aid in the diagnosis. Another feature that aids the differential diagnosis is multiple cavity effusion without metabolism distribution, especially when the percutaneous area is involved simultaneously, which is a rare manifestation in other systemic diseases. The ascitic fluid may be exudative, but the detailed mechanism is still unclear (13).

CONCLUSION

¹⁸F-FDG PET/CT is a useful tool for evaluating patients with suspected POEMS syndrome. ¹⁸F-FDG PET/CT may contribute to the diagnosis, evaluation, and follow-up of patients with POEMS syndrome by providing systematic findings of the bone lesions, lymphadenopathy, liver or spleen involvement, serous cavity effusion, and the metabolic status of the lesions.

DISCLOSURE

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