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Original Article

Usefulness of Fluorodeoxyglucose-positron emission tomography/computed tomography (PDG-PET/CT) scan on diagnosis of kikuchi disease

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Abstract: Kikuchi Disease (KD) or histiocytic necrotizing lymphadentitis is a rare cause of lymphadenopathy. The aim of this study was to analyze the diagnostic pathway of KD and clarify the usefulness of Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT). Twenty-four patients who had fever with unknown origin and lymphadenopathy were prospectively recruited. ^{18}F-FDG PET/CT scan was performed. Clinical manifestation, laboratory examination, bone marrow and biopsy of lymph node were recorded. PET/CT scan revealed diverse FDG uptake in the organs and lymph nodes in all the 24 patients. The pathological results identified lymphoma in five patients, KD in five patients, plasma cell dyscrasia in one patient, and cholangiocarcinoma in one patient. Six patients were diagnosed with autoimmune disease. One patient was confirmed with tuberculosis. Another 5 patients didn't have a definite diagnosis. In 5 KD patients, cervical and axillary lymph nodes were the most common affected lymph nodes with obvious elevated uptake of ^{18}F-FDG. All the affected lymph nodes were indicated by PET/CT for their location and sizes, which facilitates lymph node biopsy. All the KD patients recovered well and remained good situation in six months after diagnosis after the treatment of NSAIDs or glucocorticoid. Lymphoma, cancer, KD and infection should be considered for patients with fever, multiple enlarged lymph nodes with high FDG uptake. ^{18}F-FDG PET/CT could not discriminate KD and lymphoma but is helpful to differentiate with autoimmune diseases and other inflammation.

Keywords: Kikuchi disease, ^{18}F-FDG PET/CT, lymphadenopathy, histiocytic necrotizing lymphadenitis

Introduction

Kikuchi disease (KD), also known as histocytic necrotizing lymphadenitis, is a rare kind of self-limited lymphadenopathy. It is a relatively common disease in Japan, China and other Asian patients. KD was firstly reported by Kikuchi and Fujimoto [1, 2]. KD has been misdiagnosed as reactive hyperplasia of lymph node, infectious diseases, or even as malignancy [3-5]. Diagnosis of KD usually depends upon an excisional biopsy and pathological examination of enlarged lymph nodes [6, 7]. Exact diagnosis is difficult to make based on physical findings. Contrast-enhanced computed tomography (CT) findings showed that most lymph nodes were homogeneously enhanced without evidence of gross necrosis in several cases of KD [8, 9]. A definitive imaging modality for distinguishing KD and malignancy has not yet been established.

Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is a useful novel method for differentiating tumors from inflammation and normal tissues. However, several case reports and a recent study have reported that lymph nodes of KD patients showed activity in ^{18}F-FDG PET/CT imaging [10-17]. In the present study, we reviewed 24 cases with fever with unknown origin and lymphadenopathy who underwent FDG-PET/CT examination in Zhongshan Hospital Affiliated to Fudan University. Five of the 24 cases were finally diagnosed as KD with the help of pathology.

Patients and methods

Patients

All the patients presenting fever with unknown origin and lymphadenopathy at Zhongshan Hospital Affiliated to Fudan University (Shanghai, China) from April 2010 to December 2011 were recruited. Those patients who were willing to perform PET/CT and attend the study were enrolled in this study. Written consent forms were signed by all the well-informed patients according to the ethical protocols of Zhongshan Hospital, Fudan University.

Totally 24 patients, 18 males and 6 females, with a mean age of 48 years (range, 14-75 years) were enrolled. They presented fever, lymphadenopathy, fatigue, and hypodynamia. The duration of fever was 14-120 days. Physical examination revealed 11 cases had cervical lymph nodes enlargement with maximal size of 3 cm×2 cm and 5 cases had enlarged axillary lymph nodes with maximal size of 2 cm×1 cm.

Laboratory and pathological examination

All the patients underwent the laboratory examination including routine blood test, serum biochemistry test, blood culture, bone marrow cytological test and culture, autoimmune antibodies, serum virus antibody detection containing Epstein-Barr virus (EBV), cytomegalovirus (CMV), and Coxsackie. After FDG-PET/CT scan, the biopsy of lymph node was suggested for all the patients with obviously elevated FDG uptake. Subsequently, all the samples were fixed in 10% formalin, embedded in paraffin, sectioned consecutively at 4mm and stained by hematoxylin and eosin. Then immunohistochemistry staining was carried on with the first antibody CD3, CD68, CD20, CD45RO and Perforin.

^{18}F-FDG-PET/CT investigation

All whole-body PET scans with FDG were performed with a combined PET/CT scanner (Discovery VCT; GE Medical Systems), which permits simultaneous acquisition of 35 image slices in 3-dimensional acquisition mode with interslice spacing of 3.25 mm. The PET/CT scanner incorporates an integrated 64-slice multidetector CT scanner, which was used for attenuation correction and diagnosis. The CT parameters were as follows: peak tube voltage of 120 to 400 mAs, rotation time of 0.5 seconds, reconstruction thickness of 5 mm, pitch of 1. After at least 4 hours fasting, patients received an intravenous injection of 185 MBq FDG and image acquisition began 60 minutes after injection. A whole-body emission scan was performed from the head to the inguinal region with 2 minutes per bed. A senior radiologist reported the results independently.

Image analysis

For PET/CT image analysis, single ROIs as large as possible were placed over the cervical lymph node showing the highest FDG uptake using information obtained from CT images by the consensus of 2 experienced nuclear medicine physicians. Standard uptake value (SUV) was determined as the highest activity within an ROI and the maximum diameter of the lymph node was recorded per patient.

Results

Laboratory examination

Routine blood test and serum biochemistry test: Among the 24 patients, the routine blood test revealed 8 cases with leucopenia and 17 cases with an elevated erythrocyte sedimentation rate (ESR). Serum biochemistry test showed 21 cases with elevated C-reactive protein (CRP), 18 cases with elevated level of lactate dedydrogenase (LDH), and 5 cases with elevated aminotransferase level.

Pathogen test: There was no positive result with blood and bone marrow cultures in all the 24 patients. There was no serologic evidence of infection by Epstein-Barr virus (EBV). Besides, PPD tests were negative or weak positive. For cytomegalovirus (CMV) antibody tests, 1 case showed IgM positive while 6 cases IgG positive. For Coxsackie virus antibody tests, 4 cases showed IgM positive while 3 cases IgG positive. In summary, there was no evidence of bacteria infection in all these patients. Though there were some positive results as to the antibody of virus, the manifestation of the patients cannot be simply attributed to virus infection.

Autoimmune antibody and rheumatoid factor test: Among all the 24 patients, autoimmune antibody test exhibited 2 case had increased level of antinuclear antibody, 3 case had elevated level of antibody to double-stranded DNA

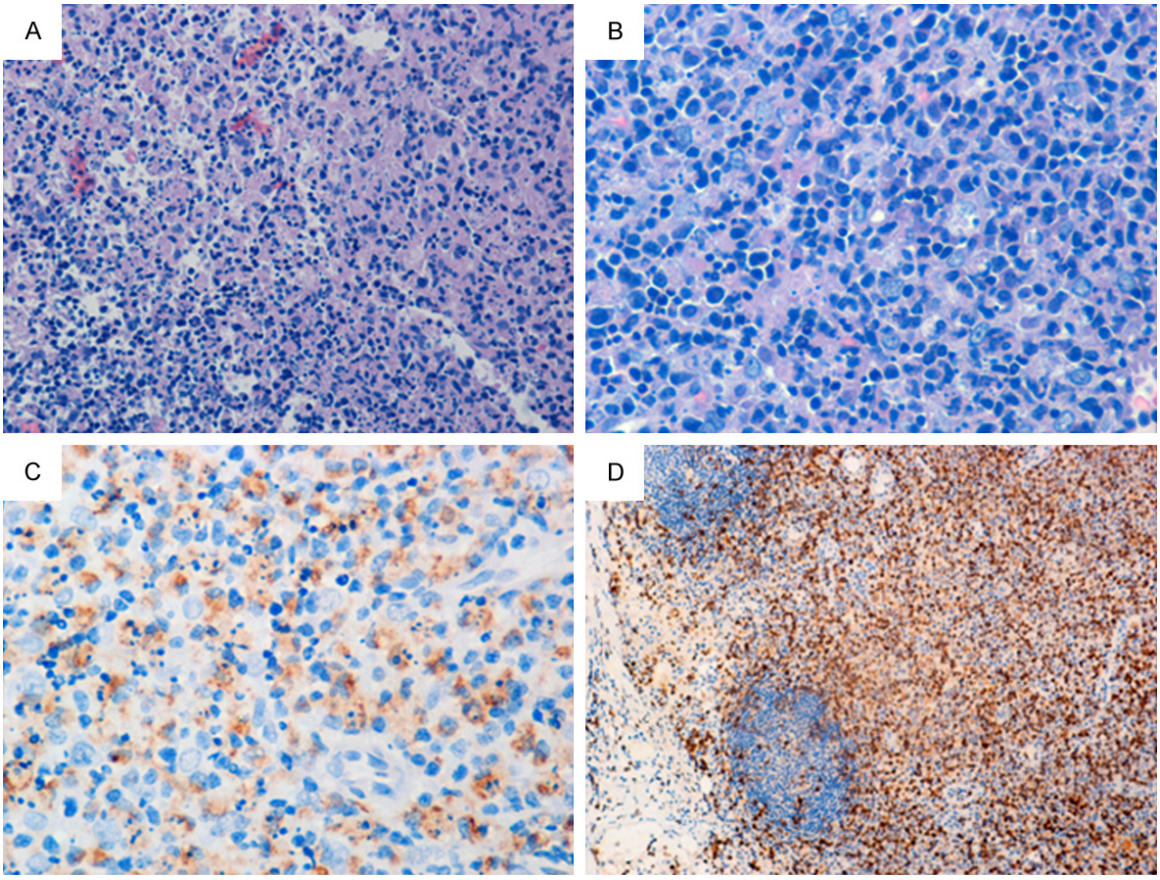

Figure 1. Histological features of lymph nodes in one of KD patients. A: HE stain: Massive necrosis and piecemeal necrosis were seen in the lymph node, indicating Kikuchi disease (×10). B: HE stainin: Histiocytes reactive hyperplasia in the lymph nodes (×40). C: Immunohistochemical staining: Histiocytes showed CD68+ in the lesional areas (×40). D: Immunohistochemical staining: Lymphocytes showed Perforin+ in the lesional areas (×10).

(dsDNA), 2 cases had positive rheumatoid factor (RF), 2 cases had positive anticardiolipin antibody (ACA). On the complement detection, 9 cases had decreased complement C3, 7 case had decreased complement C4, and 11 cases had decreased C50. Summarily, some patients had abnormal results in dsDNA and RF, which suggested autoimmune disease.

^{18}F-FDG PET/CT scan

FDG-PET/CT scan revealed multiple areas of FDG uptake in the organs and lymph nodes in all the 24 patients, including liver, spleen, bone, cervical lymph nodes, axillary lymph nodes, supraclavicular lympho nodes, mediastinum and hilum of lung lymph nodes, retroperitoneum lymph nodes, hilum of liver lymph nodes, mesenterium lymph nodes, and inguinal lymph nodes. The SUV_{max} of their organs and lymph nodes varied from 1.5-20.9, the largest lymph node was mediastinum lymph nodes (47.8× 35.8 mm). On the basis of the size and SUV_{max} of the enlarged lymph nodes and organs, the patients were initially diagnosed inflammation, lymphoma, malignant tumor, and KD, respectively by the radiologist.

Pathological results

According to the various clinical character and initial diagnosis of FDG-PET/CT, bone marrow biopsy was suggested in the patients with multiple lymphadenectasis (23 patients) and the biopsy of lymph nodes was suggested in the patients with obviously elevated uptake of FDG in multiple lymph nodes. In our study, bone marrow biopsy and lymph node biopsy was performed in 23 and 12 patients, respectively (**Figure 2**). Labial gland biopsy was performed in one patient who was suspected with Sjogren's syndrome. In the total 5 cases of lym-

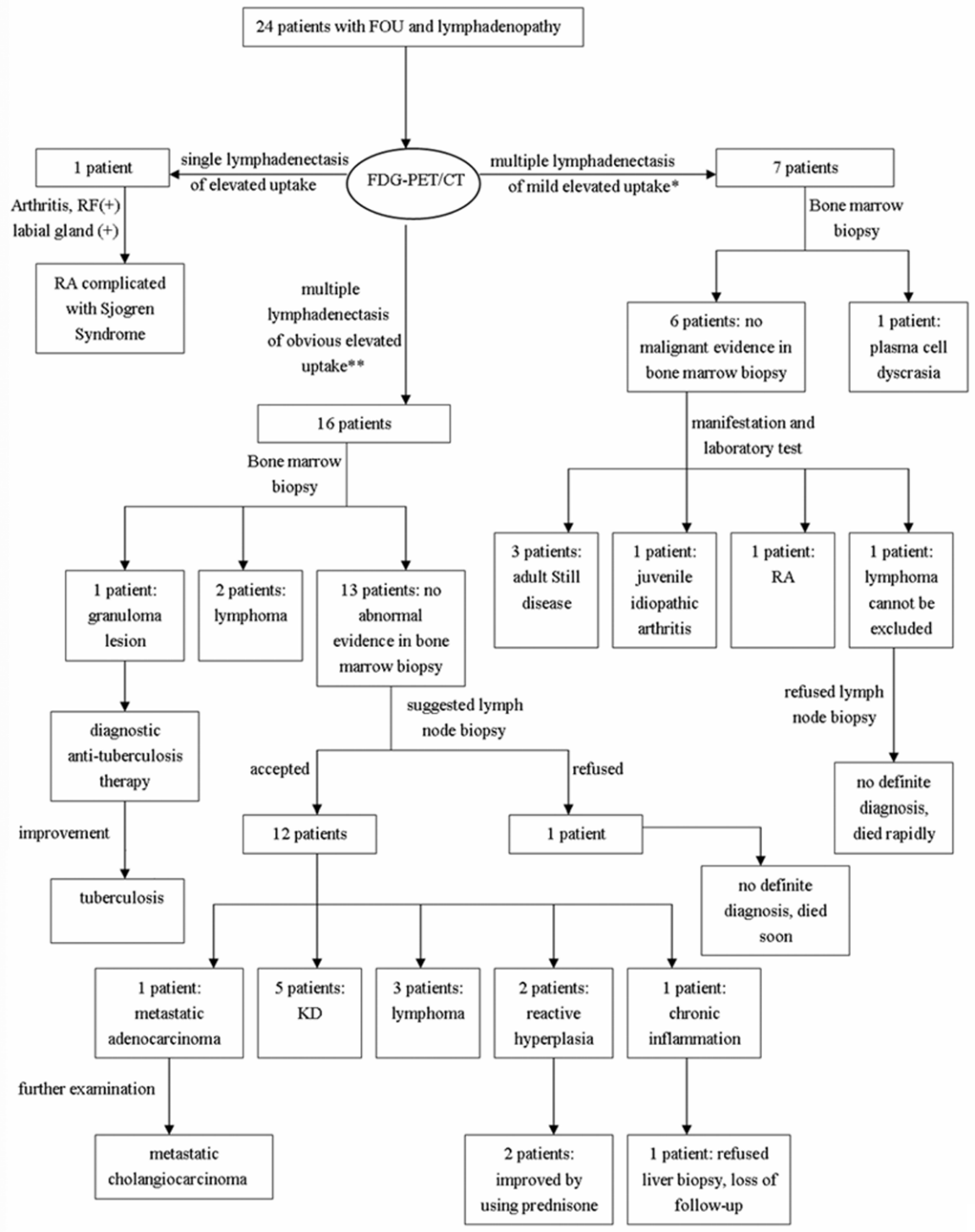

Figure 2. The diagnosis process of 24 patients with FOU and lymphadenopathy. RA: Rheumatoid arthritis. Mild elevated uptake*: $SUV_{max} \leq 4$ in PET/CT scan. Obvious elevated uptake**: $SUV_{max} > 4$ in PET/CT scan.

phoma, 5 cases of KD, 1 case of plasma cell dyscrasia, and 1 case of cholangiocarcinoma were diagnosed based on the pathological results of bone marrow and/or lymph node biopsy and other clinical findings. Six patients were finally diagnosed with autoimmune disease by clinical manifestation, autoimmune antibody, rheumatoid factor and labial gland biopsy, including 3 adult Still disease, 1 rheumatoid arthritis (RA), 1 juvenile idiopathic

Table 1. Characteristics of five KD patients and laboratory data

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	M	M	M	F	M
Age (years)	43	53	23	22	33
Symptoms	Fever	Fever, oral cavity ulcer	Fever, oral cavity ulcer, rash	Fever	Fever
WBC (×10^9/L)	8.4	2.5	6.1	1.9	2.8
CRP (mg/L)	14.2	28.8	55	/	18.2
LDH (U/L)	236	591	1200	539	448
ANA	-	-	-	+	-
RF	-	-	-	-	-
PPD test	-	-	-	-	-
Position with elevated ^{18}F-FDG PET/CT uptake (SUV_{max})	Cervical (6.15), retroperitoneal (6.84)	Cervical (12.79), mediastinal (10.0), hilum of lung (11.4) axillary (R6.9, L5.3), hilum of liver (5.1)	Cervical (6.62), axillary (4.35), root of peritoneal (7.8), retroperitoneal, inguinal (3.05)	Cervical (NA), axillary (NA)	Cervical (NA), axillary (NA), retroperitoneal (NA)
Site with the highest ^{18}F-FDG uptake	Retroperitoneal	Cervical	Peritoneal	Cervical	Cervical
Days before PET/CT investigation after outbreak	59	41	41	22	15
Biopsy site	Cervical	Cervical	Cervical	Cervical	Cervical
Treatment	No treatment	Chinese medicine	Voltaren	Methylprednisolone	Methylprednisolone

arthritis, and 1 rheumatoid arthritis complicated (RA) with Sjogren Syndrome. One case was diagnosed tuberculosis by bone marrow biopsy and diagnostic anti-tuberculosis therapy. 5 patients had not a definite diagnosis during hospitalization: two patients refused lymph node biopsy even the deterioration of disease led to death rapidly, two patients showed reactive hyperplasia by lymph node biopsy and improved after the treatment of prednisone, another patient who showed reactive hyperplasia by lymph node biopsy refused to perform liver biopsy (SUV_{max} of liver = 11.85) and died in several months.

KD patients

Of all the 24 patients, five patients were diagnosed as Kikuchi disease pathologically, four by cervical lymph node resection and the other by cervical lymph node needle biopsy. They all showed wide areas of necrotizing process with paracortical hyperplasia and histocytes with reactive proliferation. Massive necrosis and piecemeal necrosis in the lymph nodes (**Figure 1A**) were found. On the other hand, histiocytes reactive hyperplasia was seen in the lymph nodes (**Figure 1B**). Immunohistochemical analysis revealed abundant CD3, CD20, CD68 (**Figure 1C**), LCA, CD45RO, and Perforin (**Figure 1D**) positive.

For the PET/CT detection, more than 2 lymph nodes showed aberrant FDG uptake of all the 5 patients, in which 1 case showed aberrant FDG uptake in 6 different lymph nodes (**Table 1**). The most common involved lymph node (5/5) was cervical lymph node with the highest SUV_{max} 6.9 g/ml (size 17.1 mm×10 mm). The second common involved lymph node (4/5) was axillary lymph node with the highest SUV_{max} 12.79 g/ml (size 10 mm×6 mm). The following common involved lymph nodes were retroperitoneal, inguinal mediastinum, porta hepatis, hilus of lung, and mesenterium lymph nodes. Unexpectedly, their PET/CT results all exhibited high SUV_{max} (the highest SUV_{max}>6 g/ml) in multiple lymphadenectasis and organs mimicking lymphoma so that it was hard to distinguish KD from lymphoma only by PET/CT.

During the hospitalization, antibiotic treatment was failure to all the 5 patients, including aminoglycosides, penicillins, and quinolones. Three patients' temperature returned to normal after prescribed with Diclofenac sodium (75 mg, bid, po). 1 female case was given hormone (Medrol 8 mg, tid, po) treatment. She recovered gradually and stopped using Medrol in three months. 1 case recovered spontaneously without any treatment. No recurrence was found in all the five cases after 10 months follow-up. The long-term follow-up is extraordinary essential for the further research.

Discussion

KD, also known as histiocytic necrotizing lymphadenitis, is a rare self-limiting cause of cervical lymphadenopathy, predominantly affecting

Table 2. SUV_{max} and orthogonal diameters of the affected lymph nodes in patients in literature

Position with elevated ^{18}F-FDGPET/CT uptake (SUV_{max})	Lymph nodes counts (≥10 mm)	Mean of SUV_{max} (Mean ± SD)	Mean of the lymph nodes size (mm)
Cervical	17	7.17±2.17	(15.33±0.25)×(9.53±3.87)
Axillary	14	5.61±4.34	(12.88±8.54)×(7.10±4.53)
Mediastinal	3	4.29±0.43	(17.07±5.49)×(11.20±1.45)
Inguinal	2	/	/
Superclevical	7	/	/
Hilum of lung	2	/	/
Hilum of liver	2	/	/
Peritoneal and retroperitoneal region	3	/	/
Below carina	1	/	/
Total counts	51	6.13±3.19	(15.08±6.74)×(9.41±4.50)

Table 3. General condition and PET/CT results of KD patients in literature

Reference	Age	Gender	Position with elevated ^{18}F-FDGPET/CT uptake (SUV_{max})	Site with the highest ^{18}F-FDG uptake	Biopsy site	$Size_{max}$ (mm)	Treatment
Ito et al [10]	36	F	Cervical (R9.67, L8.57) axillary (R4.68, L2.05) mediastinal (3.89)	Cervical (R)	Cervical	13.0×12.4	One patient required steroid therapy , others were followed without therapy
Ito et al [10]	23	M	Cervical (R4.05, L10.25) axillary (R4.68, L2.93) mediastinal (4.50) inguinal (3.50)	Cervical (L)	Cervical	23.4×12.7	
Ito et al [10]	31	F	Cervical (L4.90)	Cervical (L)	Cervical	20.4×11.2	
Ito et al [10]	28	F	Cervical (R2.19, L4.85)	Cervical (L)	Cervical	23.8×13.1	
Ito et al [10, 11]	25	F	Cervical (R5.23)	Cervical (R)	Cervical	17.8×10.8	
Ito et al [10, 11]	43	F	Cervical (R) axillary (R13.94, L5.87)	Axillary (R)	Cervical	27.8×14.8	
Ito et al [10]	66	F	Cervical (R6.45, L8.23) axillary (R4.34, L12.90)	Axillary (L)	Cervical	13.8×11.1	
Liao et al [12]	26	F	Cervical (R) axillary (L) superchvical (B) mediastinal hilum of lung (L)	Cervical (R)	Cervical	NA	No treatment
Kim et al [13]	10	F	Cervical (R) superchvical (B) hilum of liver retroperitoneal	Cervical (R)	Cervical	NA	Steroid
Kaicher et al [14]	19	F	superchvical (L10.50) hilum of lung (L4.00) below carina (2.60)	Superchvical (L)	Cervical	NA	NA
Lee et al [5]	8		Cervical (B) parotid (R) axillary (B) superchvical (B) retroperitoneal inguinal (NA)	Cervical (R)	Cervical	NA	symptomatic
Ohta et al [15]	30	F	Axillary (R) breast (R2.10)	breast (R)	Axillary breast	NA	NA
Chen et al [17]	18	M	Cervical (L7.67) axillary (B1.34) peritoneal (3.98) retroperitoneal (NA) spleen (2.62) mandible (B)	Cervical (L)	Cervical	NA	Methylprednisolone Methylprednisolone
Chen et al [17]	17	F	Cervical (B8.45) axillary (B3.28) hilum of liver (5.74) mandible (L)	Cervical (R)	Cervical	19.5×20.4	Methylprednisolone
Zhang et al [16]	18	F	Cervical (R17.03), Supraclavicular fossa (11.05), axillar (B10.72), retroperitoneal (16.38)	Cervical (R)		NA	Steroid

Southeast Asian women younger than 30 years of age. KD is histopathologically characterized by cortical and paracortical necrosis with lymphoreticular infiltration and the absence of granulocytic infiltration [8, 18]. The major clinical symptoms include high fever, lymphadenopathy, and leukopenia. Some patients may have mild weight loss and night sweat. The clinical and imaging presentation tend to be mistaken for malignant lymphoma and tuberculosis. In our study, all the 5 cases presented high fever as the first symptom. The fever last for a long time with the mean time 29 days. Superficial, peritoneal, and mediastinal lymph nodes were found to be enlarged with unknown reason. Biopsy and pathology showed fibrinoid necrosis in the paracortical areas. Benign histiocytes, plasmacytoid monocytes, and small lympho-

cytes were observed around the necrotic areas while granulocytes are absent. These are the typical presentation of KD [15].

^{18}F-FDG-PET/CT, a noninvasive technique, is also a whole body metabolic imaging technique, as this method correlates with the functional imaging and anatomy imaging. FDG PET/CT is often used in the diagnosis and differential diagnosis of malignancy. It analyzes the lesions from physiological, biochemical, and cellular levels, other depending on the size and architecture alterations. SUV_{max} is an important marker for quantitating ^{18}F-FDG uptake, thus widely used in the clinical malignancy diagnosis [19].

Chamulak *et al*. [20] reported that about 40% of KD patients were firstly misdiagnosed as lymphoma. Furthermore, some untypical lymphomas were misdiagnosed as benign lesion in clinic. Lymphoma is observed in all the organs of the whole body [21], while KD is also seen in various organs, including the rare position, such as eyes, root of tongue, nasopharynx, and appendix, which make it easier to be missed diagnosed and misdiagnosed.

Literature searching found 8 English reports and 1 Chinese report involving 15 patients of KD who underwent ^{18}F-FDG-PET/CT [10-18] (**Tables 2**, **3**). They were 2 males and 13 female, with a mean age of 27 years (range, 8-66 years). 51 lymph nodes with diameter ≥10 mm were found in the cervical space (17/51, 33.3%), axillary space (14/51, 27.5%), upper clavicle (7/51, 13.7%), interpleural space (3/51, 5.9%), porta hepatis (3/51, 5.9%), inguinal (2/51, 3.9%), hilus of the lung (2/51, 3.9%), mesentery and retroperitoneum (2/51, 3.9%), and below carina (1/51, 2.0%). SUV_{max} value was between 1.34 and 13.94 with the mean about 6.13±3.19 in the 29 lymph nodes which gave the detail SUV_{max} ratio. Furthermore, there were 27 lymph nodes with SUV_{max} value over 2.5. In the literature, of the 25 lymph nodes given the size value, there were 24 lymph nodes larger than 10 mm in diameter, and the largest one was 27.8×14.8 mm (analogue, SUV_{max} value was 13.94). In 14 cases who had biopsy performed, 13 cases were taken biopsy in cervical lymph nodes and the other in axillary lymph node. Recently, Tsujikawa et al. [22] performed a study to compare PET/CT imaging findings in KD patients and non-Hodgkin lymphoma (NHL) patients. KD lesions tended to be smaller (13.8±5.4) than those of indolent (25.4±11.8) and aggressive (29.7±18.8) NHL without significance. And the value of corSUV might help to differentiate KD and indolent NHL.

In our study, all the 24 patients presenting fever and lymphadenopathy underwent PET/CT scan. PET/CT scan played an important role in the diagnosis because it could show us the severity and range of lesion. Of the 16 patients with multiple lymphadenectasis of obvious elevated uptake (highest SUV_{max}>4), five lymphoma patients, five KD patients, and one bile duct cancer patient were identified pathologically, one tuberculosis patient was identified by diagnostic anti-tuberculosis therapy, another four patients still had not a definite diagnosis (**Figure 2**). Among them, two patients refused to have biopsy and died rapidly, two patients showed reactive hyperplasia by lymph node biopsy and improved after the treatment of prednisone. The above result indicated that if patients had fever and multiple obviously increased FDG uptake of lymph node or organs, lymphoma, malignant tumor, and KD should be concerned. What's more, the biopsy of lymph node and bone marrow will make the ultimate diagnosis. The follow-up is essential since malignant tumor and lymphoma cannot relieve before chemotherapy and KD is a self-limited disease. Besides, one patient with single lymphadenectasis of elevated uptake was diagnosed RA complicated with Sjogren Syndrome ultimately. On the other hand, of the 7 patients with multiple lymphadenectasis of mild elevated uptake (highest SUV_{max}≤4), 5 patients were diagnosed with autoimmune disease, one patient was diagnosed plasma cell dyscrasia, the other patient died rapidly before a confirmed diagnosis was achieved. The PET/CT reports of the 7 patients all suggested inflammation changes. However, for those single lymphadenectasis or multiple lymphadenectasis of mild elevated uptake, except inflammatory disease like autoimmune disease, malignancy and hematologic neoplasm of low grade should also be considered.

Of the five KD patients, the highest SUV_{max} (12.79) was in the cervical lymph node, which was consistent to the literature [10]. Besides, we found abnormal increased ^{18}F-FDG uptake in the lymph nodes within axillary space, medi-

astinal space, root of mesentery, porta hepatis, retroperitoneal region, and inguinal space. According to the PET/CT results, we cannot distinguish KD from lymphoma. Therefore, the final diagnosis depends on the pathological examination. In our study, the final pathological impression is consistent with KD.

We also concluded that selecting the lymph nodes with elevated ^{18}F-FDG uptake as the biopsy position will improve the diagnosis. Four out of the 5 cases had small cervical lymph nodes which were impalpable. Although ^{18}F-FDG PET/CT scan can not clearly discriminate between lymphoma and KD, it is very useful to find the exact lesion position and aids pathological biopsy. It was reported that the lymph nodes with abnormal elevated ^{18}F-FDG uptake were mostly more than 10 mm in diameter, and the ^{18}F-FDG uptake is obviously increased in lymph nodes of cervical and axillary space with SUV_{max} values are 7.17±2.17 and 5.61±4.34. In our study, cervical and axillary lymph nodes were also the most common affected lymph nodes. Mediastinal, retroperitoneal, porta hepatic, hilus of lung, and inguinal lymph nodes were also involved, indicated by the whole body imaging of PET/CT.

In conclusion, ^{18}F-FDG PET/CT indicates all the enlarged lymph nodes in KD patients, which is useful for differentiation and choosing the biopsy site. KD should be considered as one of the differential diagnosis in the patient with generalized lymphadenopathy.

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Disclosure of conflict of interest

None.

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