Lymph node tuberculosis mimicking malignancy on ^{18}F-FDG PET/CT in two patients: A case report

RUI-LIN DING[1], HONG-YING CAO[2], YUE HU[1], CHANG-LING SHANG[1], FANG XIE[1], ZHEN-HUA ZHANG[1] and QING-LIAN WEN[1]

Departments of [1]Oncology and [2]Emergency, The Affiliated Hospital of Luzhou Medical College, Luzhou, Sichuan 646000, P.R. China

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Abstract. ^{18}F-fluorodeoxyglucose positron emission/computed tomography (^{18}F-FDG PET/CT) imaging, an established procedure for evaluation of malignancy, reports an increased ^{18}F-FDG uptake in acute or chronic inflammatory condition. Lymph node tuberculosis (LNTB) is the most common form of extrapulmonary tuberculosis. However, the absence of clinical symptoms and bacteriological basis makes it difficult to diagnose. In the current case report, two patients with LNTB mimicking malignant lymphoma are presented by ^{18}F-FDG PET/CT. The objective of the present report is to emphasize that LNTB should be considered as a noteworthy differential diagnosis in patients with enlarged lymph nodes, particularly in tuberculosis-endemic countries, and that lymph node biopsy serves a vital role in diagnosing LNTB.

Introduction

^{18}F-fluorodeoxyglucose positron emission/computed tomography (^{18}F-FDG PET/CT) is an important molecular imaging technique in cancer diagnostics, which is widely used in detecting and evaluating malignancy (1). ^{18}F-FDG uptake is reflective of the glycolytic activity of the cells, which is increased in the context of malignant tumors and during inflammation (2). ^{18}F-FDG is not a tumor-specific agent, thus, the diagnostic efficiency of ^{18}F-FDG PET/CT remains controversial (3,4). However, standardized uptake values of 2.5 or greater have been used as a cutoff value indicative of malignancy (5). Due to this, false positive results of PET/CT imaging in tuberculosis (TB) have been reported in previous studies (6,7). LNTB is the second most common form of TB following pulmonary TB (PTB) (8). However, LNTB presents a greater difficulty in diagnosis due to an absence of clinical symptoms. Similarly to PTB, LNTB may also mimic malignancy on ^{18}F-FDG PET/CT (8,9). The current report presents two patients with LNTB who were misdiagnosed with malignancies by ^{18}F-FDG PET/CT. The patients gave informed written consent for publishing these data, as approved by the Luzhou Medical College Human Study Committee (Luzhou, China).

Correspondence to: Professor Qing-Lian Wen, Department of Oncology, The Affiliated Hospital of Luzhou Medical College, 25 Taiping Street, Luzhou, Sichuan 646000, P.R. China
E-mail: wql7315@163.com

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Case report

A 68-year-old female patient, previously diagnosed with chronic renal failure and renal anemia in July 2014, presented with bilateral cervical swelling and mild dyspnea for more than one month. This patient presented with no fever, cough, expectoration or nighttime sweating. There was no history of TB or human immunodeficiency virus infection. Physical examination during a routine medical examination at The Affiliated Hospital of Luzhou Medical College (Luzhou, China) in October 2014 revealed bilateral hard, swollen lymph nodes on her neck. The maximal diameter of these swollen lymph nodes was >2 cm. The lesions were then detected with a cervical ultrasound examination; this reported multiple hypoechoic nodules on her neck, and diffused nodules on the thyroid gland were also detected. A CT scan of the chest (images not shown) revealed swollen lymph nodes in the bilateral hilar, mediastinal region and left axilla. Furthermore, a section with decreased density was indicated in the thyroid gland, and the left lobar thyroid was enlarged. The CT scan also revealed the presence of node involvement in the retroperitoneal and bilateral inguinal regions.

The characteristics of these lesions on CT appeared similar to malignant diseases, such as cancer. For this reason, the patient was sent to the Department of Nuclear Medicine, the Affiliated Hospital of Luzhou Medical College (Luzhou, China) for an ^{18}F-FDG PET/CT scan for additional characterization. This scan revealed the presence of ^{18}F-FDG uptake in the lesions of the bilateral neck, bilateral axilla, mediastina and bilateral inguinal regions. The maximal SUV (SUV_{max}) of ^{18}F-FDG in these lesions was 3.8; the presence of malignant lymphoma was therefore suggested (Fig. 1A). In the neck region, another area of light uptake was identified, indicating that the thyroid gland had an increased volume and decreased

density, accompanied by increased FDG uptake (SUV_{max}, 3.6); however, the nature of this lesion could not be determined (Fig. 1B). Additionally, bilateral pleural effusion was also detected by PET/CT scan (Fig. 1B).

To make a definitive diagnosis, the patient underwent a lymph node biopsy of the cervical lesion, a lymph node specimen (5 μm sections, hematoxylin and eosin, original magnification, x100) confirmed tuberculous lymphadenitis without malignance (Fig. 2). The serum polymerase chain reaction (PCR) for *M. tuberculosis* indicated a positive presence of this bacterium. The real-time PCR was performed using the ABI PRISM® 7500HT Real-Time PCR System (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA). The following primer sets were used (Takara Biotechnology, Co., Ltd., Dalian, China): *M. tuberculosis* IS6110, 5'-TTGGAAAGGATGGGGTCA-3' (forward) and 5'-CGCAGCCAACACCAAGTAG-3' (reverse); and β-actin, 5'-AGTTGCCTTACACCCTTTATTG-3' (forward) and 5'-TCACCTTCACCGTTCCAGTTT-3' (reverse). The *M. tuberculosis* primers provided an amplicon of 156 bp; the β-actin primers provided an amplicon of 149 bp. Thermal cycling conditions were as follows: Initial denaturation at 95˚C for 1 min; amplification for 40 cycles of 95˚C for 5 sec and 60˚C for 30 sec; dissociation at 95˚C for 15 sec, followed by extension at 60˚C for 1 min; and finally melting at 95˚C for 15 sec. Each PCR reaction (20 ml) contained the following: SYBR Premix Ex Taq II (2x, 10 ml; Takara Bio, Inc., Otsu, Japan), forward primer (10 mM, 0.8 ml), reverse primer (10 mM, 0.8 ml), ROX reference dye (50x, 0.4 ml; Takara Bio, Inc.), DNA template (50 ng in 2.0 ml), and distilled water (6.0 ml).

Due to the results described above, a clinical diagnosis of LNTB was subsequently made. The patient then received antituberculosis drugs, which included isoniazid (200 mg per day; Tianjing Lisheng Pharmaceutical Co., Ltd., Tianjing, China), rifapentine (480 mg per day; Changzheng Pharmaceutical Co., Ltd., Chengdu, China), and pyrazinamide (1,200 mg per day; Jinghua Pharmaceutical Co., Ltd., Chengdu, China). The patient's neck swelling gradually became smaller following this therapeutic approach for 10 months. A repeat CT scan on December 4 2015, revealed a total regression of neck lymph nodes (data not shown).

The second patient reported herein was a 20-year-old male, admitted to the Department of Oncology at the Affiliated Hospital of Luzhou Medical College (Luzhou, China) in June 2015, with a history of night sweats, weight loss (~2 kg), and bilateral cervical lymphadenectasis for >10 days. This patient was clinically diagnosed with pulmonary TB 2 years prior to the current admission at Luzhou People's Hospital (Luzhou, China), but only accepted antituberculosis therapy for 1 month there. Physical examination of the neck revealed bilateral swollen lymph nodes on the patients neck; these were abnormally sized and characteristic of malignancy, being fixed and not tender. The maximal and minimal diameter of these enlarged lymph nodes were 6 and 1 cm, respectively. A nasopharynx CT routine scan revealed multiple swollen and confluent lymph nodes in the bilateral neck, lower mandible, bilateral supraclavicular fossa, right-sided parapharyngeal space and superior mediastinum. The same results were obtained from an MRI scan.

The patient underwent a whole body ^{18}F-FDG PET/CT scan, which demonstrated a number of mass-like areas with an intense ^{18}F-FDG uptake in the right parapharyngeal space, bilateral carotid sheath, cervical region bilateral supraclavicular fossa, mediastina and para-abdominal aorta (Fig. 3). The SUV_{max} of ^{18}F-FDG in these lesions was 5.8. Additionally, a mass of cavitary phthisical lesions were also discovered in bilateral lung tissue, with an SUV_{max} of 6.8 (Fig. 3). Another intense ^{18}F-FDG uptake lesion was presented in the thickened right ascending colon wall, with an SUV_{max} of 6.0 (Fig. 3). Upon evaluation of these images, this patient was suspected to suffer from malignant lymphoma, but the characteristics of the lesions in the bilateral lung tissue were consistent with PTB.

The patient was finally diagnosed with PTB and LNTB due to the result of the biopsy specimen obtained from his right cervical region. The patient underwent a lymph node biopsy in June 2015. The tissues were fixed in 10% formalin at room temperature for 24 h, embedded in paraffin and sectioned at 5 μm thickness. This examination of pathology (hematoxylin and eosin, original magnification, x100) revealed a chronic inflammatory granulomatous reaction with caseous necrosis, which was consistent with the characteristics of TB (Fig. 4). No evidence of neoplasia was found in the biopsied specimen. Furthermore, an acid-fast stain of the patient's phlegm was performed. The patient's sputum samples were collected, smeared, air dried and heat fixed. The staining was performed using Carbol fuchsin, acid alcohol and methylene blue (Sigma-Aldrich; Merck Millipore, Darmstadt, Germany). The result confirmed the diagnosis, as acid-fast *Bacillus* was identified in the patient's sputum samples. Following the diagnosis of PTB and LNTB, the patient started the antituberculosis standard treatment while admitted to hospital for 3 more months, which included isoniazid (200 mg per day), rifapentine (480 mg per day) and pyrazinamide (1,200 mg per day).

Discussion

TB remains a major health problem worldwide, especially in developing countries. It has been ranked as the second leading cause of death from an infectious disease other than the human immunodeficiency virus (HIV) (10). Early diagnosis promotes effective treatment and leads to a reduced onward transmission of TB. However, patients with sputum-negative PTB and extrapulmonary TB (EPTB) are difficult to diagnose due to an absence of clinical signs and bacteriological basis, resulting in a significant delay of the appropriate treatment. LNTB is considered to be the most common form of EPTB (8,9), and the most frequently affected site is the cervical lymph nodes, followed by the mediastinal lymph nodes (11). Despite the reduction in the incidence of PTB worldwide, there has been no decrease in the frequency of LNTB. Lymphadenopathy, fever, weakness, night sweats, and weight loss are the most common clinical presentations of LNTB, causing a notable risk of confusing LNTB with lymphomas (12,13). Diagnostic imaging also presents challenges in the diagnosis of LNTB, as symptoms of LNTB may mimic those of other diseases such as neoplasms or sarcoidosis (6).

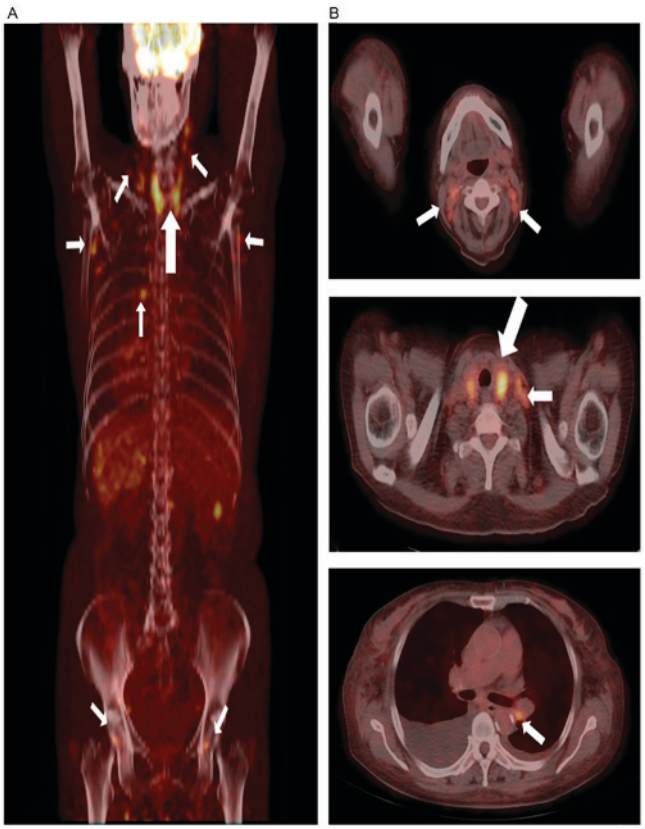

Figure 1. (A) Coronal FDG PET/CT image of the patient in case 1. (B) Axial FDG PET/CT images of the patient. The images revealed the presence of ^{18}F-FDG uptake in the lesions of the bilateral neck, bilateral axillary, mediastina and bilateral inguinal regions (smaller white arrows). The SUV_{max} of these lymph nodes was 3.8, and the presence of malignant lymphoma was suggested. In addition, the images revealed another lesion with increased FDG uptake (SUV_{max}, 3.6) in the neck region (large white arrows); however, the nature of this lesion could not be determined. FDG PET/CT, F-fluorodeoxyglucose positron emission/computed tomography; SUV, standard uptake value.

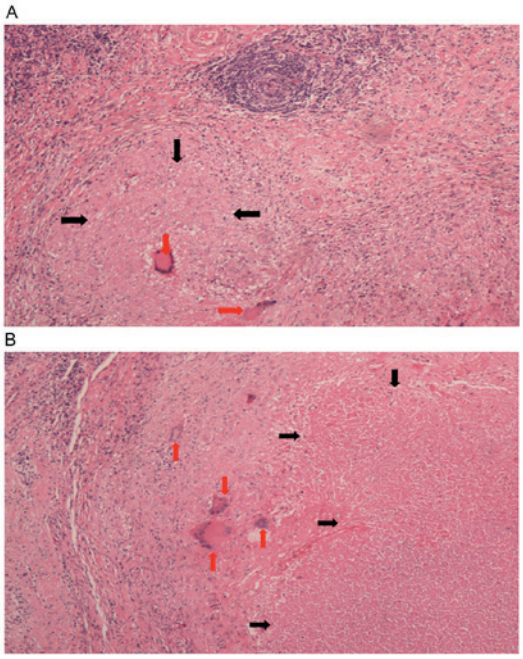

Figure 2. (A and B) Pathological examination (hematoxylin and eosin; magnification, x100) of the biopsy specimen from the cervical lymph node. The images indicate no malignant cells, caseous necrosis (black arrows) and Langhans giant cells (red arrows). The result was consistent with the characteristics of tuberculosis.

^{18}F-FDG PET/CT is a non-invasive imaging method that has been used widely for the differentiation of malignant from benign lesions (6). Increased FDG uptake has been reported in almost all tumor types with an accuracy of 96.8% and a specificity of 78% (14). However, ^{18}F-FDG is not a tumor-specific agent; it may also accumulate in inflammatory cells such as neutrophils, activated macrophages, and lymphocytes at the site of inflammation or infection, causing false-positive results (15,16). Goo *et al* (17) studied 10 patients suffering from histopathologically determined PTB, in which 9 of 10 cases reported FDG uptake in a PET scan. There are also several studies on TB lesions in which ^{18}F-FDG uptake has mimicked malignancy (18-20), proving the difficulty in distinguishing active TB from malignant tumors using FDG PET/CT imaging. The SUV_{max} measure has been widely used for detection and differentiation of malignant lymph nodes in cancer patients (21,22). Payabvash *et al* (23) studied the role of PET/CT in differentiating malignant from benign cervical lymph nodes in patients with head/neck cancer, showing that the SUV_{max} of ≥2.5 can detect malignant lymph nodes with 19% specificity, whereas a cutoff of ≥5.5 has 100% specificity for detection of malignant lymph nodes. However, in the present cases, an enlarged lymph node with SUV_{max} of 5.8 was also identified as TB.

The mechanism responsible for increased FDG uptake in tumor cells is an increased number of glucose transporter proteins and increased intracellular hexokinase and phosphofructokinase levels, which promote glycolysis (5). Cancer cells often have abnormally high rates of glycolysis, even under the sufficient oxygen conditions, and they preferentially generate energy using anaerobic glycolysis followed by metabolism of pyruvate into lactic acid. In addition to elevated glycolysis, tumors often have increased expression of glucose transporters (GLUTs) (1). Similarly to glucose, FDG is transported into tumor cells by means of GLUTs and subsequently phosphorylated by hexokinase to FDG-6-phosphate, finally accumulating within the cells (24,25). Furthermore, the glucose transporter activity of tumor cells will increase under hypoxic conditions; as the tumor grows in size and more central hypoxic areas appear, additional FDG uptake will occur (26). LNTB is typically drained from PTB through the lymphatics (9); following intense interaction between mycobacterial virulence and individual response in the tuberculous lymph nodes, the monocytes, the macrophages, the lymphocytes, the epithelial cells and the other chronic inflammatory cells will accumulate. The activated inflammatory cells, similarly to cancer cells, may then markedly increase glycolysis (5,27). The hexose monophosphate shunt is stimulated by phagocytosis, with increases of 20-30 times that of baseline values, thereby increasing FDG uptake (5). Furthermore, a previous study has also reported that the macrophages may have higher FDG uptake than the viable malignant cells despite localization in the same tissue sample (28). For this reason, the

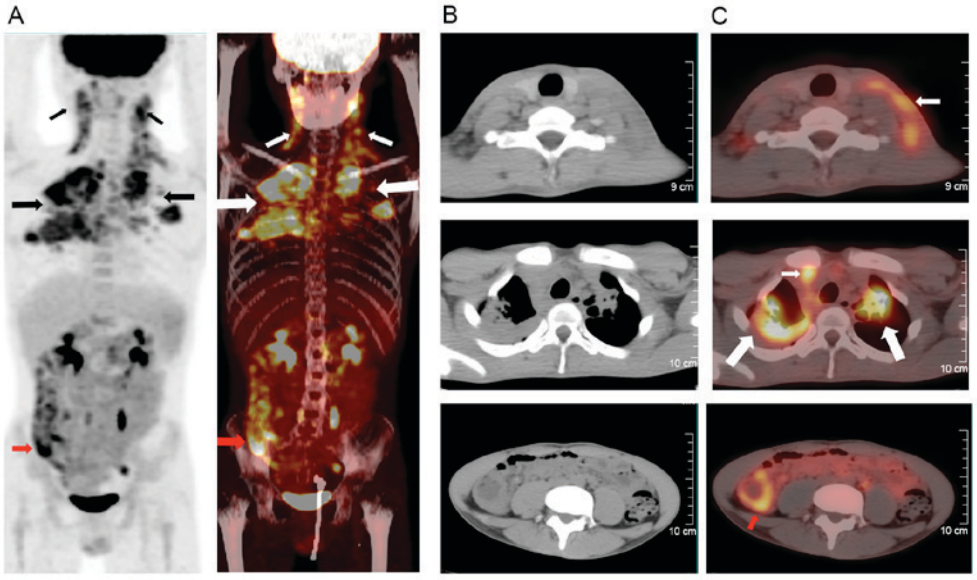

Figure 3. (A) Coronal FDG PET/CT image of the patient in case 2. (B) Axial CT images of the patient. (C) Axial PET/CT images of the patient. The images revealed enlarged lymph nodes with increased FDG uptake (SUV_{max}, 5.8) in the right parapharyngeal space, bilateral carotid sheath, cervical region, bilateral supraclavicular fossa and mediastina (smaller white arrows). A mass of cavitary phthisical lesions were also demonstrated in bilateral lung tissue, with an SUV_{max} of 6.8 (large white arrows). A thickened right ascending colon wall with increased FDG uptake (SUV_{max}, 6.0) was also detected (red arrows). FDG PET/CT, F-fluorodeoxyglucose positron emission/computed tomography; SUV, standard uptake value.

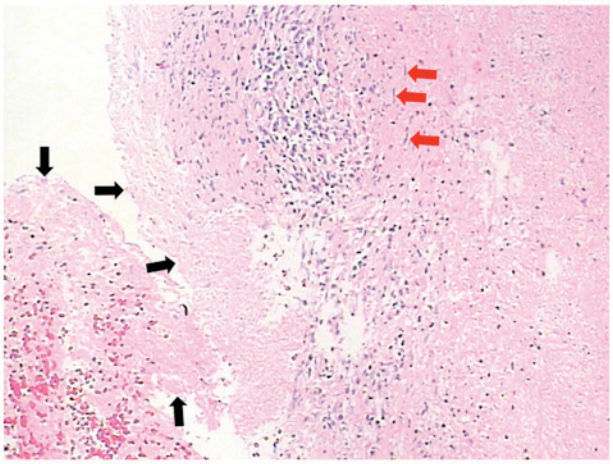

Figure 4. Pathological examination (hematoxylin and eosin; magnification, x100) of the biopsy specimen from the cervical lymph node. Caseous necrosis (black arrows) and epithelioid cells (red arrows) are reported in this field of view.

^{18}F-FDG PET/CT imaging characteristics of LNTB may be easily confused with malignancy.

In the current cases, the CT and other images of the enlarged lymph nodes did not demonstrate characteristics of LNTB, and the significant elevation of FDG uptake was detected through the PET/CT scan. Therefore, these cases could be easily misdiagnosed as lymphoma. To make a definite diagnosis of LNTB, the lymph node biopsy and pathological examination appear necessary. However, lymph node biopsy is an invasive examination. How to appropriately use the PET/CT scan to distinguish the active TB lesion, especially the LNTB, from malignancy is an urgent problem.

To solve this, various other PET tracers have been investigated, including ^{11}C-choline (29), ^{18}F-FLT (30,31), ^{68}Ga-citrate (27), with some promising results. For example, Hara *et al* (29) compared ^{18}F-FDG vs. ^{11}C-choline uptake in cancer and TB in their study, concluding that whereas lesions report elevated ^{18}F-FDG uptake, only cancer shows high uptake with choline, and TB lesions are hardly visualized. In addition, dual time point imaging (DTPI) or double phase technique of PET/CT has been suggested in several studies to boost the differentiation between benign and malignant lesions (32,33). FDG uptake in inflammatory/infectious tissues was reported to reach its peak in about 60 min after the time of injection, but then it gradually decreased with time. Conversely, malignant lesions have been shown to keep increasing the FDG uptake up to several hours (34,35). However, Razak *et al* (35) suggested in their study that DTPI of PET/CT may not be a useful technique in differentiating between EPTB and non-EPTB lesions, so the value of DTP FDG PET/CT imaging remains controversial.

The most important clinical application of ^{18}F-FDG PET/CT in LNTB is the assessment of treatment response (6,27). A previous study suggested that a SUV_{max} cut-off value of 4.5 could be used to differentiate LNs responding to TB treatment from nonresponding LNs (36), and the role of FDG PET/CT on differentiating active from inactive disease in patients with TB was also identified (27).

In summary, TB can easily be confused with malignancy, due to its clinical presentation. LNTB is the most common form of EPTB, but absence of clinical signs and bacteriological basis makes it difficult to diagnose. The current cases indicated that LNTB may increase FDG uptake in ^{18}F-FDG PET/CT, causing false-positive results. Therefore, when a patient suffers from enlarged lymph nodes, the increased FDG uptake may not necessarily be an indication of malignant disease, and LNTB should be considered, especially in patients from endemic areas; pathological examination still serves a vital role in LNTB diagnosis.

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