Inflammatory myofibroblastic tumor mimicking lymphoma on ^{18}F-FDG PET/CT. Report of a case and review of the literature

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Abstract
Inflammatory myofibroblastic tumor (IMT) is an uncommon neoplasm that has been described in various locations throughout the body, but is rarely observed in systemic lymph nodes. We present a case of a 63 years old woman with left inguinal lymphadenopathy accompanied by low-grade fever. Fluorine-18-fluoro-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) revealed abnormal higher ^{18}F-FDG uptake on the neck, axillar, pulmonary hilar, mediastinal, mesenteric, retroperitoneal, pelvic and inguinal lymph nodes. These findings led to an initial misdiagnosis of lymphoma. Final histological diagnosis revealed an IMT. The patient was treated with oral steroids. Ultrasound assessments showed a complete resolution of systemic enlarged lymph nodes at the end of 1 month of therapy. There has been no evidence of recurrence through 12 months of post-treatment monitoring. This case suggests that IMT should be considered as a possible differential diagnosis in apparent cases of lymphoma. Further, it indicates that steroid therapy may serve as an effective treatment for IMTs that systemically affect lymph nodes.

Introduction

Inflammatory myofibroblastic tumor (IMT) was originally observed in lung and described by Bunn in 1939 [1]. It is an uncommon mesenchymal tumor of unknown etiology consisting of neoplastic myofibroblasts and a conspicuous inflammatory infiltrate, which can arise in a wide variety of anatomic locations throughout the body and typically occurs in children and young adults [2, 3]. Multiple terms have been used to describe this type of lesion, including inflammatory pseudotumor, fibrous xanthoma, plasma cell granuloma, pseudosarcoma, lymphoid hamartoma, myxoid hamartoma, and inflammatory myofibrohistiocytic proliferation [4]. These diverse terms reflect the uncertainty regarding the etiology of the lesion [1]. In 1954, Umiker and Iverson renamed this lesion as IMT because of its mimicry of the clinical, radiological, and histopathological signs of malignant neoplasm [5]. Inflammatory myofibroblastic tumor is a rare neoplasia, occurs most commonly in the lungs, liver and gastrointestinal tract [1], accounting for 0.04%-1.2% of all lung tumors [6]. To our knowledge, few cases only of IMT of systemic lymph nodes have been reported in the literature.

Conventional imaging modalities, such as ultrasound, computed tomography (CT), and magnetic resonance imaging, are commonly used as initial diagnostic technologies for tumor detection. However, their diagnostic capabilities to differentiate between benign and malignant lesions are limited [7]. Kim et al. (2009) have reported that clear radiologic differentiation of an abdominal IMT from other likely malignancies is difficult [8]. On the contrary, ^{18}F-FDG PET/CT has attracted increasing interest, and it has been used in the field of oncology, especially in diagnosis and treatment of lymphoma. Fluorine-18-FDG PET/CT imaging of IMT affecting lung and abdominal tissue have been represented in a limited number of studies [9, 10], whereas the ^{18}F-FDG PET/CT characteristics of primary IMT in lymph nodes have been even more rarely described. Herein, we present ^{18}F-FDG PET/CT findings in a case of IMT affecting lymph nodes in a systemic fashion, with the suggestion that clinicians consider this type of IMT as a differential diagnosis in apparent cases of lymphoma.

Case Report

A 63 years old women presented with a gradually increasing painless swelling in her left groin over the last 20 days accompanied by low-grade fever over the last 7 days, and was admitted to our Department of Oncology. She had unremarkable medical history with respect to trauma, cancer, tuberculosis, or surgery. On clinical examination, a firm, partly fixed, nodular mass, measuring 3.0cm in maximal diameter was founded in the left groin. Laboratory investigations revealed normal levels of red and white blood cells and unremarkable liver chemistry, including measurements of alanine aminotransferase and aspartate aminotransferase. Serum toluidine red unheated serum test (TRUST) and Treponema pallidum particle agglutination assay (TPPA) showed positive titers at 1:4 (normal range: negative) and 1:640 (normal range: 0-80), respectively. Epstein-Barr virus (EBV) (EBV-IgM and EBV nuclear antigen), antinuclear antibodies, and antiextractable-nuclear antigens were negative. C-reactive protein (CRP), at 10.93mg/L (normal range: 0-8) and D-dimer, at 2.24mg/L (normal range: 0-0.5) were slightly to moderately elevated. The initial ultrasound showed multiple enlarged lymph nodes in the inguinal area bilaterally with the largest node in the left groin (2.9cm length×1.5cm width).

The lymph node in the left groin underwent excisional biopsy. The specimen was fixed in 10% neutral buffered formalin. During macroscopic analysis of cut sections, we found a well-localized, well-demarcated, smooth discrete whitish fibrotic mass, measuring 4.0cm×2.5cm×2.0cm. The cut sections did not display infiltrative tumors in the intra-luminal compartment. No signs of necrosis, hemorrhage, or calcification were found.

During microscopic, histological analysis, we found that the tumor was composed mainly of collagenous fibrotic tissue and spindle-shaped myofibroblasts with diffuse infiltration of numerous inflammatory cells (Figure 1). Immunohistochemical staining of the tumor demonstrated the presence of smooth muscle actin (SMA) (Figure 2A), CD68 (KP-1) (Figure 2B), Ki-67 (Figure 2C), and the absence of anaplastic lymphoma kinase (ALK) (Figure 2D), desmin (Figure 2E), and P53 (Figure 2F). Two days after excisional biopsy of the lymph node in the left groin, ^{18}F-FDG PET/CT (Siemens Biograph mCT; injection of 212.01MBq ^{18}F-FDG) suggested systemic presence of the tumor, revealing multiple lymph nodes with intense ^{18}F-FDG uptake as shown on the maximum intensity projection images.

In selected transaxial PET/CT slices, we found increased ^{18}F-FDG accumulation in bilateral neck lymph nodes with a maximum standardized uptake value (SUVmax) of 4.67 (Figure 3A), bilateral axillary lymph nodes with SUVmax of 2.76 (Figure 3B), mediastinal lymph nodes with SUVmax of 5.70 (Figure 3C), pulmonary hilar lymph nodes with SUVmax of 5.70 (Figure 3D), mesenteric lymph nodes with SUVmax of 6.36 (Figure 3E), retroperitoneal lymph nodes with SUVmax of 3.42 (Figure 3F), pelvic lymph nodes with SUVmax of 4.85 (Figure 3G), and inguinal lymph nodes with SUVmax of 6.99

(Figure 3H & 3I). Nearly all lymph nodes exhibited uniformly intense ^{18}F-FDG accumulation, and most of them showed signs of lymphadenectasis (from 1.8cm×1.4cm to 3.2cm×2.5cm in size).
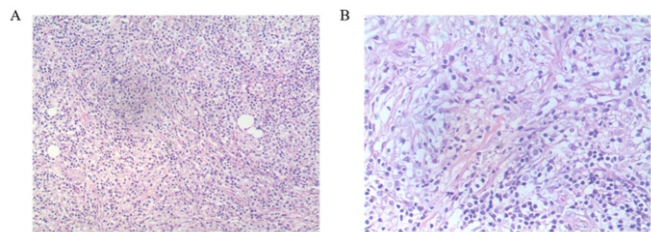

Figure 1. Hematoxylin and eosin analysis of a lymph node in the left groin. (A) Low-powered magnification demonstrating prominent storiform and fascicular pattern collagenized areas and chronic inflammatory cells (magnification, ×100). (B) High-powered magnification demonstrating the presence of spindle shaped cells (myofibroblasts), mature plasma cells and lymphocytes (magnification, ×200).
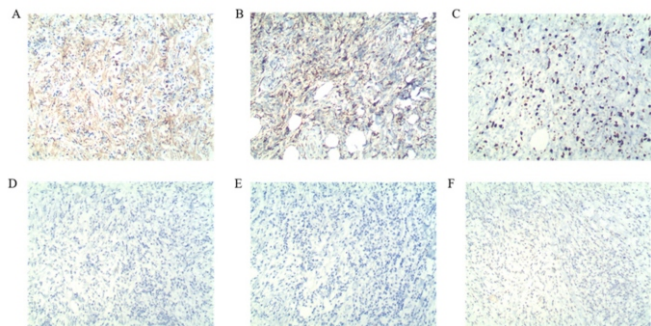

Figure 2. Immunohistochemical analysis of a lymph node in the left groin, showing positive staining with SMA (A), CD68 (B), and Ki-67 (C), negative staining with ALK (D), desmin (E), and P53 (F) (magnification, ×100).
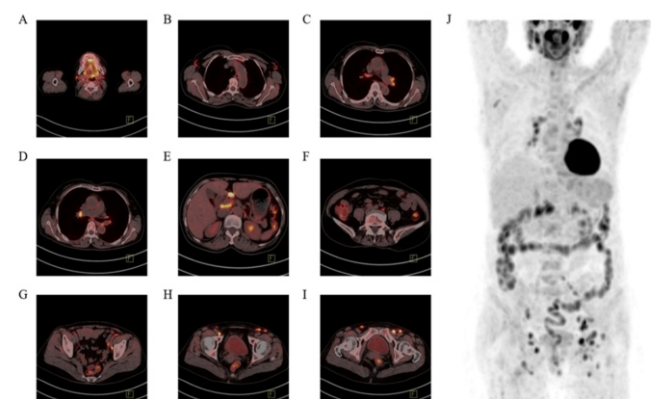

Figure 3. ^{18}F-FDG PET/CT imaging of systemic IMT of the lymph nodes. (A) Neck lymph nodes; (B) Axillary nodes; (C) Mediastinal lymph nodes; (D) Pulmonary hilar lymph nodes; (E) Mesenteric lymph nodes; (F) Retroperitoneal lymph nodes; (G) Pelvic lymph nodes; (H) and (I) Inguinal lymph nodes. (J) MIP image.

Our ^{18}F-FDG PET/CT findings suggested possible malignancy. However, the patient only reported a 7 day history of low-grade fever. Moreover, no signs of calcification or necrosis were found in the hypermetabolic lymph nodes, and no obvious pulmonary abnormalities were observed on CT scans. Based on patient's medical history and our imaging fin-

dings, lymphoma was first considered. Histology confirmed the final diagnosis of IMT. Because of the involvement of multiple lymph nodes, a complete excision of the affected lymph nodules was difficult to achieve.

The patient was treated with 0.5mg/kg of oral prednisone daily for 1 month. The ultrasound showed a complete resolution of systemic enlarged lymph nodes at the end of 1 month of therapy. There has been no evidence of recurrence through 12 months of post-treatment monitoring.

Our patient provided a written informed consent for the case report. The consent procedure was approved by the Ethics Committee of Zhongshan Hospital Xiamen University.

Discussion

According to the World Health Organization classification, IMTs are considered a mesenchymal neoplasm of intermediate malignant potential, since its histology is characterized by proliferation of fibroblasts and myofibroblasts combined with lymphocytes, plasma cells, eosinophils, and histiocytes [11]. Some IMTs can show however malignant biological behaviors, with a low risk for local recurrence (<5% of cases) and a moderate risk of distant metastasis [11].

The etiologic factors responsible for the development of IMT remain uncertain. Several hypotheses have been proposed, suggesting that it may be related to autoimmune or infectious mechanisms, noninfectious agents, or that it may be a true tumor [12]. It has been also reported, in 30% of patients with IMT, that the presence of the tumor was associated with recurrent infections caused by mycoplasma, nocardia, actinomycetes, EBV or human herpes virus species [6, 12]. In addition, trauma, abdominal surgery, and genetic factors have been associated with the presence of Inflammatory myofibroblastic tumor [13]. No previous history of trauma or abdominal surgery was reported in the presented case. Both TRUST and TPPA were positive, with elevated levels of CRP and D-dimers, suggesting an association with a syphilis infection.

The reported radiological characteristics of IMT have been variable and nonspecific [14]. Compared to conventional CT, ^{18}F-FDG PET/CT examination can provide two types of information: morphological and metabolic. Several authors have reported cases of IMT exhibiting increased ^{18}F-FDG uptake, as it is a metabolically active tumor mass [9,10]. IMT may be thus misdiagnosed as a neoplastic/recurrent disease when there is a prior history of cancer [10, 15]. Inflammatory myofibroblastic tumor positivity on ^{18}F-FDG PET/CT is explained by the fact that ^{18}F-FDG is absorbed by tumor cells, as well as macrophages, granulocytes, and inflamed tissues. The metabolic activity of IMT appears to be variable, with a SUVmax ranging from 3.8 to 20.8 [9], making distinction between IMT and malignant neoplasms impossible. In our case, the SUVmax was relatively intense, ranging from 2.76 to 6.99. Three factors may lead to increased glucose uptake degree within an IMT, such as high tumor cellularity, the presence of nuclear atypia and a relatively high proliferative index [9, 16]. Activated immune cells, including neutrophils and macrophages, over-express gluco-

se transporters that facilitate ^{18}F-FDG uptake through the cell membrane. Therefore, the use of ^{18}F-FDG PET/CT imaging in differentiating inflamed tissues from malignant lesions is limited, whereas it is useful for detecting metastasis and recurrent cancer, and for monitoring treatment response in patients with IMT. Kubo et al. (2012) reported a case of mediastinal ^{18}F-FDG-avid IMT with multiple metastases in the thoracic vertebra and lymph nodes. After three cycles of chemotherapy, ^{18}F-FDG PET/CT revealed tumor regression with significant reduction of ^{18}F-FDG uptake in all lesions [17]. Dong et al. (2014) reported a case of ^{18}F-FDG-avid lung IMT reccurent locally 7 months after resection [9].

Primary IMT in lymph nodes is a rare location with less than 10 cases reported so far. Its systemic occurrence in multiple lymph nodes is even less common. Gandhi et al. (2015) reported a case of IMT which presented as inguinal lymphadenopathy with fever. Initially, the patient was clinically misconstrued as lymphoma because cytology could not exclude a lymphoma. Immunohistochemical staining revealed IMT of the inguinal lymph nodes [19]. Important differential diagnosis might include lymphoma. Lymphoma also has no typical symptoms and may manifest with painless enlarged lymph nodes and fever. Therefore, differentiating between lymphoma and systemic IMT of the lymph nodes is difficult based solely on clinical and imaging manifestations. The key patholoanatomical differentiations of IMT are: spindle-shaped myofibroblastic cells and an intense inflammatory process, mainly involving lymphocytes and plasma cells [20]. The confirmation of the presence of SMA-positive myofibroblasts is important for the differential diagnoses from lymphoma that is confirmed SMA-negative [21]. Although controversial, ALK has been considered as a promising biomarker for improving the diagnostic accuracy of IMT [22]. ALK-protein positivity has been detected in 50 %-60% of cases with IMT due to ALK-gene rearrangement [23]. In our case, the tumor cells demonstrated expression of SMA, CD68 (KP-1) and Ki-67; they did not show expression of ALK, desmin, or P53. These results were consistent with previous reports [21-24].

The therapy for IMT includes surgical resection, steroids or non-steroidal anti-inflammatory drugs, radiation therapy, chemotherapy, and immunomodulators. These treatment modalities alleviated signs and symptoms with varying success rates [24]. Among these, complete surgical resection is the optimal therapeutic approach for IMT. Systemic steroid therapy yields rapid response, with 31%-78% of tumors disappearing completely in 24-48 hours; however, steroid therapy may be associated with a high relapse rate [25]. In this case, surgical resection was deemed not feasible due to multiple lesions, so we administered steroid therapy. The ultrasound showed a complete resolution of systemic enlarged lymph nodes at the end of 1 month of therapy. There has been no evidence of recurrence through 12 months of post-treatment monitoring. Our findings suggest that steroid therapy is a viable medical alternative when tumor resection is not feasible.

In conclusion, systemic IMT of the lymph nodes is a very rare tumor and its specific clinical manifestations and imaging findings have not been extensively described. Inflammatory myofibroblastic tumor easily mimics lymphoma as

both entities are ^{18}F-FDG avid. Histological examination is crucial for an accurate diagnosis of IMT. This case suggests that IMT should be considered as a differential diagnosis in lymphoma. Moreover, it suggests that oral steroid therapy may be a useful treatment for systemic IMT of the lymph nodes.

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