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Case Report Open Access

A Case of Anti-Synthetase Syndrome in Which Skeletal Muscle Uptake on ^{18}Fluorine Fluorodeoxyglucose-Positron Emission Tomography Imaging was the Initial Clue

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Abstract

A 73-year-old woman was diagnosed as interstitial pneumonia and treated with corticosteroids. Seventeen months later, she developed persistent fever. Considering the possibility of a malignancy, ^{18}fluorine fluorodeoxyglucose-positron emission tomography ([^{18}F]-FDG-PET) was performed, only to detect mild accumulation in the proximal skeletal muscles. She then presented muscle weakness with a myogenic pattern on electromyography. She was consequently diagnosed as polymyositis and then as anti-synthetase syndrome. [^{18}F]-FDG-PET was the key to the diagnosis of myositis in patients without muscle symptoms.

Keywords: Anti-PL-7 antibody; Anti-synthetase syndrome; [^{18}F]-FDG-PET; Interstitial pneumonia; Polymyositis

Introduction

It is well known that interstitial pneumonia is associated with collagen vascular diseases (CVDs) such as polymyositis/dermatomyositis (PM/DM) and rheumatoid arthritis (RA) [1]. Although CVD and interstitial pneumonia are often diagnosed almost simultaneously, the onset of interstitial pneumonia may precede the onset of CVD [2] resulting in the tentative diagnosis of idiopathic interstitial pneumonia. We encountered a case in which there were no findings of myositis or elevated creatine phosphokinase (CPK) at the time of onset of interstitial pneumonia. Seventeen months later, [^{18}F]-fluorodeoxyglucose-positron emission tomography ([^{18}F]-FDG-PET), performed in search of latent malignancy for the cause of persistent fever, showed mild accumulation in the proximal skeletal muscles, which led to the diagnosis of PM. Although the usefulness of [^{18}F]-FDG-PET has been widely recognized in the detection of malignant tumors, there have been few reports regarding [^{18}F]-FDG-PET in myositis. This was a rare case in which [^{18}F]-FDG-PET provided the key to the diagnosis of myositis.

Case Report

A 73-year-old woman who had never smoked was admitted to our hospital for examination and treatment of dyspnea on exertion. Chest X-ray (Figure 1a) showed reticular shadows in the bilateral lower lungs, and chest computed tomography (CT) (Figure 2a) showed ground glass opacity (GGO), reticular shadows, bullous formation, interlobular septal thickening and traction bronchiectasis at the pleural side of the bilateral lower lungs and around the bronchovascular bundles. Transbronchial lung biopsy (TBLB) performed in the right lung (Figure 3) demonstrated thickening of alveolar septa and moderate infiltration by small round cells, which was histologically compatible with interstitial pneumonia. Although the patient exhibited bilateral wrist pain and her mother had RA, RA was considered unlikely based on the affected sites and number of joints, blood tests (RF < 15 U/ml, anti-CCP antibody < 0.6 U/ml) and X-ray findings of the affected joints. The patient was negative for all other autoantibodies tested.

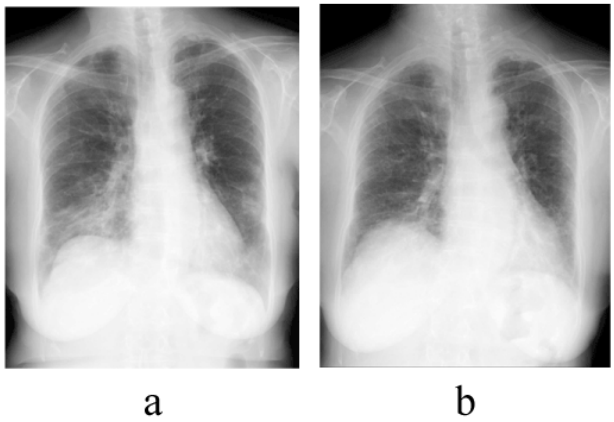
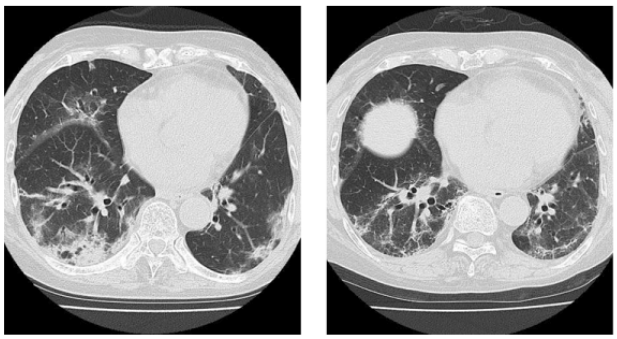


Figure 1: Chest X-ray on the initial visit (Figure 1a) showed reticular shadows in the bilateral lower lung fields which improved after the first steroid pulse therapy. At the time of re-hospitalization (Figure 1b), both lungs showed reticular shadows predominantly at the periphery with reduced lung volume.



a b

Figure 2: Chest CT on the initial visit (Figure 2a) showed GGO, reticular shadows, bullous formation, interlobular septal thickening and traction bronchiectasis at the pleural side of the bilateral lower lungs and around the bronchovascular bundles which improved after steroid pulse therapy. At the time of admission (Figure 2b), reticular shadows, curvilinear shadows and traction bronchiectasis were seen bilaterally predominantly in the periphery.

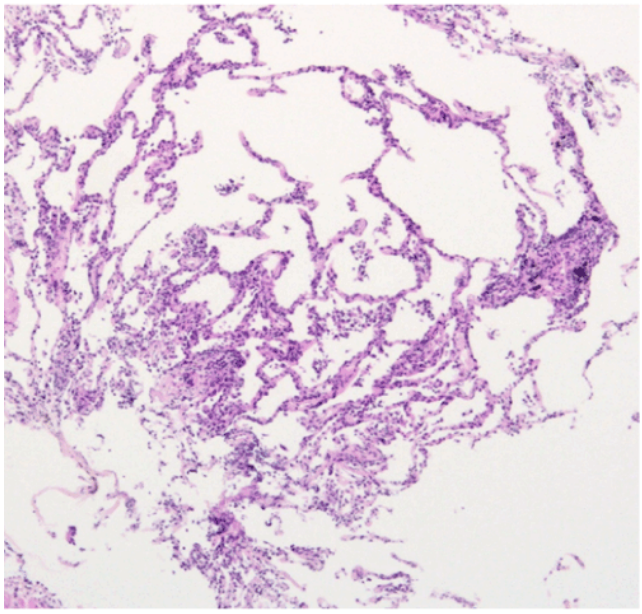


Figure 3: Histology of TBLB samples demonstrated thickening of alveolar septa and moderate infiltration of small round cells. Interstitial pneumonia was diagnosed. H&E stain, 40x.

Corticosteroid pulse therapy was performed for interstitial pneumonia, followed by oral prednisolone of 30 mg/day, to improve radiological findings and exertional dyspnea. Because of arthritis, the patient was suspected of having CVD with preceding interstitial pneumonia and was followed at our hospital on an outpatient basis.

Twelve months after onset, although the patient was maintained with prednisolone at 5 mg/day, she demonstrated worsening of chest X-ray findings and a slight increase in CPK level to 240 IU/L without muscular symptoms. Anti-Jo-1 antibody was negative. Prednisolone was increased to 30 mg/day and then tapered to 20 mg/day 5 months later (17 months after initial onset), when she developed fever. The patient was admitted for the second time because the fever persisted. She was not aware of any muscle weakness or muscle pain.

Her vital signs on admission included body temperature of 38.3ºC, blood pressure 106/80 mmHg, pulse rate 98/minute, and SpO_2 97% (O_2 nasal cannula 1L/minute). Her physical examination revealed no abnormal findings except for fine crackles heard from the bilateral lower lungs on the back.

Laboratory findings (Table 1) indicated marked leukocytosis, slightly elevated LDH, CPK, and CRP levels and an elevated KL-6 level. Anti-nuclear antibodies showed a cytoplasmic pattern at a titer of 160x, but all other autoantibodies tested, including anti-Jo-1 antibody, were negative.

Hematology							
WBC	23,500/μl		AST	25 IU/l		RF	<10 IU/ml
Neut	95%		ALT	20 IU/l		Anti-ssDNA Ab	(−)
Lym	2%		BUN	15.8 mg/dl		Anti-dsDNA Ab	(−)
Mon	2%		Cre	0.70 mg/dl		Anti SS-A Ab	(−)
Bas	0%		Na	139 mEq/l		Anti SS-B Ab	(−)
Eos	1%		K	4.2 mEq/l		Anti RNP Ab	(−)
RBC	448 ×10^4/μl		Cl	99 mEq/l		Anti Jo-1 Ab	(−)
Hb	13.1 g/dl		CPK	261 IU/l		Anti Scl-70 Ab	(−)
Ht	40.7%		GLU	75 mg/dl		IgG	871 mg/dl
Plt	32.7×10^4/μl		HbA1c	5.60%		IgA	167 mg/dl
						IgM	112 mg/dl
Biochemistry			**Serology**			KL-6	1,583 U/ml
TP	6.4g/dl		ANA	160×		SP-D	67.3 ng/ml
Alb	3.0 g/dl		speckled	40×		CRP	5.44 mg/dl
LDH	414 IU/l		cytoplasmic	160×			

Table 1: Laboratory Findings on Admission.

Chest X-ray (Figure 1b) demonstrated reticular shadows predominantly at the periphery of bilateral lower lobes. Compared with the chest X-ray at the first visit, volume reduction of the bilateral lower lungs was observed. Chest CT (Figure 2b) exhibited reticular shadows, thickening of the interlobular septa, curvilinear shadows and traction bronchiectasis predominantly at the periphery. The lung function tests demonstrated restrictive impairment, vital capacity (VC) 1.36L, %VC 63.3%, and forced expiratory volume for 1 second ($FEV_{1.0}$) 1.22L.

Whole body CT, bacteriological culture tests and transesophageal echocardiography were performed to detect the focus of infection, but there were no significant findings. Latent malignancy was suspected and [^{18}F]-FDG-PET imaging was performed (Figure 4), which illustrated mild uptake in the proximal skeletal muscles. Thereafter, the CPK and aldolase levels rapidly increased to 1,032 IU/L and 21.8

U/L, respectively, and muscle pain in the neck appeared. The extremities exhibited mild muscle weakness predominantly at the proximal muscles (Manual muscle testing 4) with electromyography (EMG) showing a myogenic pattern. Three of 4 diagnostic criteria of PM, defined by Peter and Bohan [3,4], were fulfilled (muscle biopsy was not performed), suggesting PM with high probability. After administration of corticosteroid, fever and muscle pain disappeared (Figure 5). Anti-aminoacyl-tRNA synthetase autoantibodies (Anti-ARS antibodies) were measured in the serum and anti-PL-7 antibody was detected. Therefore, this case was diagnosed as having anti-synthetase syndrome.

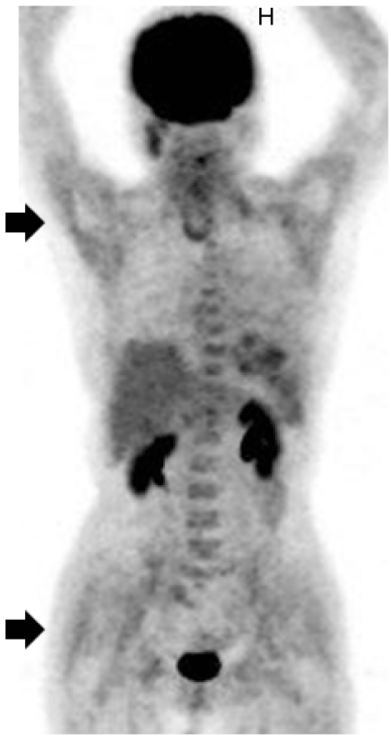


Figure 4: [^{18}F]-FDG-PET imaging showed mild accumulation in the proximal skeletal muscles. No accumulation suggestive of a malignant tumor was seen.

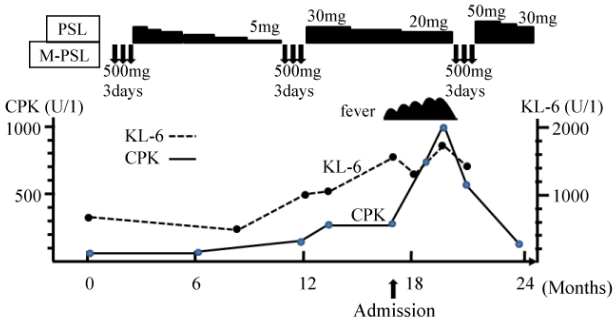


Figure 5: Clinical course.

M-PSL: methylprednisolone, PSL: prednisolone.

Discussion

During her first admission, the patient demonstrated bilateral wrist pain and interstitial pneumonia apparently associated with CVD. Since specific autoantibodies or other physical findings suspicious of CVD were not detected, the diagnostic criteria of any CVD were not met. [^{18}F]-FDG-PET performed for examination of persistent fever showed mild uptake in the proximal skeletal muscles, which became a clue to the diagnosis of PM and anti-synthetase syndrome with the positive result of anti-PL-7 antibody.

It is well known that interstitial pneumonia is associated with many CVDs such as PM/DM, RA, systemic lupus erythematosus (SLE) and systemic scleroderma (SSc) [1]. The onset of interstitial pneumonia may precede the onset of CVD such as in this case. In particular, cases of non-specific interstitial pneumonia (NSIP) followed by onset of CVD have been reported frequently [2]. In this case, marked increase in CPK and muscle pain was observed 17 months after the diagnosis of interstitial pneumonia. There was a report of a case of interstitial pneumonia in which the onset occurred 24 months prior to myositis [5]. Long-term careful observation for the onset of CVD is required in patients with interstitial pneumonia of unknown cause.

Anti-ARS antibodies are myositis-specific autoantibodies and eight types (anti-Jo-1 antibody, anti-PL-7 antibody, anti-PL-12 antibody, anti-OJ antibody, anti-EJ antibody, anti-KS antibody, anti-Zo antibody and anti-YRS antibody) have been identified to date. Among patients with polymyositis/dermatomyositis, the positive rate of anti-Jo-1 antibody was the highest at approximately 20% and that of anti-PL-7 antibody was 2-4% [6,7]. Positivity for anti-ARS antibody was frequently associated with myositis, interstitial pneumonia, and arthritis, referred to as anti-synthetase syndrome [8,9]. It has been reported that the rate of positive anti-ARS antibody was high among cases of PM/DM preceded by interstitial pneumonia such as this case [10].

A recent report demonstrated that there were differences in the clinical features among anti-synthethase syndrome cases, depending on the type of autoantibody [8]. Positivity for anti-PL-7 antibody, which was detected in this case, was frequently associated with myositis, interstitial pneumonia and sclerodactyly [11] with milder elevation of myogenic enzymes than in anti-Jo-1 antibody-positive cases [7]. Since muscular symptoms are mild in patients with anti-synthetase syndrome with anti-PL-7 antibody and symptoms remain dormant with steroids which are administered for the preceding interstitial pneumonia, diagnosis of myositis is difficult to make.

[^{18}F]-FDG-PET makes images of glucose metabolism by utilizing the fact that [^{18}F]-FDG is taken up into cells by the glucose transporter and accumulates. It has been used for the diagnosis of malignant tumors. Since glucose metabolism is also increased at the site of active inflammation caused by infectious and autoimmune diseases, [^{18}F]-FDG-PET imaging is useful in the search for the cause of fever of unknown origin [12].

In this case, [^{18}F]-FDG-PET revealed mild accumulation in the bilateral lower lungs and proximal skeletal muscles, which gave us a clue to the diagnosis of myositis. Reports on [^{18}F]-FDG-PET in myositis cases are rare [13-17]. Liu et al. [13] reported that accumulation was seen in the proximal muscles of the extremities in a patient with DM with increased CPK value of 755 IU/L. On the other

hand, in a study of 4 cases of inflammatory myopathies, accumulation in the skeletal muscles was observed only in one myopathy case due to statins with CPK value of 442 IU/L [14]. This report suggested that muscle uptake in [^{18}F]-FDG-PET imaging was not always associated with high CPK value, seemingly dependent on the inflammatory mechanisms of the disease. Though this report also suggested the usefulness of follow-up FDG-PET to evaluate treatment response, we did not perform because of radiation exposure and medical economy.

A recent study reported the validity of [^{18}F]-FDG-PET examination for the diagnosis of myositis (n=24); the sensitivity was 33% and specificity 97% [16]. No significant difference was detected in CPK concentration between patients with positive and negative [^{18}F]-FDG uptake. Patients with positive muscular uptake on [^{18}F]-FDG exhibited a myogenic pattern on electromyogram and inflammatory cell infiltration into the endomysium by muscle biopsy. Another study (n=12) suggested a sensitivity of 75% and specificity of 100% [17]. A large-scale study would be necessary to determine the validity of [^{18}F]-FDG-PET for the detection of myositis.

Although magnetic resonance imaging (MRI) is frequently used for diagnostic imaging of myositis, MRI can evaluate muscles of only one area at a time in contrast to PET. Studies of myositis patients using scintigraphy, which also detects abnormalities in the whole body, have also been reported. Some reported that Ga^{67} scintigraphy and ^{99m}Tc-PYP scintigraphy were useful in myositis [18], but others reported that the sensitivity was low at 50% [19].

We have encountered a patient who developed fever during steroid therapy for interstitial pneumonia. She underwent [^{18}F]-FDG-PET imaging, which showed mild uptake in the proximal skeletal muscles, leading to the diagnosis of PM and anti-synthethase syndrome. [^{18}F]-FDG-PET can be a useful imaging modality in the diagnosis of inflammation of the muscles of the whole body.

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