

[ CASE REPORT ]

## Paraneoplastic Syndrome Presenting with Polymyalgia Rheumatica-like Accumulations on <sup>18</sup>F-fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography

Ayaka Umetsu<sup>1</sup>, Toshimasa Shimizu<sup>1,2</sup>, Naoki Iwamoto<sup>1</sup>, Keiichi Hashiguchi<sup>3</sup>, Mizuna Eguchi<sup>1</sup>, Momoko Okamoto<sup>1</sup>, Yushiro Endo<sup>1</sup>, Sosuke Tsuji<sup>1</sup>, Ayuko Takatani<sup>1</sup>, Takashi Igawa<sup>1</sup>, Remi Sumiyoshi<sup>1</sup>, Tomohiro Koga<sup>1</sup>, Shin-ya Kawashiri<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Mami Tamai<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Tomoki Origuchi<sup>1,4</sup> and Atsushi Kawakami<sup>1</sup>

### Abstract:

A 70-year-old woman presented with a fever and pain in both lower extremities and the right shoulder and right upper arm continuously for approximately 3 months. <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography/computed tomography (<sup>18</sup>F-FDG/PET-CT) revealed the accumulation of FDG in the right shoulder, lumbar spinous processes, both ischial tuberosities, and both hips and greater trochanters, indicating polymyalgia rheumatica (PMR). In addition, upper gastrointestinal endoscopy revealed esophageal carcinoma. After endoscopic submucosal dissection was performed, her musculoskeletal symptoms spontaneously improved, and the <sup>18</sup>F-FDG/PET-CT findings decreased. In light of these findings, she was diagnosed with paraneoplastic syndrome. When atypical features of PMR, such as asymmetric symptoms occur, we should search for malignancies.

**Key words:** paraneoplastic syndrome, polymyalgia rheumatica, <sup>18</sup>F-FDG/PET-CT

(Intern Med 58: 861-864, 2019)

(DOI: 10.2169/internalmedicine.1847-18)

### Introduction

Polymyalgia rheumatica (PMR) is a common systemic inflammatory disease characterized by pain and stiffness of the proximal extremities (1). Previously existing malignancies sometimes induce rheumatic disease-like symptoms. These conditions are called paraneoplastic syndrome, which sometimes mimics PMR (2).

Recently, several studies have reported that <sup>18</sup>F-fluorodesoxyglucose positron emission tomography/computed tomography (<sup>18</sup>F-FDG/PET-CT) is useful for the detailed examination of fever of unknown origin (FUO) and rheumatic diseases, such as PMR (3, 4). However, little is

known about the pathophysiology of paraneoplastic syndrome that causes PMR-like symptoms and what types of findings present on <sup>18</sup>F-FDG/PET-CT.

We herein report a case of paraneoplastic syndrome in which <sup>18</sup>F-FDG/PET-CT showed findings suggestive of PMR but a subsequent detailed examination indicated the presence of esophageal carcinoma.

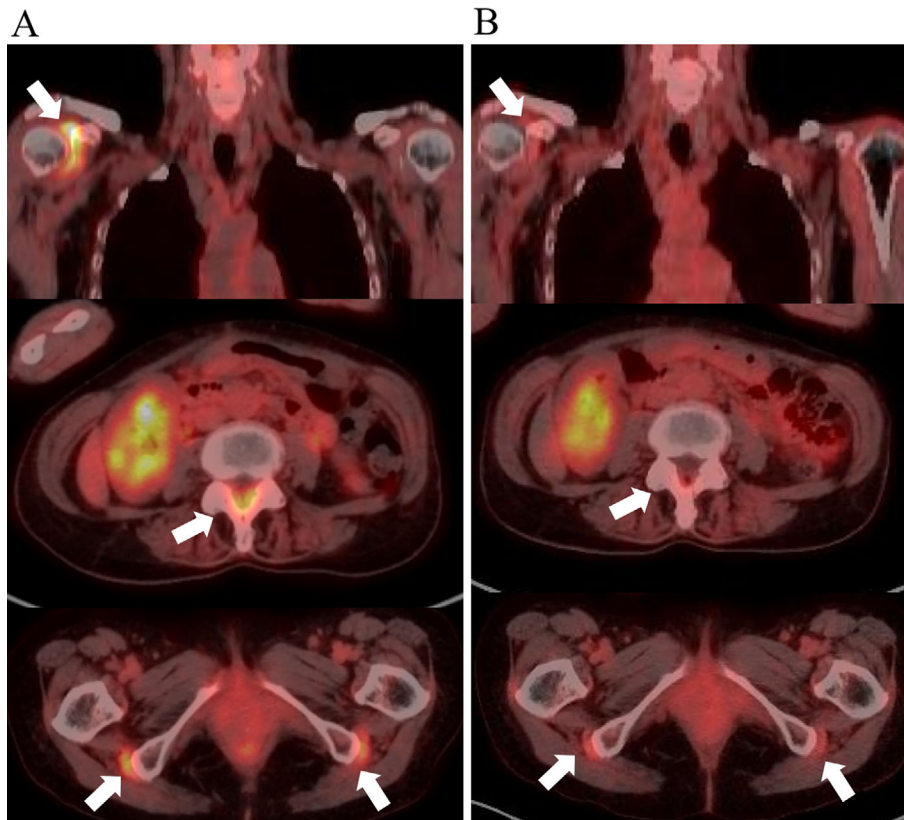
### Case Report

A 70-year-old woman experienced the sudden onset of a slight fever (approximately 37.5°C) and pain in both lower extremities in early April 2017. In mid-June 2017, she experienced an exacerbated fever (upwards of 38.0°C) as well as

<sup>1</sup>Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Japan, <sup>2</sup>Clinical Research Center, Nagasaki University Hospital, Japan, <sup>3</sup>Department of Endoscopy, Nagasaki University Hospital, Japan and <sup>4</sup>Department of Rehabilitation Sciences, Nagasaki University Graduate School of Biomedical Sciences, Japan

Received: July 19, 2018; Accepted: August 26, 2018; Advance Publication by J-STAGE: November 19, 2018

Correspondence to Dr. Toshimasa Shimizu, toshimasashimizu2000@yahoo.co.jp



**Figure 1.**  $^{18}\text{F}$ -FDG/PET-CT images. A: The images at the onset of paraneoplastic syndrome. The accumulation of FDG was observed in the right shoulder, lumbar spinous processes, and bilateral ischial tuberosities (white arrows). B: The images after treatment. The accumulation of FDG decreased (white arrows).

pain in the right upper arm and right shoulder, and she visited our hospital in early July 2017.

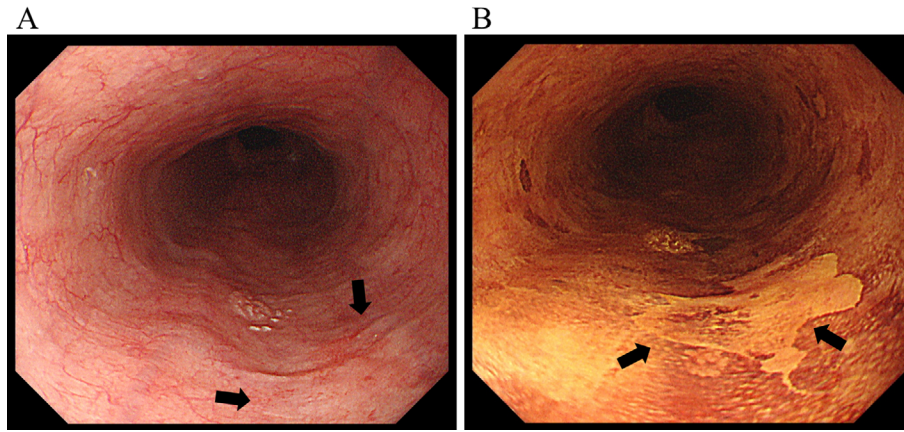
Her vital signs were as follows: body temperature,  $37.0^{\circ}\text{C}$ ; pulse rate, 77/min; blood pressure, 104/53 mmHg; oxygen saturation, 97% on room air; and clear consciousness. A physical examination revealed tenderness of the right shoulder, both hip joints, and both thighs. The range of motion (ROM) of the right shoulder was restricted. There was no swelling or tenderness at the peripheral joints, such as the wrists, fingers, or ankles. The superficial temporal artery showed no swelling or tenderness. Thoracic and abdominal findings were normal. She had no history of smoking or alcohol consumption.

Laboratory tests showed the following results: white blood cell (WBC) count  $5,900/\mu\text{L}$  (neutrophils 71%, lymphocytes 21%), hemoglobin (Hb) 11.8 g/dL, platelet (PLT)  $24.1 \times 10^4/\mu\text{L}$ , C-reactive protein (CRP) level 1.90 mg/dL, erythrocyte sedimentation rate (ESR) 70 mm/h, creatine kinase (CK) 55 IU/L, and no abnormalities on a urinalysis or with regard to the renal function. Rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibody, anti-nuclear antibody, myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), and proteinase-3 (PR3)-ANCA were not detected. Two sets of blood cultures and the viral markers for hepatitis B and C were all negative. We performed a cytokine multiplex array to measure the serum lev-

els of 42 cytokines as described previously (5). Her serum level of interleukin 6 (IL-6) was 11.8 pg/mL (interquartile range of healthy controls: 0.1-1.9 pg/mL), while the other cytokines were not elevated. Radiographs of both shoulders, hands, fingers, hips, knees, ankles, and toes revealed no abnormalities, including no erosion or joint space narrowing. Thoracoabdominal contrast-enhanced CT revealed no abnormal findings.

To identify the cause of the fever and the pain,  $^{18}\text{F}$ -FDG/PET-CT was performed. This revealed the accumulation of FDG in the right shoulder, lumbar spinous processes, bilateral ischial tuberosities, both hips, and both greater trochanters (Fig. 1A). Such accumulation suggesting vasculitis or malignancy was not observed. Musculoskeletal ultrasound of both shoulders revealed right biceps tenosynovitis and right subdeltoid bursitis.

These findings prompted us to consider the possibility of PMR. However, the asymmetric symptoms were atypical of PMR. Therefore, we performed additional imaging studies to search for malignancies. Although she had no associated symptoms, such as heartburn, upper gastrointestinal endoscopy revealed a reddish flat lesion (superficial flat type: 0-IIb) just under 10 mm in size in the middle esophagus (Fig. 2A). When Lugol's solution was applied, it was shown to be an irregularly unstained area (Fig. 2B). Biopsy findings taken from this site led to the diagnosis of squamous



**Figure 2.** Upper gastrointestinal endoscopy findings. **A:** A reddish flat lesion located in the middle esophagus (arrows). **B:** Application of Lugol's solution revealed an irregularly unstained area located in the middle esophagus (arrows).

cell carcinoma. Endoscopic submucosal dissection (ESD) was performed in September 2017, and postoperative staging indicated pT1aN0M0, Stage 0.

After ESD was performed, her PMR-like symptoms spontaneously improved and the inflammatory response was reduced without the use of corticosteroids; she was thus diagnosed with paraneoplastic syndrome. Additional  $^{18}\text{F}$ -FDG/PET-CT performed in April 2018 revealed improvement in the FDG accumulation, and no metastases were found (Fig. 1B). At the same time as the additional  $^{18}\text{F}$ -FDG/PET-CT was performed, her blood inflammatory markers decreased (CRP, 0.15 mg/dL; ESR, 10 mm/h; IL-6, 1.04 pg/mL).

## Discussion

$^{18}\text{F}$ -FDG/PET-CT is used to search for malignancies, determine staging and recurrence of malignancies, and assess their therapeutic effect. In recent years, it has come to be used not only for the detailed examination of malignancies but also for identifying the cause of FUO and inflammation of unknown origin as well as for assessing the diagnosis and disease activity of rheumatic diseases, such as PMR, rheumatoid arthritis, and large-vessel vasculitis (3, 4).

PMR is a systemic inflammatory disease that is characterized by the sudden onset of symmetric proximal muscle pain and stiffness from 50 years of age (1). The  $^{18}\text{F}$ -FDG/PET-CT findings associated with PMR include the accumulation of FDG in both shoulders, lumbar spinous processes, both ischial tuberosities, both hips, and both greater trochanters, indicating bursitis (4). A previous study investigating the usefulness of  $^{18}\text{F}$ -FDG/PET-CT in the diagnosis of PMR revealed that when the accumulation of FDG was found in two or more locations (ischial tuberosities, greater trochanters, and lumbar spinous processes), the diagnostic probabilities (sensitivity 85.7%, specificity 88.2%) were high (6). In our patient, the accumulation of FDG was found in the ischial tuberosities, greater trochanters, and lumbar

spinous processes, suggesting PMR. In addition, several reports have compared pre- and post-therapy imaging findings, showing that the accumulation of FDG disappeared after treatment, which is useful in determining the therapeutic effectiveness for PMR (7). However, it is still unclear what  $^{18}\text{F}$ -FDG/PET-CT findings of paraneoplastic syndrome that cause PMR-like symptoms.

Paraneoplastic syndrome is a condition caused by the indirect effects of malignancies and is associated with symptoms such as musculoskeletal pain, similar to rheumatic diseases. Its symptoms are alleviated by treatment of the malignancy and worsen when the malignancy worsens. Symptoms that mimic PMR are often observed (2). The relationship between PMR and malignancy is controversial. A previous study indicated that PMR does not increase the risk of malignancies (8), whereas another study conversely found that PMR does indeed increase the risk of malignancies, particularly in the first 6 to 12 months after the diagnosis (9). However, when atypical features of PMR are seen, such as an onset under 50 years of age, asymmetric symptoms, ESR of  $\leq 40$  mm/h or  $\geq 100$  mm/h, and a lack of improvement after the initiation of low-dose corticosteroids, paraneoplastic syndrome should be suspected (10). As our patient had asymmetric symptoms, which is an atypical feature, we searched for a malignant lesion.

Although the onset mechanism of paraneoplastic syndrome is not fully known, it is thought to be caused by an immune response and humoral factors such as inflammatory cytokines released from tumor cells (2). IL-6 is an important cytokine involved in the pathophysiology of PMR (1). Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome occasionally occurs as paraneoplastic syndrome. It has been reported that, in two cases of RS3PE syndrome complicated with prostate cancer, the serum IL-6 levels declined after treatment for prostate cancer, suggesting that the T cells activated by the tumor cells promoted the production of IL-6 (11). In our patient, the serum IL-6 levels were high at the time of the diagnosis and de-

clined after treatment for esophageal carcinoma, suggesting that IL-6 plays an important role in paraneoplastic syndrome as well as PMR.

In our patient, upper gastrointestinal endoscopy led to the discovery of esophageal carcinoma despite the fact that no abnormal accumulation in the esophagus was found on  $^{18}\text{F}$ -FDG/PET-CT. While  $^{18}\text{F}$ -FDG/PET-CT is generally used to search for malignancies, some types of malignancies are difficult to detect based on abnormal findings on  $^{18}\text{F}$ -FDG/PET-CT. The tumor size and invasion depth can also influence the usefulness of  $^{18}\text{F}$ -FDG/PET-CT. Although  $^{18}\text{F}$ -FDG/PET-CT can detect findings of large esophageal carcinoma (i.e. T3 and T4 tumors) in almost 100% of cases, it has a reduced sensitivity of only 43% for T1 tumors (12). It is therefore important to use other imaging modalities to search for early malignancies.

In conclusion, we encountered a patient with paraneoplastic syndrome that presented with PMR-like accumulations on  $^{18}\text{F}$ -FDG/PET-CT, suggesting that periarticular inflammation, such as arthritis and bursitis, can be caused by paraneoplastic syndrome. In cases with atypical features of PMR, we should aggressively search for malignancies, even if no evidence of malignancies is seen on  $^{18}\text{F}$ -FDG/PET-CT.

**The authors state that they have no Conflict of Interest (COI).**

Ayaka Umetsu and Toshimasa Shimizu contributed equally to this work.

## References

- Matteson EL, Dejaco C. Polymyalgia Rheumatica. *Ann Intern Med* **166**: ITC65-ITC80, 2017.
- Racanelli V, Prete M, Minoia C, Favoino E, Perosa F. Rheumatic disorders as paraneoplastic syndromes. *Autoimmun Rev* **7**: 352-358, 2008.
- Schönau V, Vogel K, Englbrecht M, et al. The value of  $^{18}\text{F}$ -FDG-PET/CT in identifying the cause of fever of unknown origin (FUO) and inflammation of unknown origin (IUO): data from a prospective study. *Ann Rheum Dis* **77**: 70-77, 2018.
- Yamashita H, Kubota K, Mimori A. Clinical value of whole-body PET/CT in patients with active rheumatic diseases. *Arthritis Res Ther* **16**: 2014.
- Koga T, Migita K, Sato S, et al. Multiple serum cytokine profiling to identify combinational diagnostic biomarkers in attacks of familial mediterranean fever. *Medicine (Baltimore)* **95**: 2016.
- Yamashita H, Kubota K, Takahashi Y, et al. Whole-body fluorodeoxyglucose positron emission tomography/computed tomography in patients with active polymyalgia rheumatica: evidence for distinctive bursitis and large-vessel vasculitis. *Mod Rheumatol* **22**: 705-711, 2014.
- Takahashi H, Yamashita H, Kubota K, et al. Differences in fluorodeoxyglucose positron emission tomography/computed tomography findings between elderly onset rheumatoid arthritis and polymyalgia rheumatica. *Mod Rheumatol* **25**: 546-551, 2014.
- Bahlas S, Ramos-Remus C, Davis P. Clinical outcome of 149 patients with polymyalgia rheumatica and giant cell arteritis. *J Rheumatol* **25**: 99-104, 1998.
- Ungprasert P, Sanguankeo A, Upala S, Knight EL. Risk of malignancy in patients with giant cell arteritis and polymyalgia rheumatica: a systematic review and meta-analysis. *Semin Arthritis Rheum* **44**: 366-370, 2014.
- Naschitz JE. Rheumatic syndromes: clues to occult neoplasia. *Curr Opin Rheumatol* **13**: 62-66, 2001.
- Sibilia J, Friess S, Schaefferbeke T, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE): a form of paraneoplastic polyarthritis? *J Rheumatol* **26**: 115-120, 1999.
- Kato H, Miyazaki T, Nakajima M, et al. The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. *Cancer* **103**: 148-156, 2005.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).