

Three different CT and FGD PET/CT findings of pulmonary involvement in methotrexate-associated lymphoproliferative disease

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Keywords

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Abstract

Lymphoproliferative disease (LPD) is one of the complications of methotrexate (MTX) therapy. In MTX-associated LPD (MTX-LPD), LPD lesions limited to the lungs are rare and show various types of opacity. A 75-year-old woman with rheumatoid arthritis (RA) presented with myalgia. She had been taking MTX for 11 years. Chest computed tomography (CT) scans showed a nodule in the left lower lobe that had grown significantly and a new nodule in the right lower lobe. ¹⁸F-fluorodeoxyglucose (FDG)/positron emission tomography (PET)/CT revealed significant FDG uptake in these nodules. Transbronchial biopsy specimen showed diffusely distributed CD20-positive lymphoid cells, and we made a diagnosis of MTX-LPD. All lung lesions disappeared within months after the immediate discontinuation of MTX. We also had two other patients with MTX-LPD lung lesions that had high FDG uptake. FDG PET/CT might be a useful diagnostic tool as it may reflect disease progression and help identify separate lesions.

Introduction

Methotrexate (MTX) is one of the key drugs for treating rheumatoid arthritis (RA) and other autoimmune arthritis. Lymphoproliferative disease (LPD) is a complication of low-dose MTX therapy, MTX-associated LPD (MTX-LPD), has recently gained increasing attention. Because localized pulmonary lesions in MTX-LPD are relatively rare, to our knowledge, there have been no literature reviews focusing on their radiological features. It is challenging to diagnose MTX-LPD because this disease shows the various types of lung shadows seen on chest computed tomography (CT). We describe three cases of MTX-LPD where we conducted chest CT and ¹⁸F-fluorodeoxyglucose (FDG)/positron emission tomography (PET)/CT. This report focuses on the radiological findings of MTX-LPD, including FDG PET/CT, based on these cases. RA and other immunosuppressant also increase the risk of LPD, but in our cases, we diagnosed MTX-LPD because the

lesions have shown spontaneous regression after withdrawal of MTX.

Case Series

Case 1

A 75-year-old woman with RA presented with myalgia. She had been taking MTX 10 mg for 11 years, and salazosulfapyridine 1000 mg for three years. She had no history of smoking. On presentation at the hospital, she had no fever or other significant findings. Physical examination revealed no abnormalities except for ulnar deviation; there were no crackles.

Laboratory data showed slightly elevated soluble interleukin-2 receptor (953 U/mL). Blood cell counts, lactate dehydrogenase, and tumour marker for lung cancer were within the normal range. Chest CT showed a nodule in the left lower lobe that had grown drastically (from

13 mm to 28 mm) in three months; a new nodule was also noted in the right lower lobe (Fig. 1A,B). FDG PET/CT initially showed slight FDG uptake in the left lower lobe nodule. Subsequently, much higher uptake was seen in the same lesion, in the new nodule that developed after three months, and in the cervical and axillary lymph nodes (Fig. 1C).

She underwent transbronchial lung biopsy twice because we could not obtain specific findings from the first biopsy. The rapid growth of the nodules, appearance of new lesions, and high FDG uptake on FDG PET/CT at those sites led us to suspect she had MTX-LPD, and we repeated the biopsy. Immunopathological examination showed diffusely distributed CD20-positive lymphoid cells, some of which were also Epstein–Barr encoding region-positive; some CD3-positive cells were also seen. We then made a diagnosis of diffuse large B-cell lymphoma (DLBCL) based on these three findings. Obtained samples were Epstein–Barr encoding region (EBER) positive.

Case 2

A 63-year-old woman with RA, who had been taking MTX for 8 years, started to feel malaise and appetite loss. Laboratory data showed elevated soluble interleukin-2 receptor (5366 U/mL) and lactate dehydrogenase (331 U/L). She had bilateral homogenous expanding consolidations on chest CT, suspected to be interstitial pneumonia

due to RA. FDG-PET/CT showed higher than expected FDG uptake for interstitial lung disease of RA in the same regions and in the mediastinal lymph nodes (Fig. 2A,B). Consolidation worsened in a few weeks. Therefore, we performed transbronchial lung biopsy, and made a diagnosis of DLBCL type MTX-LPD. EBER was negative.

Case 3

A 42-year-old man with psoriasis, who had been taking MTX for 16 years, came to our hospital because of cough and fever of unknown origin. Laboratory data showed slightly elevated soluble interleukin-2 receptor (1300 U/mL) and carcinoembryonic antigen (5.2 ng/mL), but lactate dehydrogenase was not elevated (232 U/L). He had a rapidly progressing cavitation in the right upper lobe, which was the only lesion. Bronchoscopy survey done at the previous hospital could not yield a definitive diagnosis. We confirmed that the cavity only had high FDG uptake at the periphery (Fig. 2C,D). Antibiotics and antifungal drugs were ineffective. We finally performed resection of the right upper lobe, and also made a diagnosis of DLBCL type MTX-LPD based on pathological findings. EBER was positive.

We immediately discontinued MTX after the diagnosis of DLBCL. All lung lesions spontaneously disappeared within months after simply stopping MTX, and there has been no recurrence for more than 2 years.

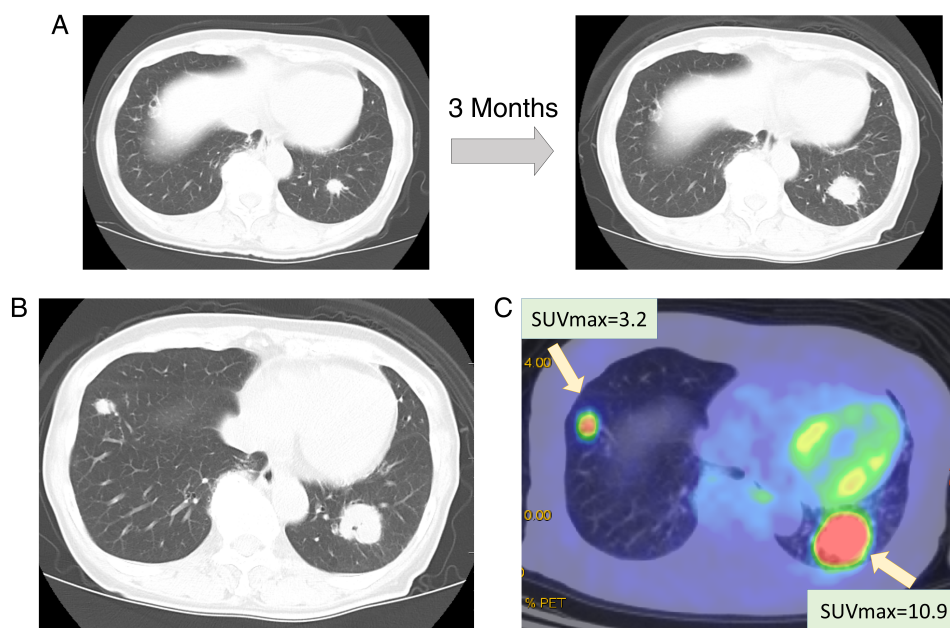


Figure 1. Chest computed tomography (CT) and ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT images of Case 1. (A) A nodule in the left lower lobe that had grown drastically (from 13 mm to 28 mm) in three months (in the upper section). (B) A new nodule was also noted in the right lower lobe. (C) FDG PET/CT showed high FDG uptake in the same regions of CT images.

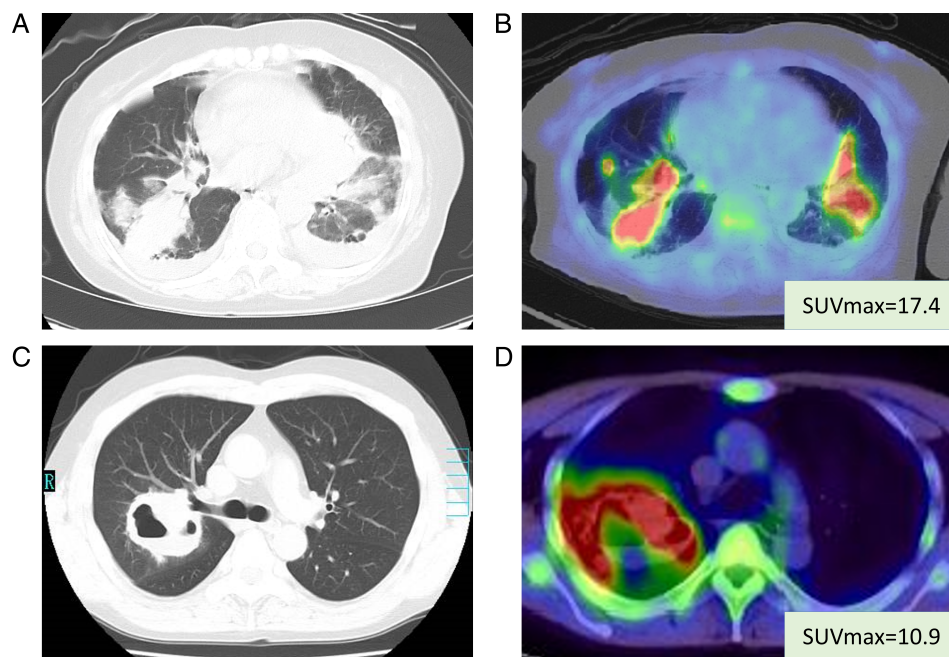


Figure 2. Chest computed tomography (CT) and ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT images of Cases 2 and 3. (A) Bilateral homogenous expanding consolidations on chest CT. (B) FDG PET/CT showed FDG uptake in the same regions and in the mediastinal lymph nodes. (C) Rapidly progressing cavitation in the right upper lobe on chest CT. (D) The cavity only had high FDG uptake at the periphery.

Discussion

MTX is often prescribed as one of the key drugs for RA or autoimmune arthritis, but MTX use occasionally leads to some forms of interstitial lung disease. The association between LPD and MTX has been discussed since the incidence of neoplasms suspected to be associated with MTX was first reported in 1985 [1]. Due to the increasing use of MTX, the number of reports of MTX-LPD increased during the 2000s. The 2008 WHO classification of lymphoid neoplasms categorized MTX-LPD as other iatrogenic or immunodeficiency associated (OIHA-LPD) [2]. MTX-LPD cases are mainly reported in Asian countries. The relationships between MTX-LPD and race or genetic components are not known. However, EBV reactivation has been thought to induce MTX-LPD [3]. Patients with chronic active EBV infection and EBV-associated haemophagocytic lymphohistiocytosis are reported more frequently in East Asia, so it is possible that Asians are more susceptible to developing MTX-LPD. RA solely increases the risk of LPD from 2 to 5.5 times [4]. Some of immunosuppressant, other than MTX, are also known to increase the risk of LPD when they are used. Previous report has shown that 25% of OIHA-LPD is associated with non-MTX drugs [5]. Furthermore, longstanding chronic inflammation is one of the risk for LPD [6]. But we diagnosed our three patients' illness as MTX-LPD, because MTX cessation simply caused disease regression.

In MTX-LPD, the primary focus may spread to involve other sites, and about a half of cases appear extranodal [7]. However, LPD lesions limited to the lungs are rare [8,9]. MTX-LPD shows a wide range of behaviour. Previous reports have shown that spontaneous regression sometimes occurs after withdrawal of MTX, but recurrence and/or residual disease was observed in 46% of cases, and some patients died despite receiving chemotherapy/radiotherapy [10,11]. MTX-LPD lesions may regress spontaneously, so we should consider the possibility of MTX-LPD in all patients receiving MTX to avoid unnecessary harmful procedures. However, because MTX-LPD could present with various types of lung shadows but with few symptoms, it is difficult to diagnose based on radiological appearance alone.

MTX-LPD has various histopathological features. The most commonly reported cases are DLBCL (35–60%) and classical Hodgkin's lymphoma (12–25%) types [2]. Multidetector CT findings of lung lesions of MTX-LPD are heterogeneous and reflect the wide spectrum of clinical manifestations and pathology. The most common radiological presentation of DLBCL is as solitary or multiple nodules, sometimes with cavitations [12]. However, our three cases, all with the DLBCL-type of MTX-LPD, had totally different CT findings. We could not make a diagnosis of MTX-LPD based on CT scan alone, and needed to perform a biopsy. FDG PET/CT might facilitate the diagnostic process as it is widely accepted in staging, monitoring treatment response,

and predicting the prognosis for cancer, and also for many types of lymphomas [13]. In terms of detecting MTX-LPD lesions, a few authors have reported its usefulness. Watanabe et al. reported that FDG PET/CT showed 90.2% sensitivity and 97.4% specificity, which were significantly higher than those of multidetector CT scan [14]. This particular report included four patients who had lung lesions but no obvious FDG PET/CT findings specifically for the lung lesions. Takanashi et al. reported that FDG PET/CT could indicate the prognosis of MTX-LPD [15]. This is the first report which focuses on the effectiveness of FDG PET/CT for MTX-LPD pulmonary lesions. A previous report showed that the histological type of DLBCL was associated with poor prognosis [12]. However, our three patients have to date remained disease-free.

In Case 1, the nodules seen on the chest CT images initially suggested lung cancer. Metastatic cancers, bacterial or fungal infections, and organizing pneumonia should also be considered as differential diagnoses. We decided to conduct follow-up studies on these nodules, as sputum and lung tissue collected through bronchoscopy was not suggestive of lung cancer. Immunostaining was not performed. Furthermore, a rapidly growing shadow over several months, and a new lesion that emerged on the contralateral side were not suggestive of lung cancer, but of MTX-LPD. We performed FDG PET/CT to evaluate disease activity, with repeat transbronchial biopsy, on suspicion that these lesions were MTX-LPD. In Case 3, the patient had to undergo surgery, because the centre of the mass had become necrotic and only necrotic tissue was obtained from several transbronchial lung biopsies. In retrospect, FDG PET/CT before the surgery could have shown the high FDG uptake only at the periphery, as it may have reflected disease activity.

Based on previous studies and our cases, FDG PET/CT could be used to objectively monitor disease activity and identify the optimum sites for biopsy specimens. Furthermore, FDG PET/CT might be a useful diagnostic tool in reflecting disease progression with high sensitivity and specificity, helping to identify separate lesions, and further highlighting the prognosis of MTX-LPD.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case series and accompanying images. Ethical approvals were provided by the institutional review board of the National Center of Global Health and Medicine (NCGM-G-002520-00).

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