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【 CASE REPORT 】

Methotrexate-associated Lymphoproliferative Disorder: A Rare Differential Diagnosis of Wheezes

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Abstract:
A 70-year-old woman was admitted for the evaluation of wheezes and a nodular lesion in the left lung field. She had been diagnosed with rheumatoid arthritis at 45 years of age and was continuously treated with methotrexate (MTX) at 8 mg/week. Bronchoscopic aspiration histology of a hilar lymph node suggested a lymphoproliferative disorder (LPD). After discontinuation of MTX, the lung nodule and wheezes disappeared. Although wheezes are not a usual manifestation of LPD, her clinical course clearly demonstrated an obvious relationship between LPD-induced airway narrowing and wheezes.

Key words: rheumatoid arthritis, methotrexate, lymphoproliferative disorder, wheezes, Epstein-Barr virus

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Introduction

Wheezes are a common manifestation of pulmonary diseases. The pathogenesis of wheezes is usually regarded as simply diffuse narrowing of the airways. For example, patients suffering from a bronchial asthma attack show prolonged expiration plus expiratory wheezes, both of which disappear following inhalation of bronchodilating agents. In such cases, reversible airway narrowing is caused by contraction of the bronchial smooth muscle. Other pathologic abnormalities are known to sometimes cause wheezes (1, 2). Cardiac asthma, a well-known disorder that should be differentiated from bronchial asthma, can display temporary wheezes that are resistant to bronchodilators, since the airways are diffusely narrowed due to mucosal edema and congestion, rather than bronchial smooth muscle contraction. Viral bronchiolitis and lymphangitis carcinomatosa are also capable of causing wheezes due to diffuse involvement of the airways. Thus, the differential diagnosis of wheezes may involve a wide array of diseases, both benign and malignant.

Methotrexate-associated lymphoproliferative disorder (MTX-LPD) is considered to be an iatrogenic immunodeficiency-related LPD caused by dose-independent, long-term MTX therapy. This disorder is usually not accompanied by any changes in the lung sounds. We herein report a rare case that exhibited wheezing for months associated with extranodal MTX-LPD in the lung.

Case Report

A 70-year-old Japanese woman was referred to our hospital for the evaluation of wheezes, dyspnea on exertion (mMRC grade 3) and a lung nodular lesion. She had been diagnosed with rheumatoid arthritis (RA) at 45 years of age. She had been treated with prednisolone (4 mg/day) and MTX (8 mg/week) for the past 15 years. The wheezes and dyspnea had gradually worsened for several months before her visit.

She presented with wheezes in both lungs and had a slightly decreased SpO_2 (94%) on room air. She showed no B symptoms (fever, weight loss, night sweats). Superficial

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lymphadenopathy was absent on a physical examination. She had no history of smoking or asthma symptoms. Since her family history included asthma predisposition in her father and two sisters, bronchial asthma was initially suspected as the cause of her wheezes. Budesonide and formoterol combined inhalation was tried, but her wheezes and dyspnea did not improve.

Blood tests showed normal values for hemoglobin (12.5 g/dL), serum IgE (11 IU/mL) and the eosinophil ratio (0%) but elevated values for C-reactive protein (5.4 mg/dL) and soluble interleukin-2 receptor (sIL-2R) (1,898 U/mL). An arterial blood gas analysis indicated slightly decreased oxygen and carbon dioxide partial pressures (PaO_2 74.3 Torr; $PaCO_2$ 30.7 Torr). Lung function tests showed irreversible obstructive impairment, based on a vital capacity (VC) of 2.33 L, forced vital capacity (FVC) of 1.77 L, forced expiratory volume in one second (FEV_1) of 0.77 L, forced expiratory volume in 1 second % (FEV_1%) of 43.5%, FEV_1 after inhalation of procaterol of 0.80 L and air trapping index [(VC-FVC)/VC×100] of 24%. We therefore deemed a diagnosis of bronchial asthma unlikely. Although the diffusion capacity (DLco) could not be assessed due to her dyspnea, a diagnosis of chronic obstructive pulmonary disease (COPD) was also ruled out, since she had no history of severe exposure to tobacco smoke or air pollution. Chest X-ray and computed tomography (CT) revealed bilateral hilar and mediastinal lymphadenopathy in addition to a nodular lesion adjacent to the left hilum (Fig. 1A and B), but extrathoracic lymphadenopathy and hepatosplenomegaly were absent. High-resolution CT (HRCT) showed the bronchial wall to be diffusely thickened. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed a strong uptake in the nodule and enlarged lymph nodes (Fig. 1C, left); an apparent uptake was also observed in the highly thickened bronchial walls (Fig. 1C, right) but not outside of the thoracic area, including the bone marrow.

Epstein-Barr virus capsid antigen-specific IgG (×40) and nuclear antigen (×20) were positive, suggesting a remote infection. A bronchoscopic examination found no endobronchial network formation or nodular lesions. Extreme bronchial fragility was not observed. It was difficult to approach the pulmonary nodule via fiberoptic bronchoscopy. An aspiration biopsy specimen of a left hilar lymph node demonstrated a lymphoproliferative abnormality (an increased number of large abnormal lymphocytes with variation in the nuclear size and shape and with nucleolar enlargement; Fig. 2A). Immunostaining of these lymphocytes was negative for CD3 (Fig. 2B) but positive for CD20 (Fig. 2C) and EBV-encoded small RNA (EBER) (Fig. 2D). Vascular invasion and necrosis, i.e. findings suggestive of lymphomatoid granulomatosis (LYG), were not observed. These findings suggested diffuse large B-cell lymphoma (DLBCL) or MTX-LPD, and MTX was thus discontinued. Accordingly, prednisolone was increased from 4 to 6 mg per day. Ten days after the withdrawal of MTX, both wheezes and dyspnea on exertion were greatly improved. One month later, CT showed shrinkage of the pulmonary nodule. The nodular lesion, mediastinal and bilateral hilar lymphadenopathy and diffuse thickening of the bronchial wall were clearly improved three to four months after the withdrawal of MTX (Fig. 3A). The patient was completely free of wheezes and dyspnea (mMRC grade 0), and her SpO_2 was good (98%).

The serum sIL-2R level gradually decreased to the normal range after four months. Lung function tests performed 5 months after the withdrawal of MTX showed improvement (VC 2.31 L, FVC 2.30 L, FEV_1 0.99 L, FEV_1% 42.5%, air trapping index 0.4%) (Fig. 3B), and there was no dissociation between the VC and FVC as had been seen in the initial tests. The disappearance of wheezes was thus accompanied by functional improvement of the airway obstruction and air trapping and by a structural change in the bronchial wall thickness (Fig. 3C and D). Two years after the withdrawal of MTX, there were no signs of recurrence of LPD. The symptoms of RA were well controlled on prednisolone at 6 mg per day. We finally concluded that her wheezes, dyspnea and lung nodule had been caused by MTX-LPD.

Discussion

This case clearly showed that wheezes lasting for months can be caused by a lymphocytic disorder. This is the first reported case of MTX-LPD presenting with wheezes. Importantly, the wheeze showed a self-limiting course in parallel with the functional and morphological improvement in the airways.

Wheezes are rarely seen as a manifestation of LPD. Based on the pattern of airway involvement, endobronchial lymphoma is classified into two types: diffuse submucosal infiltrates due to vascular or lymphangitic spread in the presence of systemic lymphoma, and airway involvement by a localized mass either due to direct invasion of lymphoma from adjacent lymph nodes or arising *de novo* from bronchus-associated lymphoid tissue (BALT). The latter lesions are generally associated with signs of airway obstruction, such as cough or wheezes (3). Jiang et al. reported a patient diagnosed with primary pulmonary DLBCL who complained of shortness of breath and intermittent wheezing (4). Bronchoscopy revealed an endobronchial lesion and partial stenosis at the distal end of the middle segment bronchus, suggesting the coexistence of the aforementioned two types of endobronchial lymphoma. An endobronchial biopsy specimen showed infiltrative atypical lymphoid tissue (4). In general, wheezes are associated with airflow limitation, and the pitch of an individual wheeze is determined not by the diameter of the airway but by the thickness of the airway wall, bending stiffness and longitudinal tension (1). Although we did not perform a bronchial mucosa biopsy due to worsening of the dyspnea during bronchoscopic study, we suspect that the first mechanism was the etiology of the wheezes, with the accumulation of lymphocytes and lymphatic edema likely inducing diffuse thickening and narrowing of the airways, resulting in expiratory wheezes. The pre-

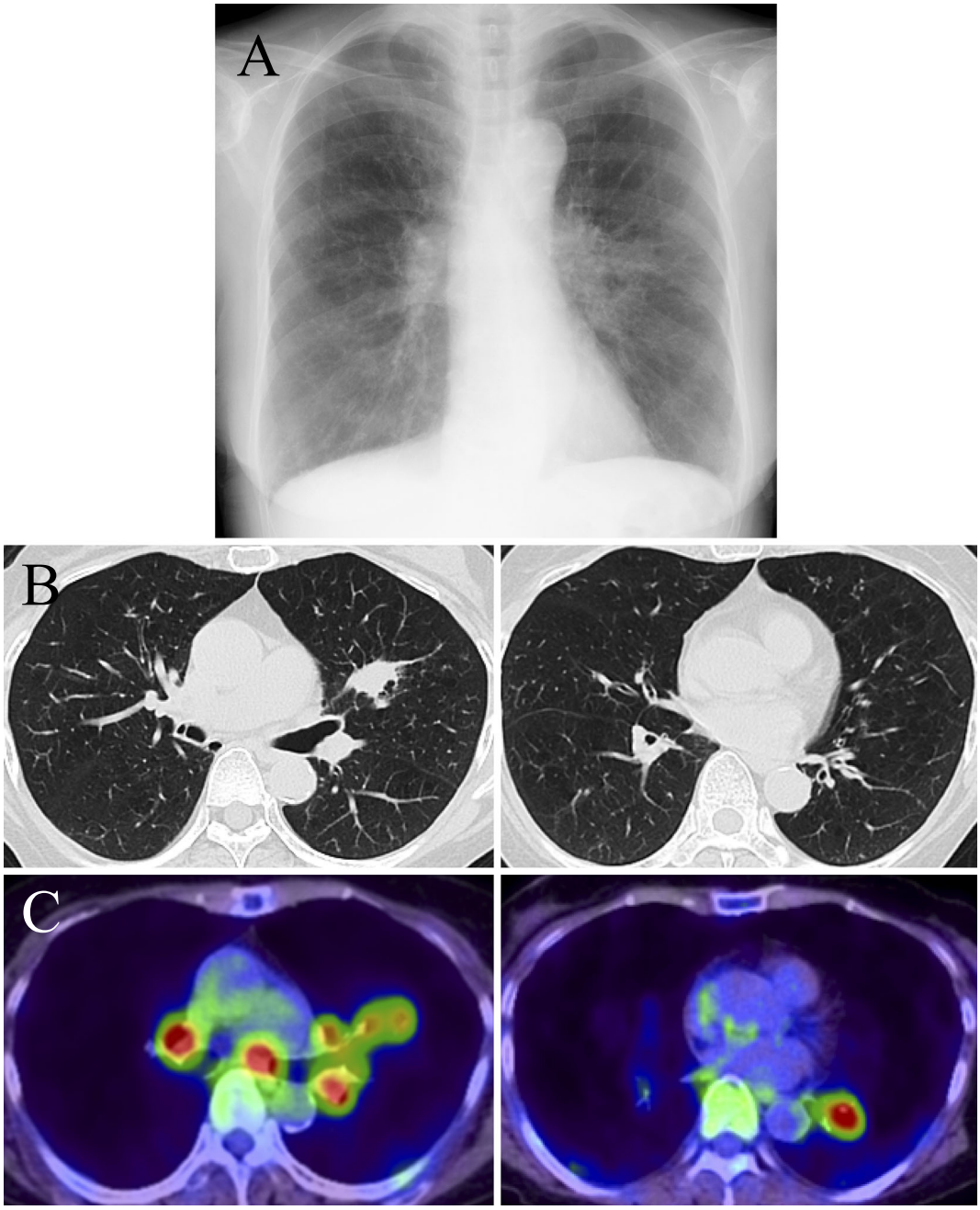

Figure 1. **A: Chest X-ray taken on admission to our hospital shows bilateral hilar lymphadenopathy and a nodular lesion (2.5 cm in diameter) adjacent to the left hilum. B: Chest CT image. A nodular lesion (left S3) (left), highly thickened bronchial walls (right) and emphysematous changes are seen. C: FDG-PET image, corresponding to the CT image in (B). A strong uptake is observed in the lung nodule and hilar and mediastinal lymph nodes (left) as well as in the highly thickened bronchial wall (right).**

sent case shows that not only the lung parenchyma but also the airways are affected by MTX-LPD (Fig. 1C, 2C). It is important to note that some other disorders can also present with wheezes due to similar mechanisms, such as sarcoidosis and IgG4-related disease (5, 6). We believe that a diagnosis of sarcoidosis would be inappropriate, based on the bronchoscopy and biopsy specimen findings as well as the normal level of serum angiotensin-converting enzyme (8.4 U/L). LYG, IgG4-related disease and multicentric Castleman's disease were also ruled out based on the pathological findings and the patient's clinical course showing recovery after the withdrawal of MTX.

LPD is rarely observed in RA patients taking MTX. Although the precise pathogenesis of MTX-LPD remains unclear, dysregulation of the host immune system due to the effects of RA and MTX is presumed to be involved in the development of LPD. Approximately half of MTX-LPD cases are reportedly positive for EBV; this virus is thought to trigger dysregulated lymphocytic proliferation, as was seen in the present case. Discontinuing MTX is essential for

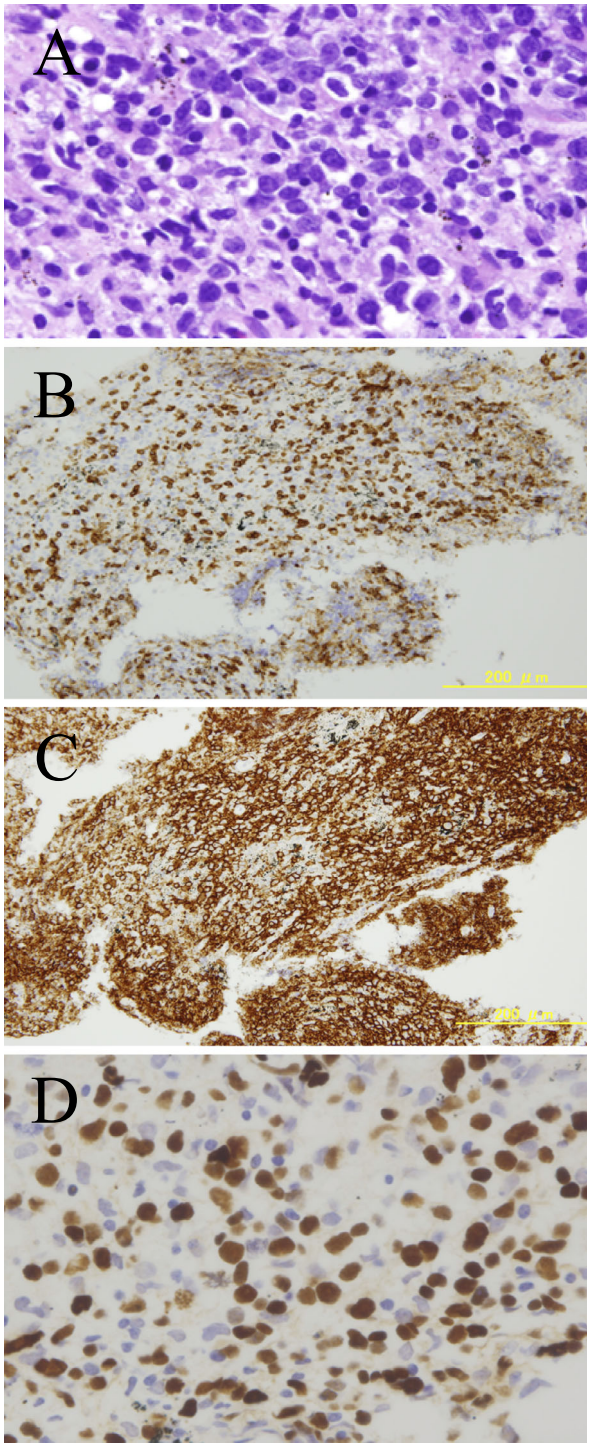

Figure 2. **A histological analysis of an aspiration biopsy specimen from a left hilar lymph node. Hematoxylin and Eosin staining (A) and immunostaining (B, C and D). B: Negative CD3 staining. C: Positive CD20 staining. D: Positive EBER staining (magnification of objective lens: ×40).**

patients with suspected MTX-LPD (7). In our present case, the lung nodular lesion completely disappeared four months after the discontinuation of MTX. However, careful monitoring is usually needed, since a small number of patients may later develop B-cell lymphoma (8).

One important aspect of the present case is that an obstructive abnormality remained on the follow-up lung function test (FEV_1% 42.5%). Her lungs were emphysematous, but she had never experienced pneumothorax. Co-existence of a rare cystic lung disease, such as lymphangioleiomyomatosis, was considered unlikely. There might have been residual MTX-LPD lesions in the airways even after the discontinuation of MTX that prevented her spirogram results from fully returning to the normal range. The extent of any persistent lesions, however, is difficult for us to estimate, as we lack access to her pre-MTX-LPD lung function results and HRCT findings. Another more plausible explanation is that her RA affected her lungs; indeed, it has been reported that

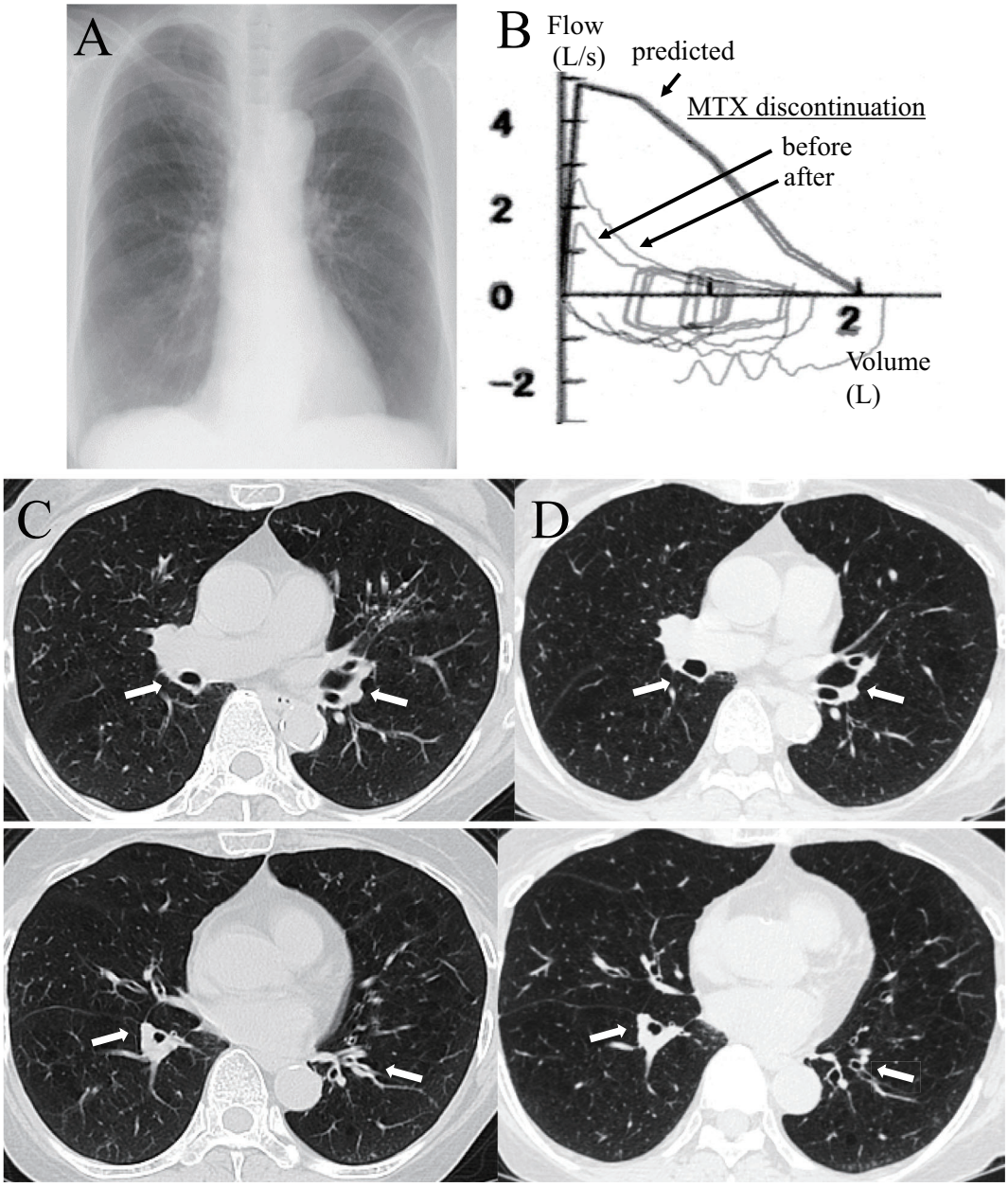

Figure 3. **A: Chest X-ray taken three months after the discontinuation of MTX shows improvement of the nodular lesion and bilateral hilar lymphadenopathy. B: Flow-volume curves on admission and at five months after the discontinuation of MTX. C: HRCT findings before the withdrawal of MTX. The bronchial wall is thickened (arrow). D: HRCT shows that the bronchial wall thickening was reduced by four months after the discontinuation of MTX (arrow).**

patients with RA often show an obstructive pattern on spirograms, reflecting airway involvement, such as bronchiolitis (9). We therefore suspect that the wheezes in the present patient may have been caused by a combination of a baseline abnormality (i.e., a chronic abnormality that was present before the development of MTX-LPD) with MTX-LPD-associated active inflammatory changes throughout the airways. However, the rapid resolution of wheezes after the withdrawal of MTX suggested that the MTX-LPD-associated changes were more deeply involved in the development of wheezes than any baseline abnormality.

Since various disorders of the airways can be involved in the development of wheezes, it is important to evaluate the functional and structural abnormalities of the airways in order to more precisely understand the pathogenesis of wheezes.

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

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