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CASE REPORT

Methotrexate-associated lymphoproliferative disease with multiple pulmonary nodules in a patient with rheumatoid arthritis

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SUMMARY

A 62-year-old woman with rheumatoid arthritis and secondary Sjögren's syndrome took methotrexate (MTX) 5 mg three times a week regularly but gradually developed an intermittent fever, oral ulcers and productive cough with mucopurulent sputum for about 2 weeks. Image study found multiple nodular lesions and lymphadenopathies in bilateral lungs. Empirical antibiotics for 1 week failed to alleviate the fever. A transbronchial biopsy in the right fourth bronchus showed infiltration of abnormally enlarged lymphoid cells with a surface marker of CD20, some of which also stained positively in situ with Epstein-Barr virus-encoded small RNA and some CD3(+) cells. After a diagnosis of MTX-associated lymphoproliferative disease had been made, MTX was discontinued immediately and intravenous methylprednisolone 125 mg/day was given for 1 week. The clinical condition improved dramatically within 1 month and there was no recurrence after 3-year follow-up.

BACKGROUND

Methotrexate (MTX) is often prescribed as a first line drug for rheumatoid arthritis (RA). Lymphoproliferative disease (LPD) is a rare complication of low-dose MTX therapy for patients with RA. MTX-associated LPD can affect nodal as well as extranodal sites. In extranodal LPD, skin, lungs, gastrointestinal tract, spleen, oral cavity and kidneys may be implicated.[1–3] However, multiple nodular lesions in bilateral lungs as a manifestation of MTX-associated LPD is uncommon. To the best of our knowledge, there have been only a few such cases in the literature.[4–6] The present patient is valuable because she has been followed up for 3 years without any evidence of recurrence after stopping MTX.

CASE PRESENTATION

The presenting symptoms of this 62-year-old woman included 2 years of symmetrical polyarthritis in hands, xerostomia and conjunctiva sicca. After the diagnosis of RA with Sjögren's syndrome was made, she took MTX 5 mg three times a week regularly for several weeks but developed insidiously intermittent fevers up to 39°C, oral ulcers and productive cough with copious mucopurulent sputum within 2 weeks after start of the medications. There was no chest tightness, abdominal pain, diarrhoea or dysuria. On presentation to the hospital, body temperature was 37.9°C, heart rate 103/min, respiratory rate 20/min and blood pressure 115/67 mm Hg. Physical examination revealed neck and axillary lymphadenopathies (LAP) as well as fine crackles in bilateral lower lungs. After initial exclusion of neoplasm (such as alveolar cell carcinoma or metastatic lung cancers), empirical antibiotics was given for 1 week but could not alleviate fever.

INVESTIGATIONS

Laboratory investigations failed to demonstrate any abnormalities except for an elevated C-reactive protein (10.74 mg/dL) and a slightly shift to left of the neutrophils (83%). The RA activity was also low (rheumatoid factor (RF)<15 IU/mL). All body fluid cultures failed to yield microorganisms or virus. However, a chest high-resolution CT (HRCT) demonstrated numerous nodular lesions in bilateral lungs as well as LAP in bilateral upper and lower paratracheal and prevascular regions of mediastinum and left axilla (figure 1). After failure of empirical antibiotic therapy, a bronchoalveolar lavage (BAL) revealed mild lymphocytosis (15%), but failed to demonstrate evidence of infections or neoplasms. Besides, a transbronchial biopsy in the right fourth bronchus showed infiltration of abnormally enlarged CD20 positive lymphoid cells (figure 2), some of which also stained in situ with Epstein-Barr virus-encoded small RNA (EBER) and some CD3 (+) cells. Grocott-Gomori's methenamine silver or acid fast stain failed to demonstrate microorganisms within the biopsy.

DIFFERENTIAL DIAGNOSIS

The diffuse nodules demonstrated in the chest HRCT images suggested multiple metastatic cancers or alveolar cell carcinoma. But the patient did not have any history of cancer before MTX administration. BAL and biopsy results also did not support the diagnosis. Bacterial, viral and other atypical infections were excluded due to negative culture results and poor response to antibiotics. Pneumonitis was another consideration based on some of the symptoms but the image as well as pathology did not support. Organising pneumonia (OP) due to MTX or other disease modifying antirheumatic drugs is also an important differential diagnosis; however, our patient had relatively low RA activity, a presence

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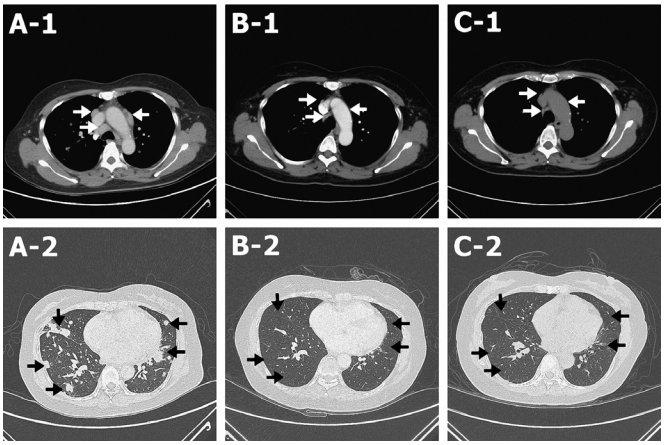

Figure 1 Chest high-resolution CT performed during the early time of disease course (A), 3 months (B) and 3 years (C) after stop of the drug, respectively. (A-1) white arrows indicate numerous lymphadenopathies in paratracheal and prevascular regions. (A-2) black arrows indicate nodular lung lesions. White arrows in (B-1, C-1) and black arrows in (B-2, C-2) indicate that the lesions in (A-1, A-2) had almost disappeared 3 month and 3 years after stop of the methotrexate.

of extrapulmonary lymph node enlargement and EBER(+) pathology, so it was less likely to be OP. A diagnosis of MTX associated-LPD was eventually made because of the image results, presence of extrapulmonary LAPs as well as the infiltration of atypical large CD20 +lymphoid cells in the parenchyma of the lung tissue.

TREATMENT

After the diagnosis was made, MTX was discontinued immediately and short-term daily intravenous methylprednisolone (125 mg/day) was given.

OUTCOME AND FOLLOW-UP

The clinical cardiopulmonary embarrassment, febrile episodes, chillness, nausea/vomiting and anorexia alleviated dramatically 1 month after stopping MTX. Up to now, there has been no recurrence of any pulmonary inflammation or LPD although she still received hydroxychloroquine, sulfasalazine, leflunomide and non-steroidal analgesics for RA within the subsequent 3 years.

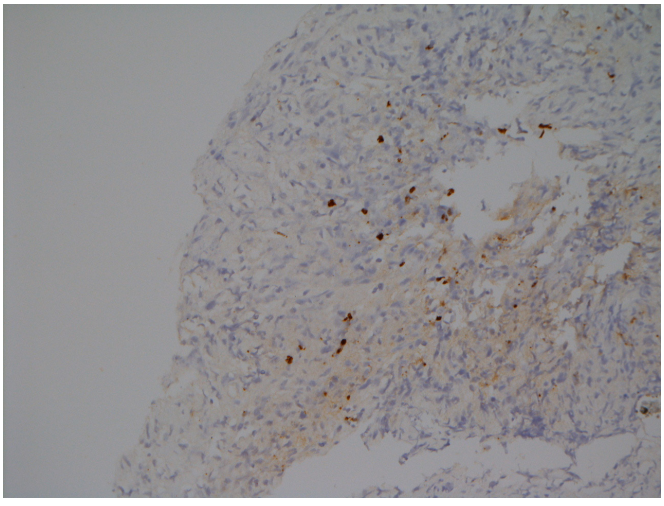

Figure 2 The transbronchial biopsy revealed scattered atypical enlarged B cells (Horseradish peroxidase stain, 5–20/HPF), x400.

DISCUSSION

The issue about LPD and MTX has been discussed fervently before since the first report on a patient with RA treated with MTX who developed lymphoma.[7 8] The 2008 WHO classification of lymphoid neoplasms has categorised MTX-associated LPD as either iatrogenic or immunodeficiency associated.[9] Our patient has been treated with MTX only for several weeks before suddenly developing multiple nodular lesions in bilateral lungs. The associated manifestations included intermittent fever, oral ulcers, productive coughs with mild dyspnoea, weight loss, nocturnal sweat and chest pain. These symptoms, except for fever, are different from the similar cases reported before.[4–6]

EB virus has been claimed to induce MTX-associated LPD. Feng *et al* demonstrated that MTX could induce the reactivation and virion release/spreading of EBV.[10] Hoshida *et al* reported higher prevalence of EBV infection in MTX-associated LPD than in sporadic LPD but not in common non MTX-LPD.[1] The overall 5-year survival rate of LPD (MTX-LPD and non-MTX-LPD) in patients with RA is significantly worse than that in sporadic LPD.[1] Withdrawal of MTX has been observed to result in its spontaneous remission.[10 11] Also, those with spontaneous regression had a higher EBV positivity than those without regression.[12] Our patient with EBV positivity also has a smooth remission after MTX stop, which is consistent with previous studies.

Another differential diagnosis issue that should be considered is a possibility of OP, either primary or secondary to MTX or other disease-modifying antirheumatic drugs (DMARDs). Although as mentioned above, all manifestations and pathological reports were in favour of MTX-LPD, OP was still kept in our mind as a possibility in our subsequent follow-up of the patient.

Regarding to the primary foci of MTX-LPD, a nodal or extranodal occurrence has been reported equally, in contrast to the post-transplant LPD in which extranodal was more prevalent.[1] Extranodal LPD may implicate various sites including skin, lungs, gastrointestinal tract, spleen, oral cavity and kidneys. However, the presentation of MTX-LPD in the form of multiple pulmonary nodules such as in this particular patient is rare. Our patient's lung manifestation was easily misinterpreted as neoplasm at a first glance. Fortunately, a prompt decision of stopping MTX together with the administration of steroid avoided the subsequent unnecessary and potentially harmful procedures. Thus, we suggest a carefully monitoring on the patient suspected to have MTX-associated LPD after discontinuation of culprit drug, wait and see for a while before considering any aggressive treatment.

Learning points

- Methotrexate (MTX)-associated lymphoproliferative disease (LPD) can present in the form of diffuse multiple pulmonary nodules.
- MTX-associated LPD mimicking malignancy can easily resolve on simple discontinuation of MTX together with a short-term administration of methylprednisolone.
- A patient under MTX therapy who is suspected to have metastatic lung disease should be carefully evaluated for the presence of MTX-induced LPD before considering an aggressive treatment.

Contributors W-FL wrote the manuscript, Y-PC amended the manuscript, C-WL took care of the patient and collected the pertinent data and C-YT verified all the data as well as supervised the whole study.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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