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LETTERS TO THE EDITOR

Methotrexate-associated pneumonitis: usefulness of lung ultrasound

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Dear Editor,

Methotrexate (MTX) remains the first-line therapy for rheumatoid arthritis (RA)[1]. Although effective and widely used, MTX can rarely induce an idiosyncratic hypersensitivity reaction known as methotrexate-associated pneumonitis (MTX-Pneu), with reported incidence ranging from 0.3% to 11.6%[2,3]. This acute, potentially severe toxicity contrasts with the long-term protective effect of MTX against RA-associated interstitial lung disease (RA-ILD)[3,4].

We report a 75-year-old woman with late-onset, seropositive RA (rheumatoid factor 99 U/L; anti-citrullinated peptide 999 U/L) who was started on MTX 15 mg/week and prednisolone 10 mg/day. Two weeks later she was presented with fever, cough, and dyspnea. Examination showed tachycardia (105 bpm), tachypnea (21 breaths/min), and bibasilar crackles. The respiratory infectious panel was negative. Lung ultrasound (LUS) revealed multiple bilateral, confluent B-lines with loss of A-lines and thickened, irregular pleural line (Figure 1B), consistent with an interstitial syndrome, and high-resolution computed tomography (HRCT) demonstrated bilateral ground-glass opacities across all lobes, with mosaic attenuation, interlobular septal thickening, and posterior basal consolidations (Figure 1A–B). Differential diagnosis included RA-ILD versus MTX-Pneu; hypersensitivity pneumonitis was considered unlikely due to absence of exposure. MTX was withdrawn and corticosteroids were escalated to 1 mg/kg/day with taper. At one-month follow-up, symptoms had resolved and both LUS and HRCT normalized (Figure 1C–D), confirming MTX-Pneu. Maintenance therapy included prednisolone 5 mg/day and sulfasalazine up titrated to 3 g/day. At three months she remained asymptomatic and in RA remission.

MTX-Pneu has been described up to age 87[3,5–7], and risk factors may include male sex, age >60, prior DMARDs, hypoalbuminemia, type 2 diabetes, and chronic kidney disease[2,3]. Our patient's only risk factor was age. Although often seropositive, MTX-Pneu also occurs in seronegative RA[8]. Onset usually occurs within 12 months of exposure[3,9], but cases range from 7 days to 5 years and from doses as low as 8 mg/week[3,5–7]. Presentations vary from incidental/asymptomatic findings[7] to severe hypoxemic respiratory failure that warrants empiric antibiotics until infection is excluded[6]. Diagnosis is clinical-radiological; several criteria exist but none are validated, making MTX-Pneu a diagnosis of exclusion[10]. HRCT commonly shows ground-glass opacities[7], centrilobular nodules[7], consolidations, septal thickening, and, with progression, fibrotic signs; radiologic resolution may occur in 31 days on average[3], and delayed recognition can be fatal[5]. MTX withdrawal is the key intervention and may suffice in some cases[7]; corticosteroids are frequently required[3]. While MTX re-challenge without recurrence has been reported, severe lung injury and death have also occurred; therefore, re-exposure is generally discouraged[3].

Crucially, current evidence indicates that MTX is not associated with the development of RA-ILD. In fact, large RA cohort studies suggest MTX may delay the onset and slow progression of RA-ILD[4,9],and MTX is not contraindicated in patients with RA-ILD[1]. This distinction is clinically important to avoid depriving RA-ILD patients of an effective disease-modifying therapy due to concern about MTX-Pneu, a rare idiosyncratic event.

This case highlights the importance of recognizing MTX-Pneu as an acute, reversible hypersensitivity reaction distinct from RA-ILD. Notably, LUS proved useful both for early detection, by demonstrating B-lines that paralleled HRCT ground-glass opacities, and for monitoring resolution. LUS may therefore serve as a valuable bedside tool in the evaluation and follow-up of MTX-Pneu.

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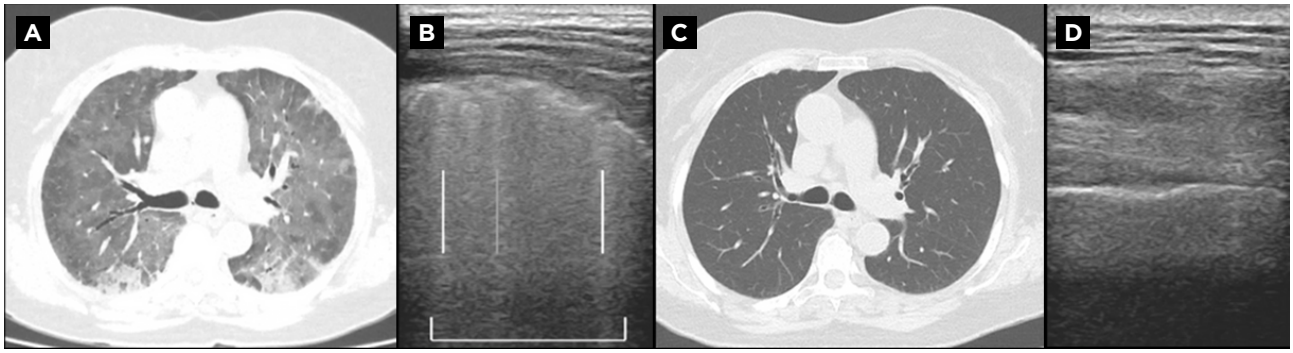

Figure 1. Baseline and Follow-up Imaging in MTX-Associated Pneumonitis. Axial high-resolution chest computed tomography and lung ultrasound showing findings consistent with methotrexate-associated pneumonitis (1A, 1B), with follow-up images demonstrating resolution (1C, 1D).

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