Interstitial lung disease in rheumatoid arthritis treated with methotrexate: A pragmatic approach

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Interstitial lung disease (ILD) is an increasingly recognized complication of rheumatoid arthritis (RA) with an approximate incidence of 10%. Adding to the complexity of ILD observed in rheumatic disease, therapeutic interventions with disease modifying antirheumatic drugs, such as methotrexate (MTX), predispose patients with RA to the development of either opportunistic infections or drug-related ILD. As a consequence, the combination of RA and MTX-treatment may create significant diagnostic dilemmas for clinicians. Numerous publications on RA- or MTX-associated pulmonary pathology commonly approach the subject from an etiological perspective, listing autoimmune diseases, drugs, and infectious agents, followed by associated histological reaction patterns.[1]

Generally histology does not represent the first-line investigative modality in diagnosing ILDs associated with RA, MTX, or infections. However, because of superior sensitivity, histology may provide the fastest way to establish a diagnosis. When evaluating lung biopsies, histological subtyping of ILDs can be simplified by recognizing a certain reaction pattern which is indicative of a specific underlying disease. However, in the context of ILD in patients with RA treated with MTX, I favour another approach by considering four differential diagnostic possibilities. These include RA-associated ILD, MTX-associated ILD, opportunistic infections, and iatrogenic lymphoproliferative disorder. Distinction of these entities is essential since therapeutic intervention is different. In open lung biopsies histological features, such as rheumatoid nodules and follicular bronchiolitis, are regarded as highly suggestive for RA-ILD. Nevertheless, RA may present with all seven patterns of interstitial pneumonias described in the ATS/ERS consensus classification, with patterns like usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), or organizing pneumonia (OP) being especially frequent.[2] In contrast to the idiopathic interstitial pneumonias, different reaction patterns, such as UIP, NSIP, OP, and follicular bronchiolitis may co-exist which helps to establish the diagnosis RA-ILD.

On the other hand, RA is the most frequent underlying disease in patients with MTX-associated ILD. Histologically MTX-pneumonitis may demonstrate a DAD pattern, type II cell hyperplasia, interstitial infiltrates with mild tissue eosinophilia, and small granulomas resembling hypersensitivity pneumonitis. Because these histological changes are non-specific and may also be encountered in RA, correlation with the clinical presentation is important to distinguish RA- from MTX-associated ILD. Especially a subacute onset of symptoms and the presence of peripheral blood eosinophilia point to MTX-associated ILD.

Long-term treatment with MTX may result in immune suppression and predisposes patients with RA to ILDs secondary to infections, particularly Pneumocystis pneumonia. Histologically, *Pneumocystis jiroveci* infection presents with a DAD pattern showing alveolar spaces filled with a foamy exudate. Silver stains or immunohistochemistry are required to demonstrate the micro-organisms.

The most common iatrogenic lymphoproliferative disorder in non-transplant settings are those associated with MTX treatment for RA. Most cases resemble diffuse large B-cell lymphomas or Hodgkin's lymphomas. Epstein-Barr virus (EBV) is detectable in a significant proportion of cases using *in situ* hybridisation. In addition, increased EBV viral load is detectable in peripheral blood.

In summary, the context of RA treated with MTX may present with a wide variety of often over-

lapping reaction patterns that may be compatible with both RA- or MTX-associated disease or attributable to an opportunistic infection. In such cases knowledge concerning the four potential differential diagnoses may simplify the process from both a clinical and pathologic perspective. However, a multidisciplinary approach involving clinicians, radiologists and pathologists is advocated to optimize diagnostic accuracy, especially in those cases where an affirmative diagnosis cannot be achieved on clinical and radiological information alone.

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