Pneumonia in a Patient with Rheumatoid Arthritis

TAKAAKI ISHIDA, TAKUYA KOTANI, TOHRU TAKEUCHI and SHIGEKI MAKINO

J Rheumatol 2012;39;1104-1105
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Pulmonary Toxicity After Initiation of Azathioprine for Treatment of Interstitial Pneumonia in a Patient with Rheumatoid Arthritis

To the Editor:

Pulmonary involvement of rheumatoid arthritis (RA) includes drug-induced pulmonary toxicity, interstitial pneumonia (IP) due to RA itself, airway lesions, pleural lesions, and pulmonary infections due to the use of immunosuppressants. It is sometimes difficult to differentiate between these conditions. Pulmonary toxicity has been reported to be often induced by methotrexate and leflunomide but rarely by azathioprine (AZA). We describe a patient with RA and IP, in whom AZA induced pulmonary toxicity.

The patient was a 72-year-old man diagnosed with RA (Steinbrocker stage III, class 2), treated with 5 mg/day prednisolone (PSL) and with clinically low disease activity. He developed a nonproductive cough 2 years ago. Chest radiograph and high-resolution computed tomography (HRCT) of the chest at that time revealed ground-glass opacities (GGO) in the bilateral peripheral lung fields and honeycomb-like cysts in the dorsal side of both lower lung fields, leading to a diagnosis of IP. Pulmonary function tests showed a vital capacity (VC) of 99.3%, and DLCO 54.2%.

After he developed exertional dyspnea (Hugh-Jones Grade II) in March 2006, he was referred to our hospital and was admitted on June 20, 2006. Fine crackles were audible in both lower lung fields. Blood tests showed a white blood cell (WBC) count 10,940/µl (73% neutrophils), C-reactive protein (CRP) 2.08 mg/dl, erythrocyte sedimentation rate 59 mm/h, and a Krebs von den Lungen-6 level of 335 U/ml. SpO₂ (room air) was 96%. Chest radiograph and HRCT of the chest revealed ground-glass opacities (GGO) in the bilateral peripheral lung fields and honeycomb-like cysts on the dorsal side of both lower lung fields, leading to a diagnosis of IP. Pulmonary function tests showed a vital capacity (VC) of 99.3%, and DLCO 54.2%.

Pulmonary lesions such as IP concomitantly develop in a high proportion of patients with collagen disease including RA, and it is important to differentiate these lesions from drug-induced IP. In particular, in our patient, it was difficult to differentiate AZA-induced IP from the acute exacerbation of RA-IP. In patients with the acute exacerbation of RA-IP, a GGO involving the entire lungs is detected on chest CT, showing rapid enlargement. However, in our case, a localized consolidation and GGO involving the right superior lung were observed, differing from the imaging characteristics of acutely exacerbating RA-IP. Further, incidental, addi-
tional AZA administration resulted in the reexacerbation of the pulmonary shadow. Based on this, a diagnosis of AZA-induced IP was made, ruling out the acute exacerbation of RA-IP.

AZA treatment can result in both allergic toxicities and dose-dependent toxicities. Bedrossian, et al reported that 4 kidney transplant patients treated with AZA died of pulmonary toxicity that was dose-dependent4. Stetter, et al, Rubin, et al, and Ananthakrishnan, et al reported cases of pulmonary toxicity in which the patients initially presented with fever, cough, and dyspnea within 6 weeks after AZA administration3,6,8. IP improved after the discontinuation of AZA and steroid administration, suggesting an allergic mechanism. In our patient, IP exacerbation with fever and dyspnea occurred 6 days after beginning the administration of AZA and improved after discontinuation. Resumption of AZA therapy was followed by the recurrence of pulmonary shadows on chest HRCT on the same day. These observations suggest that the pulmonary toxicity occurring in this patient was related to an allergic mechanism.

TAKAAKI ISHIDA, MD; TAKUYA KOTANI, MD, PhD; TOHRU TAKEUCHI, MD, PhD, Department of Internal Medicine (I), Osaka Medical College, Daigaku-Machi 2-7, Takatsuki, Osaka 569-8686, Japan. Address correspondence to Dr. Ishida; E-mail: t-takeuchi@poh.osaka-med.ac.jp

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J Rheumatol 2012;39:5; doi:10.3899/jrheum.111415