Clozapine-Induced Lymphocytic Alveolitis

To the Editor: Drug-induced lung disease is often nonspecific and represents a diagnostic challenge. We present the rare case of pulmonary toxicity associated with clozapine in a patient with a history of psychiatric illness.

"Mrs. A" was a 41-year-old, Hispanic woman with a history of schizoaffective disorder who was transferred from the psychiatric ward to medical service for evaluation of pulmonary infiltrates. Chest x-ray (Figure 1) and chest computerized tomography (CT) showed diffuse bilateral ground-glass opacities (Figure 2). The patient complained of only mild dyspnea and was able to ambulate without difficulty. She had no cough, chest pain, fever, or chills. She denied any sick contacts or environmental exposures and had stopped smoking several months prior. Her physical examination was unremarkable, and oxygen saturation on room air was 95%.

The patient had a medical history of diabetes, hypertension, and hypothyroidism. Her medications included clozapine, oxcarbazepine, atorvastatin, metformin, and levothyroxine. Two months prior, she had an episode of refractory psychosis and was initiated on clozapine and titrated to a dose of 650 mg/day.

FIGURE 1. Chest X-Ray of a Patient With Clozapine-Induced Pulmonary Toxicity

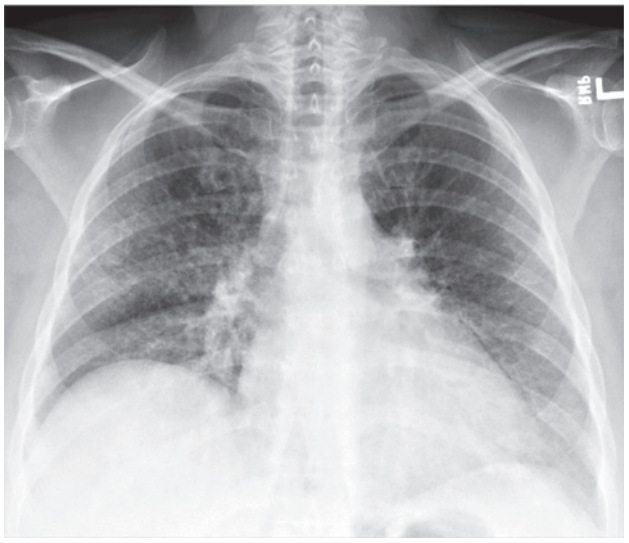
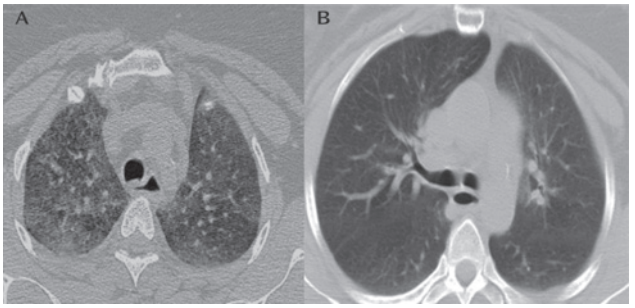


FIGURE 2. Computerized Tomography Scan of a Patient With Clozapine-Induced Pulmonary Toxicity[a]



[a]The images depict diffuse bilateral ground-glass opacities (A) and confirmed resolution of infiltrates (B).

Laboratory data revealed thrombocytosis (689 × 10^3/μl), elevated liver function (aspartate transaminase level: 75 U/l; alanine transaminase level: 103 U/l), and an increased erythrocyte sedimentation rate (130 mm per hour). There was no peripheral eosinophilia. Rheumatologic serologies and urine toxicology findings were negative, and echocardiogram results were normal. The patient was unable to provide reliable pulmonary function data.

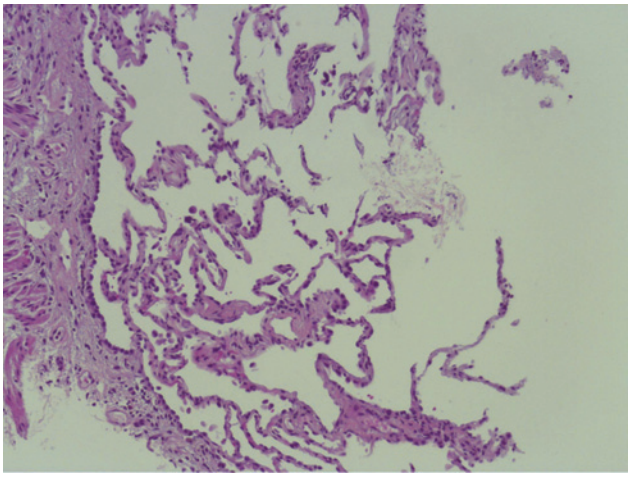
Bronchoalveolar lavage and lung biopsies were performed. Bronchoalveolar lavage showed a predominance of lymphocytes at 54% and eosinophils at 2%. Flow cytometry demonstrated a cluster of differentiation (CD)4/CD8 cell ratio of 0.7. Viral, bacterial, and mycobacterial cultures were negative. Lung biopsies revealed mild chronic inflammation without granulomas (Figure 3).

As a result of the temporal relationship between the initiation of clozapine and abnormal pulmonary findings and the absence of alternative diagnoses, a presumptive diagnosis of clozapine-induced pulmonary toxicity (lymphocytic alveolitis) was made. Clozapine was tapered and discontinued. There were no other changes made to the patient's medication regimen, and she did not receive antibiotics. Two months after discontinuation of clozapine, a repeat chest CT confirmed resolution of infiltrates (Figure 2).

The diagnosis of drug-induced lung disease is dependent upon the following three main elements: 1) appropriate temporal relationship between exposure and clinical presentation, 2) exclusion of other etiologies, and 3) resolution after drug withdrawal. In the present case, clozapine was the most recent drug exposure. We did not identify any environmental exposures, infections, or rheumatologic processes that could account for the patient's infiltrates. Finally, these infiltrates resolved after clozapine was discontinued.

There is only one other report, to our knowledge, of extrinsic alveolitis attributed to clozapine (1), and important similarities between our patient and the patient in the other case report are worth mentioning. In both cases, the patients are described as relatively well appearing, without respiratory distress but with diffuse infiltrates on chest imaging and an elevated erythrocyte sedimentation rate. However, unlike the patient in the previously reported case, our patient did

FIGURE 3. Lung Biopsy in a Patient With Clozapine-Induced Pulmonary Toxicity



not have significant peripheral eosinophilia, which suggests that clozapine may cause alveolitis via more than one mechanism in susceptible individuals. Clinicians should consider clozapine-induced lymphocytic alveolitis in patients who develop pulmonary infiltrates while receiving clozapine treatment.

Reference

1. Benning TB: Clozapine-induced extrinsic allergic alveolitis. Br J Psychiatry 1998; 173:440–441

SIXTO A. ARIAS, M.D.
PAUL COHEN, M.D.
JEFF S. KWON, M.D.
Bridgeport, Conn.

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Aripiprazole Adjunctive to Antidepressant Therapy

TO THE EDITOR: We would like to clarify the dosing for aripiprazole adjunctive to antidepressant therapy in patients with major depressive disorder as suggested in the American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Major Depressive Disorder (1), published as a supplement to the October 2010 issue of the *Journal*. The medication product information states that for adjunctive treatment of major depressive disorder, aripiprazole should be initiated at 2–5 mg per day, with a target dose of 5–10 mg per day and a maximum dose of 15 mg/day. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week, and no dosage adjustments are needed for the current antidepressant.

The current guidelines state that adjunctive aripiprazole is typically initiated at 2.5–5 mg/day and titrated upward as tolerated to a maximum dose of 30 mg/day. In the study cited for this recommendation (2), adjunctive aripiprazole was initiated at 5 mg/day and, if tolerability permitted, increased to the target dose of 10 mg/day at the start of week 2. The dose could be reduced to 2 mg if necessary for tolerability. The maximal dose in the study was 20 mg/day. There is no recommendation in the product information for a maximum dose of 30 mg/day for aripiprazole adjunctive to antidepressants. When making treatment decisions, it is important to consider the doses that were studied in three large, placebo-controlled, double-blind clinical trials for aripiprazole adjunctive to antidepressants in the treatment of major depressive disorder (2–4), and these data provide the foundation for the recommended doses in the product information.

References

1. American Psychiatric Association: American Psychiatric Association Practice Guideline for the Treatment of Patients With Major Depressive Disorder. Am J Psychiatry 2010; 167(suppl):A34
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RONALD M. MARCUS, M.D.
Wallingford, Conn.
RAYMOND SANCHEZ, M.D.
Princeton, N.J.
MARIANNE FROST, M.S.
Wallingford, Conn.
ROBERT D. MCQUADE, PH.D.
Princeton, N.J.

Dr. Marcus has received support from Bristol-Myers Squibb; and he is employed by Bristol-Myers Squibb. Dr. Sanchez has received support from Otsuka Pharmaceutical Development and Commercialization, Inc. Ms. Frost has received support from Bristol-Myers Squibb; and she is employed by Bristol-Myers Squibb. Dr. McQuade has received support from Otsuka Pharmaceutical Development and Commercialization, Inc; he is employed by Otsuka Pharmaceutical Development and Commercialization, Inc.; and he is a shareholder with Bristol-Myers Squibb.

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Response to Marcus et al. Letter

TO THE EDITOR: We thank Dr. Marcus et al. for bringing this error to our attention. The upper dose of aripiprazole studied for adjunctive treatment of major depressive disorder is 20 mg/day, and the upper recommended dose is 15 mg/day. A correction will be made in the guideline text published on PsychiatryOnline.com.

JOEL YAGER, M.D., CHAIR,
APA STEERING COMMITTEE ON PRACTICE GUIDELINES
Denver, Colo.
ALAN J. GELENBERG, M.D., CHAIR,
APA WORK GROUP ON MAJOR DEPRESSIVE DISORDER
Hershey, Pa.
LAURA J. FOCHTMANN, M.D., MEDICAL EDITOR,
APA PRACTICE GUIDELINES
Stony Brook, N.Y.

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Propofol Addiction Initiated by Anesthetic Use

TO THE EDITOR: Propofol is a safe anesthetic agent, acts rapidly, and allows a fast recovery from anesthesia. Despite its abuse potential by activation of the gamma-aminobutyric acid receptor type A ($GABA_A$), only several cases of propofol depen-