
Lung Disease Associated with Orally Administered Mesalamine for Ulcerative Colitis*

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Pulmonary symptoms, bilateral interstitial infiltrates and gas exchange abnormalities developed in a patient with ulcerative colitis treated with orally administered mesalamine. Improvement of symptoms and objective findings occurred after drug discontinuation. To the best of our knowledge, this is the first report of lung toxicity associated with orally administered mesalamine.

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5-ASA = 5-aminosalicylic acid; Dco = diffusing capacity for carbon monoxide; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; FRC = partial pressure of oxygen; Svo2 = blood oxygen saturation; FPCO2 = partial pressure of carbon dioxide; FPD = purified protein derivative (tuberculin test)

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Sulfasalazine has been used to treat ulcerative colitis for over 40 years. Several reports have described sulfasalazine toxicity involving multiple organ systems, including the lungs. The clinically beneficial component of sulfasalazine for reducing inflammation of the colon is mesalamine (5-ASA). Mesalamine has been thought to be free of most side effects. In contrast, sulfapyridine, the carrier component of sulfasalazine, has been considered to be responsible for most adverse symptoms. Several preparations of orally administered mesalamine are being assessed. Herein, we report the first case of pulmonary disorders related to the toxicity of orally administered mesalamine.

CASE REPORT

A 64-year-old nonsmoking woman was well until April 1986 when ulcerative colitis was diagnosed. Initial treatment with sulfasalazine had to be discontinued because a rash developed. She was first seen in our institution in May 1986 and a regimen of orally administered mesalamine (Asacol, Norwich-Eaton Pharmaceuticals, Inc.) was begun at a dosage of 3.6 g/day as part of a "compassionate use" program. Her bowel symptoms remitted, and she was well at follow-up intervals of six months. A chest roentgenogram in 1986 was normal.

Mild dyspnea on exertion was first described by the patient (to her local physician) in mid-1988. No relevant occupational exposure for lung disease had been noted. A chest roentgenogram and pulmonary function studies in September 1988 were normal except for a reduced Dco of 0.54 ml/min/mm Hg (predicted value, 13.7 ml/min/mm Hg). Symptoms persisted, and a chest roentgenogram in May 1989 showed bibasilar interstitial infiltrates; pulmonary function studies showed a Dco of 5.05 ml/min/mm Hg. The patient was referred back to our institution for further assessment.

On evaluation in June 1989, the patient reported no cough, sputum production or wheezing but did complain of low-grade fever and night sweats. No bowel symptoms were reported. Bibasilar rales were noted, but there was no fever, digital clubbing, cyanosis, edema or adenopathy. The Dco was 11 ml/min/mm Hg (predicted

![Figure 1. Pulmonary function tests before and after stopping oral administration of mesalamine (5-ASA).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21644/ on 04/28/2017)
value, 14 to 20 ml/min/mm Hg). A chest roentgenogram compared with the roentgenogram from May 1989 appeared improved, and oral administration of mesalamine was continued at a reduced dosage of 3.5 g/day.

The symptoms of dyspnea were still present (but had not worsened) when the patient returned in October 1989. A chest roentgenogram showed scattered interstitial infiltrates in the lower parts of the lungs; this had not been previously noted on the June 1989 film. The DCO was 12 ml/min/mm Hg. Arterial blood gas studies performed when the patient was resting and breathing room air showed the following: PaO₂, 65 mm Hg; SaO₂, 92 percent; and Paco₂, 35 mm Hg. Significant hypoxemia occurred with desaturation during exercise (PaO₂, 46 mm Hg; SaO₂, 81 percent; and Paco₂, 32 mm Hg). Further studies were advised and were performed by her local physician. These included PPD, induced sputum test for tuberculosis and fungi, fungal serologic studies and mammography; all results were negative. A two-dimensional echocardiogram showed pulmonary hypertension.

Evaluation in our institution in January 1990 showed both a worsening of the dyspnea on exertion and a sporadic cough. She now reported a weight loss of 6.5 kg and night sweats. The patient had no knowledge of prior exposure to tuberculosis. She did not have pets or a significant travel history. She was allergic to penicillin and sulfa. At this point, she had been taking mesalazine at a dosage of 5.6 g/day for 37 months and subsequently at 3.2 g/day for seven months. No corticosteroids had been used. Significant physical findings were bibasilar end-inspiratory crackles. There was no fever, digital clubbing, cyanosis, edema or adenopathy. A chest roentgenogram showed that the infiltrates were unchanged from October 1989. The DCO had decreased to 8 ml/min/mm Hg and the arterial blood gas values (with the patient at rest, breathing room air) were PaO₂, 63 mm Hg; SaO₂, 92 percent; and Paco₂, 33 mm Hg. Fungal serologic studies, sedimentation rate, mammogram, repeat PPD, and both induced sputum and gastric lavage for acid-fast bacilli were normal or negative. A ventilation-perfusion scan indicated a low probability for pulmonary embolism. An echocardiogram suggested pulmonary hypertension. The right ventricular systolic pressure was estimated to be 70 mm Hg, ventricular function was normal and there were no regional wall-motion abnormalities.

The mesalazine therapy was discontinued in January 1990, and the patient elected to defer a proposed open-lung biopsy. Over the following months, she reported marked improvement of the exertional dyspnea. There was no difference between chest roentgenograms from March 1990 and September 1990. Pulmonary function tests were repeated, and results showed an improvement in diffusing capacity (Fig 1). Estimated pulmonary artery pressure was 52 mm Hg in September 1990. Eight months after administration of mesalazine was discontinued, she was walking 2.5 miles daily, and blood oxygen saturation during exercise was 88 percent.

**DISCUSSION**

The differential diagnosis of pulmonary problems in patients with inflammatory bowel disease includes consideration of bronchitis or fibrosing alveolitis related to their underlying disease, opportunistic lung infections in patients taking steroids and pulmonary complications caused by sulfasalazine. Drug-induced lupus primarily involving the lung, hypersensitivity pneumonitis, pulmonar inflammatory infiltrates and eosinophilia, and fibrosing alveolitis have been associated with sulfasalazine therapy for ulcerative colitis. It is unlikely that these syndromes were caused by the underlying disease, since (a) the symptoms often resolved after cessation of sulfasalazine treatment and (b) similar problems have been described in patients treated with sulfasalazine for a different illness, such as rheumatoid arthritis.

Most adverse effects to sulfasalazine are attributed to the sulfapyridine moiety, whereas the mesalamine portion is thought to cause minimal adverse effects. Initial short-term trials of orally administered mesalazine in the treatment of ulcerative colitis suggested that side effects occurred much less frequently than with sulfasalazine and at about the same rate as with placebo treatment. Pulmonary toxicity has not been reported.

Previous reports of sulfasalazine toxicity noted pulmonary symptoms within one to four months after starting treatment. One patient was challenged with sulfapyridine and had recurrent pulmonary abnormalities. Another had a history (41 years earlier) of a similar response to another sulfonamide.

In our patient, insidious pulmonary symptoms and interstitial infiltrates developed after treatment with orally administered mesalazine for two years. Subjective symptoms abated within two months after drug treatment was discontinued and objective findings eight months later were significantly better. Histopathologic findings obtained before discontinuation of the drug might have enhanced the description of the disease process, but they were not necessary for the establishment of an association between lung disease and orally administered mesalazine. The improvement in symptoms, DCO and pulmonary artery pressures after discontinuation of mesalazine strongly suggested a partially reversible drug-induced pulmonary disorder with a more insidious onset than that seen with sulfonamide-related pulmonary disorders. This leads us to conclude that adverse pulmonary reactions to mesalazine must be considered in the differential diagnosis of pulmonary involvement in patients with ulcerative colitis who are receiving therapy with mesalazine.

**REFERENCES**

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Adult T-Cell Leukemia with a Solitary Lung Mass*  
Takafumi Okura, M.D.; Rumi Tanaka, M.D.; Hiroshi Shibata, M.D.; and Hitoshi Kakita, M.D.  
A 49-year-old woman was admitted to the hospital with supraclavicular lymph node swelling. On a chest x-ray film, a 4 x 4-cm nodular shadow was observed in the right middle lung field. The white blood cell count was 10,100/cu mm, showing 44 percent abnormal lymphocytes with lobulated nuclei. Since HTLV-I antibodies were markedly positive, she was diagnosed as having ATL. Transbronchial tumor biopsy revealed accumulation of ATL cells. Our patient is the first case with only a large nodular accumulation of ATL cells without diffuse infiltration of the cells in the lung.  
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ATL = adult T-cell leukemia; HTLV-I = human T-cell leukemia virus-I; CD = cluster determination  

A 49-year-old woman was admitted to our hospital because of supraclavicular lymph node swelling. Physical examination revealed the right supraclavicular and the left axillary lymph nodes to be swollen to 1.5 to 3.0 cm in diameter. Auscultation of the lung revealed no rales. She showed neither skin rash nor hepatosplenomegaly. Laboratory findings were summarized as follows: white blood cell count, 10,100 cu mm, showing 41 percent abnormal lymphocytes with lobulated nuclei; hemoglobin level, 11.5 g/dl; platelet count, 19.3 x 10^9 cu mm; total serum protein level, 5.9 g/dl; glutamic oxaloacetic transaminase value, 18 IU/L; lactic dehydrogenase, 486 IU/L; and serum calcium, 4.5 mg/dl. Abnormal lymphocytes were revealed to be 8 percent of the total cells in the bone marrow aspiration fluid. Flow cytometric analysis of lymphocyte surface antigens revealed expression of CD3 by 76.7 percent; CD4 by 72.0 percent; and CD8 by 11.0 percent. The HTLV-I antibodies were positive. A chest x-ray film revealed a 4 x 4-cm solitary nodular tumor shadow in the right middle lung field (Fig 1). Computed tomography of the chest showed a mass with air bronchogram in segment 4 of the right lung. Biopsied specimens of the left axillary lymph node showed diffuse infiltration of medium-sized lymphocytes with convoluted nuclei. Pathologic diagnosis was malignant lymphoma, diffuse medium-size cell type according to the Leukemia Study Group Classifications. Although tumor cell infiltration could not be observed in the bronchial mucosa by a bronchoscopic examination, biopsied specimens of the tumor mass showed diffuse infiltration of leukemic cells in the lung parenchyma (Fig 2). After three cycles of the chemotherapy using a combination of adriamycin, cyclophosphamide, vincristine, prednisolone and etoposide, the number of leukemic cells in the peripheral blood was markedly decreased. In addition, lymph node swelling and tumor shadow on chest x-ray film disappeared. She died, however, of a pulmonary infection nine months later. Autopsy showed a diffuse infiltration of leukemic cells and infection of Aspergillus in both lungs. Liver, spleen and retroperitoneal lymph nodes also were affected with leukemic cells.  

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FIGURE 1. Chest x-ray film on admission shows a mass in the right middle lung field.  

FIGURE 2. Transbronchial tumor biopsy specimen shows the infiltration of leukemic cells (Hand E, original magnification X 400).