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Multiple Pulmonary Nodules: An Unusual Presentation of Fludarabine Pulmonary Toxicity: Case Report and Review of Literature

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Fludarabine monophosphate, a purine analogue is used in the treatment of lymphoid malignancies. A 73-year-old woman presented with fever and cough 2 weeks after completing the third cycle of fludarabine for chronic lymphocytic leukemia (CLL). Chest roentgenogram showed multiple pulmonary nodules. Pulmonary histopathology demonstrated a mononuclear interstitial infiltrate without evidence of malignant, infectious, granulomatous, or vascular causes. Her symptoms and pulmonary nodules resolved following treatment with corticosteroids. To our knowledge, four cases of interstitial pneumonitis associated with fludarabine have been reported in medical literature. Fludarabine induced lung toxicity must be considered in all patients who develop unexplained lung disease while receiving fludarabine. It is reversible with discontinuation of drug and administration of corticosteroids. This case extends the spectrum of fludarabine pulmonary toxicity to include pulmonary nodules. Am. J. Hematol. 70:241–245, 2002. © 2002 Wiley-Liss, Inc.

Key words: fludarabine; drug toxicity; pulmonary nodules; CLL

INTRODUCTION

Fludarabine monophosphate, a purine analogue, is an effective and generally well-tolerated agent for second-line treatment of advanced chronic lymphocytic leukemia (CLL) or in chemotherapeutic-naive patients with CLL. It also has substantial activity in non-Hodgkin's lymphoma [1].

Commonly recognized toxicities of fludarabine include myelosuppression, opportunistic infections, neurotoxicity, and autoimmune hemolytic anemia.

This report describes an unusual case of fludarabine toxicity presenting as multiple pulmonary nodules and reviews the literature on fludarabine pulmonary toxicity.

CASE REPORT

A 73-year-old female with a 7-year history of CLL was admitted with fever and nonproductive cough. Chest X ray revealed multiple pulmonary nodules (Fig. 1). Her previous chest X rays had been normal. She was on fludarabine (25 mg/m^2 for 5 days every 28 days by intravenous bolus) for worsening thrombocytopenia and had completed her third cycle 2 weeks before admission; she had a good hematologic response. She was not on any prophylactic antibiotic after fludarabine treatment. She was a nonsmoker, and there was no history of exposure to tuberculosis, toxins, recent travel, or HIV risk factors.

Her blood pressure was 130/70 mmHg, pulse was 100, respiratory rate was 16, temperature was 100.7°F, and pulse oximetry was 96% on room air. Lungs were clear, and cardiovascular examination was normal. The abdomen was soft without tenderness or hepatosplenomegaly. There was no lymphadenopathy.

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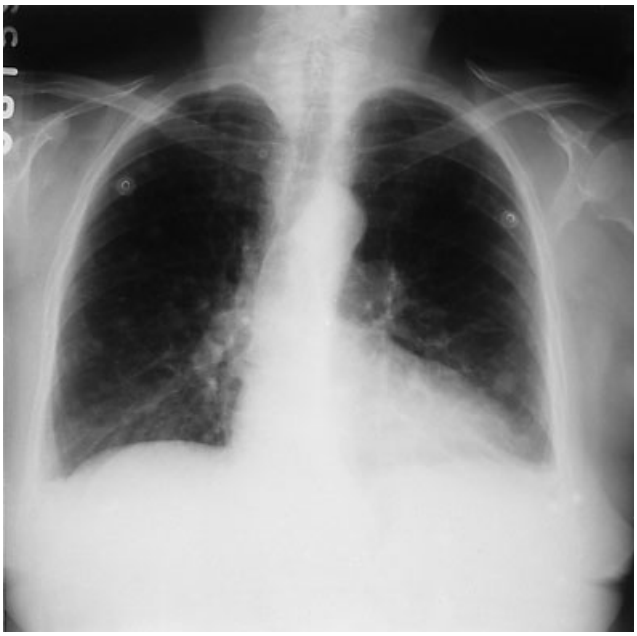

Fig. 1. Chest radiograph on admission shows multiple pulmonary nodules bilaterally.

The laboratory findings were as follows: white count 7.5×10^9/L with 49% neutrophils, 38% lymphocytes, 10% monocytes, and 3% eosinophils; hemoglobin 12.3 g/dL; platelets 112×10^9/L; ESR (Westergren) 15. Results of liver and kidney function tests were within normal limits. CT scan of the chest showed multiple nodules, the largest being on the left base measuring 1.8 cm × 1.7 cm; nodules on the right were smaller than 1 cm (Fig. 2). Routine cultures and titers for respiratory pathogens were negative. Test for PPD was negative. Tests for antinuclear antibody, rheumatoid factor, hepatitis B surface antigen, Coombs' antibody, and cryoglobulins were negative. Complement level was normal. HIV test was negative. CD4 count was 0.403×10^9/L. Fungal serologies (for aspergillosis, histoplasmosis, blastomycosis, and coccidioidomycosis) were negative.

She was empirically started on levofloxacin for typical and atypical respiratory pathogens, and further fludarabine treatment was withheld.

A fiber optic bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy was performed. Bronchoscopy showed a normal tracheobronchial tree. Bronchoalveolar lavage was negative for malignancy. Special stains and cultures were negative for bacteria, fungi, viruses, *Mycobacterium*, and *Pneumocystis carinii*.

Histological examination revealed a mononuclear interstitial infiltrate. There was no area of necrosis, acute inflammation, or granulomatous infiltration. These findings led to the conclusion that the lung toxicity was caused by fludarabine. The antibiotic was discontinued, and the patient was started on prednisone (1 mg/kg/day). Repeat chest radiograph after 2 weeks showed complete resolution of all nodules (Fig. 3) . Steroids were tapered over 1 month. Fludarabine treatment was not reinstituted.

DISCUSSION

Development of multiple pulmonary nodules in an immunocompromised host raises complex diagnostic problems, as the distinction between metastatic cancer, infections, granulomatous diseases, and drug toxicity is crucial to determine appropriate therapy [7].

A variety of diseases of diverse etiologies may produce diffuse pulmonary nodules, and an aggressive approach is indicated to establish the cause.

Multiple pulmonary nodules strongly suggest metastatic tumor [8]. There was no evidence of malignancy on bronchoalveolar lavage and histopathology. CLL itself or its tissue counterpart, small lymphocytic lymphoma, can cause bilateral pulmonary infiltrates. This can be diagnosed by bronchoalveolar lavage and transbronchial biopsy [9,10]. Open lung biopsy should be reserved for patients in whom less traumatic procedures have yielded negative results. Infection remains a major cause of morbidity and mortality in patients with CLL [11]. Fludarabine selectively depletes CD4 cells to alter the CD4:CD8 ratio and produces a clinical and immunologic picture similar to acquired immunodeficiency syndrome [12]. The spectrum of infection seen in fludarabine-treated patients includes those infections common to patients with CLL in addition to opportunistic infections caused by *Pneumocystis carinii*, *Mycobacteria*, *Nocardia*, *Listeria*, *Cryptococcus*, *Histoplasma*, *Cytomegalovirus*, *Candida*, *Aspergillus*, and Herpesvirus [2,11–15]. Patients with *P. carinii*-induced acute interstitial pneumonitis present with acute hypoxia, and it can closely mimic hypoxic presentation of fludarabine-induced interstitial pneumonitis. In our patient, various cultures, serum tests, and special stains on bronchoalveolar lavage and transbronchial biopsy did not support existence of infectious etiology for the multiple pulmonary nodules. Laboratory and histopathological data did not support the existence of rheumatoid arthritis, Wegener's granulomatosis, sarcoidosis, or bronchopulmonary amyloidosis to explain the presence of multiple pulmonary nodules.

Four case reports of interstitial pneumonitis due to fludarabine have been reported in the medical litera-

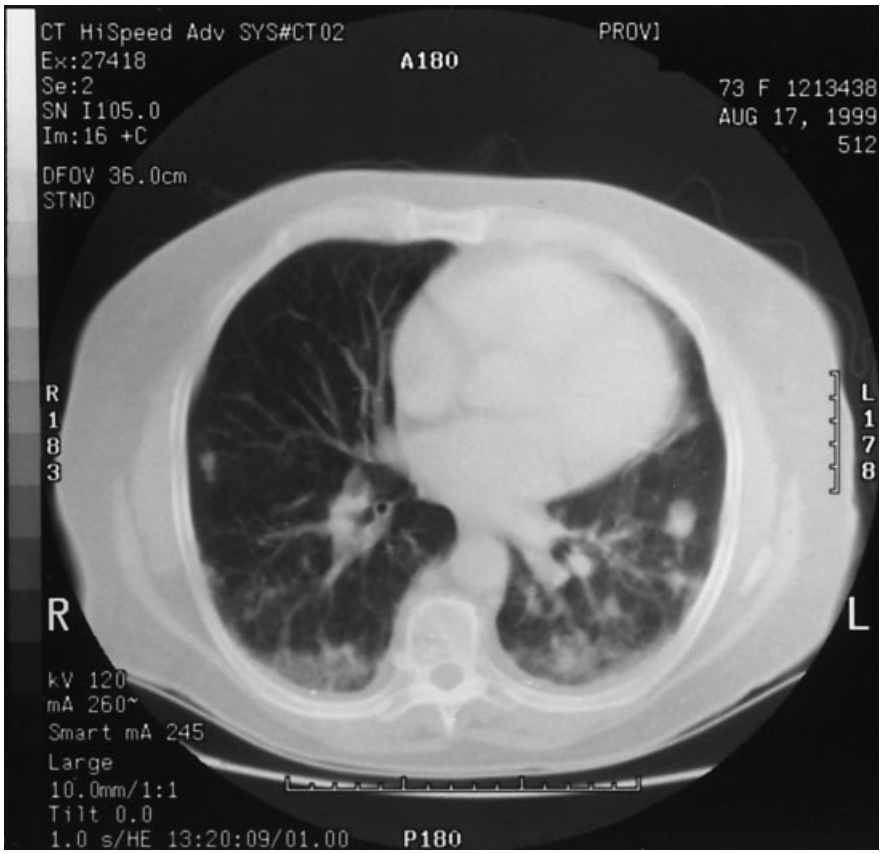

Fig. 2. CT scan shows the largest nodule on left lower lobe, measuring 1.8 cm × 1.7 cm. All right sided nodules are smaller than 1 cm.

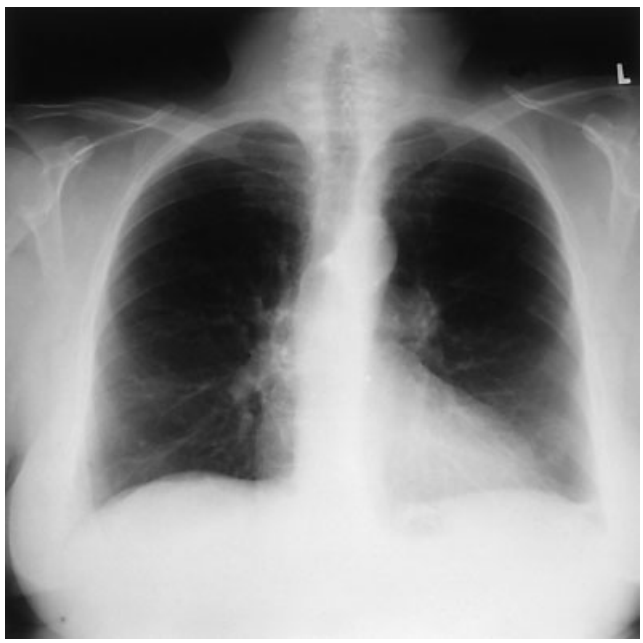

Fig. 3. Chest radiograph shows complete disappearance of pulmonary nodules.

ture [3–6]. An overview of previously reported cases of fludarabine-associated lung injury is presented in Table I.

Patients with fludarabine-induced pulmonary toxicity usually present with nonproductive cough, fever, and dyspnea usually 6 days to 2 weeks after the last dose. There is no correlation with the number of cycles previously given. In previous cases, patients presented with varying degree of hypoxia while our patient was never hypoxic. No deaths have been reported.

Radiographic changes consist mostly of diffuse reticular infiltrate with or without nodularity. Our patient is unusual because of the radiographic pattern of multiple pulmonary nodules.

The pathology of fludarabine-induced pulmonary toxicity demonstrates mononuclear cell infiltration, atypical type II pneumocytes, and proliferation of fibroblasts.

All patients had clinical and radiographic response to steroids. One patient reported in the literature had a recurrence on tapering of steroids but responded to reinstitution of the steroids [3]. There was recurrence of pneumonitis on reintroduction of drug in 2 patients [4,6].

The pathogenesis of lung injury induced by fludarabine remains unknown, but prompt response to steroids suggests the role of an immunologic mechanism, although direct toxicity cannot be ruled out.

TABLE I. Characteristics of Patients With Pulmonary Toxicity Associated With Fludarabine

Report	Age/sex and diagnosis	Dosage and time of onset	Presentation	Roentgenogram	Lung biopsy	Treatment with steroids	Response and outcome
Hurst [3]	61/M CLL	2 weeks after 3rd cycle (20 mg/m^2, days 1−5)	Fever, dyspnea, dry cough, hypoxia (pO_2 45 mmHg)	Diffuse reticulonodular infiltrate	Fibrosing interstitial pneumonitis with mono-nuclear infiltrate and fibrosing alveolitis	Yes	Response to steroids in 24 hr; recurrence on tapering dose of steroids; resolved after reinstitution of steroids
Cervantes [4]	40/M CLL	8 days after 3rd cycle (20 mg/m^2, days 1−5)	Fever, dyspnea, cough, hypoxia (pO_2 60 mmHg)	Diffuse interstitial pneumonia	None	Yes	Response to steroids; recurrence on the 2nd day of the 4th cycle, resolution after steroids
Kane [5]	74/M CLL	6 days after 1st cycle (24 mg/m^2, days 1−5)	Nonproductive cough, fever, dyspnea, hypoxia (pO_2 66 mmHg); intubation	Diffuse bilateral reticulonodular infiltrate	Patchy diffuse alveolar damage with atypical type II pneumocytes	Yes	Response to steroids within 48 hr; complete recovery
Levin [6]	71/M CLL	First admission: after 5th cycle (50 mg, days 1−5) Second admission: 1st cycle was given after 1.5 years	First admission: cough, fever Second admission: fever, cough, hypoxia; intubation	First admission: bilateral asymmetric pulmonary infiltrate Second admission: adult respiratory distress syndrome	First admission: none Second admission: resolving interstitial pneumonitis	First admission: yes Second admission: yes	First admission: response to steroids in 1 week Second admission: responded to steroids; death 2 weeks later from progressive disease
This study	73/F CLL	2 weeks after 3rd cycle (25 mg/m^2, days 1−5).	Fever, nonproductive cough	Bilateral multiple pulmonary nodules	Mononuclear interstitial infiltrate	Yes	Response to steroids within 24 hr; complete disappearance of all nodules within 2 weeks

We believe that this is the first reported case of multiple pulmonary nodules without hypoxia as a presentation of fludarabine pulmonary toxicity.

Fludarabine-induced pulmonary toxicity must be considered in all patients who develop unexplained lung disease while receiving fludarabine. Lung biopsy is usually necessary to eliminate other specific diagnosis such as opportunistic infection or malignancy.

Once the diagnosis is established, it is necessary to discontinue the drug permanently and initiate systemic steroid therapy. Early recognition of pulmonary toxicity is important because the toxic process of fludarabine is reversible with appropriate therapy.

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