A Case of Pemetrexed-Induced Acute Lung Injury in Non-small Cell Lung Cancer

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CASE REPORT

A 61-year-old woman was admitted to our hospital. Seven months before admission, she was diagnosed with NSCLC (adenocarcinoma, pT2N2M0) and treated with a right lower lobectomy. Adjuvant chemotherapy was started with vinorelbine and cisplatin, but the chemotherapeutic regimen was changed to pemetrexed after four cycles due to pleural metastasis.

Shortly after the fourth cycle of pemetrexed treatment, the patient complained of dyspnea. Chest x-rays and computer tomography scan (Figure 1B) revealed diffuse pulmonary infiltration, and the lesion progressed rapidly. No bacterial pathogen was cultured in induced sputum, and Acid fast stain was also negative. Serologic data did not show any evidence of infection, cardiac, or collagen vascular disease as a cause of the acute lung injury. As dyspnea was so severe, we could not perform the bronchoscopy and bronchoalveolar lavage for culture. The patient underwent a video-assisted thoracoscopic lung biopsy. The pathology revealed diffuse alveolar septal thickening with hyaline membranes, and Grocott’s methenamine silver stain of the biopsy specimen did not reveal any evidence of specific infiltration (Figure 2). After prednisolone 60mg/d (oral) was started, the dyspnea and pulmonary infiltrations slowly improved (Figure 1C).

Comment

Many chemotherapeutic agents have been associated with pulmonary toxicity. The onset of symptoms is unpredictable and generally rapidly progressive. Furthermore, chemotherapy-induced lung injury can manifest in many different patterns and can be severe or fatal. The diagnosis depends on clinical, radiologic, and histologic findings. However, in the clinical setting, the diagnosis is made by excluding other conditions with similar manifestations. Early withdrawal of the offending drug and judicious treatment with steroid will often lead to improvement or complete resolution of the chemotherapy-induced lung injury.

Many drugs have been associated with lung injury characterized by diffuse alveolar damage (DAD); this histologic pattern is common in a majority of patients with lung injury due to chemotherapeutic agents. Histologically, DAD is diagnosed with the findings of alveolar airspace and interstitial edema, hyaline membrane formation, and proliferation of type II pneumocytes. Mechanisms of damage include direct pulmonary toxicity and indirect effects caused by stimulation of inflammatory reactions.

Pemetrexed is a newly developed antifolate drug that targets multiple enzymes involved in DNA synthesis and folate metabolism. Pemetrexed is currently being used as a standard agent for second line chemotherapy in patients with NSCLC due to prolonged survival time and modest side effects. The most frequent toxicities reported in patients treated with pemetrexed are fatigue, neutropenia, and infection. Pulmonary toxicity resulting from treatment with pemetrexed has not been previously reported with pathologic confirmation.

There are no established criteria for the diagnosis of chemotherapy-induced lung injury and the pathologic findings of drug-related DAD. Thus, the diagnosis is possible by exclusion of other conditions that cause lung injury. In our case, the clinical history, histologic evidence of lung injury, and exclusion of other potential factors suggested the chemotherapeutic drug as the cause of the acute lung injury. This is the first case of pathologically proven lung injury due to pemetrexed.

In conclusion, this patient demonstrated an acute lung injury with the histologic pattern of DAD associated with...
pemetrexed treatment. Currently, pemetrexed is used as a standard agent for second line chemotherapy in patients with NSCLC. Because pemetrexed may cause acute lung injury in some patients, careful follow-up of patients treated with pemetrexed is required.

REFERENCES


**FIGURE 1.** Summary of chest computer tomography (CT) before presentation of acute lung injury (A), at presentation (B), and after some improvement (C).

**FIGURE 2.** The microscopic examination of the lung specimen revealed diffuse alveolar septal thickening by fibroblasts and scant chronic inflammatory cells, which was consistent with the features of an organizing stage of diffuse alveolar damage. Within the alveolar lumen, some remnants of hyaline membranes were observed (×100, hematoxylin and eosin [H and E]).