Fatal Pemetrexed-Induced Lung Injury in Patients with Advanced Mesothelioma

A Report of Two Cases

To the Editor:

Pemetrexed is an antifolate chemotherapy agent that is active in multiple tumor types including malignant mesothelioma.\(^1\) Adverse drug reactions are mild, and there have been no previous reports that pemetrexed induces fatal acute lung injury. We encountered two patients who had been given pemetrexed and developed a fatal lung injury.

The first case was a 71-year-old man admitted to our hospital for evaluation of chest pain and diagnosed as sarcomatous malignant pleural mesothelioma. The patient received chemotherapy with cisplatin (60 mg/m\(^2\)) and pemetrexed (500 mg/m\(^2\)). However, 4 weeks after initiation of the treatment, he was dyspneic. A chest computed tomography scan demonstrated diffuse ground-glass opacities in his right lung (Figure 1). The patient’s white blood cell count was 14,800/mm\(^3\), C-reactive protein was 12.7 mg/dl, and KL-6 was 2700 U/ml (normal range: <500 U/ml). No infectious, tumor-related, embolic, or cardiac causes were found after extensive workup. The patient’s clinical state deteriorated, and methylprednisolone was started at 500 mg/d. Despite the treatment, his respiratory status worsened, and he died 7 weeks after initiation of the chemotherapy.

The second case was a 77-year-old man referred to our hospital for evaluation of dyspnea and diagnosed as biphasic-type malignant pleural mesothelioma. The patient received chemotherapy with carboplatin (area under the curve = 4) and pemetrexed (500 mg/m\(^2\)). Three weeks after the start of the treatment, he presented with progressive exertional dyspnea. His chest computed tomography scan demonstrated ground-glass opacities in his left lower lobe (Figure 2). The patient’s white blood cell count was 16,900/mm\(^3\), C-reactive protein was 9.2 mg/dl, and KL-6 was 1236 U/ml. There were no infectious, embolic, tumor-related, or cardiac causes found after extensive workup. High-dose corticosteroid treatment was started at 500 mg/d of methylprednisolone. However, his respiratory status worsened, and he died 5 weeks after the start of chemotherapy; just before his death, the level of KL-6 was 2417 U/ml.

There is only one published report on pemetrexed-induced lung injury, but that was very mild and easily treated by corticosteroids.\(^2\) In both our cases, none of the examinations revealed evidence of embolic, tumor-related, cardiac, or infectious causes. Moreover both patients’ serum levels of KL-6 were increased remarkably. KL-6 is a high molecular weight, mucin-like glycoprotein classified as human MUC1 mucin. Serum levels of KL-6 are increased in patients with interstitial lung diseases including drug-induced pneumonitis but not in patients with bacterial pneumonia or normal control subjects.\(^3\) In both patients, there were no “candidates” that could have induced the acute interstitial pneumonitis other than the chemotherapy treatment.
Evaluation of Kras Gene Mutation and Copy Number in Thymic Carcinomas and Thymomas

To the Editor:

Compared with the more common epithelial cancers, current knowledge about the biology of thymic epithelial tumors is limited. Research has been hampered by the rarity of the tumor and the lack of established cell lines and animal models. Ras family plays important roles in the regulatory processes of proliferation, differentiation, and apoptosis. A recent Caucasian report demonstrated that 1 of 38 thymoma and 1 of 7 thymic carcinoma had Kras mutations. Because we previously reported the EGFR copy number and Kras mutation status using quantitative polymerase chain reaction (PCR) assay in non-small cell lung cancer, we evaluated the Kras gene mutation status and Kras gene amplification, which may bring important information for the surgically treated Japanese thymic epithelial tumor patients.

Thymic epithelial tumor tissues were obtained by surgical excision from 125 patients (107 thymomas and 18 thymic cancers). Kras mutation status at codon 12,13 mutation was analyzed by quantitative real-time PCR performed using LightCycler. Positive sample and some of the negative samples from melting analysis were directly sequenced. Using the LightCycler genotyping PCR assay, only one thymic carcinoma case was detected to have a Kras mutation. A heterozygous G to T substitution at nucleotide position 35 in exon 1 of Kras, resulting in a valine for glycine amino acid substitution at position 12 (G12V).

Disclosure: The authors declare no conflicts of interest.

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FIGURE 1. The data for Kras gene using direct sequencing. Left, A heterozygous G to T substitution at nucleotide position 35 in exon 1 of Kras, resulting in a valine for glycine amino acid substitution at position 12 (G12V). Right, Reverse sequencing.