Alveolar Hemorrhage Associated with Pemetrexed Administration

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Abstract

We herein describe a 67-year-old man with advanced adenocarcinoma of the lung who developed an alveolar hemorrhage (AH) associated with pemetrexed. He received four courses of pemetrexed therapy with carboplatin and seven courses of pemetrexed maintenance therapy. One week after the last pemetrexed administration, the patient developed hemoptysis with deteriorating dyspnea and anemia. Chest images showed diffuse ground-glass attenuation. The diagnosis of AH was based on findings of bloody bronchoalveolar lavage (BAL) fluid, hemosiderin-laden macrophages in the BAL fluid, and a transbronchial lung biopsy sample. This report is the first to describe AH associated with pemetrexed.

Key words: lung cancer, NSCLC, pemetrexed, alveolar hemorrhage

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Introduction

Pemetrexed is one of the most active cytotoxic agents commonly used for the treatment of advanced non-squamous non-small cell lung cancer (NSCLC) (1). Drug-induced alveolar hemorrhage (AH) is a serious event observed in patients with lung cancer who undergo chemotherapy. We herein report the first case of AH associated with pemetrexed.

Case Report

A 64-year-old man, who was a former smoker, underwent heavy iron radiotherapy for the treatment of pulmonary adenocarcinoma (cT1bN0M0) in the left lower lobe at another hospital with significant effectiveness and focal radiation pulmonary fibrosis (Fig. 1A, B). Three years later, he was referred to our hospital due to lung cancer recurrence (Fig. 1C). At this point, the radiation-induced fibrotic lesion was not evident due to occupation by the recurrent tumor growth. Cytological specimens from pleural effusion confirmed the recurrence and revealed neither a mutated epidermal growth factor receptor gene nor an anaplastic lymphoma kinase fusion gene. He was treated with four cycles of carboplatin (targeted area under the curve of 5 mg h/L) and pemetrexed (500 mg/m²) administered on day 1 every three weeks which led to a stabilization of the disease (Fig. 1D). Pemetrexed (500 mg/m²) maintenance therapy was administered every three weeks for seven cycles. One week after the last pemetrexed treatment, the patient was admitted with hemoptysis, anemia and dyspnea. He had no history of anticoagulation therapy.

Hematological investigations revealed a hemoglobin level of 4.4 g/dL, reticulocyte count of 93‰ and platelet count of 237×10³/mm³. His C-reactive protein level was 1.5 mg/dL, KL-6 was 149 U/mL and the brain natriuretic peptide level was 26.5 pg/mL. Coagulation tests revealed a prothrombin time of 10.7 seconds, active-partial thromboplastin time of 30.4 seconds, and D-dimer of 0.8 μg/mL. The carcinoembryonic antigen (CEA) level was 17.8 ng/mL. Urinalysis was normal. With oxygen supplementation (FiO₂ of 0.31), an arterial blood gas analysis showed a PaO₂ of 64 Torr. Anti-neutrophil cytoplasmic antibodies, anti-glomerular...

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basement membrane antibodies, and anti-nuclear antibodies were all normal. The laboratory findings did not show any evidence of inflammatory diseases or infections.

Chest radiography and computed tomography (CT) findings showed no progressive disease in terms of tumor size and pleural effusion (Fig. 1D, compared with Fig. 1C) or bilateral diffuse ground-glass attenuation, notably in the right middle lobe, which was on the other side of the tumor (Fig. 1E). Esophagogastroduodenoscopy revealed no evidence of bleeding in the upper gastrointestinal tract. Echocardiography showed normal ejection fraction of the left ventricular without evidence of valvular diseases.

Bronchoscopy showed diffuse bleeding in the bilateral bronchi (Fig. 2A-D). The bronchoalveolar lavage (BAL) was persistently bloody in appearance and gradually increased during four sequential lavage aliquots from the right upper lobe (Fig. 2E). Hemosiderin-laden macrophages were seen in the BAL fluid and in a transbronchial lung biopsy sample (Fig. 2F). A diagnosis of AH was established.

Methylprednisolone pulse therapy (1 g/day) was administered for three days followed by prednisolone therapy (60 mg/body). On the ninth hospital day, his symptoms gradually improved. The CT scan images were almost completely clear on the 25th hospital day (Fig. 1F). The dose of prednisolone was tapered by 10 mg every 2 weeks. On the 33rd hospital day, however, hemoptysis recurred and a CT scan revealed diffuse bilateral ground-glass attenuations (Fig. 1G). The patient’s symptoms, physical examinations and laboratory tests failed to suggest infectious events. Additional pulse therapy with methylprednisolone followed by prednisolone (60 mg/body) and immunosuppressive therapy with cyclophosphamide and cyclosporine, together with anti-microbial and anti-fungus agents, was administered. However, the respiratory failure was progressive. The patient died on the 83rd hospital day. An autopsy was not performed in accordance with his family’s request.

**Discussion**

The patient developed AH during the 11th cycle of pemetrexed treatment, followed by a significant amelioration due to the discontinuation of pemetrexed and the administration of high-dose corticosteroid therapy; however, the AH recurred one month after the first onset of AH. The diagnosis of AH seemed definitive based on typical clinical manifestations and the exclusion of other differential diseases. Tumor hemorrhage seemed unlikely because of the diffuse nature of the bleeding. An exhaustive effort to exclude any other possible causes finally led us to link the AH with the pemetrexed treatment. This plausible inference, however, raises two questions: 1) does the timing of the onset make it reasonable to consider AH as an adverse effect of pemetrexed, and 2) is the recurrence of AH without the resumption of the pemetrexed treatment reasonable? Putative etiology of drug-induced pulmonary injury generally includes direct cytotoxicity of the causative agent and an im-

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**Figure 1.** A chest CT image illustrates the left lower lobe before treatment with heavy-iron irradiation (A). The radiotherapy yielded a partial response, with pulmonary fibrosis located exclusively in the irradiated area, however, there was no evidence of extended radiation-induced pneumonitis (B). Three years later, the tumor recurred at the left lower lobe (C). Chemotherapy consisting of carboplatin and pemetrexed for 4 cycles followed by maintenance with pemetrexed for 7 cycles resulted in stable disease until AH developed (D), when another CT image showed diffuse bilateral ground-glass opacities, notably in the right middle lobe (E). The CT image obtained on the 25th hospital day revealed a significant improvement in the diffuse lesion (F). The CT image obtained on the 33rd hospital day again revealed diffuse bilateral ground-glass opacities predominantly in the left lung (G).
agents (2, 3). In addition, a cluster of studies have reported of years after the start of administration of the causative ably, ranging from a sudden to a late onset with an interval the timing of the onset of drug-induced AH varies consider-ations seem to contradict the timing of the onset and recur-

munological mechanism. Both the former and latter explana-
tions seem to contradict the timing of the onset and recur-
rence of AH in the present case, thus making it difficult to pinpoint the etiology. According to the pertinent literature, the timing of the onset of drug-induced AH varies consider-
ably, ranging from a sudden to a late onset with an interval of years after the start of administration of the causative agents (2, 3). In addition, a cluster of studies have reported the recurrence of AH without the resumption of the causa-
tive agents (3-6). In these cases, severe respiratory failure developed after long-term exposure of causative drugs. The findings seem concordant with the present case because the patient developed severe respiratory failure after the long-
term exposure of pemetrexed. Although it is still not fully understood, the etiology of drug-induced AH includes pul-
monary vasculitis, increased vascular permeability, any im-
une reaction, and lung injuries (2, 7, 8). As some cyto-
toxic agents cause diffuse alveolar damage resulting in AH (3, 9, 10), pemetrexed may have the potential to cause AH. Pemetrexed has been previously reported to cause lung damage (11). The outcome of AH associated with cytotoxic drugs is reportedly poor with a mortality ranging from 50 to 100% (3). High dose corticosteroid administration is recom-

mended for drug-induced AH, however, there is still no clear evidence to support its effectiveness.

In conclusion, the present patient is the first reported case in which treatment with pemetrexed most likely induced AH. The possibility of fatal AH as a result of pemetrexed treatment even after prolonged administration should therefore be noted, especially since pemetrexed is widely used as a maintenance therapy in patients with advanced non-

The authors state that they have no Conflict of Interest (COI).

References
1. Shih C, Chen VJ, Gossett LS, et al. LY231514, a pyrrolo [2,3-d] pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 57: 1116-1123, 1997.
2. Dhillon SS, Singh D, Doe N, Qadri AM, Ricciardi S, Schwarz MI. Diffuse alveolar hemorrhage and pulmonary capillaritis due to propylthiouracil. Chest 116: 1485-1488, 1999.
3. Schwarz MI, Fontenot AP. Drug-induced diffuse alveolar hemorrhage syndromes and vasculitis. Clin Chest Med 25: 133-140, 2004.
4. Locke IC, Worrall JG, Leaker B, Black CM, Cambridge G. Autoantibodies to myeloperoxidase in systemic sclerosis. J Rheu-
matol 24: 86-89, 1997.
5. Nomiyama Y, Yatera K, Kawajiri T, et al. A case of MPO-ANCA positive vasculitis associated with diffuse alveolar hemorrhage and various cardiac conducting system abnormalities following pro-

pylthiouracil treatment. Nihon Kokyuki Gakkai Zasshi 42: 324-
329, 2004 (in Japanese, Abstract in English).
6. Fujii A, Arimura Y, Minoshima S, et al. [MPO-ANCA related vasculitis with pulmonary hemorrhage during propylthiouracil (PTU) therapy]. Ryumachi (Official Journal of Japan College of Rheumatology) 37: 788-793, 1997 (in Japanese, Abstract in English).

7. Husari A, Beydoun A, Sheik Ammar A, Maakaron JE, Taher A. The untold story of Dabigatran etexilate: alveolar hemorrhage in an elderly patient with interstitial pulmonary fibrosis. J Thromb Thrombolysis 35: 81-82, 2013.

8. Pavlakis N, Bell DR, Millward MJ, Levi JA. Fatal pulmonary toxicity resulting from treatment with gemcitabine. Cancer 80: 286-291, 1997.

9. Ioachimescu OC, Stoller JK. Diffuse alveolar hemorrhage: diagnosing it and finding the cause. Cleve Clin J Med 75: 258, 260, 264-265, 2008.

10. Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. Chest 137: 1164-1171, 2010.

11. Nagata K, Kaji R, Tomii K. Fatal pemetrexed-induced lung injury in patients with advanced mesothelioma: a report of two cases. J Thorac Oncol 5: 1714-1715, 2010.