

## Gemcitabine-induced Pulmonary Toxicity

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**Abstract.** *Background: Gemcitabine is the only approved cytotoxic agent for the treatment of pancreatic cancer by the Food and Drug Administration. In addition, gemcitabine is also commonly used for the management of breast, ovarian, and non-small cell lung cancer. Myelosuppression is the most common toxicity of gemcitabine therapy. Pulmonary toxicities due to gemcitabine have, however, been reported. Dyspnea occurs in approximately 25% of patients treated with gemcitabine, whereas serious pulmonary toxicities are much less common, approximately 0.3%. Here, we present a case of gemcitabine-induced pneumonitis, encountered during treatment of pancreatic cancer, and review the literature of this rare, but dangerous complication. Case Report: A 56-year old male being treated for stage IV pancreatic cancer developed progressive dyspnea on exertion, chest tightness, and palpitations. Oxygen saturation was 82-84%. Computerized-tomography (CT) angiography of the chest demonstrated new diffuse groundglass opacities in the bilateral lower lobes when compared to the CT of the chest without intravenous contrast, 5 weeks prior. Mild to moderate emphysema was also seen, but no pulmonary emboli were detected. Myocardial infarction was ruled-out by normal electrocardiogram and normal cardiac biomarkers. Conclusion: We report another case of gemcitabine-induced pneumonitis. Physicians seeing such patients should be aware of this rare but real pulmonary toxicity. A delay in diagnosis and treatment can lead to potentially fatal outcomes.*

Gemcitabine (2',2'-difluorodeoxycytidine) is a widely used antineoplastic agent and is considered the standard-of-care in a variety of oncology settings, including pancreatic cancer. Pancreatic cancer is a devastating diagnosis to patients and their families, with median overall survival ranging from 6-

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9 months at the time of diagnosis. Burris et al. demonstrated superiority of gemcitabine monotherapy over fluorouracil in metastatic pancreatic cancer with a two-month benefit in progression-free survival (3.7 versus 5.8 months) (2).

Gemcitabine is generally well-tolerated with common toxicities including myelosuppression, peripheral edema, gastrointestinal toxicity and electrolyte abnormalities (4). Gemcitabine-induced pulmonary toxicities are common with an incidence rate of 23% (5). These complications can range from mild (dyspnea and bronchospasm) to severe (pulmonary fibrosis and acute respiratory distress syndrome). These more serious complications are rare, but can potentially be fatal or have a significant detriment on the quality of life, resulting in severely reduced functional capacity and dependency on supplemental oxygen.

We have previously published two cases of gemcitabine-related toxicities in the adjuvant setting for pancreatic cancer, and here we discuss a third case of toxicity of gemcitabine administered in the metastatic setting. An excellent clinical outcome was achieved for this patient by maintaining a high index of suspicion for pulmonary toxicity. We believe that maintaining a high index of suspicion for this rare, but potentially fatal adverse event is of great importance in preserving a patient's quality of life in an already devastating disease.

### Case Report

The patient is a 56-year-old man with a 50 pack/year smoking history diagnosed with stage IV (pT3, pN1, M1) poorly-differentiated adenocarcinoma of the pancreatic head with a single 1.8-cm hepatic metastasis. The patient underwent a pylorus-sparing Whipple procedure, followed by five cycles of adjuvant chemotherapy under a study protocol. The regimen comprised of gemcitabine ( $1000 \text{ mg/m}^2 \times 2.15 \text{ m}^2 = 2300 \text{ mg i.v.}$ ) and study drug or placebo *p.o.* on days 1-21 out of a 28-day cycle. Cycles were repeated every four weeks. The patient demonstrated a complete response by cycle 3 on magnetic resonance imaging (MRI), and the decision was made to continue under the study protocol. By cycle 5, the patient received a cumulative dose of 32,300 mg of gemcitabine. Upon

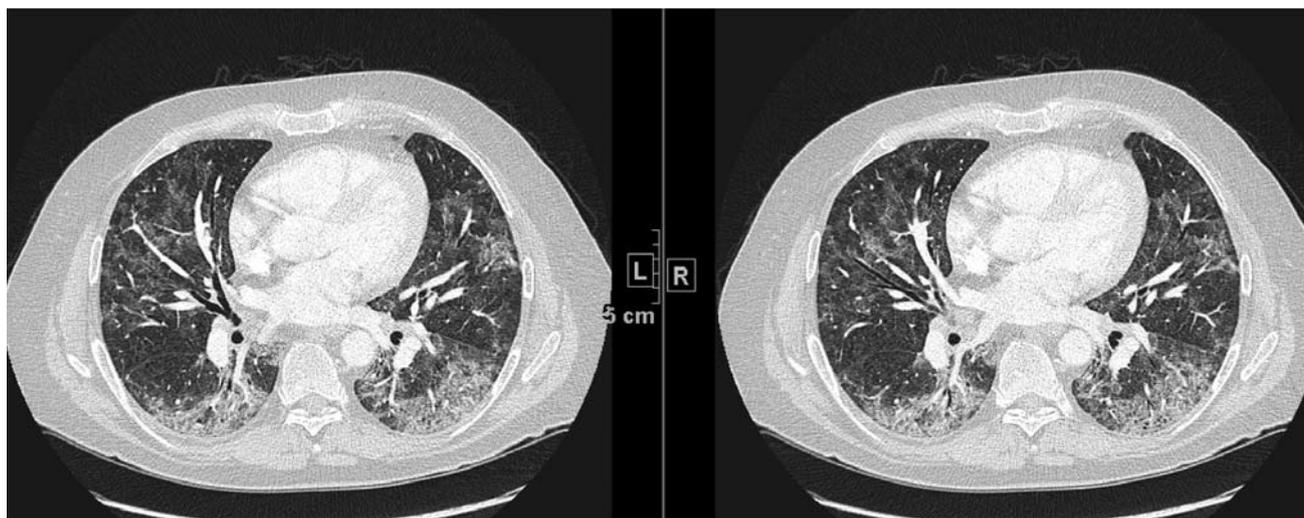


Figure 1. Representative axial images from a computerized tomography (CT) angiography of the chest at the time of presentation.

presentation for cycle 6, the patient reported several days of progressive dyspnea on exertion, chest tightness, and palpitations. Oxygen saturation was 82-84% on room air by pulse oximetry, which improved to 92% on 2 L of supplemental oxygen by nasal cannula. The patient also had a low-grade fever of 100.3°F/37.9°C. CT angiography of the chest demonstrated new diffuse groundglass opacities in the bilateral lower lobes when compared to the CT of the chest without *i.v.* contrast, five weeks prior (Figure 1). Mild to moderate emphysema was also seen, but no pulmonary emboli were detected. Myocardial infarction was ruled-out by normal electrocardiogram and normal cardiac biomarkers.

The patient underwent an extensive infectious work-up including serial blood cultures, urine culture, *Streptococcus pneumoniae* urinary antigen, *Legionella* urinary antigen, cultures of expectorated sputum and bronchoalveolar lavage for bacterial and viral (influenza, respiratory syncytial virus, parainfluenza, adenovirus, rhinovirus, metapneumovirus), fungal (*Pneocystis*, *Asperillus*) and acid-fast bacilli. The patient's HIV status was also confirmed as being negative. This work-up failed to identify an infectious etiology for dyspnea.

Bronchoscopy was visually normal. Cytological analysis of bronchoalveolar lavage showed no evidence of malignancy, but showed numerous pulmonary alveolar macrophages. An immunocytochemical stain for cytomegalovirus was also negative. Transbronchial biopsy showed a pattern of diffuse alveolar damage with intra-alveolar fibrinous exudates. Again, special stains of the biopsy specimen failed to reveal an infectious etiology.

Upon presentation, the patient was immediately started on high-dose corticosteroids and empiric broad-spectrum anti-infectives, including azithromycin, piperacillin-tazobactam,

sulfamethoxazole/trimethoprim, vancomycin, tobramycin, and oseltamivir. All anti-infective medications were discontinued as infectious etiologies were ruled out and at the time of discharge, the patient was prescribed with only an oral corticosteroid.

During the first five days of hospitalization, the patient required increasing supplemental oxygen requirements to maintain oxygen saturation above 90%, but did not require endotracheal intubation, mechanical intubation, or bilevel positive airway pressure (BPAP). By hospital day 10, the patient was able to wean off nasal cannula, but still required supplemental oxygen up to 6 L on ambulation. At the time of discharge, the patient's ambulatory oxygen saturation was 84% on room air and 94% with 4 L supplemental oxygen by nasal cannula. The patient was discharged with home oxygen. At six weeks' follow-up after discharge, the patient completed slow steroid taper and no longer required supplemental oxygen. The patient had also noted an increase in his functional status and exercise tolerance. Follow-up imaging at five weeks showed improvement of ground-glass opacities.

## Discussion

Gemcitabine-induced pulmonary toxicity is a diagnosis of exclusion. Infectious etiologies are of significant concern given the immunocompromised status of many patients who are undergoing cytotoxic chemotherapy and must be thoroughly evaluated before a diagnosis of drug toxicity is made. We present both radiographic and microscopic documentation of this toxicity in a patient with pre-existing pulmonary disease with a 50 pack/year smoking history and radiographic evidence of emphysema, but no evidence of pulmonary metastases.

This case illustrates the importance of early detection and treatment of gemcitabine-induced pulmonary toxicity in maintaining the quality of life for patients with pancreatic cancer. As more chemotherapeutic regimens become available for metastatic pancreatic cancer, consideration of alternate chemotherapies may be warranted for patients with significant pulmonary disease. We believe that further investigations into the risk factors for this toxicity will aid clinicians in the preservation of a patient's functional status and maximizing a patient's quality of life.

### Conflicts of Interest

The Authors have no potential conflicts of interest.

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