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A Rare Case of ARDS: Combination of G-CSF and Chemotherapy for Pancreatic Cancer

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Abstract

Herein, we describe a case of acute respiratory distress syndrome (ARDS) during granulocyte colony-stimulating factor (G-CSF) administration after chemotherapy for pancreatic cancer. The patient received gemcitabine + nab-paclitaxel therapy. In one week, antibiotics and G-CSF were administered for febrile neutropenia with pneumonia. After a remarkable increase in neutrophil count, lethal ARDS occurred, and the patient succumbed despite intensive treatment including methylprednisolone administration. Thus, attention should be paid to the emergence of ARDS after the combination of anti-cancer drugs and G-CSF use for pneumonia, even though anti-cancer drugs have a low risk of interstitial pneumonia.

Keywords: ARDS, G-CSF, Chemotherapy

Introduction

Malignancy is the leading cause of death worldwide, and a variety of anti-cancer agents are routinely used. The risk of adverse events is well documented in clinical trials. In particular, interstitial pneumonia is one of the severe adverse events that should be considered including acute respiratory distress syndrome (ARDS). However, ARDS is rarely reported as an adverse event of anticancer agents, and its etiology remains unknown. Some reports have mentioned lung injury caused by mature neutrophils that rapidly proliferate with granulocyte colony-stimulating factor (G-CSF) [1-4]. G-CSF is commonly used for febrile neutropenia which is one of the major adverse events of anti-cancer agents [5]. Severe neutropenia with pneumonia may cause lung injury after the rapid proliferation of neutrophils with G-CSF. In the following case report, we experienced lethal ARDS in pancreatic cancer patient, which occurred after using G-CSF for febrile neutropenia with pneumonia.

Case Report

A 75-year-old man was admitted to our hospital for chemotherapy of pancreatic cancer. Three months prior, he had received 5-Fluorouracail, Folic Acid, Irinotecan, and Oxaliplatin (FOLFIRINOX) therapy, and after 1 month, computerized tomography (CT) showed progressive disease with increased hepatic metastasis and ascites (Figure 1). The patient received gemcitabine + nab-paclitaxel therapy after admission as second-line chemotherapy. On the 7th day, the neutrophil decreased to 319/μl with high fevers. He was diagnosed with febrile neutropenia with mild pneumonia in the lower right lung field (Figure 2), and received meropenem and five consecutive 75 μg doses of G-CSF. The sputum culture grew *Klebsiella pneumoniae* and *Haemophilus parainfluenzae*, which were both sensitive to carbapenems, whereas blood and urine cultures were negative. On the 12th day, the neutrophil count increased to 23881/μl; however, oxygen saturation gradually decreased with slight infiltration of the lung on chest radiography (Figure 3). On the 14th day, the oxygen saturation rapidly decreased to 88% with massive interstitial infiltration (Figure 4). Computed tomography (CT) showed diffuse interstitial infiltration of the lung with bilateral pleural effusions, while pancreatic cancer and hepatic metastasis showed no progression (Figure 5). He was diagnosed with ARDS and administered methylprednisolone (1 g). On the same day, he experienced cardiopulmonary arrest, received mechanical ventilation, and succumbed despite intensive treatment. Consent for pathological analysis and autopsy was not obtained.

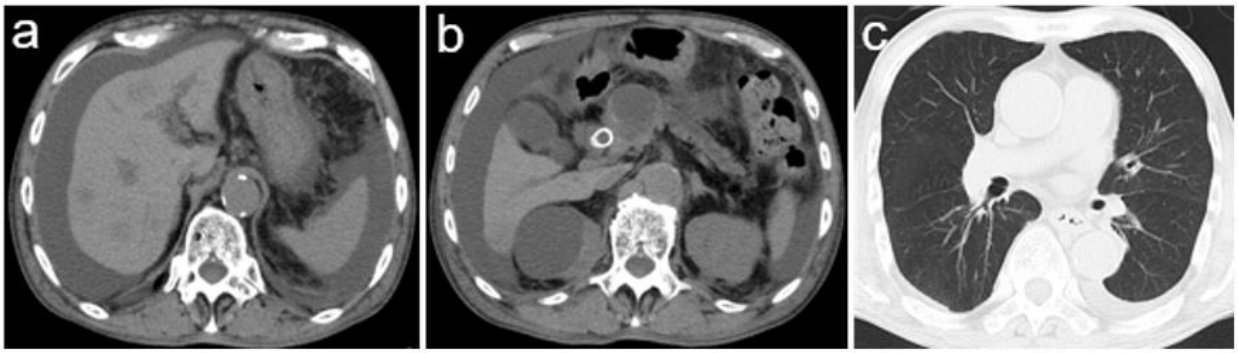

Figure 1: (a) Computed tomography (CT) shows liver metastasis. (b) CT shows pancreatic head cancer. (c) Lung CT scan shows no infiltration

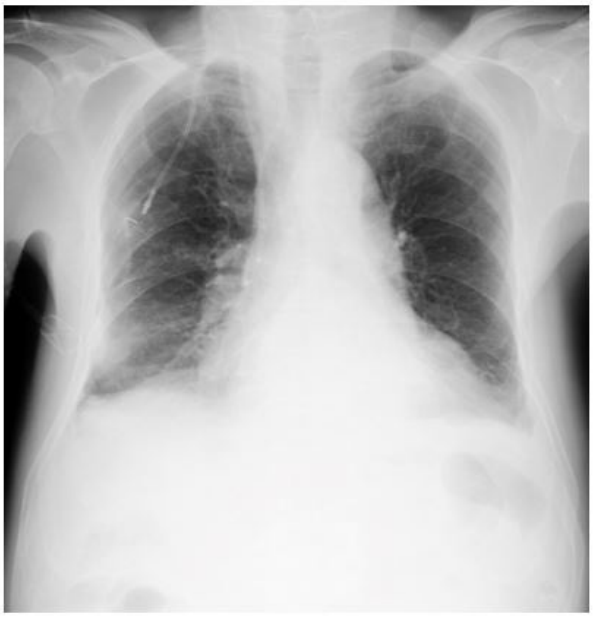

Figure 2: Chest X-ray shows mild consolidation in the right lower lung

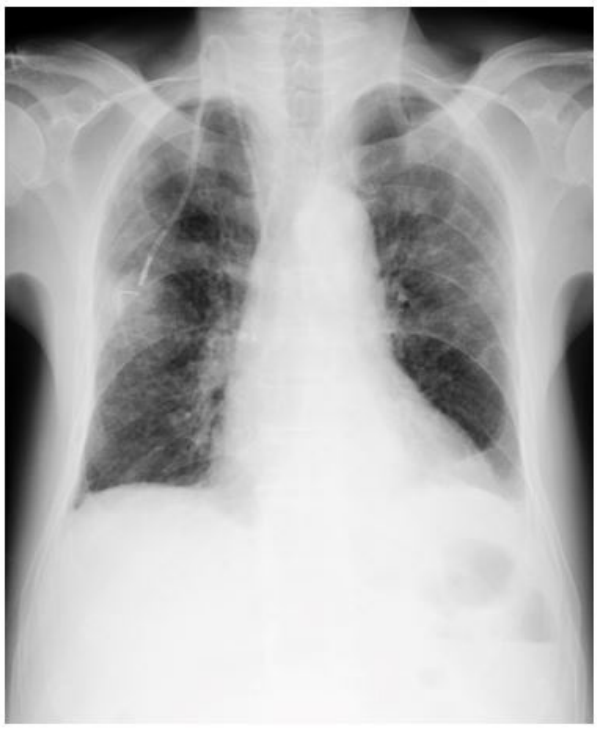

Figure 3: Chest X-ray shows mild infiltrations in both the lungs

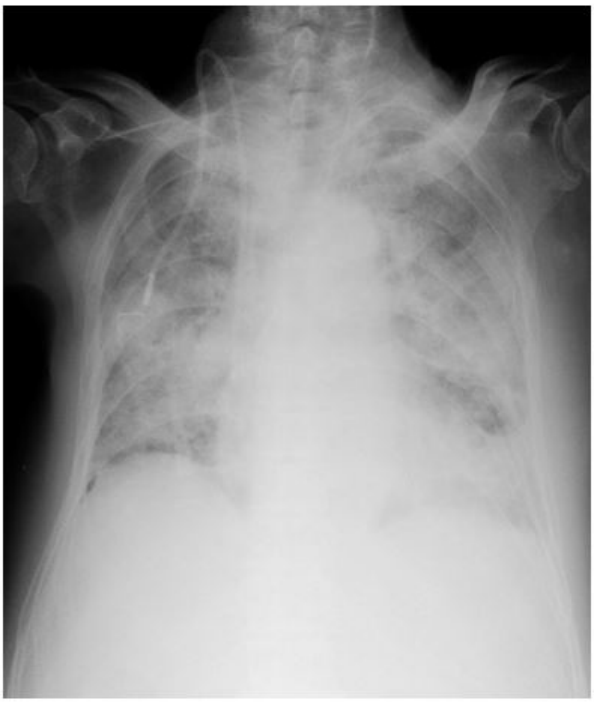

Figure 4: Chest X-ray shows mild infiltrations in both the lungs

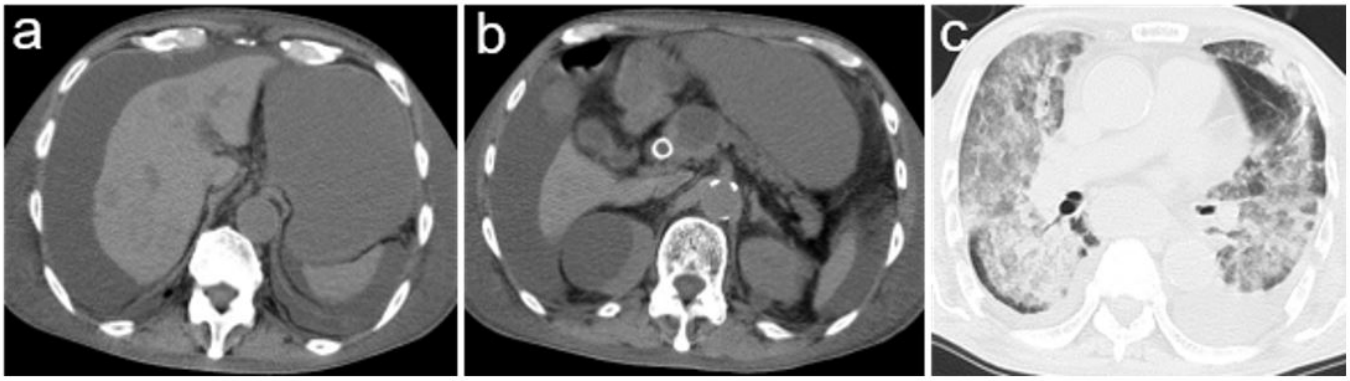

Figure 5: (a) Computed tomography (CT) shows no progression of liver metastasis. (b) CT shows no progression of pancreatic head cancer. (c) CT shows dense infiltrations in both lungs with few pleural effusions

Discussion

We encountered a case of ARDS due to G-CSF administration for febrile neutropenia during chemotherapy for pancreatic cancer. ARDS is an acute respiratory failure that cannot be explained by heart failure, renal failure, or intravascular hyperhydration. The pathology of ARDS shows non-specific hyperinflammation caused by neutrophils in the alveolar region and pulmonary edema due to hyperpermeability of pulmonary microvessels resulting from extensive lung damage [6]. The causes of ARDS include drug-induced lung injury, cancerous lymphangiopathy, pulmonary tumor thrombotic microangiopathy (PTTM), respiratory infection, and exacerbation of interstitial pneumonia. To investigate the cause of ARDS, it is important to consider the clinical course, physical findings, and blood test results including interstitial pneumonia markers and chest radiography or CT scans. In the present case, the patient had no history of interstitial pneumonia. CT showed no interlobular septal thickening or diffuse tree-in-bud opacities, which are characteristic of cancerous lymphangiopathy and PTTM, respectively [7, 8]. Therefore, we considered the cause of ARDS to be a combination of anti-cancer drug-induced lung injury, pneumonia, and G-CSF administration.

Several studies have reported that the use of G-CSF is associated with ARDS. Some reports indicated that ARDS occurs during neutrophil proliferation following G-CSF administration in the presence of lung injury [9-11]. G-CSF leads to the rapid proliferation of mature neutrophils, resulting in the accumulation of neutrophils stimulated by cytokines in the lungs. Activated neutrophils damage the pulmonary vascular endothelium and alveolar epithelium, resulting in ARDS [1-4]. Furthermore, G-CSF alone can cause transient respiratory disturbances in healthy donors undergoing allogeneic peripheral blood progenitor cell transplantation [12].

There are a few reports of ARDS following the use of G-CSF during chemotherapy for lymphoma, leukemia, and breast cancer [13-16]. Especially, bleomycin has a high incidence of interstitial pneumonia (10%) and may increase the risk of lung injury with G-CSF [17]. In patients with hematologic malignancies, the occurrence of pneumonia during neutropenic episodes was reported to be associated with an increase in ARDS after G-CSF administration [11]. To our knowledge, there are no reports of ARDS following the use of G-CSF during chemotherapy for pancreatic cancer. In this case, we used gemcitabine and nab-paclitaxel, the combination of which has a low incidence of interstitial pneumonia (3.0%) [18]. However, a rapid deterioration of oxygenation occurred with the rapid proliferation of neutrophils after G-CSF administration, suggesting that the combination of anti-cancer drugs and G-CSF promoted the development of ARDS. Medications for ARDS include methylprednisolone (30 mg/kg/day) [19] and neutrophil elastase inhibitors [20] in the early phase. In this case, methylprednisolone (1 g/day) was started as steroid pulse therapy immediately after rapid deterioration of the respiratory condition; however, the patient died the same day despite intensive care. Clinicians must be vigilant for ARDS when G-CSF is used during anti-cancer therapy in the presence of lung diseases such as pneumonia.

In summary, a striking case of ARDS during the administration of G-CSF after gemcitabine and nab-paclitaxel therapy for pancreatic cancer was encountered. Even though anti-cancer agents have a low incidence of interstitial pneumonia, the combination of G-CSF use and pneumonia may unexpectedly increase the risk of ARDS, and the clinician should be prepared for sudden deteriorations in oxygenation.

Conflict of Interest

None

References

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