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Case Report

Pleomorphic Carcinoma of the Lung Producing Granulocyte Colony-Stimulating Factor: Report of a Case

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Abstract
We herein report a case of acute respiratory distress syndrome (ARDS) that appeared to be related to a granulocyte colony-stimulating factor (G-CSF)-producing lung cancer. A 77-year-old man with arterial sclerotic obstruction (ASO) underwent reconstructive surgery of the left femoral artery. He developed ARDS on the 5th postoperative day, which resolved following mechanical ventilation with steroid pulse treatment. Four months later, he was admitted with a fever and right arm pain. Chest computed tomography showed a malignant lesion in the right apical lung, and percutaneous needle biopsy demonstrated adenocarcinoma. Laboratory data revealed neutrophilia with elevated serum G-CSF levels. He underwent a right upper lobectomy with chest wall resection, and administration of sivelestat sodium to treat his postoperative pre-acute lung injury state. Pathology revealed a G-CSF-producing pleomorphic carcinoma. Retrospectively, a tumor shadow was noted on chest X-ray at the time of ARDS just after ASO surgery. The relationship between an abnormal G-CSF level and ARDS was considered, and the implications are herein discussed.

Key words Granulocyte colony-stimulating factor · Lung cancer · Pleomorphic carcinoma · Acute respiratory distress syndrome

Introduction

Granulocyte colony-stimulating factor (G-CSF), an inflammatory cytokine that is essential for neutrophil production, has been shown to enhance the functional activity of mature neutrophils in vitro and following systemic administration. Acute respiratory distress syndrome (ARDS), a critical state that results from diffuse alveolar–capillary injury, is often associated with multiorgan failure and a high mortality rate. Although abnormal G-CSF level have been implicated in ARDS, the underlying mechanism has remained unclear. While several cases of ARDS after administration of G-CSF during chemotherapy or hematopoietic stem cell transplantation have been reported,[1] no studies about ARDS associated with G-CSF-producing lung cancer have been published. We herein report a case of G-CSF-producing lung cancer in a patient who had experienced ARDS just before the diagnosis of the lung cancer.

Case Report

A 77-year-old man with a slight fever and right arm pain was referred to our hospital with an abnormal shadow in the right apical lung. Reconstructive surgery of the left femoral artery for arterial sclerotic obstruction (ASO) had been performed 4 months prior to presentation. After ASO surgery he had developed ARDS, from which he recovered following ventilator management with steroid pulse treatment. He was formerly a smoker, but had not smoked for 20 years. Laboratory examinations showed leukocytosis (14 200/mm^3) with neutrophil predominance and no atypical cells, as well as elevated C-reactive protein (CRP; 2.0 mg/dl). Tumor marker levels were within normal limits. Chest X-ray and computed tomography (CT) showed a 40 × 28-mm mass involving the chest wall in the right apical lung. Because transbronchial biopsy revealed no malignancy, the lesion was suspected to be a lung abscess. Despite antibiotic treatment, the fever continued and the mass shadow gradually expanded (Fig. 1C,D). Therefore, a CT-guided percutaneous needle biopsy was performed, which revealed adenocarcinoma. Thereafter, the patient

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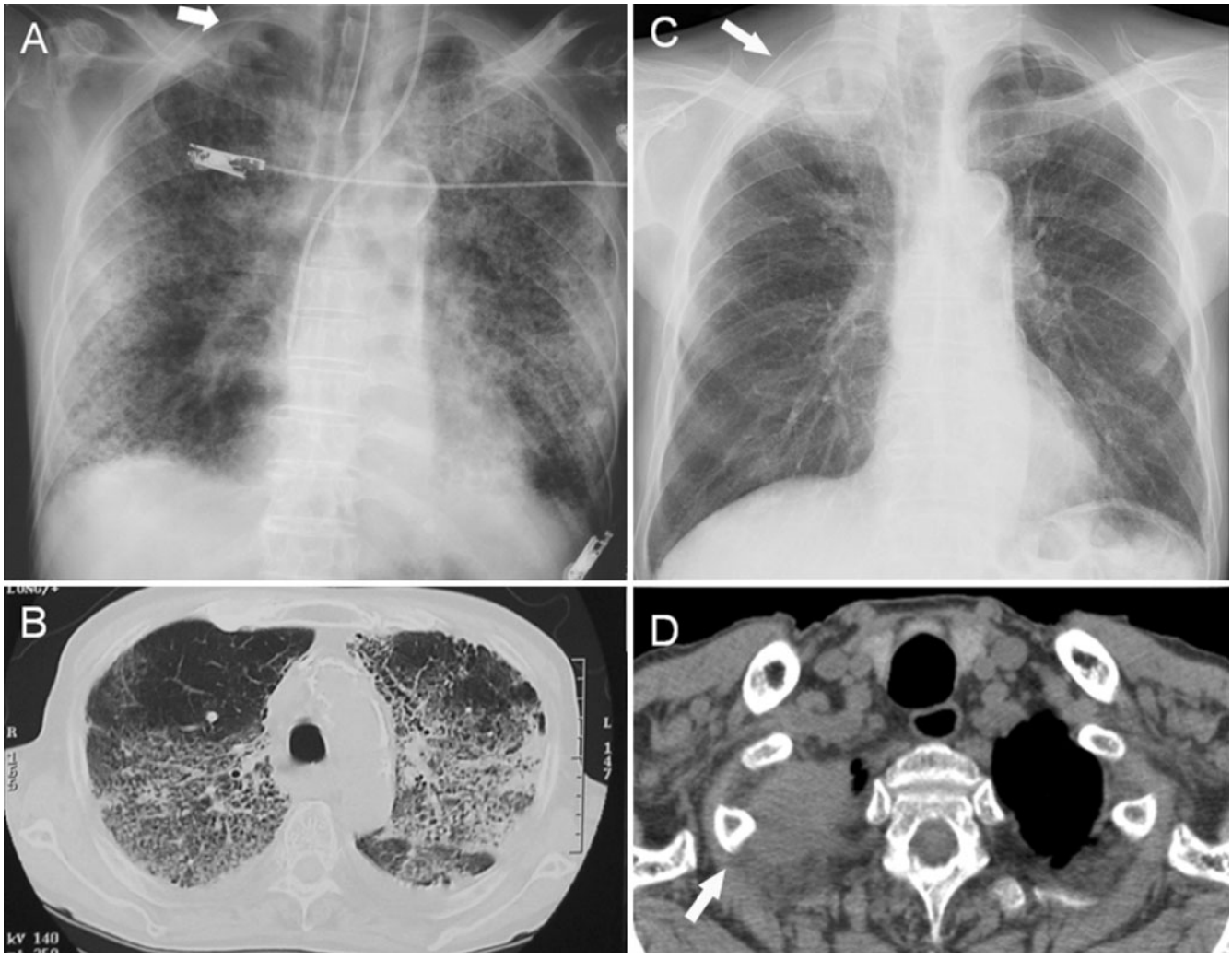

Fig. 1. **A** X-ray showing bilateral diffuse reticular shadows with a nodular shadow in the right apical lung 5 days after vascular reconstruction surgery (*arrow* points to nodule). **B** Computed tomography scan showing a bilateral reticular shadow 5 days after vascular reconstruction surgery. **C** X-ray showing a rapidly expanding tumor in the right apical lung (*arrow*). **D** Computed tomography scan showing involvement of the right second rib (*arrow*)

continued to experience a high fever with elevated white blood cell (WBC) count (37 400/mm^3) and an abnormal G-CSF level (248 pg/ml). These clinical symptoms were hypothesized to be due to the presence of lung cancer, and surgical treatment was therefore indicated.

The patient underwent a right upper lobectomy combined with chest wall resection. The tumor was 62 × 56 × 52 mm in size, and was completely resected. Histologically, the tumor tissue consisted of giant cells, poorly differentiated adenocarcinoma, and squamous cell carcinoma (Fig. 2A–C). Giant cells occupied >10% of the tumor, and immunohistochemical staining results for G-CSF were positive (Fig. 2D). The tumor invaded the parietal pleura but not the rib cage, and lymph nodes were intact. Finally, the tumor was diagnosed as a G-CSF-producing pleomorphic carcinoma without interstitial pneumonia, and was concluded to be pathological stage IIB (T3N0M0). We retrospectively reviewed the chest X-ray and CT image acquired at the time of ARDS. Indeed, a nodular shadow was clearly apparent in the right apical lung in these images (Fig. 1A,B).

On the first postoperative day (POD), sivelestat sodium was administered for the patient's pre-acute injury state, which was noted by radiologic imaging as a diffuse ground-glass shadow in the remnant right lobes. The shadow on the chest X-ray disappeared 8 days later (Fig. 3A,B). The patient's leukocyte count and serum level of G-CSF decreased to normal levels on POD 15. The patient was discharged on POD 33, but unfortunately developed a local recurrence in the chest wall 3 months later. Despite radiation treatment at a total of

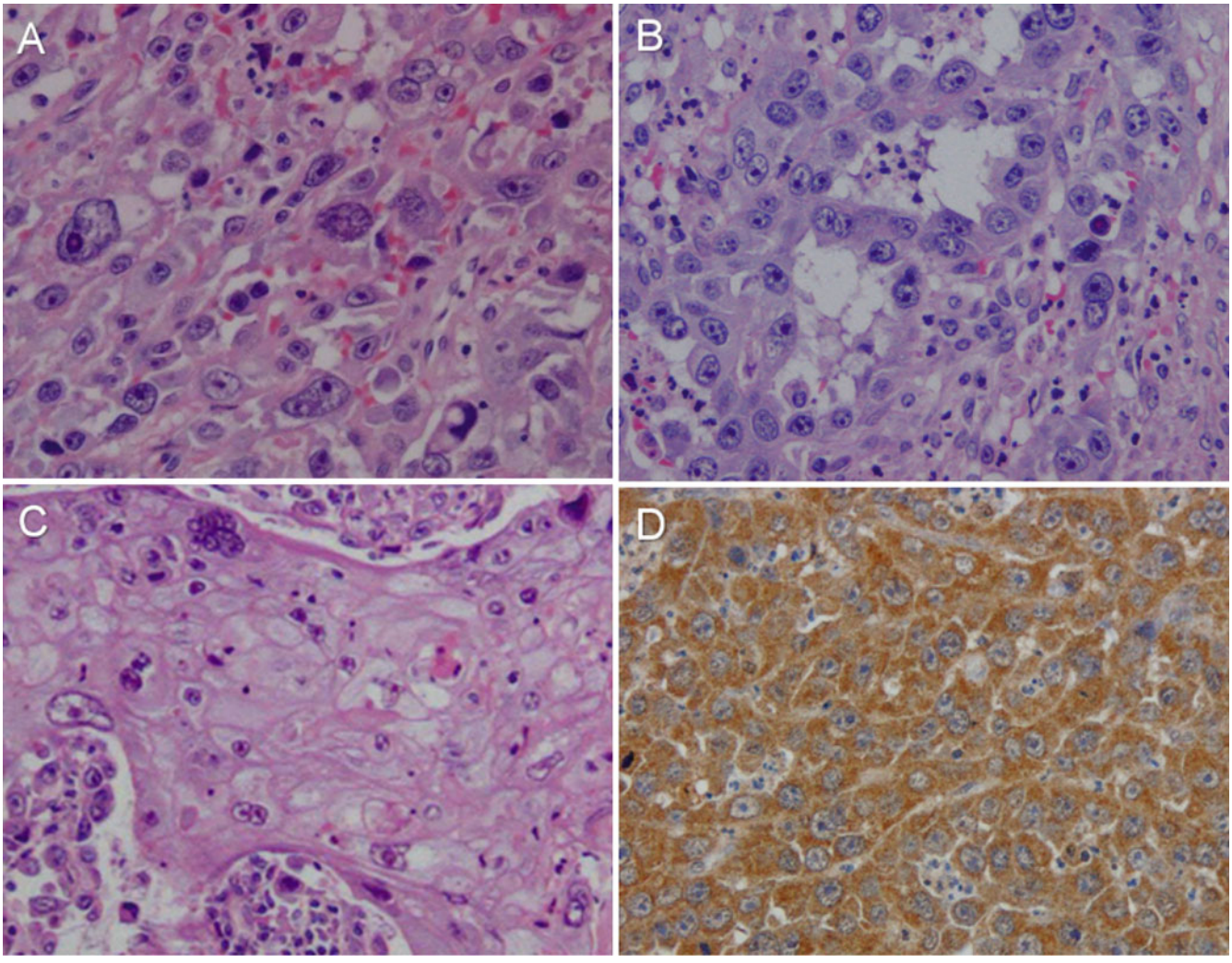

Fig. 2A–D. Histological findings (×400). **A** Giant cells with loose intercellular adhesions. **B** Poorly differentiated adenocarcinoma with vague tubular formation. **C** Squamous cell carcinoma with eddy formation and a little keratinization. **D** Immunohistochemical staining for granulocyte colony-stimulating factor (G-CSF). The poorly differentiated component and few giant cells were positive

60 Gy/30 fractions, he died 9 months after surgery (Fig. 4).

Discussion

Granulocyte colony-stimulating factor-producing tumors, which were first identified in 1977,[2] are defined by the following criteria: (1) extreme leukocytosis, (2) increased serum G-CSF levels, (3) improvement of leukocytosis following tumor resection, and (4) positive G-CSF immunohistochemical staining. The present case fulfilled all of these criteria. These tumors have high malignant potential and a poor prognosis. Pei et al. reported that G-CSF promotes the invasion and metastasis of human lung cancer cell lines.[3] Mizuguchi et al. also reported a 1-year survival rate of 17%, and the median survival time was 5 months.[4] Many cases of G-CSF-producing lung carcinoma were pathologically reported to be diagnosed as giant cell carcinomas. Pleomorphic carcinoma of the lung defined in the 1999 WHO classification[5] partially includes the previous classification of giant cell carcinoma. Therefore, in pleomorphic carcinoma of the lung, there may be a considerable number of cases that were previously classified as giant cell carcinomas.

Granulocyte colony-stimulating factor promotes the proliferation, differentiation, and maturation of progenitors in the neutrophil lineage, and mobilizes hematopoietic stem cells from the bone marrow into the blood. It also activates mature neutrophils, and prolongs their survival.[6] Furthermore, G-CSF is thought to form

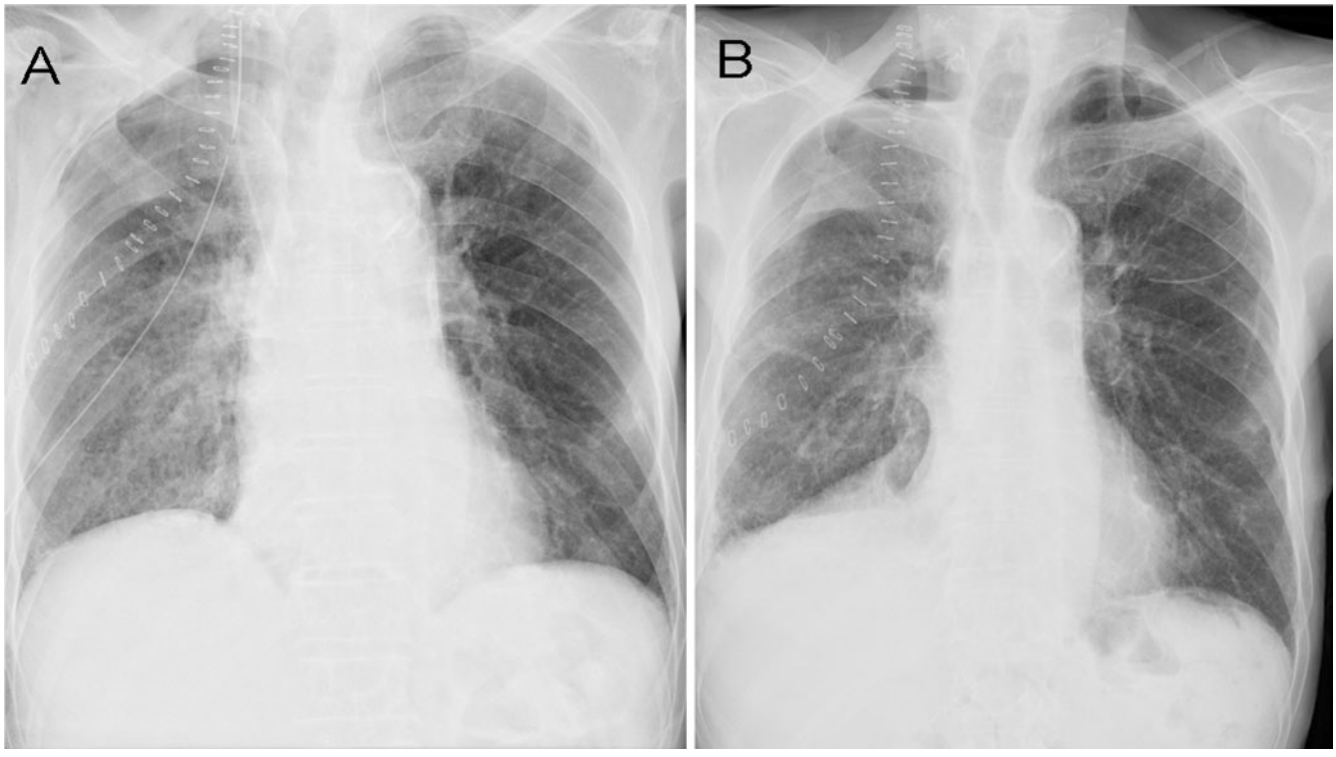

Fig. 3. X-ray showing a diffuse ground-glass shadow in the remnant right lobes on the first postoperative day (**A**) and 8 days later when the shadow had disappeared (**B**)

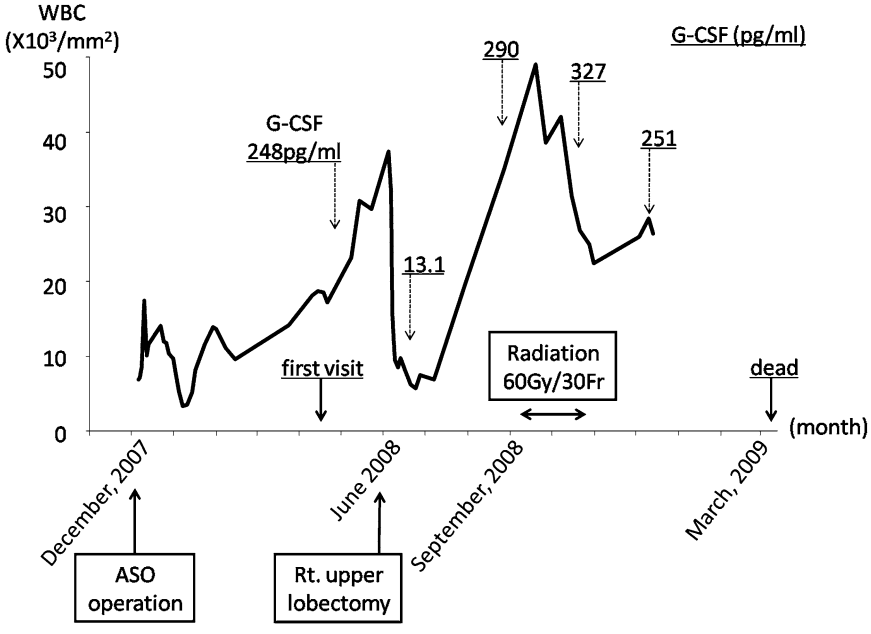

Fig. 4. Clinical course of the patient with perioperative changes in the white blood cell count and serum G-CSF level

a "CSF network" along with granulocyte/macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) that is associated with interleukin (IL)-1 and tumor necrosis factor (TNF) activity in various inflammatory and/or autoimmune conditions.[7]

While the mechanism through which G-CSF induces ARDS remains unclear, ARDS may develop due to a direct pulmonary endothelial disorder via activated neutrophils, and the activation of various cytokines and superoxide. Aggarwal et al. demonstrated that G-CSF and IL-8 levels, which increase the number and infiltra-

tion of leukocytes, were increased in the bronchioloalveolar lavage fluid of ARDS patients. These results suggested that G-CSF and IL-8 are involved in the mechanisms underlying pulmonary neutrophilia in ARDS.[8] Takatsuka et al. reported the clinical features in the onset of ARDS after administration of G-CSF to be fever and an inflammatory response at the time of the WBC nadir, and increased TNF-α and IL-8 levels during ARDS; thus, they concluded that a G-CSF-mediated cytokine storm may be related to the onset of ARDS.[1]

Although G-CSF is associated with inflammatory cytokines, G-CSF alone cannot induce an inflammatory reaction such as fever or CRP elevation. In the present case, a slight fever of unknown origin was observed before ASO surgery, and a high fever was observed just prior to lung cancer surgery, despite the use of a fever reducer; thus, it appears that other inflammatory cytokines may have been produced in addition to G-CSF. In a study that compared postoperative pulmonary function following abdominal aortic surgery versus peripheral vascular surgery, levels of postoperative inflammatory mediators, including G-CSF, were significantly elevated in patients who underwent major vascular surgery as compared to peripheral surgery.[9] We hypothesized that while ASO surgery is not sufficient to induce pulmonary injury, the occurrence of ARDS following neutrophil activation may result from the release of cytokines, including G-CSF, from the pleomorphic lung cancer. Because G-CSF-producing lung cancer may induce ARDS through neutrophil activation, we managed the pre-acute lung injury state occurring at POD 1 by the early administration of sivelestat sodium (Ono Pharma, Osaka, Japan), which is a specific inhibitor of polymorphonuclear elastase used to treat acute lung injury. Special care should be taken during the intensive management for surgical resection of a G-CSF-producing tumor, especially lung cancer, because the tumors are known to be highly aggressive and invasive.

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