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A case of primary lung squamous cell carcinoma mimicking malignant mesothelioma producing granulocyte colony stimulating factor with chemotherapy (cisplatin and gemcitabine)-associated thrombotic thrombocytopenic purpura (TTP); An autopsy case report

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ABSTRACT

Objectives: Thrombotic thrombocytopenic purpura (TTP) is a rare form of thrombotic microangiopathy. In recent years, an extensive variety of drugs, including certain cytotoxic agents, have been reported to be associated with TTP. Additionally, several studies have reported that granulocyte colony-stimulating factor (G-CSF) was produced by lung carcinoma. G-CSF-producing carcinoma also produces various other cytokines, which may cause vascular endothelial damage and trigger TTP development. However, there has been no report describing G-CSF-producing carcinoma combined with TTP. We report a rare case of pseudomesothliomatous squamous cell lung carcinoma producing G-CSF along with chemotherapy associated TTP.

Materials and Methods: A 66-year-old man with pseudomesotheliomatous primary squamous cell lung carcinoma was treated with chemotherapy consisting of cisplatin and gemcitabine as the first line treatment. However, thrombocytopenia, acute renal dysfunction and acute respiratory failure occurred after starting the first chemotherapy cycle. As a result, the patient died, and an autopsy was performed.

Results: According to the autopsy findings, a diagnosis of primary lung squamous cell carcinoma producing G-CSF associated with TTP was made.

Conclusion: Chemotherapy-related TTP should be considered when anemia and thrombocytopenia progress rapidly in patients who are under chemotherapy treatment. Furthermore, the current case may provide a possible link between TTP and G-CSF-producing tumor.

1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare form of thrombotic microangiopathy, characterized by the classic pentad of haemolytic anemia, thrombocytopenia, fever, renal impairment, and neurological complications. Early identification of TTP is essential for instituting early treatment and improving survival. An extensive variety of drugs, including certain cytotoxic agents, have been reported to be associated with TTP [1].

Pseudomesotheliomatous carcinoma is a malignant tumor that extends along the pleura, similar to malignant mesothelioma. Almost all cases originate from lung cancer, particularly adenocarcinoma [2]. There have been few reports of squamous cell-type pseudomesotheliomatous carcinoma that were evaluated by autopsy.

TTP induced by a combined chemotherapy of cisplatin and gemcitabine for primary squamous cell lung carcinoma has not previously been described. We herein report a case of pseudomesothliomatous squamous cell lung carcinoma producing granulocyte colony

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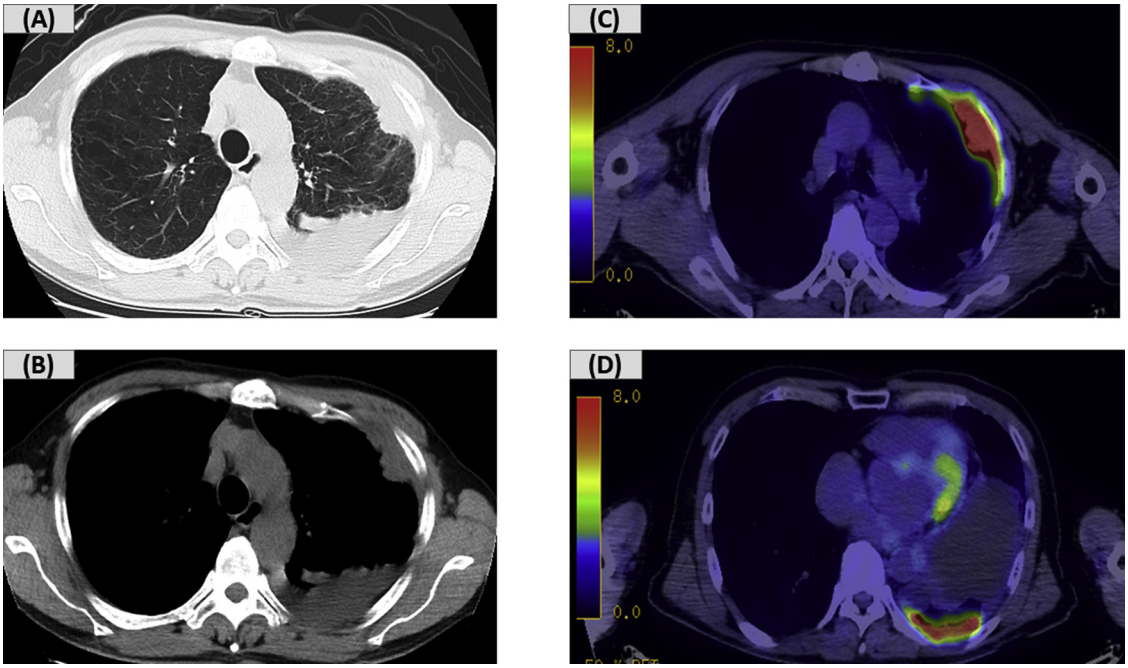

Fig. 1. Chest CT scans and trans-axial PET-CT images.
(A–B) Chest CT showed pleural effusion and pleural thickening on the left side, but there were no nodules in the lungs. (C–D) PET-CT revealed high 18-FDG accumulation in the thickened pleura. CT, computed tomography. PET-CT, positron emission tomography-computed tomography. FDG, fluorodeoxyglucose.

stimulating factor (G-CSF) along with chemotherapy (cisplatin and gemcitabine)-associated TTP. The current report calls attention to TTP following chemotherapy

2. Case description

A 66-year-old man complaining dyspnea over the previous 3 months was referred to our outpatient clinic for treatment. He had a past history of smoking with 66 pack-years. There was no known history of allergy, respiratory disorders or asbestos exposure. Computed-tomography (CT) scanning of the thorax revealed pleural effusion and pleural thickening on the left side, but there were no nodules in the lungs with emphysematous background (Fig. 1A-B). Positron emission tomography (PET)-CT demonstrated high 18-fluorodeoxyglucose (18-FDG) accumulation in the thickened pleura (Fig. 1C-D).

A CT-guided percutaneous needle biopsy was performed on the thickened pleura. Histopathological and immunohistochemical (IHC) staining demonstrated squamous cell carcinoma with carcinomatous pleuritis.

The patient received systemic chemotherapy, consisting of cisplatin (80 mg/m^2, day 1) and gemcitabine (1000 mg/m^2, day 1 and day 8) as the first line treatment. However, serious adverse events occurred 2 weeks after starting the first chemotherapy cycle.

The blood platelet count decreased dramatically from a baseline of 25.4×10^4/μL to 2.2×10^4/μL. The white blood cell count and hemoglobin level also slightly decreased. Since these were primarily the result of myelosuppression due to chemotherapy, a 20-unit platelet transfusion was performed. Nevertheless, thrombocytopenia was not sufficiently recovered; furthermore, acute renal dysfunction and acute respiratory failure occurred 2 days after platelet transfusion. The patient was then transferred to our hospital to receive intensive treatment.

Physical examination showed a moderate brain injury with a score 11 on the Glasgow Coma Scale (E4V2M5), and low blood pressure. Laboratory findings on admission revealed microangiopathic hemolytic anemia with schistocytes on peripheral blood smear. On the basis of his clinical course and laboratory findings, we suspected TTP. We did not perform platelet transfusion again, and examined a disintegrin and metalloprotease with thrombospondin type I motif, member 13 (ADAMTS13) activity and the anti-ADAMTS 13 autoantibody level. As a result, the patient's ADAMTS13 was 26% (reference range, 70–120%), and his anti-ADAMTS 13 autoantibody level was < 0.5 Bethesda units/mL. Therefore, we eventually diagnosed the patient as having TTP according to the symptoms of thrombocytopenia, microangiopathic hemolytic anemia, neurological abnormalities, renal dysfunction, and a decreased level of ADAMTS13. Additionally, since his white blood cell count increased steeply from 12,400 /μl to 39,200 /μl within a week after admission to our hospital, lung tumor was suspected of producing G-CSF. We measured serum G-CSF and found it to be elevated at 210 pg/ml.

Unfortunately, the patient's general condition deteriorated with the progression of respiratory dysfunction, thrombocytopenia, and anemia. He died on day 26 after admission. An autopsy was performed after securing his family's permission.

3. Autopsy and pathological findings

The whole left lung showed severe adhesion to the left pleural cavity, and the left parietal pleura was thickened overall. The tumor directly invaded the left dorsal side of the first to twelfth rib and diaphragm (Fig. 2A). There were metastases at the pericardium and hilar lymph nodes. Tumor cells were characterized by the sheets of cells with a central comedo-type pattern of necrosis and well-formed intercellular bridges. Immunohistochemically, the tumor cells were positive for p40, and negative for calretinin and TTF-1 (Fig. 2B-E). Furthermore, immunohistochemical staining with specific monoclonal antibodies against G-CSF was positive (Fig. 2F).

The patient did not have a history of chronic inflammation caused by pleural empyema, pilonidal sinuses or fistulae over the previous 10 years, and squamous metaplasia with atypia were diffusely seen in the emphysema under the pleura. From these findings, we speculate that the tumor did not occur in the pleura but the lung.

Finally, we made a diagnosis of a primary lung squamous cell carcinoma producing G-CSF. On the other hand, multiple microvascular thrombus were observed in the micro capillaries of the heart and

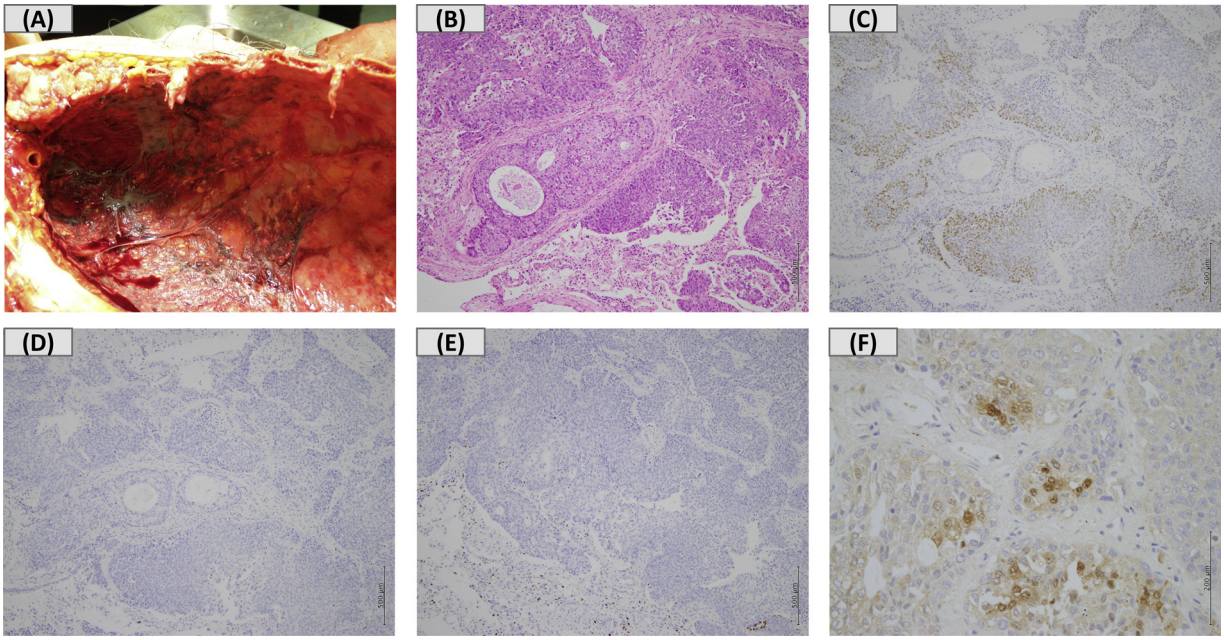

Fig. 2. Histological and immunohistochemical findings obtained from pleural tumor in the autopsy.
(A) Macroscopic appearance of the whole left lung showed severe adhesion to the left pleural cavity and the tumor directly invaded the left dorsal side of the first to twelfth rib and diaphragm. (B) Microscopic evaluation following hematoxylin-eosin staining of the tumor tissue revealed squamous cell carcinoma. (C) IHC examination revealed p40 expression for the pleural tumor. (D) IHC examination revealed negative calretinin expression. (E) IHC examination revealed negative TTF-1 expression; (F) IHC examination revealed granulocyte colony stimulating factor expression. IHC, immunohistochemical.

kidney. These thrombus were positive for CD42b, and phosphotungstic acid hematoxylin stain was not detected. These findings suggest that the thrombus consisted of platelets, which were compatible with TTP.

4. Discussion

To the best of our knowledge, there has been no report describing G-CSF-producing carcinoma combined with TTP. G-CSF influences the proliferation of endothelial cells and induces cytokines involved in vascularization of endothelial cells [3]. G-CSF-producing carcinoma also produces various other cytokines [4], which may cause vascular endothelial damage and trigger TTP development. Particularly, interleukin-1 (IL-1) is a key element for the regulation of G-CSF production [5], and angiogenesis [4]. Furthermore, hemolytic uremic syndrome (HUS) is a kind of thrombotic microangiopathy (TMA) that is caused by a verocytotoxin-1 (VT-1) producing *Escherichia coli* strain 157 infection. Since IL-1, in vitro, is associated with the synthesis of the VT-1 receptor [6], it may play an important role in the pathogenesis of HUS. Similarly, IL-1 may affect the pathogenesis of TTP. Although we measured serum IL-1β in the present case, it was not elevated (IL-1β; < 10 ng/ml). Further investigations are needed to elucidate the relationship between G-CSF-producing carcinoma and TTP.

TTP, one of the typical phenotypes of TMA, is characterized by the classic pentad, as previously described. TTP cases are divided into either hereditary cases or acquired cases, the latter of which are caused by drugs, infection, autoimmune disorders, post-hematopoietic stem cell transplantation, malignancy, or pregnancy [7]. In the current case, we did not evaluate ADAMTS13 gene mutation for the patient, but hereditary TTP was unlikely because he had no past medical history or family history that indicated TTP. Furthermore, there were no manifestations associated with infection, such as diarrhea before the onset of TTP. Thus, considering the background of the patient, as well as the clinical course of onset after chemotherapy, we diagnosed him as having chemotherapy-associated TTP. TTP associated with chemotherapy is a rare but serious complication [8].

Although the mechanism of chemotherapy-associated TTP has not yet been fully elucidated, two key pathogenesis may be considered for endothelial cell injury. The first possible mechanism is immunological disorder, in which immune complexes induced by chemotherapeutic agents contribute to endothelial cell injury. Synder et al. reported that prognosis of chemotherapy-associated TTP improved when serum immune complexes, complements C3 and C4, were normalized by treatment with extracorporeal immunoadsorption therapy [9]. This finding suggests that immune complexes are both direct and indirect components of endothelial injury in chemotherapy-associated TTP. Since the occurrence of TTP in this mechanism is independent of chemotherapeutic agent-dose, TTP can occur at an early phase of chemotherapy. The second possible mechanism is direct chemotherapy-induced endothelial cell toxicity, which is caused by decreased tissue plasminogen activator and increased plasminogen activator inhibitor, resulting in thrombotic microangiopathy [10]. Regarding gemcitabine-associated TTP, the mechanism has been previously reported by Zupancic M. et al. According to their study, endothelial cell injury is involved in and gemcitabine dose is related to the mechanism [8]. Further study is needed to investigate whether the patient's genetic predisposition may cause a chemotherapy-associated TTP or not.

In the present case, primary lung squamous cell carcinoma closely resembles a malignant pleural mesothelioma. Attanoos et al. reported that pseudomesotheliomatous carcinoma constitutes approximately 6% of all pleural malignancies [2]. In their study, 53 pseudomesotheliomatous carcinoma cases were evaluated. Adenocarcinoma was the most frequent subtype among primary lung cancers (34 of 47 cases), and squamous cell carcinomas were only detected in four cases. Since it is difficult to differentiate between pseudomesotheliomatous squamous cell carcinoma and malignant mesothelioma from the viewpoint of radiological findings, pathological examination using immunostaining is especially important.

In conclusion, we here described a case of pseudomesotheliomatous lung squamous cell carcinoma producing G-CSF accompanied by chemotherapy-associated TTP. Autopsy revealed that G-CSF-producing carcinoma cells had spread to the overall left parietal pleura. We should pay particular attention to chemotherapy-related TTP, even in the early

phase of chemotherapy, because chemotherapy against G-CSF-producing carcinoma may trigger TTP development. In the future, it is necessary to accumulate cases such as that in the present report, in order to determine the relationship between G-CSF and TTP.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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