Progressive Diffuse Pulmonary Interstitial Opacities due to Complications of Pulmonary Tumor Emboli: An Autopsy Case Report

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Abstract

A 76-year-old man complaining of exertional dyspnea was admitted to our hospital. Chest computed tomography revealed bilateral diffuse ground-glass opacities and small nodules. A transbronchial lung biopsy revealed tumor cell emboli in the pulmonary arteries. The patient was diagnosed with gastric adenocarcinoma using an endoscopic stomach biopsy; however, the interstitial opacities progressively worsened and he died of acute respiratory failure. An autopsy revealed extensive pulmonary tumor embolisms (PTE) with associated ischemic damages, e.g., infarctions, alveolar wall thickening with cuboidal metaplasia, hemorrhage, and diffuse alveolar damage. The ground-glass opacities in the chest computed tomography findings appear to correlate with the pathological ischemic changes associated with PTE.

Key words: diffuse interstitial opacities, pulmonary tumor embolism, pulmonary infarction

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Introduction

Pulmonary tumor embolism (PTE) is a classic manifestation of cancer metastasis to the lung. The occlusion of pulmonary microvasculature by tumor cells accompanied by thrombi typically produces a subacute and progressive clinical presentation resembling thromboembolic disease (1). Although pulmonary infarction and hemorrhaging are typical pathological findings associated with PTE (2), a correlation between the pathological findings and the radiological findings remains to be determined.

We herein report the case of a 76-year-old man presenting with bilateral ground glass opacities (GGO) resembling interstitial pneumonia on chest computed tomography (CT). On the autopsy, GGO appeared to be related to hemorrhaging, interstitial pneumonia-like lesions, and diffuse alveolar damage (DAD). Thus, based on the autopsy, we posthumously diagnosed the patient with PTE.

Case Report

A 76-year-old man presented to a local clinic with a dry cough and exertional dyspnea. Because his symptoms were refractory and progressively worsened over the course of a month, he was admitted to our hospital for further examination. His body weight had decreased by 10 kg over the previous 3 months. The physical examination on admission revealed no significant abnormalities, and the superficial lymph nodes were not palpable. Laboratory tests revealed anemia and coagulation abnormalities (hemoglobin concentration, 12.2 g/dL; prothrombin time-international normalized ratio, 1.36; activated partial thromboplastin time, 35.9 s; and fibrinogen level, 697 mg/dL). The level of surfactant protein-D (SP-D) was elevated (151.1 ng/mL), whereas the level of Krebs von den Lungen-6 (KL-6) was within the normal range. The laboratory tests also indicated elevated levels of C-reactive protein (4.7 mg/dL) and carcinoembry-

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Figure 1. Radiological findings on admission. (a) A chest X-ray showed bilateral ground-glass opacities. (b) Chest computed tomography showed small nodules and linear opacities around and inside the areas of ground-glass opacity which were predominantly located in the peripheral lung field and spared the subpleural space.

onic antigen (6.8 ng/mL). Moreover, we did not observe any immunological abnormalities, such as aberrant leukocyte counts, unusual immunoglobulin or complement levels, or autoantibodies. A blood gas analysis in the atmosphere of room air revealed hypoxia (pH, 7.44; PaO₂, 66.2 Torr; PaCO₂, 36.7 Torr).

A chest X-ray showed bilateral GGO, and a chest CT demonstrated small nodules and linear opacities around and inside GGO which were predominantly located in the peripheral lung field and spared the subpleural space (Fig. 1). A sputum culture was negative for bacteria, and no abnormal findings were detected on the sputum cytology. Based on the radiological findings, we initially considered diffuse alveolar hemorrhage or eosinophilic pneumonia as the provisional diagnosis; however, these were excluded due to the absence of hemosiderin-laden macrophages and eosinophils in the bronchoalveolar lavage fluid. A transbronchial lung biopsy (TBLB) specimen from right B¹ demonstrated marked alveolar wall thickening with cuboidal metaplasia (Fig. 2a, b). Accordingly, we tentatively diagnosed the patient with interstitial pneumonia of unknown cause. We started the patient on oral prednisolone (30 mg/day) for the hypoxia symptoms. However, the second CT examination on day 26 of admission showed deterioration of the abnormal shadows (Fig. 3). GGO and linear opacities had extended, and new cavitory nodular lesions were seen. Thus, we suspected a secondary fungal infection and discontinued prednisolone therapy.

BFS was repeated to obtain sufficient material to confirm the pathological diagnosis. The histopathological examination of the specimens from the second TBLB from right B⁵ and B⁸ demonstrated microemboli composed of cancer cells inside the pulmonary artery branches; this problem was also

accompanied by mild alveolar wall thickening in the surrounding lung (Fig. 2c, d). During the histopathological examination, no obvious intraluminal hemorrhaging was detected in either the first or second TBLB specimens. Gastrointestinal endoscopy was performed to elucidate the primary adenocarcinoma site. Converging folds were detected endoscopically, and a stomach biopsy confirmed gastric adenocarcinoma (Fig. 4a). Thus, we diagnosed the patient with PTE originating from gastric adenocarcinoma. A right heart catheterization excluded pulmonary hypertension (mean pulmonary arterial pressure was 21 mmHg).

Shortly after the diagnosis of PTE, the patient suffered from acute onset respiratory failure and his symptoms rapidly deteriorated. A third CT examination on day 39 of admission showed an extension of non-segmental GGO accompanied by multiple cavitory lesions (Fig. 3). The patient died on day 40 of admission due to a worsening of his respiratory failure.

An autopsy examination identified the primary diagnosis as advanced gastric adenocarcinoma located on the lesser curvature of the upper body (Fig. 4b). Concomitant multiple metastases were present in the liver, lungs, and lymph nodes. We also performed a detailed evaluation of the pulmonary lesions associated with PTE. Three different types of pulmonary metastasis were detected, including massive tumor emboli with organized thrombi obstructing muscular pulmonary arteries and arterioles, tiny hematogenous metastatic nodules, and lymphogenous spread.

Gross and microscopic changes associated with massive tumor emboli were present as various stages of whitish anemic infarctions and small yellowish infarctions (Fig. 5a, b). Several interstitial pneumonia-like lesions of up to one lobule in size were histologically observed. In general, these lesions were adjacent to the infarction sites and were composed of edematous/myxomatous or fibrous thickening of the alveolar wall (Fig. 6a, b), slight infiltration by inflammatory cells, cuboidal metaplasia (Fig. 6c), and centered capillaries (Fig. 6d). In addition to cord-like and nodular fibrosis (Fig. 5a, b), an alveolar wall hemorrhage (Fig. 5d), a focal intraluminal hemorrhage with hemosiderosis, diffuse alveolar damage (DAD; Fig. 4c), and cavitory lesions (Fig. 5c) were noted. Most cavitory walls were composed of infarction accompanied by bacterial and fungal infections; the fungal infection typically involved *Aspergillus* spp.

Therefore, the autopsy findings appeared to correlate with the CT findings. The bilateral diffuse GGO on admission was assumed to correspond to the interstitial pneumonia-like lesions. The nodular lesions and linear opacities on admission may represent the organized infarction and cord-like fibrosis. Therefore, cavitory lesions may represent the necrosis related to bacterial and fungal infections and the infarctions due to tumor emboli. Furthermore, the terminal extension of the non-segmental GGO appeared to reflect mainly DAD.

Figure 2. Results of the transbronchial lung biopsy (TBLB). (a) A low magnification view of the alveolar wall thickening [Elastic van Gieson staining (EvG), 4× magnification]. (b) A high magnification view of the alveolar-wall thickening with cuboidal cell metaplasia [Hematoxylin and Eosin (H&E) staining, 20× magnification]. (c) A low magnification view of tumor emboli and a forming thrombus in the muscular pulmonary artery (EvG, 4× magnification). (d) A high magnification view of micro-emboli composed of cancer cells in the pulmonary artery (H&E staining, 20× magnification).

Figure 3. The clinical course. Chest computed tomography showed deterioration of the abnormal shadows.

Figure 4. Gross pathological and microscopic findings of the stomach and lung. (a) The stomach biopsy showed adenocarcinoma [Hematoxylin and Eosin (H&E) staining, 10× magnification]. (b) Gastric cancer was seen in the lesser curvature of the upper body at autopsy. (c) Hyaline membrane (arrows), which is a representative finding in diffuse alveolar damage (DAD), and tumor emboli on the alveolar wall during autopsy is shown (H&E staining, 10× magnification).

Figure 5. Gross pathological and microscopic findings of the lung at autopsy. The cut surface of the lung showed (a) a pulmonary infarction (arrowhead) and linear fibrosis (arrows) in diffuse consolidation, (b) a yellowish infarction (arrowheads) and linear fibrosis (arrow) in diffuse consolidation, and (c) cavitation. (d) Microscopic findings showed an alveolar wall hemorrhage (between arrows) (H&E staining, 40× magnification).

Figure 6. Lung microscopy at autopsy: a lobular interstitial pneumonia-like lesion. (a) A panoramic view of a lobule-sized lesion in the center [Hematoxylin and Eosin (H&E) staining]. (b) Edematous/myxomatous thickening of the alveolar wall with cuboidal metaplasia is shown (H&E staining, 20× magnification). (c) Diffuse cuboidal cell metaplasia by immunostaining using pan-keratin is shown (keratin, 20× magnification). (d) Alveolar capillaries located in the center of the alveolar wall without attachment to the surface of the alveolar wall is shown (immunostaining for CD34, 20× magnification).

Discussion

In the present case of advanced gastric cancer with PTE, the pathological findings (acute ischemic lung damages due to PTE) correlated with the radiological findings (diffuse interstitial opacities on CT). PTE is associated with a coagulation abnormality related to cancer progression and is generally diagnosed on post-mortem examination (3, 4). PTE mainly involves muscular arteries and causes intimal fibrosis (5, 6). Pulmonary infarction and hemorrhaging are caused by insufficient pulmonary arterial blood flow resulting from thromboembolism and tumor cell emboli (3, 7, 8).

In the present case, various pathological findings were observed in addition to infarction and focal hemorrhaging, including alveolar wall hemorrhages, linear/nodular fibrosis, and interstitial pneumonia-like lesions. Moreover, an alveolar wall hemorrhage was seen in association with pulmonary infarction, and cord-like and nodular fibrosis were frequently connected to the infarction walls. These characteristic findings can be attributed to ischemia due to insufficient pulmonary arterial blood flow associated with PTE.

Intriguingly, consistent with the findings of the initial TBLB samples, interstitial pneumonia-like lesions were

lobule-sized and showed edematous or fibrous thickening with scanty inflammatory cells and separation between the epithelial and endothelial basement membranes. We have previously reported the association between this type of basement membrane separation in the alveolar wall and pulmonary infarction caused by lung tumors (9). These findings differ from non-specific interstitial pneumonia, which is usually diffuse and accompanied by moderate-to-severe inflammatory cell infiltration of the alveolar wall with luminal organization (10, 11). Therefore, the interstitial pneumonia-like lobule-sized lesions that were observed in the present case may represent the pathological changes reflecting tissue ischemia, but they are not associated with primary inflammatory reaction (i.e., idiopathic, collagen vascular disease, and drug induced). Furthermore, the ineffectiveness of the steroid treatment may support the notion of non-inflammatory nature of interstitial pneumonia-like lesions.

DAD pattern is a known complication of pulmonary infarction (12). A previous report examining 318 autopsied cases from patients who died of various cancers (excluding lung cancer) revealed that four of the 12 PTE patients presented DAD pattern during the lung examination (13). Furthermore, in our study involving patients with DAD pattern associated with subclinical idiopathic pulmonary fibrosis,

approximately 10% patients had pulmonary thromboemboli and disseminated intravascular coagulation (14) indicating that widespread PTE is a possible risk factor of DAD in the present case. In addition, we speculate that severe fungal and bacterial infection of cavitary nodular lesions is also involved in the mechanism of DAD development. These infections may therefore be attributed to the patient's weakened immune system due to steroid treatment and/or cancer progression.

In conclusion, we herein reported on the pathological-radiological correlation between the autopsy findings of acute ischemic lung damage due to PTE and pulmonary interstitial opacities on CT in a case of advanced gastric cancer. Clinicians should consider acute ischemic lung damage as a differential diagnosis of steroid-refractory progressive interstitial opacities, especially in cases with malignant tumors.

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

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