Case Report

Primary pulmonary combined scar carcinoma composed of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma: An autopsy case and literature review

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Abstract

Primary pulmonary scar carcinoma with triplicate differentiation is very rare. A 66-year-old woman presented with cough, and consulted to a private hospital, where she was pointed out to have abnormal lung shadow by chest X-P. She was admitted to our hospital for scrutiny. Imaging modalities including chest X-P, CT, and MRI revealed a main tumor (35 mm in diameter) in the right lower lobe and multiple small metastases in both lungs. Biopsies and cytology revealed an adenocarcinoma. Metastasis to the liver, iliac bone and tibia bone were also detected. She was diagnosed as stage IV lung adenocarcinoma (T2N3M1), and received chemotherapy. Soon, she complained of right hemiparesis, and brain CT revealed multiple brain metastases. She died of respiratory failure due to bronchopneumonia 7 months after admission. An autopsy revealed a lung tumor (4 × 4 × 3 cm) in the right lower lobe. Miliary micro-metastases were recognized in bilateral lungs, brain, bones, pleura, liver, brain, and systemic lymph nodes. The lungs showed bronchopneumonia. The liver was cirrhotic. Microscopically, the primary lung tumor consisted of adenocarcinoma element (70% in area), squamous cell carcinoma element (20%), and small cell carcinoma element (10%), all of which were embedded in a fibroelastic scar with calcification (scar carcinoma). There were gradual merges between the adenocarcinoma and squamous cell carcinoma elements, but the small cell carcinoma element was isolated. The liver metastases were composed only of small cell carcinoma, and other metastatic sites consisted of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. Other pathologic changes included pulmonary aspergillosis, bronchopneumonia, splenomegaly, emphysema, cardiac hypertrophy, and kidney congestion. The present case shows that a lung scar carcinoma can display triplicate differentiations.

1. Introduction

Primary lung cancer may develop in a scar. Such cancer has been called by scar cancer. It is characterized by fibroelastic scar, deposition of ducts, and peripheral localization with pleural puckering.1–5 The scar is formed by atherectasis, infarction, tuberculosis, anthracosis, and other exogenous agents. Almost all of scar cancers are adenocarcinomas. However, pulmonary scar cancers with multiple histological components have rarely reported, to the best of the author’s knowledge.

Combined pulmonary combined carcinomas consisting of more than two histological types have been reported. A review of English literature revealed 17 case studies of combined lung cancers.6–22 However, there have been no cases of combined scar carcinoma of the lung in the literature. Here, the author reports a case of primary pulmonary combined scar carcinoma composed of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma elements.

1.1. Case report

A 66-year-old woman complained of cough, and consulted to a private hospital, where she was found to have abnormal lung shadow by chest X-P. She was admitted to our hospital for scrutiny. Imaging modalities including chest X-P, CT, and MRI revealed a main tumor (35 mm in diameter) in the right lower lobe and multiple small metastasis in both lungs. Biopsies and cytology revealed an adenocarcinoma. Metastasis to the liver, iliac bone and tibia bone were also detected. She was diagnosed as stage IV lung adenocarcinoma (T2N3M1), and was treated by chemotherapy.

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Later, she complained of right hemiparesis, and brain CT revealed multiple brain metastases. She died of respiratory failure due to bronchopneumonia 7 months after admission.

An autopsy revealed a lung tumor (4 × 4 × 3 cm) in the right lower lobe (Fig. 1). The lung tumor was hard, and was heavily pigmented. The tumor involved the pleura with pleural indention. Miliary micrometastases up to 5 mm were recognized in bilateral lungs, brain, bones, pleura, liver, brain, and systemic lymph nodes. The lungs showed emphysema, bronchopneumonia, and mucin impaction. The liver was cirrhotic.

Microscopically, the primary lung tumor consisted of adenocarcinoma (Fig. 2) (70% in area), squamous cell carcinoma (Fig. 3) (20%), and small cell carcinoma elements (Fig. 4) (10%), all of which were embedded in a scar with calcification (“scar carcinoma”) (Fig. 5). The scar area contained many elastic fibers, collagen fibers, heavy duct deposition, foci of calcification, and pleural involvement (Fig. 5). There were gradual merges between the adenocarcinoma and squamous cell carcinoma elements (Fig. 6) in the lung carcinoma. However, the small cell carcinoma element was isolated, and there were no transitions between the small cell carcinoma element and the other two elements. The liver metastases were composed only of small cell carcinoma (Fig. 7). The other metastatic sites (lungs, brain, bones, pleura, liver, brain, and lymph nodes) consisted of adenocarcinoma, squamous cell carcinoma, and small cell carcinoma (Figs. 8 and 9). In these metastatic sites other than the liver, the adenocarcinoma element was closely associated with squamous cell carcinoma elements; gradual merges were noted between the two. In contrast, small cell carcinoma element in the metastatic sites was isolated, and there were no associations with the adenocarcinoma and squamous cell carcinoma elements.

An immunohistochemical study was performed with the use of Dako Envision method (Dako, Glostrup, Denmark), as described previously. The antibodies examined and the results are shown in Table 1. The adenocarcinoma element was positive for pan-cytokeratins, CK7, CK8, CK18, CK19, epithelial membrane antigen (EMA), CEA (Fig. 10), and PDGFRA. It was negative for CK5/6, CK14, CK20, TTF-1, PE10, p53 protein, chromogranin, synaptophysin, CD56, and KIT. The squamous cell carcinoma element was positive for pancytokeratin, CK5/6 (Fig. 11), CK7, CK8, CK18, CK19, epithelial membrane antigen (EMA), CEA, and PDGFRA. It was negative for CK14, CK20, TTF-1, PE10, p53 protein, chromogranin, synaptophysin, CD56, and KIT. The small cell carcinoma was positive for pancytokeratins, CK18 (Fig. 12), chromogranin, synaptophysin (Fig. 13), CD56, and PDGFRA. It was negative for CK5/6, CK7, CK8, CK14, CK19, CK20, TTF-1, PE10, EMA, CEA, p53 protein, and KIT. The Ki-67 labeling was 22% in adenocarcinoma elements, 31% in squamous cell carcinoma element, and 8% in small cell carcinoma element. Therefore, the immunophenotypes were very similar in adenocarcinoma and squamous cell carcinoma elements. The immunophenotypes of small cell carcinoma element was entirely different from those of adenocarcinoma and squamous cell carcinoma elements. The small cell carcinoma elements showed neuroendocrine features.

Other pathologic changes included pulmonary multiple aspergillosis, pulmonary edema, bronchopneumonia, splenomegaly, emphysema, cardiac hypertrophy, and kidney congestion. The cause of death was respiratory failure due to the pulmonary lesions.

Fig. 1. The primary pulmonary carcinoma of the right lobe. A 4 × 4 × 3 cm tumor is present with pleural involvement. The tumor is very hard and pigmented. The tumor fulfills the criteria of scar carcinoma.

Fig. 2. Adenocarcinoma element within the scar. HE, x200.
Scar cancer of the lung is an old term. It is rare, and characterized by peripheral lung cancer with fibroelastotic scar, pleural involvement, and pigmentation.\textsuperscript{1–5} Therefore, the present lung cancer is categorized as scar cancer. The scar cancer is rare; Auerbach et al.\textsuperscript{1} identified 82 scar cancers among 1186 lung cancers, the frequency is 7\% of all lung carcinoma. Most of the scar cancer is adenocarcinoma. For example, Shimosato et al.\textsuperscript{2} reported that of the 58 scar cancers, 48 were adenocarcinomas, 2 were large cell carcinomas, and 8 were squamous cell carcinomas. A review of the literature, there have been no cases of scar cancers with small cell carcinoma histologies and combined carcinoma histologies,\textsuperscript{1–5} to the best of the author’s knowledge. Therefore, the present case appears the first case of scar cancer with small cell carcinoma histologies or with combined carcinoma histologies. The pathogenesis of the scar of scar cancers has been unclear; infarction, tuberculosis, atherectasis, and anthracosis are proposed.\textsuperscript{1–5} The scar of the present is also unclear. It is reported that the epithelium within the scar harbors loss of heterozygosity (LOH) of tumor suppressor genes, which may be related to carcinogenesis within the scar.\textsuperscript{24} It is probable that the tumor of the present case arose from such genetically altered epithelium within the scar. It is also possible that the tumor was derived from totipotential stem cells present in the lung.

In the present case, three components, i.e. adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, were present in the pulmonary scar. Histologically, there were close merges between the adenocarcinoma and squamous cell carcinoma elements. In addition, immunophenotypes of these two elements were almost the same except for CK5/6. These finding strongly suggest that the adenocarcinoma and squamous cell carcinoma elements are the same clone. The author speculates that the squamous cell carcinoma element is derived from squamous transdifferentiation of adenocarcinoma developed in the scar. In contrast, the small cell carcinoma element is isolated in the scar, and there were no merges with the other two elements. The small cell carcinoma elements had neuroendocrine features. In addition, immunophenotypes of the small cell carcinoma was entirely different from those of adenocarcinoma and squamous cell carcinoma elements. These findings strongly suggest that the small cell carcinoma element is a tumor different from the adenocarcinoma and squamous cell carcinoma. LOH studies of these combined pulmonary carcinomas are necessary to determine the clonality.

In metastatic sites, there was a close association between the adenocarcinoma and squamous cell carcinoma elements, while the
small cell carcinoma element was isolated and there was no association with the adenocarcinoma and squamous cell carcinoma element. In the cirrhotic livers, metastases of only small cell carcinoma element were recognized. These different metastatic sites and route also strongly suggest that the small cell carcinoma is a different clone, and the adenocarcinoma and squamous cell carcinoma elements belong to another different clone.

A full review of the literature of pulmonary combined carcinoma revealed 19 papers. Hashimoto et al.6 reported a case of tumor composed of small cell carcinoma and well differentiated papillotubular adenocarcinoma. Nomori et al.7 mentioned combined oat cell carcinoma. Humphrey et al.8 reported 8 cases of pulmonary carcinoma with a sarcomatoid element. Yokose et al.9 reported that of 34 small cell lung carcinoma, 12 cases of mixed small cell carcinoma and 4 cases of combined small cell carcinoma. Hiroshima et al.10 reported a combined carcinoma composed of adenocarcinoma and spindle cell carcinoma. Tsubota et al.11 reported a combined small cell carcinoma and spindle cell carcinoma. Yang12 reported a combined carcinoma composed of small cell carcinoma and large cell carcinoma. Chetty13 reported two cases of combined large cell neuroendocrine carcinoma and spindle cell carcinoma. Shikata et al.15 reported a combined carcinoma consisting of small cell carcinoma, adenocarcinoma, and squamous cell carcinoma. This case is similar to the present case. Nicholson et al.16 examined 100 surgical cases of small cell lung carcinoma, and surprisingly described that 28 cases (28%) showed combinations with non-small lung carcinoma, with large cell carcinoma the most common, followed by adenocarcinoma and squamous cell carcinoma. Murase et al.17 reported 6 cases of combined small cell and non-small cell carcinoma; three were small cell carcinoma and squamous cell carcinoma, and the other three were small cell carcinoma and adenocarcinoma. They found LOH loci were found in combined small cell and squamous cell carcinoma, while they were not recognized in combined small cell

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and adenocarcinoma. They speculated that the combined small cell and squamous cell carcinoma has a close clonal relationship, while the combined small cell and adenocarcinoma does not. Gotoh et al.18 reported a case of combined carcinoma composed of small cell carcinoma, spindle cell carcinoma, and squamous cell carcinoma. Zhang et al.19 described the distinction between small cell carcinoma and poorly differentiated squamous cell carcinoma and reported two cases of combined small cell carcinoma and poorly differentiated squamous cell carcinoma. Hsiao et al.20 reported a case of combined small cell carcinoma, adenocarcinoma and spindle cell carcinoma with soft tissue metastases. Michal et al.21 reported two cases of primitive small cell tumor with epithelial, ganglyocytic, neuroendocrine, and mesenchymal differentiation. Fellegara et al.22 reported a combined small cell lung carcinoma, large cell neuroendocrine carcinoma, and adenocarcinoma, and suggested a monoclonal origin from pluripotent precursor cells with the use of LOH analysis. Wagner et al.23 reported 7 cases of combined small cell carcinoma, and performed LOH analyses. They showed that immunophenotypes were the same between small and non-small cell carcinomas in 6 patients, and indicated that LOH shared loss of least 1 marker in every lesion in 5 tumors. Their data suggest a clonal origin of combined small cell carcinoma of the lung. These papers indicated no particular tendency of the histological types in combined lung carcinoma. However, small cell carcinoma element and spindle cell carcinoma element are relatively frequent. The origin of the combined is obscure, but recently molecular studies have begun to disclose the clonality of combined pulmonary carcinoma. The study is in the state of a start line.

In the present study, AE1/3 and CAM5.2 were expressed in the three components, indicating that they are epithelial malignancies. CK5/6 was expressed only in the squamous cell component. It is reported that CK5/6 is expressed mesothelioma, squamous cell carcinoma, and other malignancies, but not in adenocarcinoma and small cell carcinoma.25 CK7 and CK20 patterns are well recognized. The lung adenocarcinoma and squamous cell carcinoma shows a CK7-positive and CK20-negative pattern,26,27 as is the case of the present case. Camilo et al.28 reported that CK7 was expressed in pulmonary adenocarcinoma in 94% while in pulmonary squamous cell carcinoma in 7%. In the present study, CK 7 is equally expressed in adenocarcinoma and squamous cell carcinoma element. CK 14 is known to express esophageal and pulmonary squamous cell carcinoma, but the present case was negative for CK 14 in both adenocarcinoma and squamous cell carcinoma elements.29 Little is known in the expression of CK8, CK18, and CK19 in lung carcinoma.30 Scarpatetti et al.30 reported conflicting heterogenous expression of these CK in pulmonary carcinomas. Young et al.31 reported that CK18 was frequently expressed in pulmonary adenocarcinoma, while it is infrequent pulmonary squamous cell carcinoma. The present case showed that both adenocarcinoma and squamous cell carcinoma elements were positive for CK8, CK18, and CK19, suggesting that pulmonary adenocarcinoma and squamous cell carcinoma express CK 8, CK18, and CK19. TTF-1 and PE10 (an antibody to surfactant apoprotein A) are well known antigens of lung adenocarcinoma.28,32 The percentage of TTF-1 expression of lung adenocarcinoma is 72%,33 and that of PE10 is 27%.33 In the present case, expression of TTF-1 and PE10 were absent in adenocarcinoma, squamous cell carcinoma, and small cell carcinoma elements. Leversha et al.34 reported that p53 protein is expressed in pulmonary adenocarcinoma in 67% and in pulmonary squamous cell carcinoma in 53%. In the present case, p53 protein was absent in all the three elements. Little is known about the CK expression in small cell lung carcinoma. Shumidt et al.34 reported that small cell lung carcinoma was labeled with pancytokeratin cocktail but not with CK20, While Hanly et al.35 reported that CK was expressed in 33% of small cell lung carcinoma. Probably, CK expression of small cell lung carcinoma is heterogenous, and varies from case to case. In the present case, the small cell carcinoma element was positive for AE1/3, CAM5.2 and CK18 (very strong
expression), while was negative for CK5/6, CK7, CK14, CK19 and CK20. The very strong expression of CK18 in the present study is interesting. Much more studies CK profiles in small cell lung carcinoma are mandatory. Although most of small cell lung carcinoma expresses KIT and PDGFRA, the small cell carcinoma element of the present case did not express KIT. PDGFRA expression in the adenocarcinoma and squamous cell carcinoma in the present case is interesting, and more studies are required.

Conflict of interest

The author has no conflict of interest.

References