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Case report

A unique case of a huge mixed squamous cell and glandular papilloma of non-endobronchial origin with a peripheral growth

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ABSTRACT

We report a case of a huge solitary non-endobronchial pulmonary tumor in a 76-year-old male smoker. The tumor measured 11 × 10 × 8 cm. It was ill-defined, and it was located periphery of the right lower lobe with the subpleural cystic spaces. He underwent right lower lobectomy with mediastinal lymph node dissection and is free from tumor 30 months after surgery. Microscopically, it was composed of a proliferation of squamous and ciliated columnar epithelial cells with a few mucous cells. These cells were arranged in a papillary growth fashion extending along the fibrously thickened alveolar septa together with metaplastic bronchiolar and squamous epithelia displaying an usual interstitial pneumonia-pattern. Although the histologic features of the tumor were that of a mixed squamous cell and glandular papilloma (MSCGP), it was peripherally located and showed a lepidic growth, and it was much larger than previously reported MSCGPs. It is possible that the tumor developed in association with bronchial metaplasia in the periphery of the lung, and then extended along the surface of the reconstructed air spaces, which resulted in its unique histologic appearance. Further investigations of respiratory papilloma are needed to clarify the pathogenesis of these lesions.

1. Introduction

Solitary endobronchial papilloma, a rare benign pulmonary neoplasm, accounts for < 0.5% of all lung tumors [1]. It usually originates from within the trachea or main-stem bronchi. Only a few exceptional cases are located peripherally [2–4]. Pulmonary papilloma is divided into three subtypes in the WHO classification: squamous cell papilloma, glandular papilloma, and mixed squamous cell and glandular papilloma (MSCGP) [5]. MSCGP, the rarest subtype of pulmonary papilloma, is usually < 2.5 cm in size and comprises a mixture of squamous and pseudostratified, ciliated and non-ciliated cells, admixed with few mucin-containing columnar cells, arranged in a papillary growth fashion. The association between papilloma and interstitial pneumonia has not been documented. We describe a unique case of a huge non-endobronchial pulmonary tumor with features of MSCGP that extended widely along the alveolar septa in association with interstitial pneumonia.

2. Case report

2.1. Clinical presentation

A 76-year-old Japanese man with a smoking history of 20 cigarettes daily for 40 years (equivalent to a 40 pack-year smoking history) was admitted to our hospital to evaluate a mass in the right lung, detected by chest radiograph during a physical examination. He had no respiratory symptoms. Serum tumor markers, including squamous cell carcinoma antigen [24.5 ng/mL (normal, < 1.5)], cytokeratin 19 fragment [10.3 ng/mL, (< 3.5)], carcinoembryonic antigen [7.3 ng/mL, (< 3.5)]. Serum surfactant protein D [299 ng/mL, (< 110)], which is a biomarker of interstitial lung disease, was also elevated. Chest radiograph revealed an irregular opacity in the right lower lobe (Fig. 1a). A subsequent chest computed tomography (CT) scan demonstrated a large area of consolidation with air bronchogram in the right lower lobe, and reticular opacities with honeycombing in both lungs (Fig. 1b and c).

Abbreviations: MSCGP, mixed squamous and glandular papilloma; CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; CK, cytokeratin; RRP, recurrent respiratory papillomatosis; HPV, human papilloma virus; CMPT, ciliated muconodular papillary tumor

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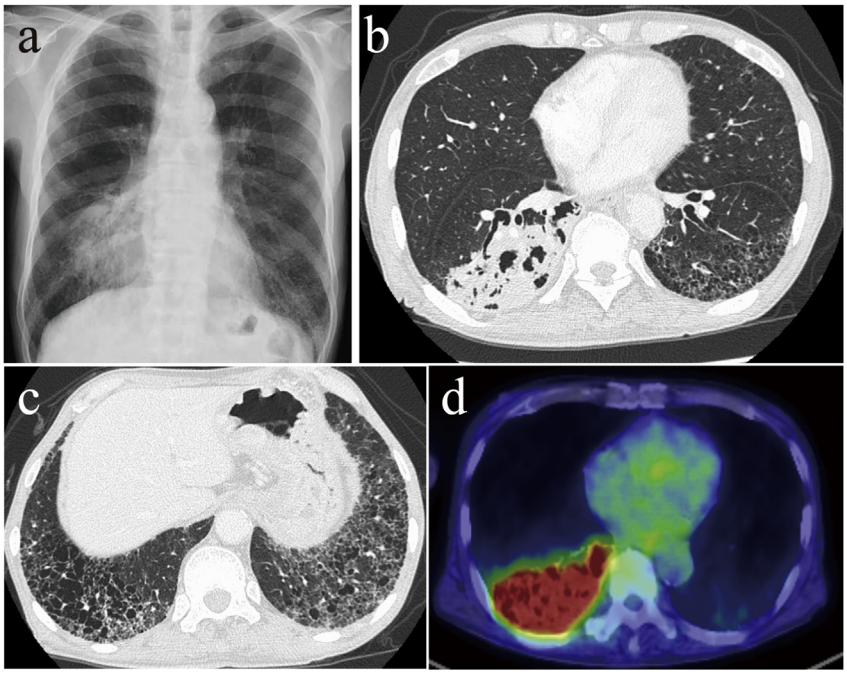

Fig. 1. Chest radiograph shows an irregular opacity in the lower lobe of the right lung (a). Chest computed tomography (CT) scan shows a large area of consolidation with air bronchogram in the right lower lobe and reticular opacities with honeycombing in both lungs (b, c). 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT shows increased uptake (maximum standardized uptake value of 13.03) in the right lung lesion (d).

The right lung lesion showed high uptake (maximum standardized uptake value at 1 hour and 2 hours 9.38 and 13.03, respectively) in the 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT (Fig. 1d). We did not observe any laryngeal or endobronchial lesion by bronchoscopic examination. We performed transbronchial lung biopsy, bronchial brushing, and bronchoalveolar lavage. Squamous cell carcinoma was suspected based on the cytological examination of the specimen. He underwent right lower lobectomy with mediastinal lymph node dissection and is free from tumor 30 months after surgery.

2.2. Pathological findings

The cytological smear of specimens obtained by bronchial brushing and washing showed high cellularity. There were many clusters of squamous epithelial cells in a sheet-like or papillary arrangement, and singly scattered cells, including keratinizing cells characterized by thick and deeply eosinophilic cytoplasm on a hemorrhagic or inflammatory background (Fig. 2a). The cells had centrally located and mildly hyperchromatic nuclei with prominent nucleoli. Therefore, the cytological findings were interpreted as squamous cell carcinoma. Additionally, there were singly scattered or clusters of ciliated epithelial cells and portions of mucous columnar epithelium without nuclear atypia (Fig. 2b and c).

Macroscopic examination of the right lower lobectomy specimen revealed that the tumor was located at the periphery of the lung It was ill-defined, measuring 11 × 10 × 8 cm in size, with a yellowish-to-whitish cut surface (Fig. 3). Variable-sized cystic spaces were seen mainly at the subpleural areas in the non-neoplastic pulmonary tissue, and in the tumor. The inferior lobar bronchus was free from the tumor. Microscopically, the tumor was composed of inflamed fibrovascular cores and papillomatous fronds covered by squamous and glandular epithelia (Fig. 4a). The squamous components were predominant (approximately 60% of the tumor) and showed several transitions from the ciliated columnar cells. The squamous epithelium was acanthotic and focally keratinizing. It coexisted with the glandular epithelium, which comprised ciliated or non-ciliated pseudostratified columnar cells and a few mucous columnar cells (Fig. 4b–d). No cell had significant nuclear atypia; stromal or vascular invasion was not evident. The tumor

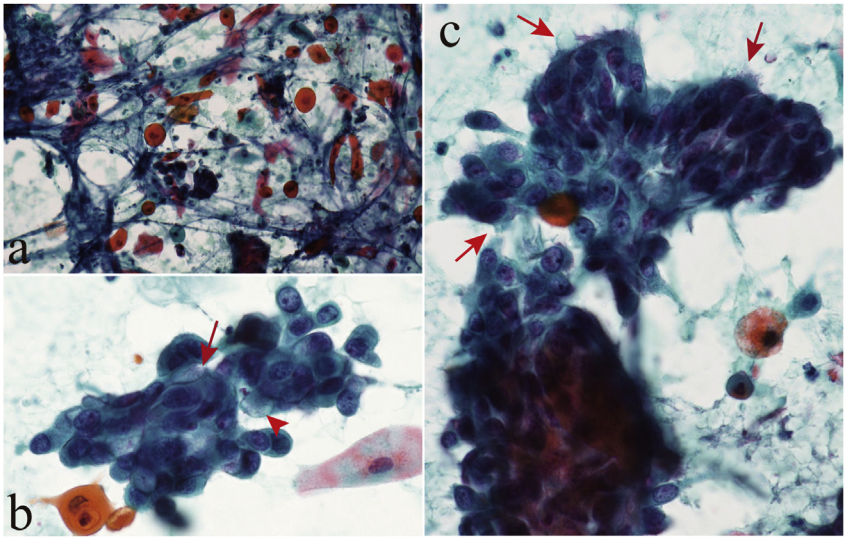

Fig. 2. Cytological findings of the tumor. The smear preparation shows clusters of squamous cells with abnormal keratinization on a hemorrhagic or inflammatory background (a), many clusters of ciliated epithelial cells (arrows), and some portions with columnar epithelium containing mucin (arrowhead) without nuclear atypia (b, c).

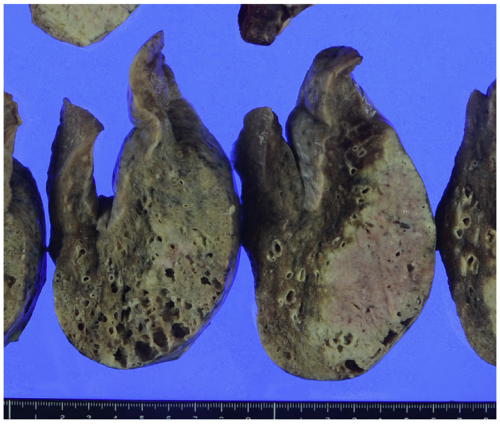

Fig. 3. The macroscopic evaluation of the resected pulmonary specimen shows a solid tumor occupying more than half of the right lobe with variable-sized cystic spaces, together with a honeycomb pattern in the non-neoplastic areas.

extended along the fibrously thickened alveolar septa or the surface of the reconstructed air spaces (Fig. 4e) with cystic structures often lined by ciliated columnar epithelium with mucopurulent content. The tumor did not involve the bronchi.

The immunohistochemical analysis revealed squamous cells that were positive for p63 and cytokeratin (CK) 5/6. Some of the ciliated cells were positive for CK 7, but both cell types were negative for CK 20. Only a few scattered cells were reactive to p16. Mucous columnar cells stained positively and focally with mucin 5AC. Ki-67 was positive mainly in the basal layer of the epithelium. The labeling index of the tumor was approximately 5%. BRAF V600E and ALK protein were negative. The non-neoplastic pulmonary tissue showed subpleural septal fibrosis with many fibroblastic foci, and bronchial or squamous epithelial metaplasia with large air spaces, representing a usual interstitial pneumonia-pattern (Fig. 4f). We observed obstructive pneumonia in the areas adjacent to the tumor. There was no tumor metastasis in the lymph nodes. Therefore, he has diagnosed with MSCGP extending along the alveolar septa in association with interstitial pneumonia.

3. Discussion

Pulmonary papillomas can be categorized according to their number, location, or histology. Considering the number of papillomas, there are solitary papilloma and multiple papillomas (or papillomatosis). Papillomatosis is used to name several conditions, including tracheobronchial papillomatosis, juvenile laryngobronchial papillomatosis, and recurrent respiratory papillomatosis (RRP). RRP is usually associated with human papilloma virus (HPV) infection, particularly with subtypes 6 and 11. Infections with these serotypes frequently occur in children and young adults and involve the larynx, nasopharynx, tracheobronchial tree, and pulmonary parenchyma [6]. Lung involvement in RRP may comprise variable sized-solid nodular or polypoid lesions containing large cavities, which is consistent with the present case. RRP without laryngeal papillomatosis is rare, and MSCGP is the rarest type of pulmonary papilloma. In the absence of HPV infection, this rare subtype affects most commonly men, particular, those in their 60's who smoke tobacco. MSCGP is composed of fibrovascular fronds covered by a mixture of squamous, pseudostratified ciliated and non-ciliated cells admixed with some mucin-containing columnar cells. The histopathological characteristics observed in the present case match this description. However, MSCGP is defined as an endobronchial tumor in the WHO classification [5]. Papillomas occurring in the periphery of the lungs are rare, with only a few reported cases [2–4]. The present tumor was located at the periphery of the right lung and it extended along the alveolar surface in a lepidic growth pattern, which is common in case of adenocarcinoma without involvement of the bronchial lumen. The origin of this tumor may be associated with other interesting histologic features of the present case: bronchiolization, goblet cell, or squamous cell metaplasia with enlarged alveolar spaces, and subpleural and septal fibrosis, representing a honeycomb change in the non-neoplastic areas. As per our knowledge, no endobronchial papilloma has been previously reported to arise in association with interstitial pneumonia. However, the present tumor may have emerged from the metaplastic epithelium in the periphery of the right lung and extended along the reconstructed alveolar septa in a papillary or sheet-like growth fashion, resulting in this unique histological appearance.

The differential diagnoses of MSCGP include variably benign and malignant pulmonary tumors. Ciliated muconodular papillary tumor (CMPT) is rare lung tumor, first described by Ishikawa et al. [7]. CMPTs are small peripheral lung nodules, measuring < 1.5 cm, that comprise a mixture of ciliated columnar, mucous, and basal cells that form glandular or papillary structures with an abundant extracellular mucin pool. The cellular elements are similar to those of pulmonary glandular papilloma or MSCGP. Thus, although a squamous cell component is not predominant, CMPT may be considered as a peripherally located MSCGP [8]. Because *BRAF*, *EGFR*, *KRAS* and *AKT1* mutations, and *ALK* rearrangements were recently identified in CMPTs [8–12], molecular genetic analyses of MSCGP and CMPT for the specific alterations may provide valuable information in understanding their pathogenesis. The characteristics of the present case, such as large tumor size, unusual pattern of extension, and lack of immunohistochemical detection of BRAF V600E and ALK protein, are not aligned with the characteristics of CMPT. Mucoepidermoid carcinoma of the lung or metastatic mucoepidermoid carcinoma from the salivary gland may mimic MSCGP because of the presence of mucous and squamous cells and papillary or cystic structures. This type of tumor arises in the central airways containing bronchial mucous glands, and lacks ciliated cells. These characteristics also differ from those of the present tumor.

Malignant transformation is reported in approximately 10% of case of squamous cell papilloma, and only rarely in case of glandular papilloma [13]. The characteristics of such tumors are exclusive of squamous cell carcinoma. These are thought to develop from the squamous epithelium in case of squamous cell papilloma or the metaplastic squamous epithelium in case of glandular papilloma [1,13,14]. Despite histologically benign features, some MSCGPs reportedly present high FDG uptake on FDG-PET/CT, as in the present case [15,16]. High FDG uptake in MSCGPs may predict malignant potential [15]. However, a localized active inflammatory response secondary to the tumor extension seems to be associated with the phenomenon. Despite the huge tumor size, the low Ki-67-index of the tumor and the lack of overt cellular atypia, as well as the constant presence of cilia and lack of stromal invasion, suggest an indolent or benign clinical course of the current lesion.

Few reports have described the cytological findings of pulmonary papillary tumors. Based on the radiological information of a large tumor in the right lower lobe, added to the cytological smear specimen revealed many clusters of squamous epithelial cells with abnormal keratinization and hyperchromatic nuclei on a necrotic background, we initially considered this lesion to be squamous cell carcinoma. However, singly scattered or clustered ciliated cells and few columnar cells containing mucin are not typical findings in squamous cell carcinoma.

We report a case of a huge MSCGP that arose in the periphery of the right lung and extended widely along reconstructed alveolar septa, in association with interstitial pneumonia. Because MSCGPs are extremely rare and the lesion described herein had unique histologic features, further investigations of pulmonary papillomas are warranted.

Disclosure

The authors declare no conflict of interest.

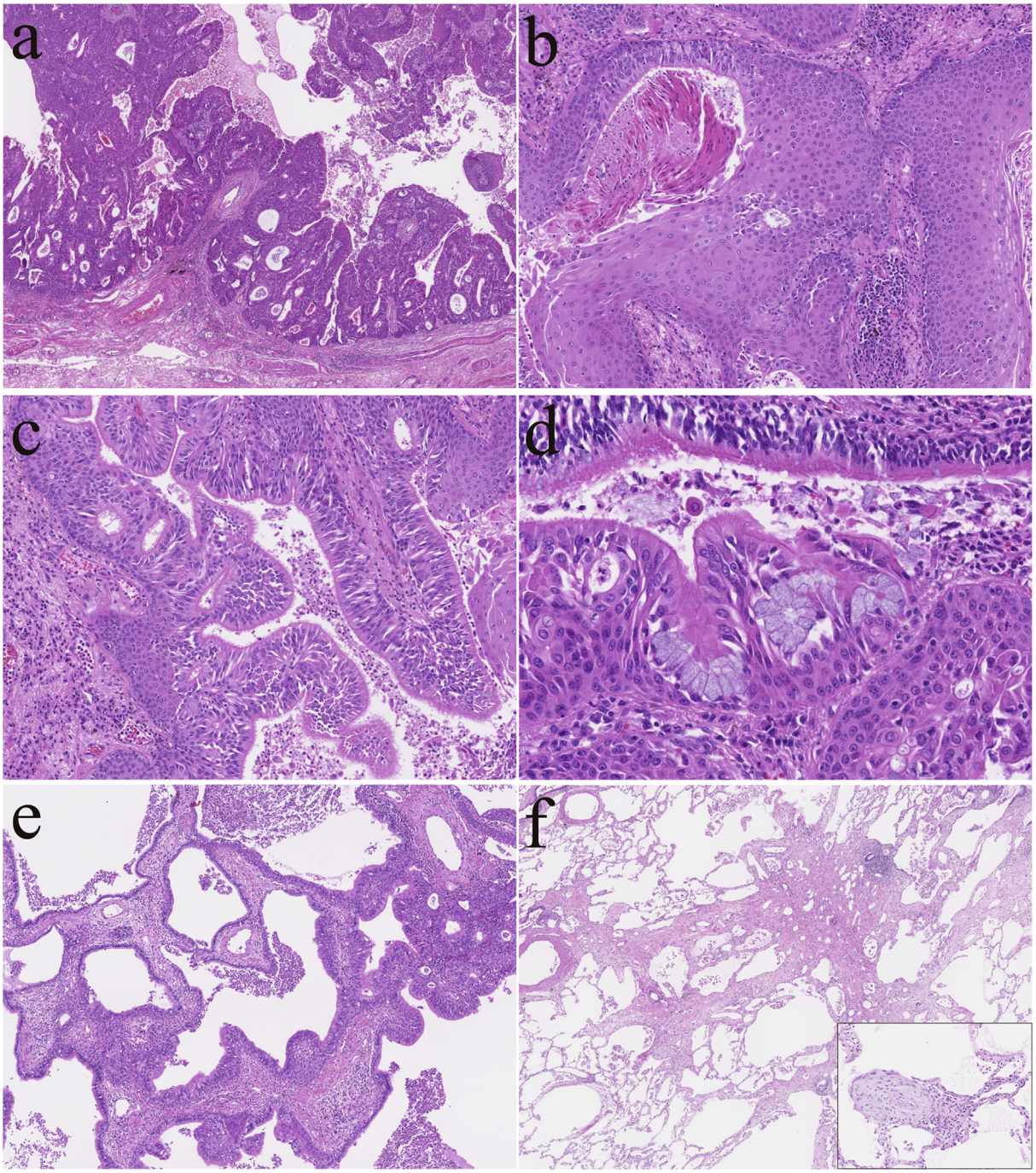

Fig. 4. The histological evaluation of the tumor shows papillary structures of epithelial cells without stromal invasion (a). The tumor is composed of squamous cells (b), ciliated columnar cells (c) and a few mucous columnar cells (d) without nuclear atypia. The tumor cells extend along the fibrously thickened alveolar septa forming cystic structures with mucopurulent content (e). The non-neoplastic pulmonary tissue showed usual interstitial pneumonia-pattern fibrosis (g) with fibroblastic foci (inset).

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