



Case report

Mixed squamous cell and glandular papilloma of the lung resembling early adenocarcinoma: A case report



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H I G H L I G H T S

- Mixed squamous cell and glandular subtype is extremely rare pulmonary papilloma.
- Initial presentation of this benign tumor had resembled early adenocarcinoma.
- This disease should be taken into account in making a differential diagnosis.

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Abbreviations:

FDG-PET

¹⁸F-fluorodeoxyglucose positron emission tomography

HPVs

human papilloma viruses

MSCGP

mixed squamous cell and glandular papilloma

SUV

standardized uptake value

A B S T R A C T

Introduction: An extremely rare case of mixed squamous cell and glandular papilloma of the lung is reported. The correlation between the radiological and the pathological features as well as the clinical pitfall in making a diagnosis is discussed.

Presentation of case: An asymptomatic 68-year-old female with a cigarette smoking habit presented with a small nodule in her peripheral lung. A wedge resection was performed though it failed on-site diagnosis which was instead obtained following pathological scrutiny. The postsurgical course was excellent with no recurrence of disease.

Discussion: A small ground glass nodule gradually enlarged and transformed to a partially solid nodule a year and a half later. This transformation falsely made us suspect an early adenocarcinoma development. Eventually, the extremely rare subtype of pulmonary papilloma, with biphasic glandular and squamous cells, had been demonstrated to obstruct the peripheral bronchiole; and the adjoining alveoli had filled with a large volume of mucus. These pathological features seemed to have constituted the inner solid portion and the marginal ground glass portion respectively in the CT images, mimicking invasive lepidic adenocarcinoma.

Conclusion: Both pre- and intra-operative diagnoses are difficult mainly because of the rareness of the disease, however, mixed squamous cell and glandular papilloma may be considered in case the presence of primary adenocarcinoma is not validated.

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1. Introduction

We report an extremely rare case of pulmonary mixed

squamous cell and glandular papilloma which showed early adenocarcinoma-like progression and was not diagnosed precisely during the operation.

2. Case presentation

The disease was found through a screening for lung cancer in a 68-year-old asymptomatic female with a history of 22-pack-year

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cigarettes smoking. She presented with a small ground glass shadow in the left upper lung field on a plain chest roentgenogram.

On initial computed tomography (CT) of the chest, the nodule had a pure ground glass density. With an approximate longest diameter of 8 mm, it was too small to allow interventional examination such as with a bronchofiberscope. The patient was recommended to undergo CT follow-up every three months. A year and a half later, the tumor had grown to 10 mm in longest diameter, and an internal solid component had gradually developed within the ground glass density (Fig. 1). ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) revealed no significant increase of uptake even after the tumor's progression had been observed.

At that time, the disease remained yet to be diagnosed and open thoracotomy with a wedge resection of the tumor was performed. The intraoperative diagnosis was like that: 'primary lung adenocarcinoma, possible'. However, the pathologists added that they were unable to confirm it because of its scarce cell atypia and that further investigation was required.

Later scrutiny showed the tumor was located in a small bronchiole with abundant mucus production, which filled the adjoining alveoli (Fig. 2). The tumor was composed of biphasic cells: mucus-producing goblet cells that formed a glandular lesion (negative for both p40 and cytokeratin 5/6) and transitional-cell-like tall columnar cells that partially transformed to a multi-layered squamous cell lesion (positive for both p40 and cytokeratin 5/6). Cell atypia was not overt and the tumor had benign features on the whole. After all these observations, pulmonary mixed squamous cell and glandular papilloma was confirmed.

Several examinations were added to investigate the involvement of human papilloma viruses (HPVs). Immunohistochemistry using an anti-p16-INK4a antibody showed diffuse overexpression of p16-INK4a protein, however, both *in situ* hybridization for HPVs mRNA and direct polymerase chain reaction for HPVs genomic DNA failed to detect HPVs.

The patient's postsurgical course was fair without complications. No recurrence of disease was noted six months after the operation.

3. Discussion

Solitary pulmonary papilloma is classified into three subtypes

by morphological features [1]. Among them, mixed squamous cell and glandular papilloma (MSCGP) is the rarest [2]. The other two subtypes are squamous cell papilloma and glandular papilloma. The characteristics of MSCGP described in previous reports are the followings: potential association with male gender, smoking habit, preference of the central airways, and irrelevance with human papilloma viruses (HPVs) infection. In our case, unusually, the patient was female and the tumor was located at the periphery of the lung. However, a cigarette smoking history and testing negative for HPVs were consistent with the typical features.

Regarding CT images, initial presentation was not of a typical solid nodule [3] but a faint density that had gradually developed to a partially solid nodule with an opaque fringe. This observation largely resembled an early *in situ* adenocarcinoma transforming to an invasive adenocarcinoma. The faint density and the inner solid portion might have represented lepidic growth of alveolar carcinoma cells and invasive central scar respectively, instead of mucus-filled alveoli followed by growth of the papilloma [4,5]. In addition, the FDG-PET failed to detect significant FDG uptake, unlike previous reports in which maximum standardized uptake values (SUV) were within the range of 3–9 [6,7].

Pathologically, MSCGP is characterized by the biphasic differentiation of both the squamous and glandular portions without malignant features. Immunohistochemical examinations are useful to distinguish these two components; they correlate well with the morphological features. HPVs involvement may better be investigated in pulmonary papilloma cases.

Preoperative diagnosis of a peripherally grown MSCGP is difficult compared to the central airway type. Because tumors may not be observed directly with a bronchofiberscope, sufficient biopsy samples cannot be easily obtained. In addition, cytological diagnosis is reported to be inadequate [8].

Obtaining a diagnosis of MSCGP by rapid examination during a surgical operation is also very difficult because of the disease's rareness and its histological similarities to mucus-producing small adenocarcinoma. In our facility, 450 pulmonary lesions have been diagnosed primarily during surgery in the last decade. Of these, there were 10 cases (2%) where diagnosis was not confirmed intraoperatively and further examination had been required: four with inflammatory lesions, three with primary lung adenocarcinoma, two with sclerosing hemangioma and one with MSCGP (the

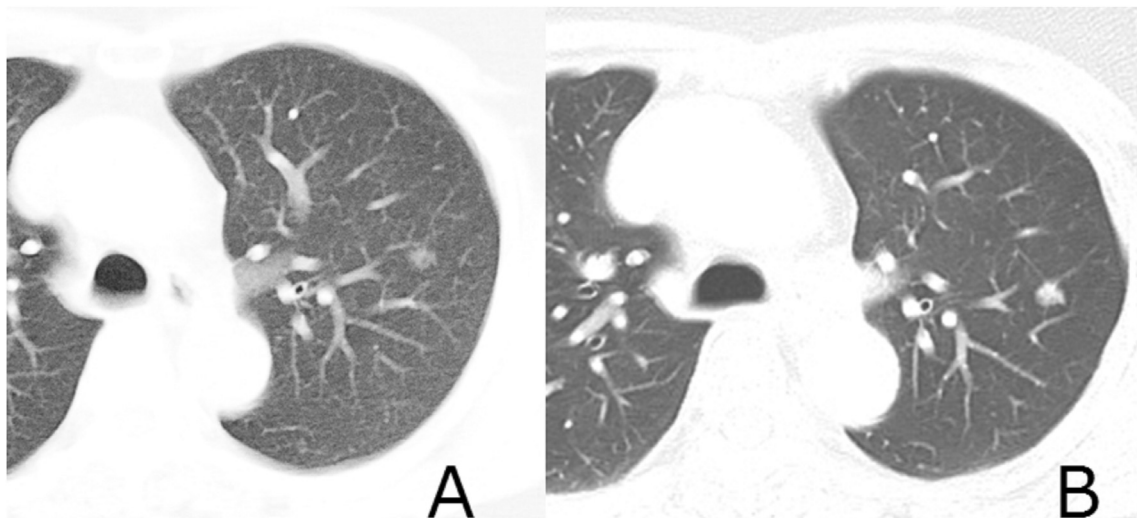


Fig. 1. A) An initial presentation CT scan of the patient. A faint ground glass small nodule was observed. B) An image of the same patient a year and a half later. A solid component had developed within the tumor and occupied approximately 60% of the mass, whereas the rest of the tumor sustained the ground glass pattern at the rim.

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