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*Case Report*

# Solitary endobronchial papillomas with false impression of malignant transformation: report of two cases and review of the literature

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**Abstract:** Solitary endobronchial papillomas (SEPs) are rare benign tumors of the lung, seldom transform to malignancy. This tumor had been reported occasionally manifest like carcinomas histologically. Herein we report 2 cases of SEPs; one is a squamous cell papilloma providing a false impression of interstitial micro-invasion. The other is a mixed squamous cell and glandular papilloma with massive lipid pneumonia gross appearance, and focally resembles adenocarcinoma with lepidic-like pattern on histological examination. A review of associated literatures was provided.

**Keywords:** SEP, lung, tumor, misdiagnosis

## Introduction

Solitary endobronchial papillomas (SEPs) are rare neoplasms [1] with around only one hundred cases reported to date in English literature [1-8]. The recent World Health Organization (WHO) classification of lung tumors subdivided these papillomas into three separate categories: squamous cell papilloma, glandular papilloma, and mixed squamous cell and glandular papilloma. Malignant transformations have been reported in a few squamous cell papilloma cases, and no malignancy has been reported in the mixed type to the best of our knowledge [9]. In several reports, SEPs have been described "mimicking" the histological appearance of malignant carcinomas [6, 8, 10, 11]. Herein, we present 2 cases of SEPs with such deceptive morphologic changes which could be easily misdiagnosed as malignancies: one case is a squamous cell papilloma, with suspicious micro-invasion on frozen sections, was finally confirmed benign on permanent sections; the other case is a mixed squamous cell and glandular papilloma with large area of lipoid pneumonia, focally showed a lepidic-like pattern which resembles an adenocarcinoma. A review of related literatures is also carried out.

## Case presentation

*Case 1*

A 65-year-old male was admitted to hospital because of a recurrent productive cough and hemoptysis of 4 months' duration. Laboratory data was unremarkable. Chest computed tomography scanning (CT-scan) revealed a peripheral solid mass in the left upper lobe of the lung, adjacent to the pleura with focal pleural infiltration (**Figure 1A**). He had a history of smoking 20 cigarettes daily for 40 years. Prior routine health examination did not show any abnormalities. As a diagnosis of lung cancer could not be completely ruled out, following pulmonary lobectomy was performed.

In gross examination, the lesion was a subpleural, grayish-tan mass of medium texture, measuring 4.5 cm×3.5 cm×3.5 cm in size, with cysts containing sallow liquid on the cut surfaces. Frozen section examination showed a typical squamous cell papilloma with mild to moderate epithelial atypia (**Figure 1B**). Notably, isolated epithelial clusters abruptly occurred in the peripheral lung tissue, which was very similar to carcinomatous interstitial micro-invasion

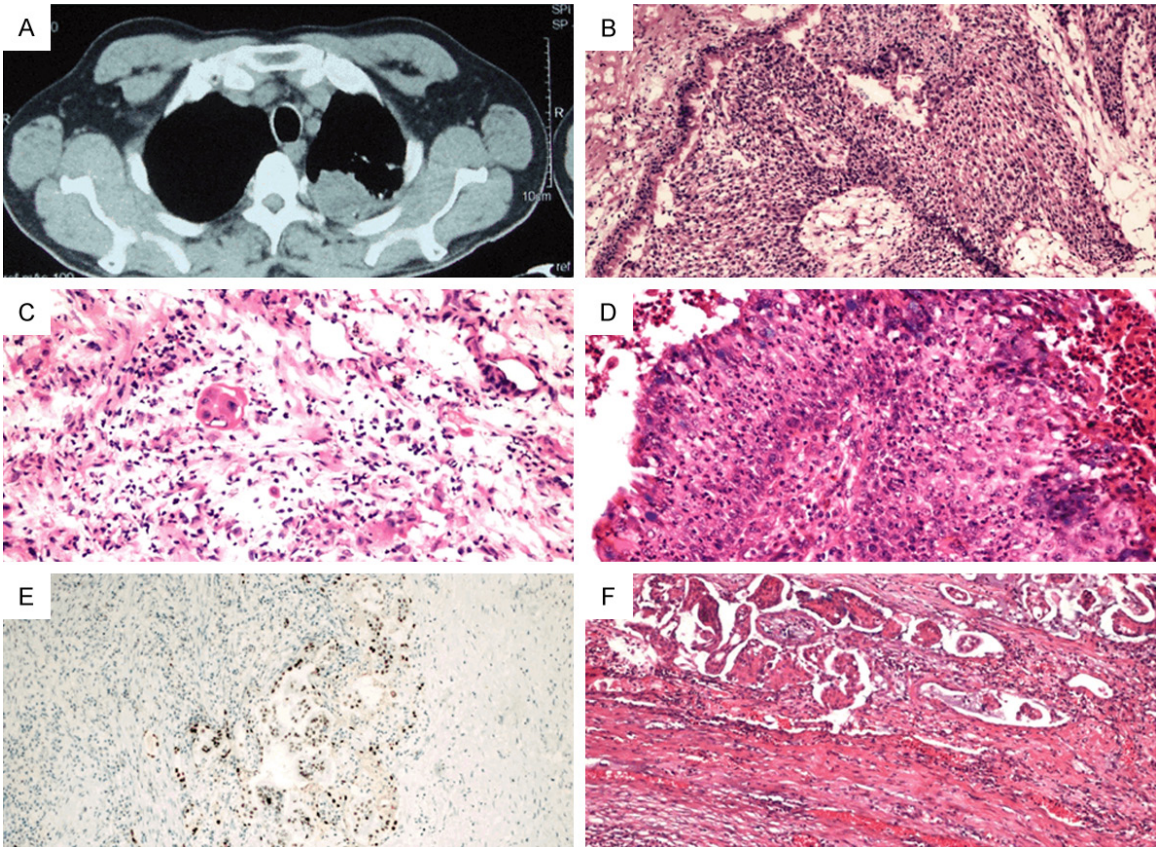


**Figure 1.** CT-scan of case 1 revealed a large solid mass adjacent to in the left upper lobe of the lung, with focal pleural infiltration (A). Intraoperative frozen HE sections showed a papillomatous tumor composed of squamous epithelium, with mild to moderate cytological atypia, featured by compact cellular arrangement and enlarged nucleus (B). Isolated epithelial clusters abruptly occurred, in the peripheral area of the main tumor, very similar to carcinomatous interstitial micro-invasion (C). On the permanent HE sections, the squamous epithelium were of mild cytological atypia, accompanied with severe inflammatory infiltrations (D). The "invasion" cell clusters were also observed embracing by vague outlines of alveolar structures (E). Immunochemistry staining of TTF-1 were positive for the "invasion" cells, and also embracing alveolus walls (F).

(**Figure 1C**). After discussion, an intraoperative pathology diagnosis of "squamous papillary tumor with high grade intraepithelial lesion and microscopic suspicious interstitial invasion" was made. Subsequent lymphadenectomy surgery was performed.

On review of the permanent sections, cystic tumor composed of fibrovascular cores and acanthotic, focally keratinizing squamous cells was evident. Mucin-filled cells also appeared within the squamous epithelium in majority of area. Acute and chronic inflammatory infiltration was remarkable. Cytological atypia of squamous epithelium were featured by increased cellular layer, compact cellular arrangement, enlarged nucleus, and nuclear hyperchromasia (**Figure 1D**), but yet not up to the standard of high grade intraepithelial neoplasia. Pathological nuclei mitosis was not found. Additional sampling revealed more areas of the suspicious interstitial micro-invasion. However, vague outlines of alveolar structures embracing the "invasion" cell clusters were also observed. These alveolus walls were ruptured and embedded within the organized fibroblasts (**Figure 1E**), which were indiscernible on the previous frozen sections. Immunohistochemistry stain showed that the isolated cell clusters were positive for TTF-1, but negative for p63. TTF-1 also stained and outlined the alveolar structures surrounding these "invasion" cells (**Figure 1F**). In the main part of the tumor, p63 was diffusely positive in the squamous cells, and TTF-1 was weakly stained in basal cells of the epithelium.

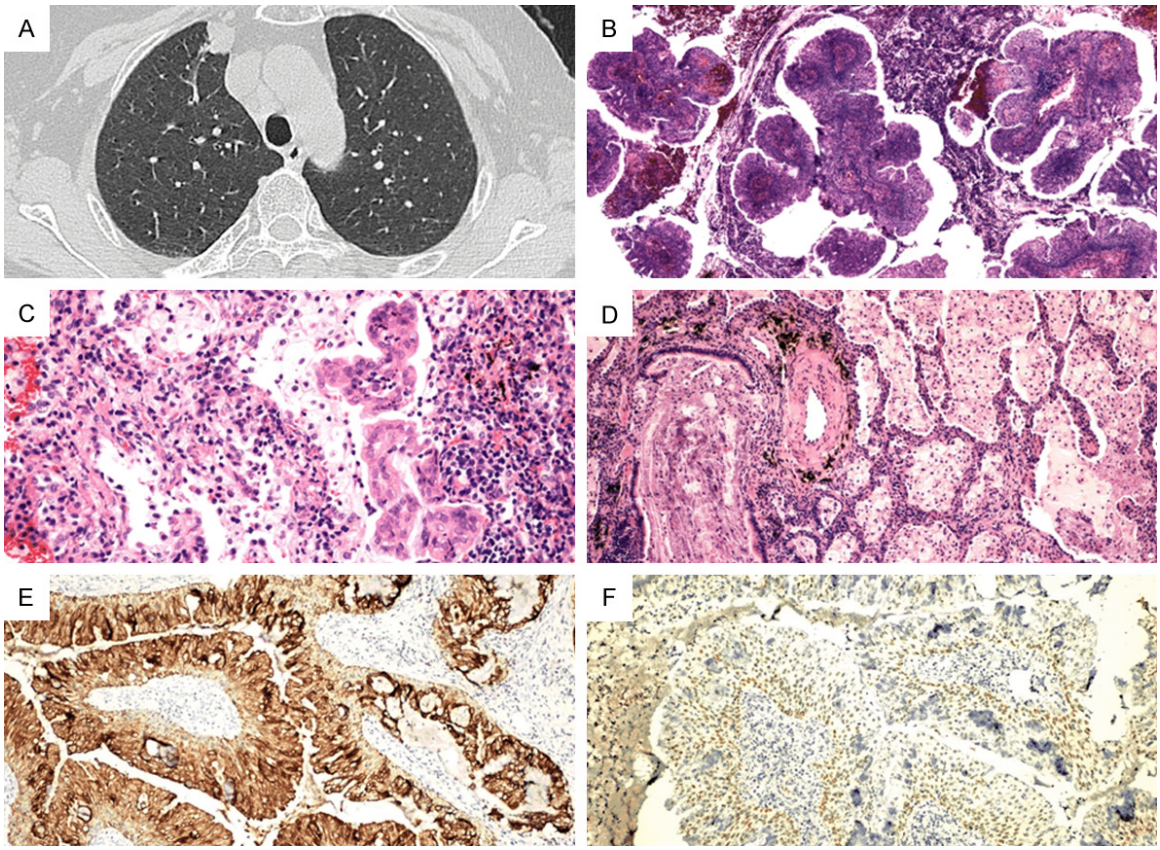


**Figure 2.** In case 2, chest CT-scan confirmed a nodular peripheral solid lesion in the upper right lobe of the lung (A). Histologically, the lesion was constituted of mixed squamous and glandular epithelium covering fibrovascular cores (B). In partial areas, tiny papillae with abundant mucus extending within the adjacent alveolar spaces were similar to the morphologic feature of adenocarcinoma with lepidic-like pattern (C). The peripheral lung tissue presented a lipid pneumonia change that massive histiocytes and cholesterol clefts accumulated in the air spaces, mixed with proliferated granulation tissue (D). Both glandular and squamous cells were strong and diffuse positive for CK7 (E). TTF-1 was also weakly stained in basal and parabasal cells of the squamous epithelium, and in basal cells of the glandular epithelium (F).

Considering that the evidences of peripheral invasion were not adequate, the final pathology diagnosis of a benign tumor was made (squamous cell papilloma). The patient recovered well after surgery, did not receive any postoperative adjuvant chemoradiotherapy. 48 month's follow-up presented a stable condition without any sign of recurrence or metastasis.

*Case 2*

A 63-year-old female nonsmoker had a complaint of malaise, active chest tightness and asthma of 1 year's history. During the latest 1 week, her condition sharply deteriorated and started with a productive cough. Echocardiography (ECG) demonstrated a rheumatic heart disease with mitral valve stenosis and moderate insufficiency, moderate tricuspid valve insufficiency, and mild aortic valve insufficiency. Chest X-ray examination showed enlarged heart shadow, and also discovered an obscure nodular opacity in the upper right lobe of the lung. Chest CT-scan confirmed that the nodule was a peripheral solid lesion (**Figure 2A**). In order to further identify the entity of the lesion, a video-thoracoscope pulmonary wedge resection was performed.

On gross examination, the lesion was a yellowish consolidated mass beneath the pleura, measuring 2.5 cm×1.5 cm×1.0 cm in size. The mass had an oily appearance on the cut surfaces and had oozed a greasy material. One piece of lesion tissue was sampled and made to frozen section. On frozen section evaluation, the most striking feature was massive histiocytes deposition and cholesterol clefts forma-

tion, accompanied with severe lymphocytes and neutrophils inflammation. Prominent epithelial changes were not seen. An intraoperative diagnosis of benign lesion was favored; thereby the wedge resection was an adequate therapy.

On review of the permanent sections, additional sampling discovered a papillomatous lesion within the yellowish mass, measuring 0.5 cm in diameter under the microscope, mainly located in a dilated bronchial lumen. Histologically, the lesion was featured by mixed squamous and glandular epithelium covering fibrovascular cores, displaying a papillary growth pattern (**Figure 2B**). The glandular epithelium was predominantly pseudo-stratified ciliated or non-ciliated columnar epithelium and massive mucous columnar epithelium, squamous differentiation components were also seen, mostly occurred in the center of the lesion. No nuclei mitosis or prominent cytological atypia was found. Notably, in partial areas, tiny papillae with abundant mucus were observed within the adjacent alveolar spaces, showing mild to moderately cellular degeneration, which resembles adenocarcinoma with lepidic-like pattern (**Figure 2C**). In the peripheral lung tissues, accumulated histiocytes and cholesterol clefts mixed with proliferated granulation tissue were accordant to the histological changes of lipid pneumonia (**Figure 2D**). Immunohistochemistry analysis showed that tumor cells (both glandular and squamous cells) were strong and diffuse positive for CK7 (**Figure 2E**). TTF-1 was weakly stained in basal and parabasal cells of the squamous epithelium, in basal cells of the glandular epithelium, and in alveolar epithelium (**Figure 2F**). p63 staining was moderately positive in basal and parabasal squamous epithelium. PAS/PASD staining confirmed that the liquid materials in the lumen contained mucin rather than glycogen.

A diagnose of "mixed squamous cell and glandular papilloma of the lung with endogenous lipid pneumonia" was established. The patient showed fine recovery after surgery. She was slightly relieved from her symptoms, but was suggested for further re-examination of ECG 3 to 6 months after discharge. A follow-up of 20 months showed no signs of local recurrence or distant metastasis.

## Discussion

Solitary endobronchial papilloma is an uncommon benign neoplasm; accounting for only 0.38% of all lung tumors [12]. Currently, the SEPs are listed under benign epithelial tumors of the lung in the WHO classification system because they rarely have malignant transformation, and the a few malignant carcinoma cases usually related to favorable prognosis [1-3]. In several reports, this benign tumor was described disguised as malignant carcinomas that tumor cells extend into adjacent bronchiolar and alveolar spaces with abundant mucus, which could have been confused with carcinoma with lepidic-like or micropapillary growth pattern [6, 8, 10, 11]. This could be especially deceptive when accompanied with fibroblastic organization or cellular atypia secondary to bronchiolar obstruction or inflammation. Therefore, the main concern for pathologists is to differentiate the false impressions caused by secondary changes from the true malignant carcinomas, to avoid unnecessary surgical intervention prompt by over-diagnosis.

In our manuscript, case 1 was initially considered as a high grade intraepithelial neoplasia due to the cytological atypia and the suspicious invasive growth pattern. However, on review of permanent sections, histological proof of malignancy became inadequate. The epithelial components displayed only mild cytological atypia without nuclei mitosis, even could be explained as regenerative atypia response to the severe inflammation. As to the "micro-invasion" area, alveolar structures confirmed by immunohistochemistry staining of TTF-1 were observed surrounding the "invasion" cells, indicating that the isolated epithelial clusters might had previously grew along the alveolar ducts rather than interstitial invasion. We speculated that some of these cells were actually benign micropapillae arisen from major papillary branches extending into adjacent bronchiolar and alveolar spaces. The immunohistochemistry staining (positive for TTF-1, negative for p63) suggested that they were glandular epithelial cells rather than squamous cells, possibly shared same origin with the mucin-filled glandular cells (positive for TTF-1). In fact, this feature had been previously mentioned in a few cases of SEPs [6, 8, 11]. Besides, we propose a hypothesis that, owing to the intercommunicated alveolar airways of the lung, small clusters of epithelial cells that exfoliated from the main tumor could have "fell" into airspaces distant from the main lesion. These cells were embedded and mixed up with organized fibrinous tissues, thus provided a false impression of malignant intersti-

tial invasion. This hypothesis could be supported by the phenomenon that, the pseudostratified ciliated columnar epithelium which belongs to major bronchus could be occasionally seen within terminal airspaces. Hence, most of the staff pathologists agreed that the suspicious micro-invasion cells were actually benign micropapillae arisen from major papillary branches or exfoliated epithelial organized by fibrinous tissues. 48 months' follow-up without radiochemistry therapies showing a stable condition partially supported the diagnosis of a benign lesion.

Similar findings were also observed in case 2 we present. Case 2 was a mixed type papilloma with glandular cells occupying more than 30% of the epithelial component [2]. The epithelial cytological changes were more of degeneration rather than atypia. Tiny papillae lined by glandular epithelium extended along alveolus with abundant mucus, similar to the feature of adenocarcinoma with lepidic-like or micropapillary growth pattern, sometimes could be mistaken for well-differentiate mucinous carcinomas. Therefore, this is another noticeable histological presentation. Lin [10] had mentioned this pattern as "mimicking" adenocarcinoma. Importantly, in this case, massive lipid pneumonia formed large area of yellowish and greasy appearance, thus led to a mis-sampling of the intrinsic lesion in the initial intraoperative gross examination. As most lipid pneumonia were caused by airway obstruction, we suggest that specimens with apparent lipid pneumonia-like appearance should be especially examined carefully to avoid missing the intrinsic lesion, and look for possible obstructions blocking within the airway, such as endobronchial tumors or foreign materials. Immunohistochemistry analysis showed that the different types of epithelial had proximate immunophenotype, that both squamous and glandular epithelium were strongly positive for CK7, and TTF-1 were stained in all epithelial basal cells. These findings were in accordance with that of Inamura *et al.* and Lin *et al.* reported, supporting the view that the tumor's different components arise from same progenitor cells [6, 10].

In conclusion, according to the 2 cases of SEPs we present, we suggest that when diagnosing this type of lung tumor, pathologists should particularly pay attention to the false impressions provoked by secondary changes, to avoid the consequent over-diagnosis. Meanwhile, when the secondary appearances are prominent in gross examination (as the apparent lipid pneumonia-like appearance in case 2), the sample should be especially carefully examined, lest for missing the intrinsic lesion.

## Disclosure of conflict of interest

None.

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