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Case Report

Pulmonary mixed squamous and glandular papilloma: diagnostic challenges of a rare lesion when the clock is ticking. How to avoid interpretation mistakes

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Summary

Pulmonary mixed squamous and glandular papillomas (MSCGPs) are rare, benign neoplasms with peculiar clinical and histological features. However, on occasion, they can present certain characteristics that overlap with other neoplasms including carcinomas. Recognising these features is hence important for treatment purposes. Molecular studies can sometimes help in further characterisation, although they should not guide the diagnosis which ultimately relies on morphology.

We report a challenging case of MSCGP with unusual features, received during intraoperative consultation. We highlight the subtle morphological features to help avoid overcalling a benign lesion as malignant.

Key words: MSCGP, frozen section, papilloma

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Case report

Solitary pulmonary papillomas are rare neoplasms. The World Health Organisation classification of lung tumours categorizes them into squamous cell papilloma, glandular papilloma and mixed squamous and glandular papilloma (MSCGP). MSCGP are rare benign neoplasms, malignant transformation has rarely been reported [1-3].

The clinical characteristics of MSCGP described in the literature are the following: the median age of the sixth decade with a male preponderance, smoking habit, predominantly central airway and endobronchial location, haemoptysis and obstructive symptoms and no association with HPV [1-2].

Macroscopically, MSCGPs are tan to red polypoidal lesions measuring 0.2-2.5 cm with a predominantly central and endobronchial location. Histologically they are composed of a mixture of mild to severely atypical squamous epithelium and the non-atypical ciliated, glandular epithelium lining fibrovascular cores [1-2].

Pre-operative diagnosis is difficult as the tumours may not be observed directly with a bronchoscope to obtain adequate diagnostic material. Intra-operative diagnosis is also difficult given the limited sampling for a rare disease which may mimic carcinomas.

Hence, we described a case of MSCGP received during intraoperative consultation presenting unusual features and discuss the diagnostic consideration.

A 77-year-old non-smoker lady, presented with weight loss and a CT scan revealed a 35 mm cavitating lesion located in the costophrenic recess of the right lower lobe. A biopsy was inconclusive hence she was referred for wedge resection with a frozen section given the clinical suspicion of lung cancer. Intraoperative macroscopic examination revealed an ill-defined, cavitating, grey-white peripheral lesion measuring 35 mm. The frozen section showed a papillary tumour with fibrovascular cores lined by columnar mucin containing glandular epithelial cells and an outer layer of squamous epithelial cells. In addition, there were separate squamous epithelial islands with keratinisation and significant nuclear atypia. A diagnosis of 'non-small cell carcinoma, favouring squamous cell carcinoma' was rendered based on the separate squamous islands showing dysplasia (Fig. 1A-C). Final histology confirmed a subpleural tumour with both squamoid and glandular components (Fig. 2A). The squamoid component showed moderate atypia with occasional mitotic figures, focal necrosis and keratinisation. The glandular proliferation was relatively monomorphic comprising columnar mucinous cells with no atypia or mitoses. Cilia were identified in paraffin sections (Fig. 2A) although were not obvious in the frozen section (Fig. 1). On immunohistochemistry, both components showed positive staining AE1/AE3 whilst showing negative staining for S100 and calponin. P40 was positive in the squamoid component (Fig. 2B) while TTF1was positive in the glandular epithelium (Fig. 2C). P16 and in-situ hybridization (ISH) HPV were negative. Molecular analysis revealed no mutations in the hot spot regions of *EGFR*, *BRAF* or *KRAS* genes. Overall, the differentials included MSCGP with dysplasia and a well-differentiated adenosquamous carcinoma. Although the squamous component showed dysplasia, the dilemma was to discern whether the glandular component was also neoplastic or entrapped/reactive. Given the extent of the glandular proliferation and its monomorphism, a diagnosis of mixed squamous and glandular papilloma was favoured.

This case was difficult to diagnose intra-operatively given the location, cavitating appearance and presence of detached squamous islands exhibiting nuclear atypia and necrosis mimicking invasive squamous cell carcinoma. Also, the limited sampling and time constrain did not allow for a comprehensive study of the lesion.

Although these lesions are considered benign, the recommended treatment is complete surgical resection due to the risk of malignant transformation [1-3]. An intra-operative diagnosis of a peripheral lesion with a squamous and glandular component should lie between an adenosquamous carcinoma and an MSCGP. The exhaustive search for the cilia in the glandular cells will give clues for diagnosis although

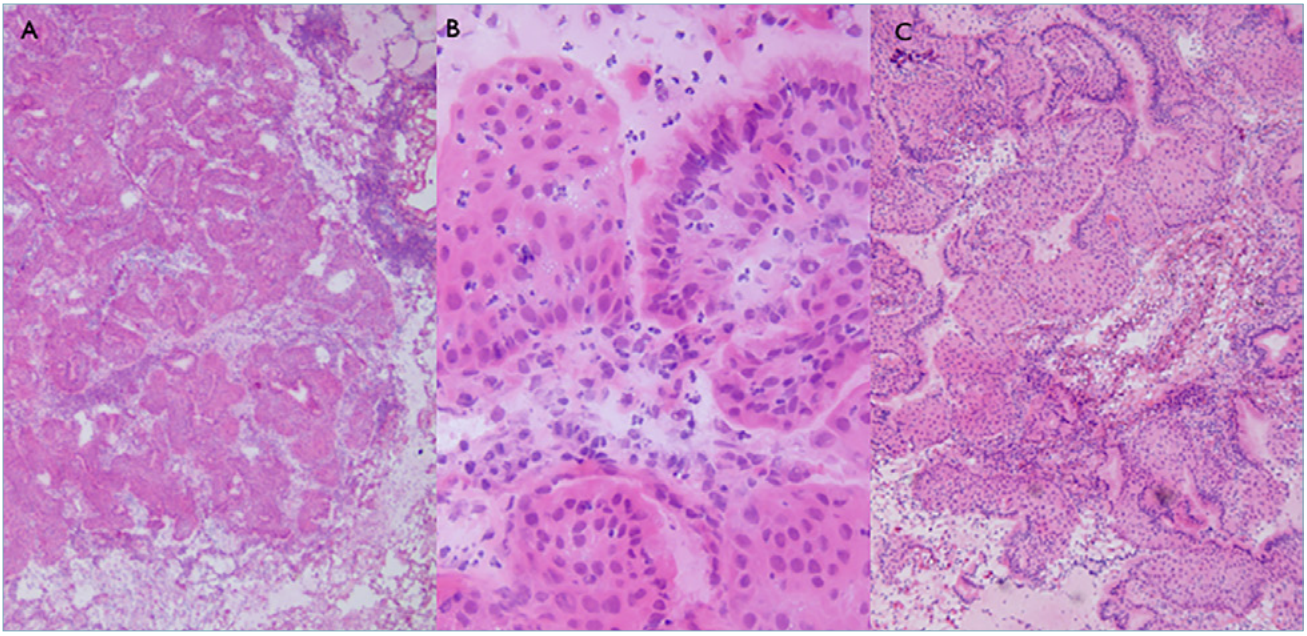

Figure 1. (A) Frozen section shows the infiltrative pattern of the lesion at low power (H&E 2.5x). (B) Frozen section showing the island of squamous cells with nuclear pleomorphisms focally lined by mucinous epithelium (H&E 10x). (C) Frozen section shows both components at low power (H&E 4x).

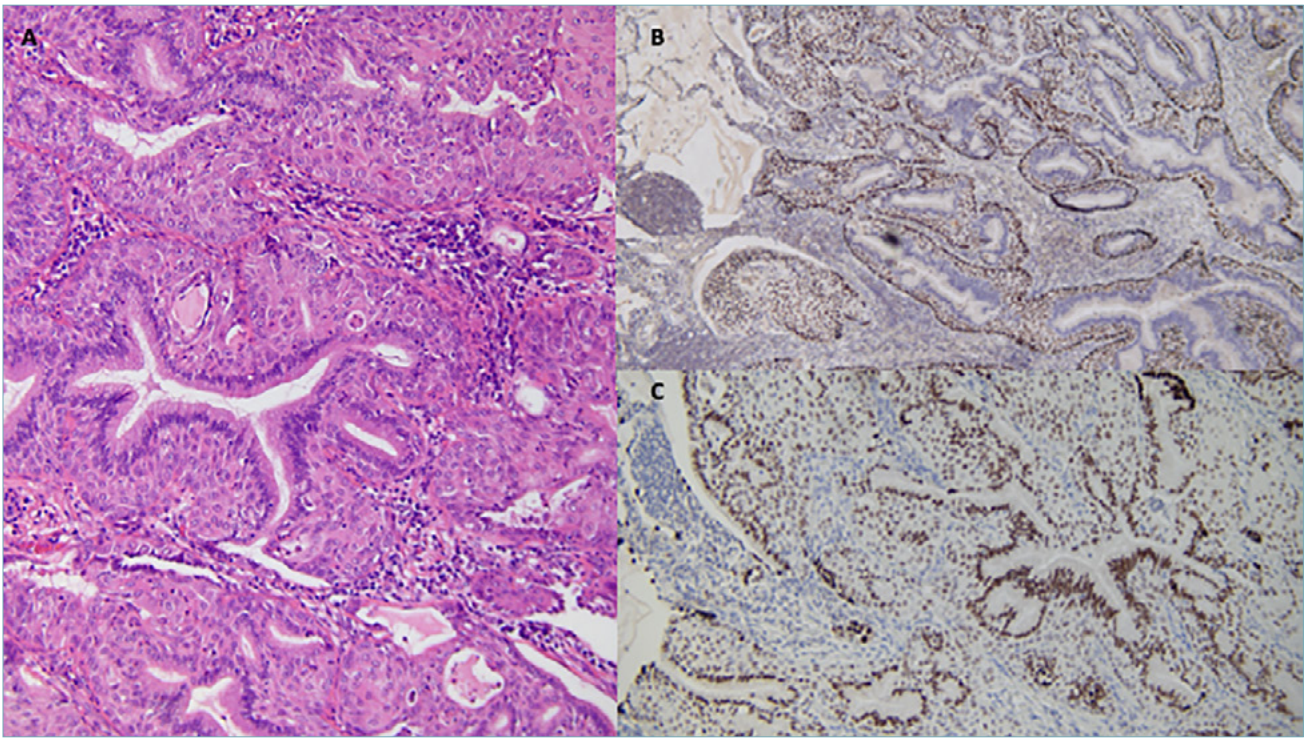

Figure 2. (A) Paraffin section shows the cytomorphological features of both components (H&E 10x). (B) The squamous cells are positive for squamous marker, while the glandular epithelium is negative (p63 4x). (C) The mucinous cells are positive for the glandular marker (TTF-1 4x).

challenging in frozen tissue. In our case, tumour cells extended into bronchiolar and alveolar spaces with mucus suggesting more aggressive behaviour, hence interpreted as malignant also given the strong clinical suspicion of cancer.

Pulmonary peripheral glandular papilloma (GP) and MSCGP have very similar histological features to the pulmonary ciliated micronodular papillary tumour (CMPT)/bronchiolar adenoma (BA). Some authors have investigated molecular alterations to differentiate these lesions. GP and MSCGP frequently harbour the BRAF V600E mutation [4]. Recently, AKT1 mutations concurrent with BRAF or HRAS mutations have been reported in these lesions as opposed to pulmonary adenomas [5]. Thus, molecular testing could be a useful tool in this setting for classification and treatment purposes. We identified no relevant mutations in our case however, and given the clear morphological features identified after generous sampling, we confidently reached the diagnosis. We reported this unusual case to raise awareness of unusual features that can occur in otherwise straightforward but uncommon lesions, especially when sampling is limited.

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Conflicts of interest

The authors declared no conflicts of interest.

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Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by IA, NG and PV.

The first draft of the manuscript was written by IA, PV and AM.

All authors read and approved the final manuscript.

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