Int J Clin Exp Pathol 2016;9(7):7674-7679
www.ijcep.com /ISSN:1936-2625/IJCEP0028401

Case Report

Solitary endobronchial mixed papilloma with prominent micropapillary pattern: a case report

Di Zhang[1,2], Nan Liu[1,2], Yang Liu[1,2], Yue-Feng Jiang[1,2], Ye-Lin Wang[1,2], Hong-Yi Cao[1,2], Liang Wang[1,2], Hong-Tao Xu[1,2], Qing-Chang Li[1,2], Xue-Shan Qiu[1,2], En-Hua Wang[1,2]

[1]Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang 110001, China; [2]Institute of Pathology and Pathophysiology, China Medical University, Shenyang 110001, China

Received March 16, 2016; Accepted May 26, 2016; Epub July 1, 2016; Published July 15, 2016

Abstract: Mixed squamous cell and glandular papilloma (mixed papilloma) is a rare, benign, pulmonary neoplasm and most commonly found in senile patients with male predilection. There were only 18 cases reported so far in the English literature. We herein present one case of mixed papilloma in a 61-year-old male patient. Contrast-enhanced computed tomography scanning revealed a solitary nodule in the inferior lobe of left lung with the obstruction of basal segmental bronchus. Histologically, the glandular component of the mixed papilloma was characterized by the prominent "Medusa head-like" micropapillae and occupied more than 70% of the whole lesion. In the current case, these micropapillary patterns were so worrisome and should be distinguished with primary or metastatic micropapillary adenocarcinoma, especially in frozen slides or if the specimen is limited. By reporting this case, we aim to remind the pathologist with this uncommon histological structure in mixed papilloma.

Keywords: Mixed squamous cell and glandular papilloma, squamous cell papilloma, glandular papilloma, pulmonary neoplasm, micropapillae, lung

Background

Pulmonary papillomas are relatively rare, benign neoplasms which are subclassified into three categories according to histological type: squamous cell papilloma, glandular papilloma, and mixed squamous cell and glandular papilloma (mixed papilloma) [1, 2]. Pulmonary papillomas usually arise from central lobar or segmental bronchi. Therefore, patients often present with obstructive symptoms including productive or paroxysmal cough, wheezing, or mild haemoptysis [1, 2]. Peripheral endobronchiolar lesions may also occur, but quite rare [1, 3-8]. Glandular papillomas and the glandular components of mixed papillomas are usually lined with ciliated or non-ciliated columnar cells, with varying numbers of cuboidal and goblet cells. Occasionally, stratified or pseudostratified columnar epithelium may form micropapillary tufts [2]. These structures pose a great diagnostic challenge, especially for determining whether the tumor is benign or malignant. Herein, we present a case of solitary endobronchial mixed papilloma with prominent "Medusa head-like" micropapillae. To our knowledge, this is the first case of pulmonary papilloma characterized by the prominent "Medusa head-like" micropapillae. The patient underwent a sleeve lobectomy of the left lower lobe and was alive with no tumor recurrence or metastasis for 6 months of follow-up.

Case presentation

Clinical history

A 61-year-old male was admitted to our hospital with chief complaint of shoulder hurt after falling down the stairs. Cardiovascular and cerebrovascular examination did not find organic disease. Contrast-enhanced computed tomography (CT) revealed a nodule with the greatest dimension of 1.78 cm in the inferior lobe of left lung with the obstruction of basal segmental bronchus. The CT value for the nodule was 28 HU and up to 59 HU after enhancement (**Figure 1**). He did not have fever, cough, wheezing, hae-

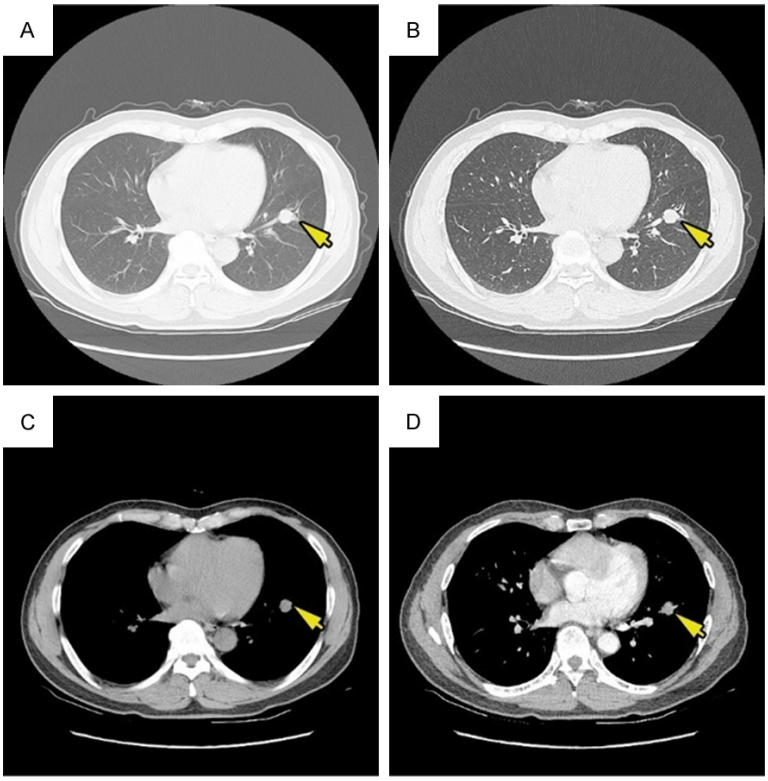

Figure 1. Imaging examination results of the patient. A-D: Contrast-enhanced CT revealed a nodule in the inferior lobe of left lung with the obstruction of basal segmental bronchus. The arrows indicate the mass.

moptysis or other pulmonary symptoms. Family history was not remarkable. A video-assisted thoracoscopic excision was performed. A pale, semi-firm lesion was found in the basal segment of left inferior lobe. The mass was well-demarcated with slight adhesion to surrounding normal tissue. Rapid intraoperative pathological diagnosis favors glandular papilloma and required the paraffin-embedded tissue and immunohistochemistry to further demonstrate. Finally, sleeve lobectomy of the left lower lobe was performed. A tumor of 1.5 × 1.0 × 0.8 cm in size was completely resected. The patient was alive with no tumor recurrence or metastasis for 6 months of follow-up.

Materials and methods

The tumor tissues were fixed in 10% formalin and embedded in paraffin. Several 4-μm sections were cut from each paraffin block, and one was stained with hematoxylin and eosin (H&E), the others were stained with immunohistochemistry (IHC). Immunohistochemical staining was performed using the streptavidin-peroxidase system (Ultrasensitive; Mai Xin Inc., Fuzhou, China) according to the manufacturer's instruction. Commercially available prediluted monoclonal antibodies against the following antigens were employed: pancytokeratin (AE1/AE3), vimentin, CK19, CK5/6, CK7, thyroid transcription factor-1 (TTF-1), p40, p63 and Ki-67. For the negative controls, the primary antibody was replaced with PBS.

Microscopic features

Histologically, the tumor was composed of mircropapillary and papillary structures. The former was characterized by a non-hierarchical branching architecture in which a myriad of fine, micropapillae, usually five times taller than they were wide, emanate directly from large, often fibrotic papillae (**Figure 2A**). Lymphocyte and plasma cell were observed within the stromal cores of the large papillae (**Figure 2B**). The micropapillae have scant or no stromal cores and in contrast to typical glandular papilloma, which contained columnar cells that are frequently ciliated, the cells of micropapillae are cuboidal with a high nuclear to cytoplasmic ratio and small, uniform, more atypical nuclei and cilia are conspicuously absent (**Figure 2C**). All these features above mimic micropapillary variant of ovarian serous borderline tumor. Hyalinized stromal stalks lined by a single layer of nonciliated columnar cells with basal nuclei were observed in focal area (**Figure 2D**). Foci of mucus retention were also observed within these hyalinized stromal stalks. In addition, the broad papillomatous fronds lined by columnar epithelium, which is the typical feature of glandular papilloma, were also identified in the current case (**Figure 2E**). Mucin-rich cuboidal and columnar cells were rare and hard to recognize in H&E slide, but can be easily identified by PAS and AB-PAS staining (**Figure 2F**, **2G**). Foci of acanthotic squamous epithelium without obvious keratinizing were observed (**Figure 2H**), but the proportion was quite low. Therefore, the final diagnosis of this case was revised to mixed papilloma. We also observed some expansive

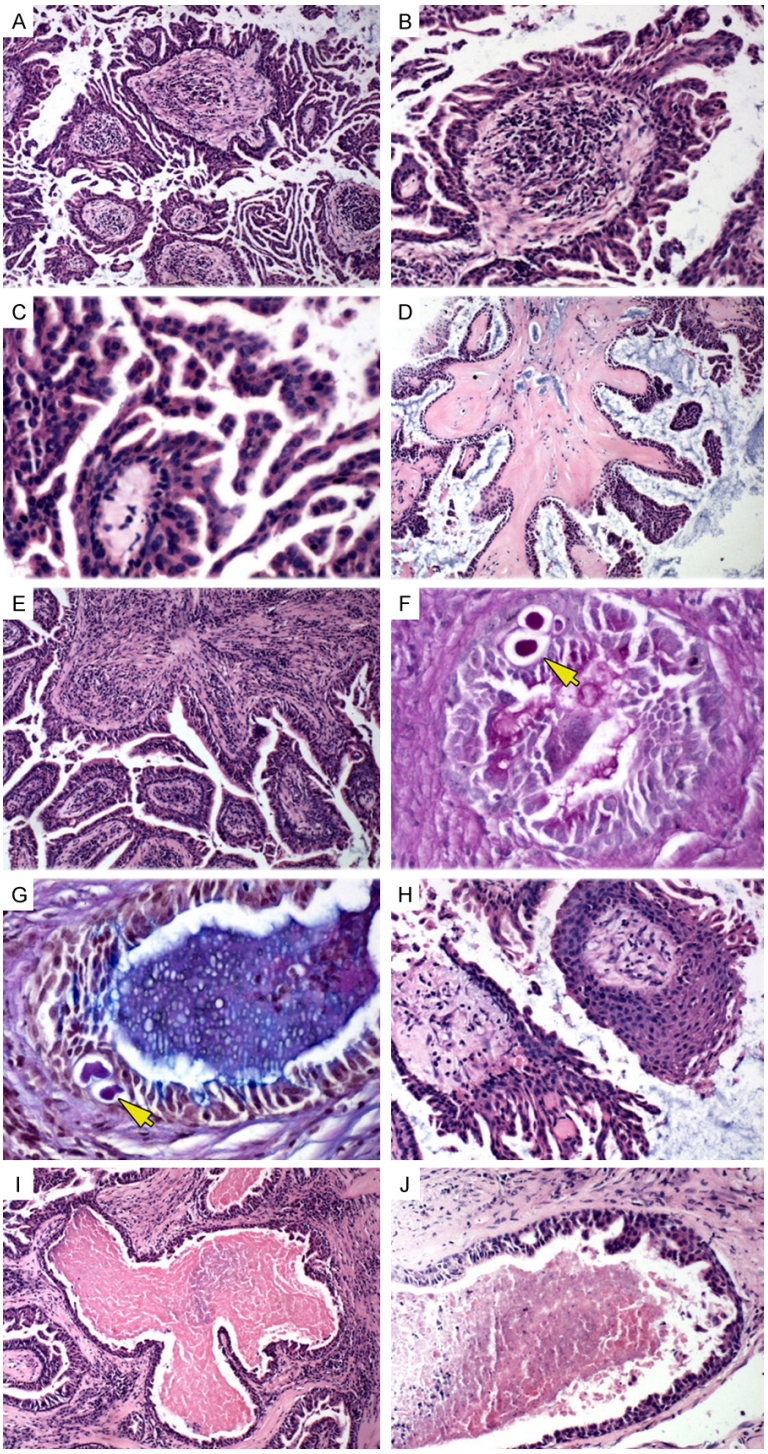

Figure 2. Histological features of this case. A: "Medusa head-like" micropapillary pattern. B: Lymphocyte and plasma cell infiltration in the stromal cores. C: Non-hierarchical branching architecture in which a myriad of fine micropapillae emanate directly from the large fibrotic papillae. The cells of micropapillae are cuboidal with a high nuclear to cytoplasmic ratio and small, uniform, more atypical nuclei. D: Hyalinized stromal stalks lined by a single layer of nonciliated columnar cells. E: The broad papillomatous fronds lined by columnar epithelium. F, G: Mucin-rich cuboidal and columnar cells were identified by PAS and AB-PAS staining. H: Foci of acanthoticsquamous epithelium without obvious keratinizing were observed. I: Expansive lumens in the large fibrotic stromal cores. J: Foci of suspicious intraluminal necrosis. The arrows indicate the "Mucin-rich" tumor cells.

lumens in the large fibrotic stromal cores (**Figure 2I**). Foci of suspicious intraluminal necrosis were also observed (**Figure 2J**), but pleomorphism and mitotic figures are absent.

Immunohistochemistry (IHC)

Tumor cells were markedly and diffusely positive for pancytokeratin (AE1/AE3) (**Figure 3A**), CK7, CK19 (**Figure 3B**) and CK5/6, but negative for vimentin (**Figure 3D**). All kinds of epithelia were positive for TTF-1 (**Figure 3C**), which was strongly immunostained in the basal cells of squamous component, while became weaker as the maturity of squamous epithelium. The basal cells beneath the columnar or cuboidal epithelium were labeled positive by p40 and p63 (**Figure 3E**). The Ki-67 labeling index was approximately 5% (**Figure 3F**).

Discussion

Pulmonary papillomas are relatively uncommon and can be classified according to number of lesions, location, and histology [1]. They have two clinical presentations which are multiple papillomas and solitary papillomas. Multiple papillomas, also known as papillomatosis, are usually related to papilloma virus infections, most often occurring in children and young adults, and involve both upper and lower respiratory tracts. In contrast to multiple papillomas, solitary papillomas are rarer, usually affect middle-aged adults and appear as a discrete polypoid nodule, and involve the trachea, the lobar and the segmental bronchi [9-12].

According to the location, pulmonary papillomas are divid-

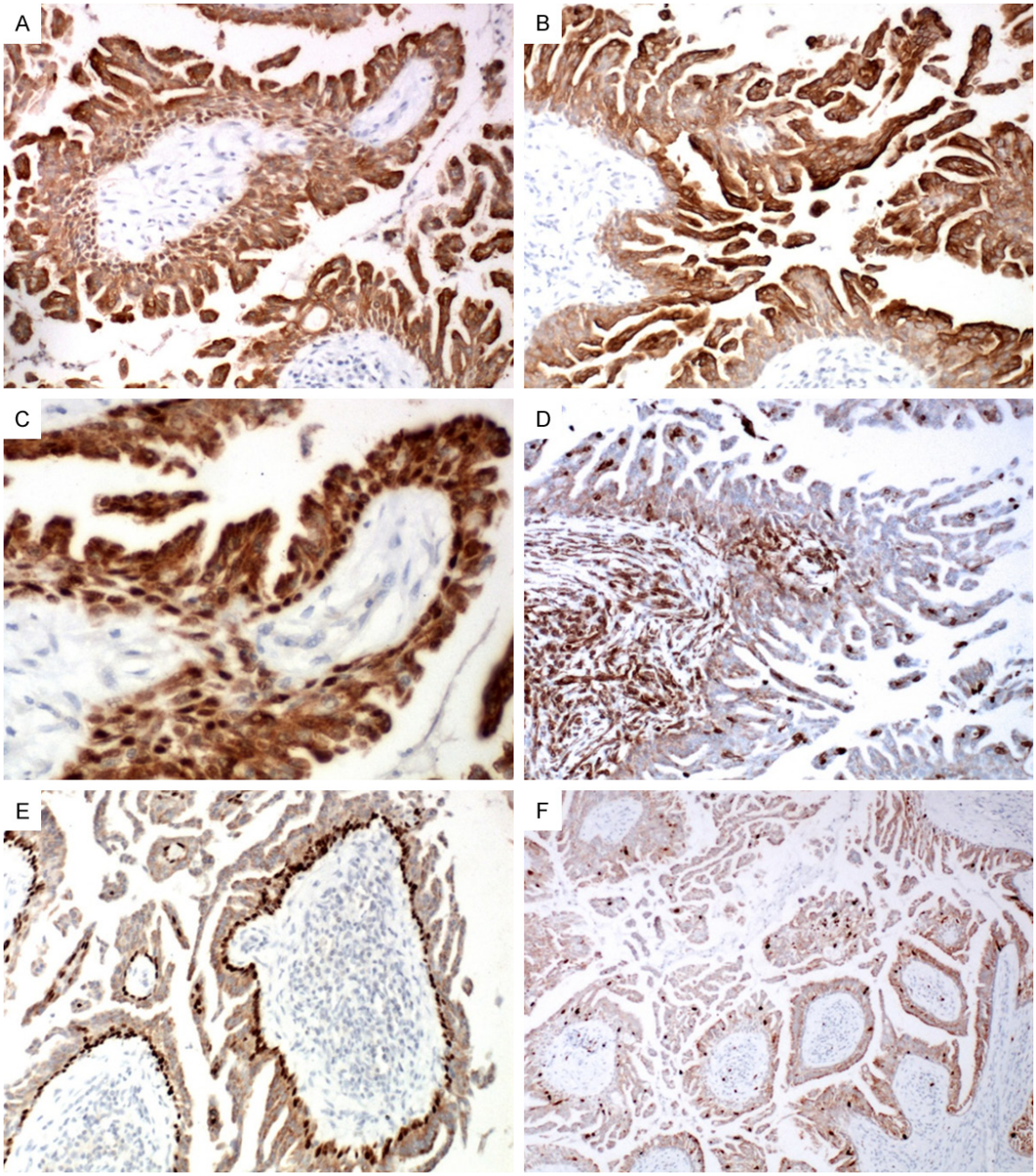

Figure 3. Immunohistological features of this case. A: Tumor cells were markedly and diffusely positive for AE1/AE3. B: Tumor cells were markedly and diffusely positive for CK19. C: All kinds of epithelia were positive for TTF-1. D: Tumor cells were negative for vimentin. E: The basal cells beneath the columnar or cuboidal epithelium were labeled positive by p63. F: The Ki-67 labeling index was approximately 5%.

ed into 2 types: endobronchial and peripheral papillomas. Endobronchial papillomas are easily detected and demonstrated by CT scanning, as the patients often present with obstructive symptoms including productive or paroxysmal cough, wheezing, or mild haemoptysis [3]. Compare with endobronchial papillomas, peripheral bronchiolar papillomas are extremely rare, and no more than 20 cases have been reported in English literature to date [1, 3-8]. However, these differences in prevalence may not reflect the real incidence rates of these lesions and the detection rates of peripheral bronchiolar papillomas may increase with the

popularization of chest radiography and high-resolution CT in health check [3].

Pulmonary papillomas are histologically divided into 3 categories according to the recent WHO classification, that is, squamous cell, glandular, and mixed types [1]. Squamous cell papillomas are the most common type, and characterized by the papillary fronds mainly covered with acanthoticsquamous epithelium. Glandular papillomas are apparently rare with only 20 cases having been reported in English literature since the first case report of bronchial glandular papilloma in 1954 by Ashmore [5, 13]. Histologically, glandular papilloma is lined by ciliated or non-ciliated columnar cells, with varying numbers of cuboidal and goblet cells. Mixed papillomas are extremely rare, with only 18 reported cases. The male-to-female ratio is 5:1, and the median age is in the sixth decade [2, 14]. Mixed papillomas show a mixture of squamous and glandular epithelium, with the glandular type constituting at least one third.

Malignant transformation of papilloma has been reported, but the exact relationship between solitary papillomas and bronchogenic carcinomas remains unclear. In the previous reports, 10 cases of squamous cell papilloma had malignant transformation (squamous cell carcinoma in 7 cases, low-grade differentiation cells of carcinoma in 3 case); 6 cases of mixed papilloma had malignant transformation (squamous cell carcinoma in 2 cases, adenocarcinoma in 2 cases, low-grade differentiation cells of carcinoma in 2 cases). Compared with the other two histological types of papillomas, there have been no reports of malignant transformation of glandular papillomas [6, 13-17].

In the current case, the main concern is the histological micropapillary structure, which is never described in the previous cases. "Micropapillary pattern" in pathology, was used to described the two histological features: 1. used to describe a non-hierarchical branching architecture in which a myriad of fine, micropapillae, usually five times taller than they were wide, emanate directly from large, often fibrotic papillae-e.g., always used to describe the micropapillary variant of ovarian serous borderline tumor. 2. used to describe the tumor cells growing in papillary tufts forming florets that lack fibrovascular cores. The tumor cells are usually small and cuboidal, with variable nuclear atypia-e.g., always used to describe the histological features of micropapillary adenocarcinoma in lung, breast and other organs and was always related with poor prognosis.

In the current case, "micropapillae" was used to describe the former histological features resembling "Medusa head" and also named as "Medusa head-like" appearance. Although the micropapillary or cellular tufts were rarely formed in glandular papilloma, this kind of micropapillary pattern is still different from that in our case. Of interest, the typical papillary pattern of glandular papilloma was also observed in the current case and these two histological patterns (micropapillary and papillary pattern) blended imperceptibly. In addition, these two histological patterns show the consistent immunophenotype (diffusely positive for CK, CK7, TTF-1, CK19 and both of them have a layer of positive basal cells which covering the large fibrotic papillae and can be labeled by p40 and p63). Considering the histological and immunohistochemical findings above, we speculate the different components arise from the same kind of progenitor cells. Thus, we believe that this "Medusa head-like" micropapillary pattern should be the histological variant of glandular papilloma. "Medusa head-like" micropapillary pattern always presents the low-grade malignant potential in other organs. We speculate that this uncommon histological pattern may be related with the low-grade malignant potential, but it is not possible to draw any kind of conclusion as there is lack of information in the majority of reported cases with this uncommon histological feature. Therefore, we considered it is necessary to report this case and so to better evaluate the real frequency and the biological behavior of the tumor with this uncommon histological feature.

In peripheral papilloma, glandular tumor cells can extend into bronchiolar and alveolar spaces with limited spread, and may have a similar appearance to peripheral adenocarcinomas of the bronchioloalveolar or papillary type. Of course, the metastatic adenocarcinoma should be also included into the differential diagnosis. Features which aid in differentiation with carcinoma are the absence of significant cytological atypia, hyperchromasia, mitoses, necrosis and two-layer cellular structure with intact basal cells. In the current case, suspicious intraluminal necrosis was also observed in focal area,

while it is hard to distinguish with the mucopurulent debris. Considering the structural multiformity, we believe that complete excision is necessary for definitive diagnosis and also the best way of treatment.

Conclusion

By reporting this case, we aim to remind the pathologist with this uncommon histological pattern in glandular papilloma and so to better evaluate the real incidence of this uncommon variant of pulmonary papilloma.

Acknowledgements

This study was supported by grants from the National Natural Science Foundation of China (No. 81302312 to Yang Liu and No. 81302192 to Liang Wang) and Natural Science Foundation of Liaoning Province (No. L2013292 to Yang Liu) and Scientific Research Foundation for the Returned Overseas Chinese Scholars (No. 2013277 to Yang Liu).

Disclosure of conflict of interest

None.

Address correspondence to: Yang Liu, Department of Pathology, The First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang 110001, China. Tel: +86 24 23261638; Fax: +86 24 23261638; E-mail: lyonliuyang@mail.cmu.edu.cn

References

[1] Flieder DB, Koss MN, Nicholson A, Sesterhenn IA, Petras RE and Travis WD. Solitary pulmonary papillomas in adults: a clinicopathologic and in situ hybridization study of 14 cases combined with 27 cases in the literature. Am J Surg Pathol 1998; 22: 1328-1342.

[2] Travis WD, Brambilla E, Burke A, Marx A, Nicholson AG; Cancer IAfRo. WHO classification of tumours of the lung, pleura, thymus and heart. International Agency for Research on Cancer 2015.

[3] Aida S, Ohara I, Shimazaki H, Dai Y, Ogata S, Ozeki Y and Tamai S. Solitary peripheral ciliated glandular papillomas of the lung: a report of 3 cases. Am J Surg Pathol 2008; 32: 1489-1494.

[4] Ashley DJ, Danino EA and Davies HD. Bronchial polyps. Thorax 1963; 18: 45-49.

[5] Ashmore PG. Papilloma of the bronchus: case report. J Thorac Surg 1954; 27: 293-294.

[6] Emerson LL and Layfield LJ. Solitary peripheral pulmonary papilloma evaluation on frozen section: a potential pitfall for the pathologist. Pathol Res Pract 2012; 208: 726-729.

[7] Inamura K, Kumasaka T, Furuta R, Shimada K, Hiyama N, Furuhata Y, Tanaka I and Takemura T. Mixed squamous cell and glandular papilloma of the lung: a case study and literature review. Pathol Int 2011; 61: 252-258.

[8] Sari I, Uzunlar AK, Buyukbayram H, Ozcelik C, Yilmaz F and Ozaydin M. Non-squamous papilloma of the bronchus. S Afr Med J 2000; 90: 867-869.

[9] Barzo P, Molnar L and Minik K. Bronchial papillomas of various origins. Chest 1987; 92: 132-136.

[10] Drennan JM and Douglas AC. Solitary Papilloma of a Bronchus. J Clin Pathol 1965; 18: 401-402.

[11] Maxwell RJ, Gibbons JR and O'Hara MD. Solitary squamous papilloma of the bronchus. Thorax 1985; 40: 68-71.

[12] Spencer H, Dail DH and Arneaud J. Non-invasive bronchial epithelial papillary tumors. Cancer 1980; 45: 1486-1497.

[13] Tryfon S, Dramba V, Zoglopitis F, Iakovidis D, Sakkas L, Kontakiotis T and Galanis N. Solitary papillomas of the lower airways: epidemiological, clinical, and therapeutic data during a 22-year period and review of the literature. J Thorac Oncol 2012; 7: 643-648.

[14] Kozu Y, Maniwa T, Ohde Y and Nakajima T. A solitary mixed squamous cell and glandular papilloma of the lung. Ann Thorac Cardiovasc Surg 2014; 20 Suppl: 625-628.

[15] Lagana SM, Hanna RF and Borczuk AC. Pleomorphic (spindle and squamous cell) carcinoma arising in a peripheral mixed squamous and glandular papilloma in a 70-year-old man. Arch Pathol Lab Med 2011; 135: 1353-1356.

[16] Lin D, Jiang Y, Wang J, Ding L, Xin F, Zhao H and Li Y. Pulmonary mixed squamous cell and glandular papilloma mimicking adenocarcinoma: a case study and literature review. J Thorac Dis 2013; 5: E129-132.

[17] Paganin F, Prevot M, Noel JB, Frejeville M, Arvin-Berod C and Bourdin A. A solitary bronchial papilloma with unusual endoscopic presentation: case study and literature review. BMC Pulm Med 2009; 9: 40.