Classic Ciliated Muconodular Papillary Tumor of the Lung With Braf Mutation: The New We Should Know

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Case Report

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Abstract

Background Ciliated muconodular papillary tumor (CMPT) was initially recognized as three typical types of cells (ciliated cells, mucinous cells and basal cells) and two typical structures (papillary and tubular). It is found that the proportion of various cells is different and papillary structure is not necessary. So some scholars propose that CMPT is a proximal-type bronchiolar adenoma (BA) which expands the concept of CMPT. At the same time they propose revising the terminology. These morphological variations bring great challenges to the diagnosis.

Case presentation: Multiple small nodules in bilateral lungs were found in 79-year old female patient. A frozen examination was performed. Grossly, there were jelly-like nodules with clear boundaries, and the maximum diameter was about 4mm. Microscopically, glandular ducts, papillary and even micropapillary structures were seen. The cavities were lined by columnar cell and mucous cells. In a low-power field the conspicuous mucin pool was observed, as well as floating tumor cells in the mucin pool. So atypical adenomatous hyperplasia of the lung was reported in intraoperative rapid diagnosis, and the surgeon performed a lobectomy for the patient. In typical HE, this tumor was made up of three kinds of cells in different proportions, including ciliated columnar cells, mucous cells, and basal cells which were confirmed by CK5/6 and P63 immunohistochemistry staining. Immunohistochemical analysis reveals thyroid transcription factor1 (TTF-1) and CK7 expression by ciliated columnar epithelial cells, basal cells, and nonciliated columnar and cuboidal epithelial cells, but not mucous cells. All the cells do not express CK20. BRAF V600E protein express in the tumor. At the same time, the tumor harbores the *BRAF* gene mutation, while *EGFR*, *KRAS*, *ALK*, *HER-2*, *RET*, *ROS-1*, *PIK3CA* and *NRAS* mutation are negative.

Conclusion We report a classic CMPT. The tumor has *BRAF* mutation and BRAF protein expression. Classic lesions are easy to identify, while for morphological variant cases, the key to the diagnosis of the disease is the diversity of cell components and the presence of basal cells.

Introduction

Ciliated muconodular papillary tumor (CMPT) is a low incidence tumor and is first described by Ishikawa [1]. Up to now almost the cases reported come from Asian. Shao et al. reviewed 41 cases of CMPT including their own two cases and summarized that the tumor could be seen in all age groups, and was prone to the elderly, with no gender difference [2].

CMPT is characterized as a papillary tumor consisting of ciliated columnar, mucous cells and basal cells. The different morphologies of CMPT reported are including partial papillary structures, and even lack of papillae, along the alveolar wall in a flat shape or forming an adenocoelomoid structure and a continuous basal cell layer in the base. All these morphological features are mimics to the morphological variation from bronchioles to terminal bronchioles. So it is speculated that CMPT originated from bronchioles. In 2017, at the US Canada pathology conference, Chang et al. proposed the concepts that CMPT were essentially the continuous changes of mucosal epithelial cells from proximal bronchioles to

distal bronchioles. Therefore, it is suggested that this kind of tumor should be named as bronchiolar adenoma and further divided into proximal type and distal type according to morphology, and CMPT is the member of BA family [3]. Zheng et al. affirmed and consolidated this view [4].

Histologically, the tumor is composed of papillary and adenoid structures lined by ciliated columnar cells, mucus cells and basal cells with different proportions[5]. The shed tumor cells can float in the mucus-filled alveolar cavity, which is easy to misdiagnose as a mucinous adenocarcinoma[6,7], especially in frozen sections. The cytoplasm of ciliated columnar epithelium is slightly rich in eosinophils, with round nuclei and nucleoli, forming micropapillary clusters in the glandular cavity, similar to cancer [8]. The basal cells are not easy to recognize and immunohistochemistry is helpful. Low Ki67 index and no stromal reaction facilitated the diagnosis[9, 10].

Molecularly, several studies have reported that CMPT has mutations in BRAF V600E, KRAS, EGFR and / or ALK genes, which further indicates that CMPT is a tumor [11-15].

At present, about 50 cases of CMPT have been reported, and none of them has recurrence or metastasis. Sub-lobectomy may be proper and adjuvant treatment should be avoided since the disease is now prone to benign lesions.

Case Report

Clinical history

We will report a case about CMPT, now known as BA. The CT scan of chest suggested that there were multiple small nodules in the upper and middle lobe of the right lung. The largest was about 0.4 cm in diameter and the border was smooth. Contrast enhancement CT scan showed no abnormal enhancement foci in the lung. No other nodules were identified (Figure 1). Intraoperative rapid diagnosis with a frozen section of the tumor indicated atypical adenoma-like hyperplasia, due to less cellular heterogeneity and lack of some basic features for diagnosing adenocarcinoma. The surgeon performed a lobectomy for the patient, with no lymph node dissection. Clinical follow-up was about 24 months without local recurrences or distant metastases.

Pathologic findings

Postoperative pathological analysis showed that the border of tumors was a little ill-defined (Figure 2A and B). The tumor was consisted of proliferated epithelium with adenoid and papillary structures, including ciliated columnar, mucous and basal cells (Figure 2D and E). The ciliated cells are rich and acidophilic in cytoplasm, and some of them form micropapillary clusters in the glandular cavity (Figure 2C). Tumor cells showed no atypia, mitosis or necrosis. Stromal reaction is slight with lymphocyte infiltration between glands (Figure 2E). Mucus could be seen in the normal alveolar cavity around the tumor (Figure 2F).

Immunohistochemical features and molecular pathology analysis

The immunohistochemical profile of the ciliated columnar and mucous cells showed that CK20 was negative, CK7 was positive (Figure 3A). Thyroid transcription factor 1 (TTF-1) was positive in ciliated cells and basal cells, with mucous cells negative (Figure 3B). CK5/6 and P63 was positive in basal cells (Figure 3C and D). The proliferating index (Ki67) is low (Figure 3E). At the same time, we detected the expression of BRAF V600E, and found BRAF V600E was positive in the tumor (Figure 3F).

Molecular detection was performed after immunohistochemical, BRAF mutation was also detected, while EGFR, KRAS, ALK, HER-2, RET, ROS-1, PIK3CA and NRAS mutation were negative.

Discussion

CMPT first was described by Ishikawa in 2002. Up to now, no more than 50 cases were reported in English and Chinese. In our case, HE and immunochemical staining which include TTF-1, NapsinA, CK5/6 and P63 show three cell types and at the same time the basal cell is complete. Papillary sturctue, even micropapillary is obvious. So this case is a classic CAMP, distal-type BA.

In our case, the ciliary micropapillary structure is more common (Fig 2C), even forming cell clusters in glandular cavity, similar to micropapillary carcinoma. If we realize that no matter which type of BA, there will be ciliated cell micropapillary structure, and at the same time, lacking other histological and cytological characteristics of cancer can be differentiated.

As shown in Figure 2, the stroma in the tumor widened and even formed acinar structure, similar to adenocarcinoma. This phenomenon is particularly prominent in frozen sections. However, by careful observation we find that the widened stroma mainly due to edema and inflammatory lesions, and often lack of thick collagen fibers. The wide range of stroma may also be related to frozen production.

In this case, the boundary of the tumor is unclear, and the focal tumor cells grow along the alveolar wall (Figure 2B), but the basal cells are all present by immunohistochemistry, and the tumor cells were mild in morphology. This growth pattern is consistent with the jumping growth pattern reported in the literature [3].

On the issue of basal cells, Chang emphasised that both distal BA and proximal BA had bilateral structures. Basal cells exist, but may not be complete. However, Zhang et al. recognized that basal cells are not a necessary condition for the diagnosis of BA [16]. And cases of partial disappearance of basal cells or even complete disappearance of basal cells are constantly found. In our case, the basal cell is intact, which indicates that it is a benign lesion.

Due to the progress and widespread application of molecular biotechnology, the detection and analysis of molecular genetic changes of CMPT is accompanied by the histological observation almost from the beginning. The results show that although BRAF mutation is the most common genetic change in BA (usually occurs in V600E of exon 15), the genetic characteristics of BA are heterogeneous, including EGFR19del, ALK rearrangement, AKT1 E17K mutation and KRAS mutation. Zheng et al. considered that

BRAF mutation rate in classical CMPT was higher than that in non classical CMPT. However, Chang et al. believed that BRAF had a higher mutation rate and was more common in distal BA. Udo et al. reviewed four cases of CMPT and performed genomic analyses. Gene mutations were detected in two of the four cases, including BRAF V600E, AKT1 E17K, KRAS G12D and KRAS G12C [14]. Because mutations of oncogenes such as EGFR and KRAS are related to the pathogenesis of lung adenocarcinoma, some researchers believe that the presence of EGFR and KRAS mutations in CMPT may be precancerous lesions or low-grade malignant tumors of mucinous adenocarcinoma. We also detect BRAF mutation in V600E of exon 15, and the BRAF V600E protein is overexpression detected by immunohistochemical.

In conclusion, CMPT also known as distal-type BA, the incidence is very low. At present, the morphological spectrum of this disease has been expanded, and the diversity of cell types and the presence of basal cells are the important features of this disease. The disease can be misdiagnosed as cancer, especially in frozen sections, so learning about the disease needs to be enhanced. The last thing I want to emphasize is that according to the published literature, the tumor may be a benign tumor, but it needs more cases and longer follow-up time to further prove.

Abbreviations

CMPT: Ciliated muconodular papillary tumor; BA: bronchiolar adenoma ; ALK: Anaplastic lymphoma kinase; CK: Cytokeratin; TTF-1: Thyroid transcription factor-1; EGFR: Epidermal growth factor receptor; HER-2: human epidermalgrowth factor receptor-2; ROS-1: reactive oxygen species 1; HE: Hematoxylin and eosin; PCR: Polymerase Chain Reaction; KRAS: V-Ki-ras2 Kirsten ratsarcoma viral oncogene homolog.

Declarations

Authors' contributions

Zhang Minfeng analyzed the data and drafting the manuscript as a major contributor, Li Zhao prepared the pictures and collected clinical data , Shaoyan Liu and Xuexian Tan participated in immunostaining and molecular analysis, Qingping Jiang conceived of the study design, and reviewed manuscript, Na Wang participated in writing the final manuscript as a corresponding author. All authors participated for data analysis and approved the final version.

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Availability of data and materials

All data is available upon request to the corresponding author.

Ethics approval and consent to participate

All procedures performed in this study were approved by the ethical committee at The Third Affiliated Hospital of Guangzhou Medical University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

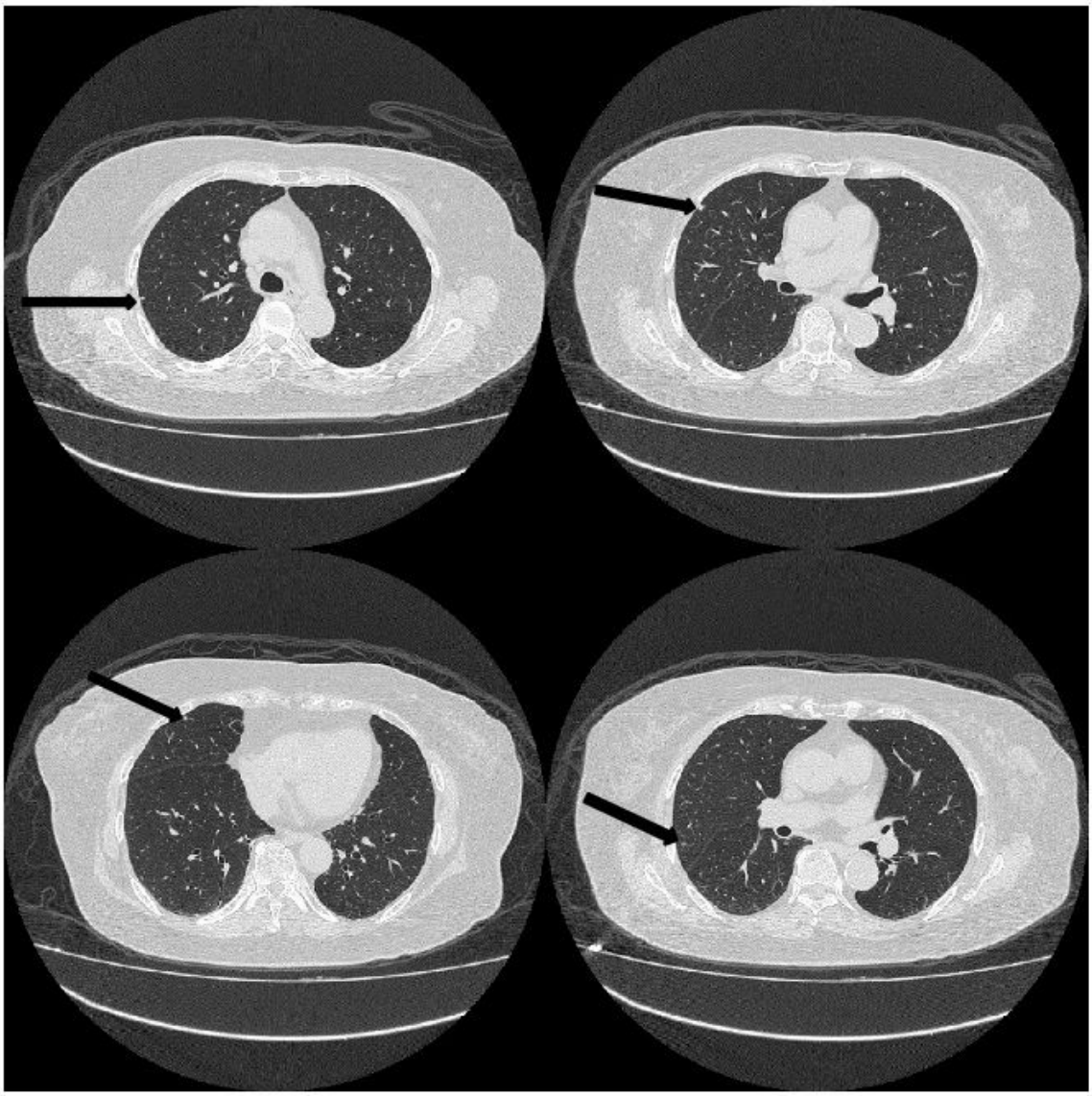

Figure 1

The arrow shows ground glass nodules.

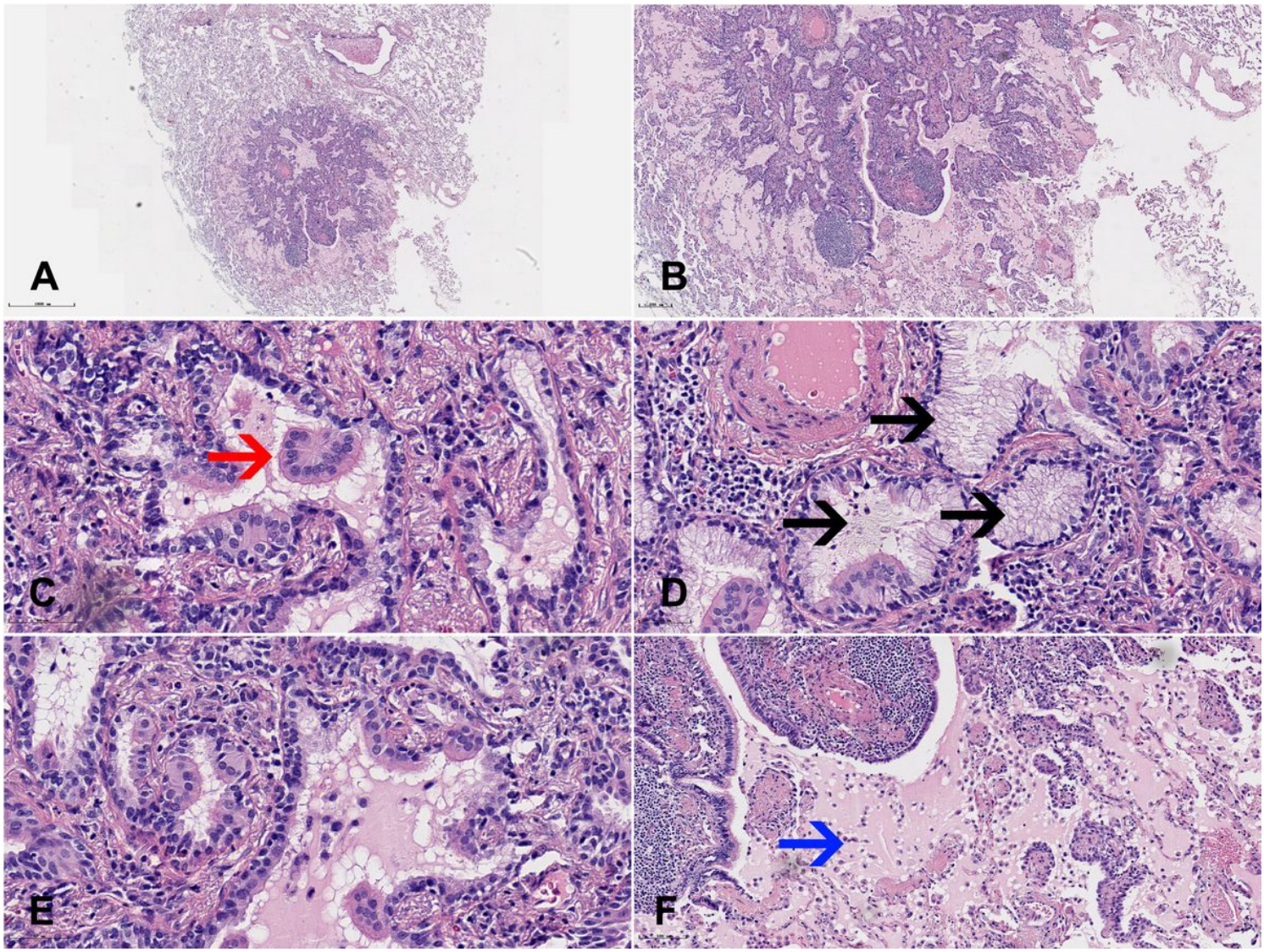

Figure 2

A. Under the low power microscope of tumor□B. The boundary of the tumor was not clear at 100□ C. Ciliated cells form micropapillary structures. D. The arrow shows the mucous cells.E. The focal area showed two layers of cells. F. Mucus pool with inflammatory cells.

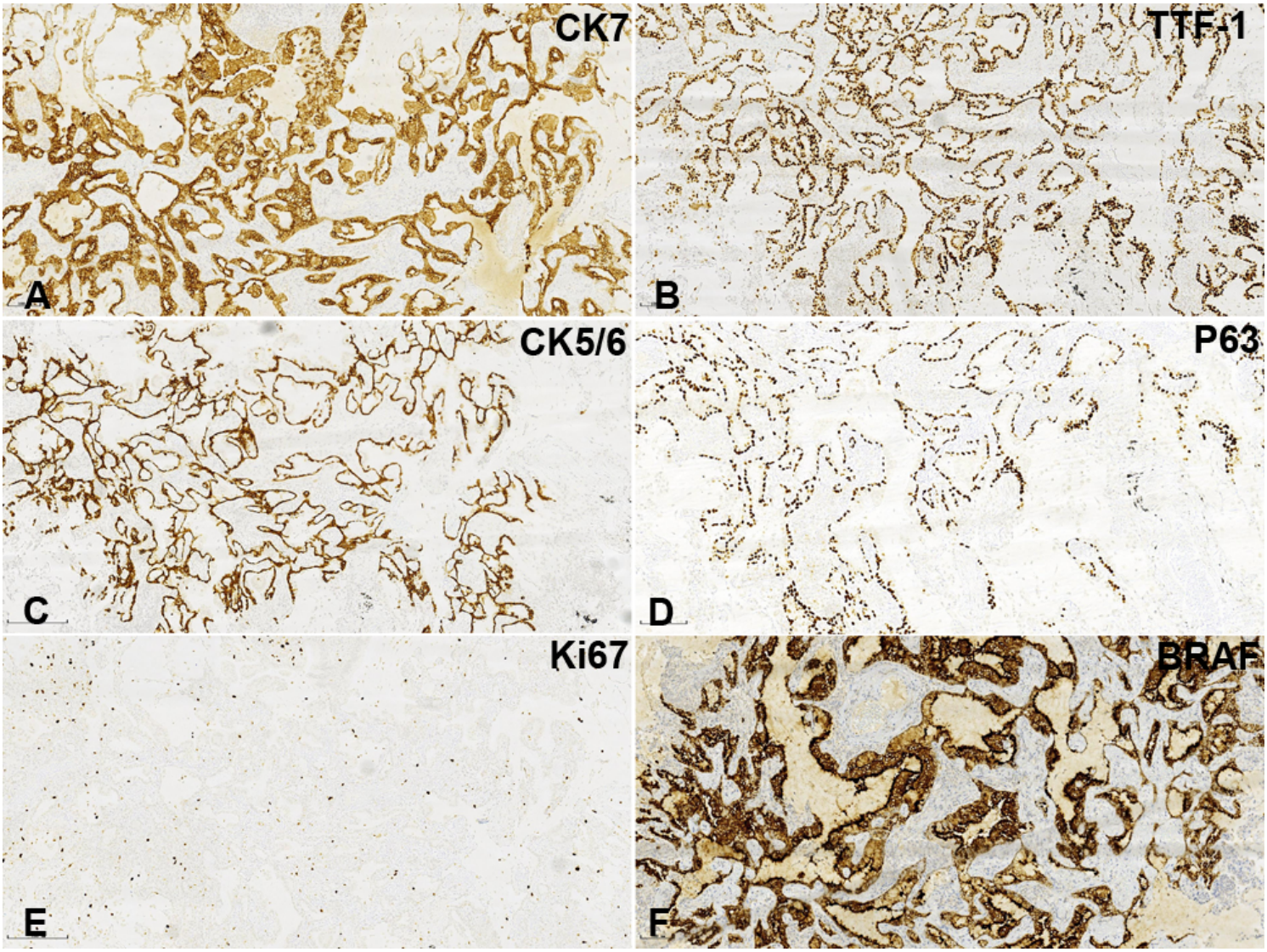

Figure 3

A.CK7 shows strong positivity in luminal cells and basal cells. B. TTF1 shows weak to moderate positivity in the basal cells, whereas it is negative in the luminal cells. C and D P63 and CK5/6 highlight a continuous basal cell layer. E. Ki67 shows a very low proliferative index. F. BRAF shows strong positivity.

Supplementary Files

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- CAREchecklistEnglish2013.pdf