

# Tracheal Solid Variant of Adenoid Cystic Carcinoma with Basaloid Features: A Case Report and Review of Literature

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## Case report

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# Abstract

**Background:** Primary tracheal adenoid cystic carcinoma (ACC) is a rare and heterogeneous group of neoplasms arising from the respiratory tract. The solid variant of ACC is a histologically distinct subtype with unfavorable clinical course. We report a case of tracheal ACC with immunohistochemical and molecular analysis together with a review of the literature.

**Case presentation:** A 31-year-old man presented with a neoplasm growing on the lower part of the total tracheal membrane, left side wall and anterior wall. The tumor was obtained via fiberoptic bronchoscopy. Histologically, the tumor is characterized by a predominant compact sheet-like and nested pattern of rounded basaloid cells. Immunohistochemically, the tumor was diffusely positive for CK and CD117. CK7 and CK5/6 was focally positive in the genuine glandular structures. P63 was completely negative in majority of neoplastic cells. Fluorescence in situ hybridization analysis revealed MYB gene rearrangement. The current case showed an almost entirely solid pattern of growth with basaloid features, and was morphologically difficult to distinguish from a variety of other round cell neoplasms.

**Conclusions:** This case report highlights the significance of various histological patterns and diagnostic modalities in making an accurate diagnosis of primary tracheal ACC at an early stage.

## Background

Adenoid cystic carcinoma (ACC) is a rare, distinctive salivary gland malignant neoplasm arising infrequently as a primary tumor in the lung[1]. ACC often arises in trachea and main bronchus. Morphologically, this subset of primary pulmonary carcinoma is histologically indistinguishable from ACC arising from other sites. ACC can have three architectural growth patterns: cribriform, tubular and solid with cribriform pattern being the most common type. The solid variant of ACC with basaloid features is a histologically distinct subtype that has been associated with an unfavorable clinical course[2,3]. We report a case of tracheal solid variant of ACC that has a striking basaloid appearance. We performed a clinicopathological, immunophenotypic and molecular analysis to delineate the characteristic features of this rare subtype. We highlight the need to recognize ACC in its solid form, discuss the differential diagnosis, and emphasize the need to establish a correct diagnosis for appropriate clinical management.

## Case Presentation

### Case presentation

A 31-year-old Chinese man presented to our hospital with the chief complaints of cough, expectoration and hemoptysis for half a month without apparent cause. He denied other symptoms including dyspnea, chest pain, fever and recent weight loss. The patient's chest computed tomography (CT) demonstrated multiple lymph nodes enlargement, tracheal and esophageal compression, and multiple lung nodules in

the horizontal mediastinal aortic window. Positron emission tomography (PET) showed lower tracheal nodules, multiple infiltrations in the lower tracheal and left main bronchial wall, multiple mediastinal lymph nodes enlargement, and multiple bone lesions throughout the body, which suggested the possibility of tracheal carcinoma with multiple metastasis. The patient underwent a fiberoptic bronchoscopy. A neoplasm was detected on the lower part of the total tracheal membrane, left side wall and anterior wall, arising at 3cm distal to the upper segment of the left main bronchus from the protrusion of trachea (Fig.1). An endobronchial fine needle aspiration (FNA) was performed on the mass under bronchoscopic guidance and FNA smears was made. The cytologic smears were highly cellular and contained 3-dimensional clusters of neoplastic basaloid cells, which were very rarely associated with hyaline basement membrane material. The individual tumor cells were homogeneous in size,. The neoplasm consisted of aggregates of basaloid cells with small to medium size, scant cytoplasm and evenly hyperchromatic nuclei.

Bronchofibroscope biopsy tissue was observed under the microscope (Fig.2): The surface of the tumor tissue was covered by pseudostratified columnar respiratory-type epithelium. The tumor exhibited a predominantly solid (>90%) architecture comprised of basaloid appearing cells. The solid nests were distributed under the mucosa and had microscopically invasive border. The solid area, showing "geographic", irregular or "garland-like" islands, also could be seen in the local shape of a sieve or trabecular structure. The intervening stroma was typically fibromyxoid or hyalinized. The neoplastic cells had a predominantly basaloid appearance characterized by small to medium cells. The surrounding cells were arranged in a palisade. The tumor cells showed scant, mildly eosinophilic cytoplasm with round to oval hyperchromatic nuclei and inconspicuous nucleoli. Nuclear atypia was moderate to marked. Mitotic activity was observed. Intercalated ducts within solid nests were poorly formed. Occasionally pseudoglandular structures were also seen with cribriform or gland with various sizes. These spaces were filled with homogenous, eosinophilic material. Focal necrosis was present in the nests of tumor cells.

The tumor tissue sections were immunostained with primary antibodies against broad-spectrum cytokeratin (CK), CK7, p63, p40, CD117 (c-kit), CK5/6, Calponin, thyroid transcription factor-1(TTF-1), NapsinA, LCA, FLI-1, S-100, Synaptophysin(Syn), Chromatin A(chgA) and CD56. All antibodies were purchased from Gene Company. After incubation with primary antibody, the detection of antibodies was accomplished using the Streptavidin-peroxidase method. Immunohistochemically, the tumor was diffusely positive for CK and CD117. CK7 and CK5/6 was focally positive in the genuine glandular structures. P63, specific for myoepithelial cells, was completely negative in majority of neoplastic cells. Focal, weak staining was seen in small area. The tumor was negative for p40, Calponin, TTF-1, NapsinA, LCA, FLI-1, S-100, Syn, chgA and CD56. The percentage of cells that stained positively for ki-67 was about 20-30% (Fig.3).

Fluorescence in situ hybridization (FISH) was performed on 5-um-thick paraffin sections (Fig.4). To detect MYB rearrangement, a dual-color break apart interphase FISH assay was performed using centromeric (BAC clone RP11-349 J5, red) and telomeric (BAC clone RP11-641019, green) probes. MYB break-apart assay: Nuclei with a positive MYB break apart signal showed nonoverlapping single centromeric (red)

and telomeric (green) signals in 1 allele of tumor cells, whereas the other allele (not rearranged) showed 1 yellow signals due to superimposed red and green signals. Tumors with greater than or equal to 10% abnormal cells were considered positive for rearrangement [4].

## Discussion And Conclusions

Tracheal ACC is a rare low-grade malignant tumor of the trachea and bronchi. It is most common in the lower third of the main bronchus and can occur at any age with a peak incidence of 40–50 years of age [5]. Because the ventilatory capacity of the trachea is obviously greater than the general actual needs of the body, early small tumors in the trachea can not cause any symptoms of airway obstruction, with only occasional chest tightness, irritant cough, phlegm, or cough blood sputum. For primary tracheal tumor, although fiberoptic bronchoscopy detection rate is low, it is unique for early occult lesions and preoperative pathological diagnosis. In our case, fibrebronchoscopy revealed new organisms on the left and front walls of the lower part of the trachea, extending from 3cm above the protrusion to the upper left main bronchus. The clinical features of this patient and the presence of fiberglass are very similar to those reported in the literature.

Primary tracheal ACC is a rare, distinctive salivary gland-type malignant neoplasm. The tumor is composed of a dual-cell population of luminal and myoepithelial / basal cells. ACC has three distinct growth patterns: tubular, cribriform and solid. Compared with typical ACC, the solid basaloid variant appears to be a high-grade variant. It is more aggressive, prone to distant metastasis and worse prognosis[2,3].The tumor cells in the basaloid variant exhibited moderate to marked atypia and pleomorphism. Increased mitotic activity is also commonly seen. Some of the cells surrounding the solid nests were arranged in a palisade pattern. In our case, in small areas which constituted less than 5% of the neoplasm, inconspicuous glandular lumen or cribriform structure can also be seen. Although very focal, the present of cribriform structures is the key morphological feature for diagnosis [6,7].The local cribriform structure can often reveal the nature of adenoid cystic carcinoma.

The two different cell types of ACC can be easily distinguished by immunohistochemistry. The basal layer cells are typically positive for myoepithelial markers (p63, S-100, Calponin), vimentin, whereas the luminal cells exhibit positivity for CK7, EMA, CK5/6 and c-kit (CD117). In our case, the tumor was uniformly positive for CK and CD117, with focal expression of CK7 and CK5/6, while myoepithelial cells were only rarely demonstrable with P63. Previous studies have revealed that the typical dual population of cell types is not always demonstrable in the solid (basaloid) variant of ACC [7].This is in concordance with our histologic results. The tumor is entirely composed of basaloid cells with only rare foci of myoepithelial cells. It has been suggested that basaloid cells represent primitive cells. They may be poorly differentiated or undifferentiated tumor cells with the potential of multi-directional differentiation into adenoid, squamous and myoepithelial cell cells. In solid variant of ACC with distinctive basaloid features, solid nests may be scattered with inconspicuous adenoid or sieve structures, which suggesting an undifferentiated or poorly differentiated ACC. Consequently, absence of cells expressing myoepithelial markers does not exclude the diagnosis of solid variant ACC [6,7].

Series studies have revealed that C-kit gene encodes a glycoprotein receptor called CD117, a member of the tyrosine kinase family. CD117 plays a role in regulating apoptosis, cell differentiation, proliferation, chemotaxis and adhesion through phosphorylation with ligands. CD117 is expressed in 92% of salivary ACC [8]. It is also the basis of differential diagnosis between salivary ACC and other head and neck malignancies. In addition to head and neck, ACC of the breast, trachea, skin and cervix also expressed CD117. Crisi, *et al* [9] have shown that in classical cribriform or tubular ACC, CD117 is mainly expressed in the inner layer of the cell nest, but CD117 was observed in all the nests in solid variant of ACC with basaloid features. In this case, the expression characteristics of CD117 are the same as those in the literature. The authors believe that in addition to the histological features, ACC as an independent tumor entity, the constant expression of CD117 can be used as an important basis for differential diagnosis from other types of malignancies.

Person, *et al* confirmed the presence of translocation t(6;9)(q22-23;p23-24) in ACC, which led to the formation of an MYB-NFIB fusion gene and has been identified as a tumor specific cytogenetic abnormality of ACC. The consequence of the translocation leads to overexpression of MYB-NFIB transcripts and activation of MYB target genes involved with cell cycle control, apoptosis, cell adhesion, and angiogenesis [6,10]. The incidence of MYB-NFIB fusion in ACC was 49-57% (mean 54%) and it is highly specific [10]. Detection of MYB rearrangement can be used as a reliable and accurate method for differential diagnosis between ACC and other tumors. In our case, FISH for MYB break-apart assay showed separate red and green signals in more than 30% tumor cells, supporting the diagnosis of solid variant of ACC. However, it should be emphasized that not all ACCs show MYB rearrangement, and a normal FISH pattern does not rule out this diagnosis.

The differential diagnosis includes several other small round tumors [6,11,12]. Poorly differentiated squamous cell carcinoma is composed of nests or cords of cells and has pseudoglandular structure without obvious keratinization. Frequently in situ carcinoma of squamous cell is found near the infiltrating area. p63 and CK5/6 are typically diffusely and strongly positive, whereas CD117 is negative. Small-cell (neuroendocrine) carcinoma shows similar features of tightly packed rounded or ovoid cells with hyperchromatic nuclei, scanty cytoplasm and nuclear molding. Markers of neural differentiation are variably expressed. CK may show a paranuclear, dot-like expression pattern. Nuclear TTF-1 expression may be prominent in more than 90% of cases, with different degrees of bcl-2 and CD117 positivity. The Ki-67 positive rate is usually more than 50%. Small cell carcinoma is generally free of the typical cribriform structure in adenoid cystic carcinoma. Nonkeratinizing squamous cell carcinoma (SCC) with basaloid features is a highly aggressive tumor with a worse prognosis. It mainly consists of clusters of basal-like cells, which are palisade-arranged around the tumor. CK5/6 and p63 have been shown to be positive in 90-100% of basaloid SCC with CD117 negative. Ewing sarcoma (ES) / primitive neuroectodermal tumor (PNET) cells are usually very bland and monotonous, sometimes with small amounts of clear cytoplasm, and are diffusely membranously positive for CD99. The tumor frequently shows rearrangements of the EWSR1 gene, leading to fusions with FLI1 gene most commonly. Mucosal melanoma is typically diffusely positive for S-100 protein and melanocytic markers. The tumor cells can be arranged in solid, glandular, epithelioma and sarcomatoid. In addition, tracheal ACC also needs to be

differentiated from other primary tracheal malignancies, especially tracheal salivary gland-type tumors such as basal cell adenocarcinoma, epithelial-myoepithelial carcinoma.

Because of its growth characteristics, tracheal ACC is prone to local recurrence and distant metastasis. Approach of surgical resection depends on the location of the tumor in the airway. Surgical resection is the optimal management in most of the cases [13]. However, in several studies, surgical resection followed by post-operative adjuvant radiotherapy had a better prognosis and hence a preferred mode of treatment [14].

In summary, we report a case of solid variant of tracheal ACC with basaloid features. Due to its relatively complex tissue structure and certain limitations in bronchoscopy biopsy, it is concluded that in case of solid aggregates predominated by poorly differentiated basaloid cells, primary tracheal ACC should be considered as an important differential diagnosis. Additional immunohistochemistry and molecular techniques could be applied to refine the diagnosis. This case report highlights the significance of various histological patterns and diagnostic modalities in making an accurate diagnosis of primary tracheal ACC at an early stage.

## **Abbreviations**

ACC, adenoid cystic carcinoma; CT, computed tomography; PET, positron emission tomography; FNA, fine needle aspiration; FISH, Fluorescence in situ hybridization.

## **Declaration**

## **Acknowledgements**

The authors declare that there are no acknowledgements.

## **Availability of data and materials**

All the data on which the conclusions of this case report are based are included in this manuscript.

## **Consent**

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## **Competing interests**

The authors declare that they have no competing interests.

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Not applicable.

## Authors' contributions

Feng Gao was responsible for the acquisition and interpretation of patient data and manuscript preparation. Lijuan Zang and Jin He performed immunohistochemical staining and in situ hybridization, respectively. Weiqing Xu was responsible for pathological diagnosis, supplementary analysis and critically revised the manuscript. All authors approved the final manuscript.

## Ethics approval and consent to participate

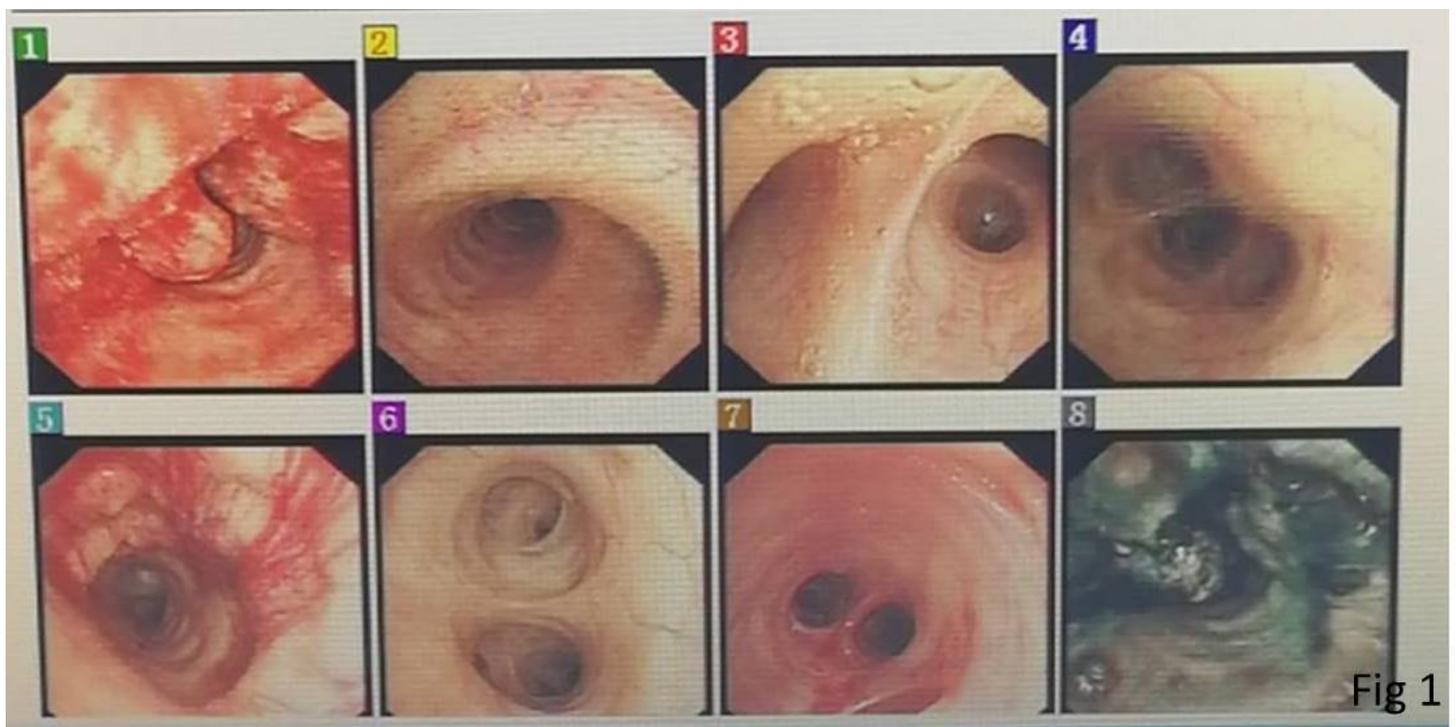
Ethical approval is obtained from the Institutional Review Boards of Shanghai General Hospital. Consents of the patient were obtained to participate to the presentation of this report.

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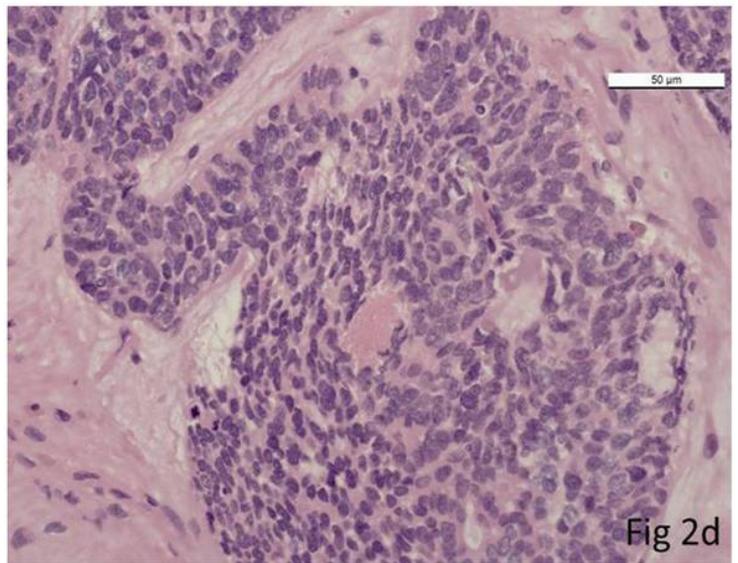
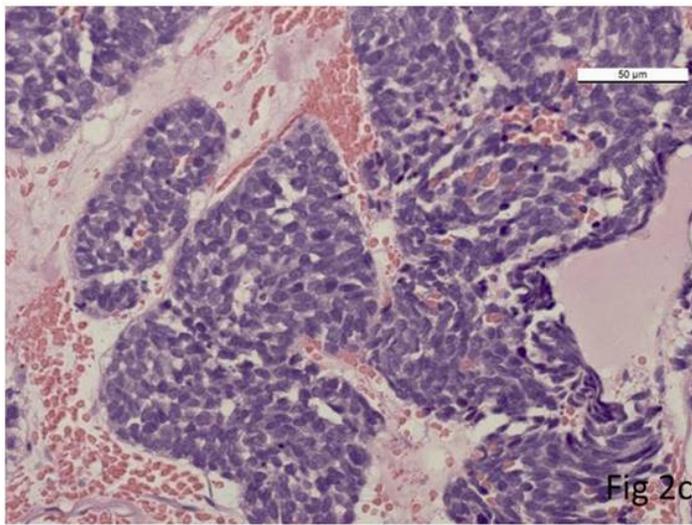
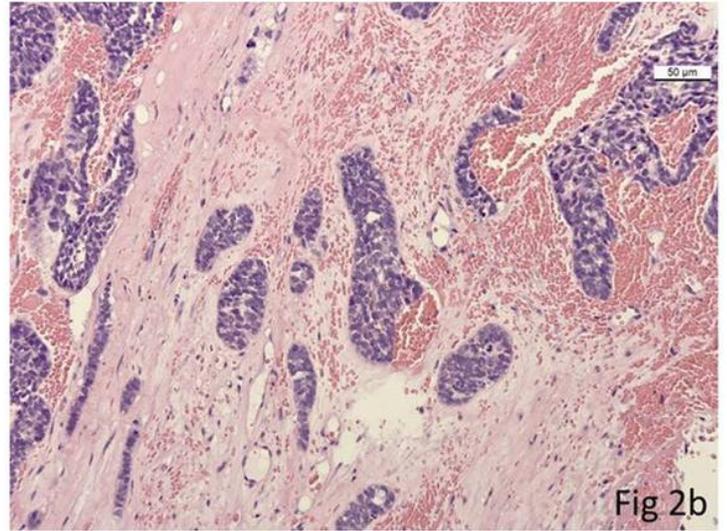
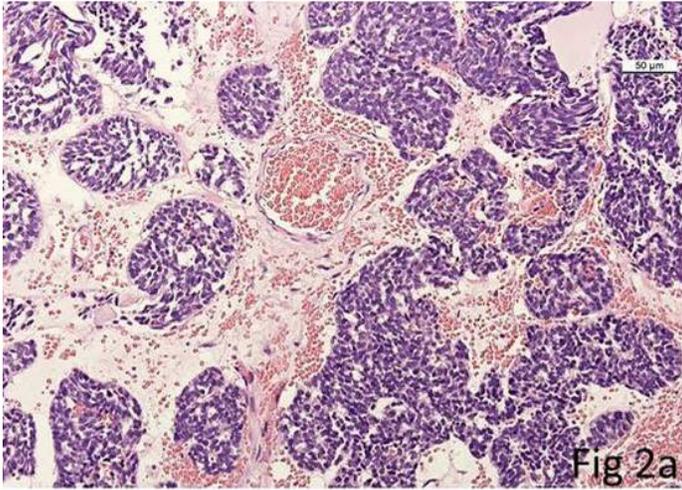
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## Figures



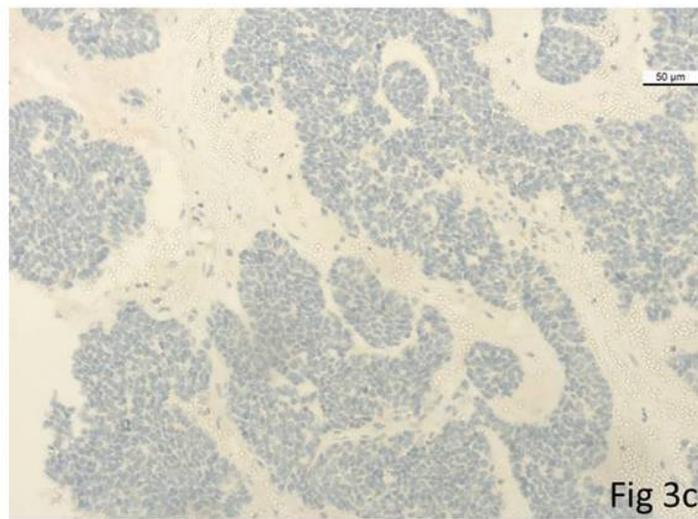
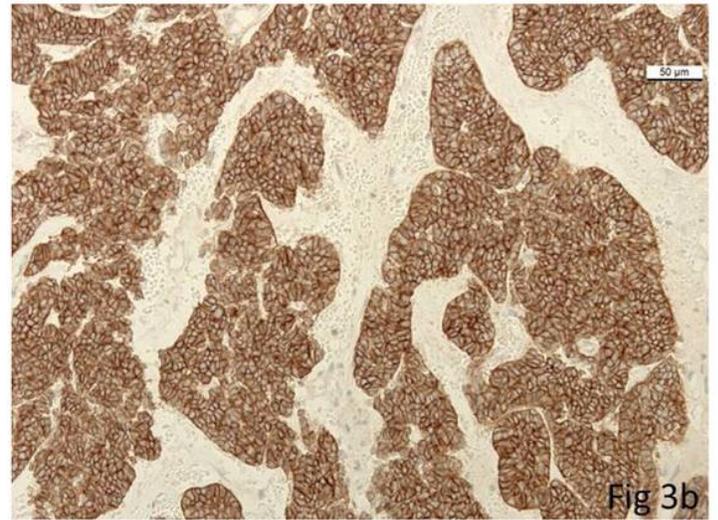
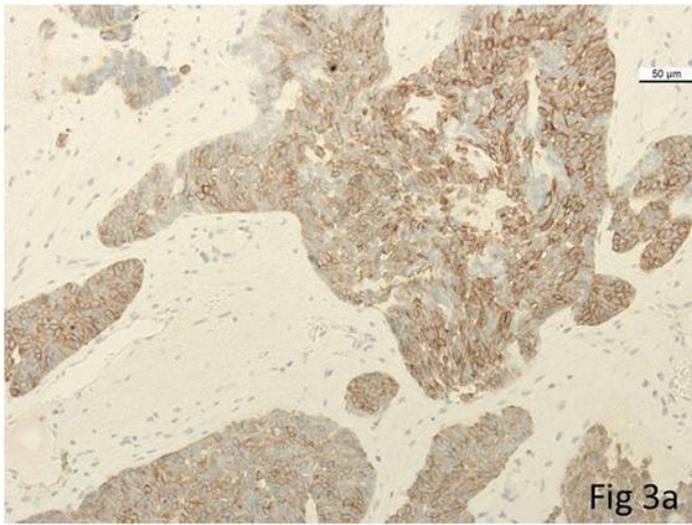
**Figure 1**

Fiberoptic bronchoscopy revealed the neoplasm was detected on the lower part of the total tracheal membrane, left side wall and anterior wall, arising at 3cm distal to the upper segment of the left main bronchus from the protrusion of trachea.



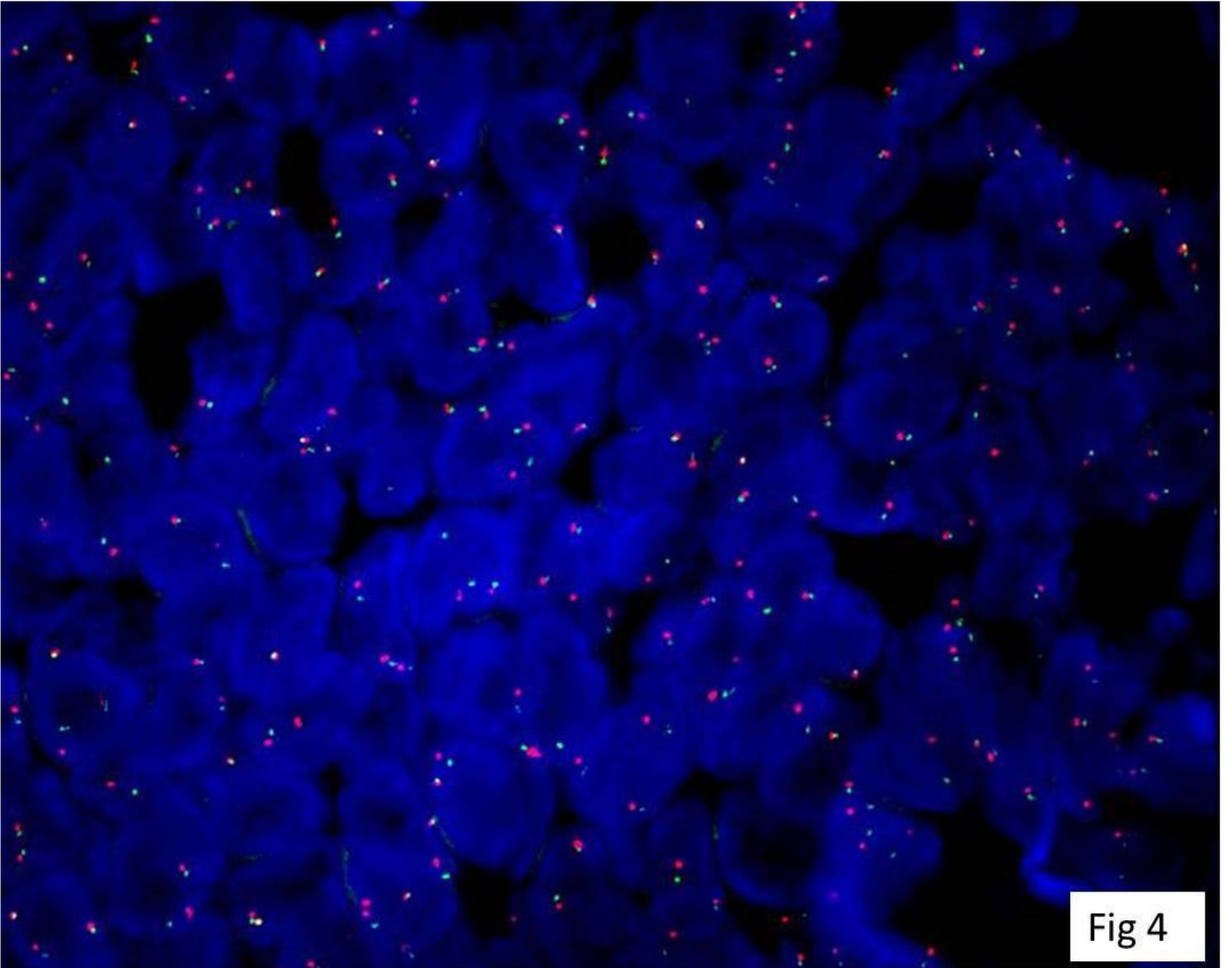
## Figure 2

Histological findings of the tumor. (a) The tumor cells were in irregular nests and distributed in fibrous stroma. (b) Some of the tumor cells grew in the shape of a beam. (c) The tumor cells were solid nests and showed basaloid features, The cells were round or ovoid with scant cytoplasm and hyperchromatic nuclei. (d) In some solid nests, the lumen-like structures were not obvious.



### Figure 3

Immunohistochemical analysis of the tumor. (a) CK7 was positive in some cells of solid cell nests. (b) The expression of CD117 was diffusely positive in tumor cells. (c) Loss of P63 expression in solid cell nests



**Figure 4**

FISH for MYB break-apart assay showed separate red and green signals in more than 30% tumor cells