The Clinicopathological Features and Unusual Immunophenotype of Primary Tracheobronchial Granular Cell Tumors

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Research

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Abstract

Background

Primary tracheobronchial granular cell tumors (GCTs) are rare. The characteristics of these tumors are unclear, and they are easily misdiagnosed. Thus, the present study aimed to investigate the clinicopathological features and immunophenotype profile of these tumors of the tracheobronchial tree.

Methods

Four patients were treated for GCTs of the tracheobronchial tree at our institution during 2009–2020. The clinicopathologic and immunohistochemical (IHC) findings were performed in all cases. In addition, seven typical GCTs involving the subcutaneous tissues (4/7) and esophagus (3/7) were also selected as control groups to evaluate the differences in IHC characteristics in different locations. Fisher's exact test was adopted in analysis of categorical data.

Results

There were four patients, two females and two males, aged 15, 22, 45 and 52. Three tracheobronchial tumors were solitary with a range from 2.0 to 3.1 cm (mean, 2.6 cm) in its large axis, while one sample was multiple. Chest computed tomography (CT) often suggested lung infectious lesions. On histopathology, three samples were typical GCTs, and the other sample was atypical with a fusiform or spindled morphology. All tumor cells stained positive for S100 protein, CD68, and Nestin and negative for Inhibin-α and thyroid transcription factor-1（TTF-1）. The Ki-67 index was less than 5%. Tracheobronchial GCTs exhibited occasional focal and weakly positive transcription factor E3 (TFE3) staining and had a lower ratio than those in other sites, while calretinin showed predominant subcutaneous expression. Two patients treated with tumor resection and the others only performed an endoscopic biopsy. Follow-up period ranged from 24 to 68 months with a mean of 42 months.

Conclusions

Primary tracheobronchial GCTs are rare and are often mimics pneumonia, which have a good prognosis even without surgical resections. Tracheobronchial GCTs had an unusual immunophenotype of TFE3 expression compared with other sites. This result may reflect a site-specific phenomenon distinguishing GCTs of the tracheobronchial tree.

Background

Granular cell tumors (GCTs), first reported as granular cell myoblastomas by Abrikossoff in 1926, are rear benign tumors of unknown origin[1]. Recent evidence from immunohistochemical studies suggests that GCTs are of neurogenic origin from Schwann cells[2–4]. However, there is no fully accepted consensus underlying GCT development.

GCTs essentially occur in the subcutaneous tissues, tongue, and esophagus[5]. This entity is characterized by abundant cytoplasm of the tumor cells filled with numerous eosinophilic granules. However, in some cases, especially in unusual sites, these tumors may pose a diagnostic challenge. Primary tracheobronchial GCTs are rare and are often misdiagnosed as bronchitis, pneumonia, asthma, lung cancer or other diseases in clinical practice and radiological examination. Since Feckner published the first endobronchial case in 1938[6], nearly 100 cases of tracheobronchial GCTs have been reported[7]. However, most of them are a single case report. Approximately 6–10% of GCTs can appear in the lower respiratory tract[5, 8].

Commonly, antibodies against S-100 protein and CD68 have been used widely as adjuvant markers in differential diagnosis. Recently, GCTs from various sites of the body were found to be positive for several new markers associated with neural or nonneural differentiation, such as transcription factor E3 (TFE3), calretinin, Nestin, inhibin-α and thyroid transcription factor-1 (TTF-1) [9–13]. However, these markers were not evaluated in tracheobronchial GCTs in previous studies.

Herein, we present the clinicopathologic features of four primary tracheobronchial GCTs and their unusual immune activities. Seven typical GCTs involving the subcutaneous tissues and esophagus were also selected as a control group to evaluate the uniformity of IHC characteristics in different locations.

Methods

Tissue samples

The archives of the Departments of Pathology at West China Hospital of Sichuan University were searched between January 2009 and October 2020 for all granular cell tumors. A total of 75 cases were reviewed; from this group, four samples of tracheobronchial GCTs were collected for study. In addition, seven typical GCTs originating from subcutaneous tissues (four cases) and the esophagus (three cases) were selected as control groups to evaluate IHC expression in different locations. Clinical data were collected from the patients' medical records, and pathological slides were reviewed independently by two pathologists. All tumors possessed histological and immunohistochemical characteristics of GCTs and did not demonstrate pathological findings attributable to other specific types of soft tissue neoplasia.

Immunohistochemistry (IHC)

The surgically resected specimens and biopsies were fixed in 10% neutral buffered formalin and embedded in paraffin. Hematoxylin-eosin staining and immunohistochemical analysis were performed on paraffin-embedded sections. The following antibodies were used: S100 protein (clone 4C4.9, MXB, China), CD68 (clone PGM-1, Dako, USA), Ki-67 (clone MIB-1, MXB, China), TFE3 (clone MRQ-37, MXB, China), inhibin-α (clone AWY82, BIO, China), Nestin (clone EP287, BIO, China), calretinin (polyclonal, BIO, China) and TTF-1 (clone 8G7G3/1, ZECA, China). Immunoreaction product deposits were visualized by the polymer-immunocomplex method using an Envision System (DakoCytomation) according to the manufacturer's protocols.

Statistical analysis

Categorical data were analyzed with chi-squared test or Fisher's exact test by SPSS 24.0 software package. Differences were considered to be statistically significant for $p < 0.05$.

Results

Clinical features

The clinical features of the four tracheobronchial GCTs are shown in Table 1. In our study, the patients aged 15 to 52 (mean, 34) at the time of diagnosis had an equal incidence by sex. Three patients had a long history of cough, two of whom had dyspnea in later stages, while the other patient presented with hemoptysis as the first symptom. It is worth mentioning that three of the four patients suffered from lung infection. The duration of symptoms between onset and diagnosis ranged from 10 days to 12 months.

Three lesions located in the tracheobronchium were single, while one case was multiple. The tumor involved the trachea (3/4, 75%) and bronchia (1/4, 25%). The mean size of the tumor was 2.6 cm, with a range from 2.0 to 3.1 cm in its large axis. Macroscopically, the lesions showed different appearances. Bronchoscopy showed irregular marked thickening, and a white lesion localized to the anterior wall of the left upper lobe bronchus (Caes1). On chest computed tomography (CT), there was a small soft tissue shadow in the upper lobe of the right lung, with nodules and patch shadows scattered around, which suggested lung infectious lesions (Fig. 1A). Granular pink nodules were scattered on the tracheal mucosa (Case 2). Chest CT revealed multiple ground glass shadows in the right lung, a cavity lesion could be seen in the apex of the upper lobe of the right lung, and a soft tissue nodule measuring 0.9 cm x 1.1 cm was seen, which was also considered an infectious lesion (Fig. 1B). A polypoid, sessile, and yellow tumor measuring 2.0 cm x 2.0 cm x 1.6 cm was located in the upper trachea (Case 3). Neck CT showed that the trachea was locally thickened and narrow at the level of the thoracic 2 vertebra (Fig. 1C) (Case 4). After radiological examination, diagnostic bronchoscopy demonstrated a 3.1 cm x 1.6 cm x 0.6 cm white-to-yellow apophysis lesion on the right wall of the thoracic trachea (Fig. 1D).

One patient suffered from secondary pulmonary tuberculosis and aspergilloma in the right upper lung (Case 2), while the remaining three cases were not accompanied by other diseases. This patient had a smoking history of at least 10 years (2-4 cigarettes/day), while the other three patients never smoked.

Histologic features

Microscopically, the tumors had an indistinct border and grew as expansile submucosal nodules (Fig. 2A) or with an infiltrative pattern entrapping submucosal glands (Fig. 2B). The neoplastic cells were comprised of polygonal or ovoid cells with abundant eosinophilic and granular cytoplasm (Fig. 2C). Tumor cells with a fusiform or spindled morphology appeared on one sample (Fig. 2D), which prompted the tumor cells to be atypical. The nuclei were small, hyperchromatic and prominent. Mitotic figures and nuclear pleomorphism were rare. All tumor cells were without necrosis.

Immunohistochemical features

The immunohistochemical data are summarized in Table 2. The results showed that the three groups of tumor cells were completely positive for S100, CD68 and Nestin diffusely (Fig. 2E-H) but negative for Inhibin-α and TTF-1 thoroughly. The Ki-67 index was completely less than 5%.

Among the three groups of eleven GCTs, seven cases (64%) demonstrated focal weak or diffuse strong positive TFE3 staining. Among the four tracheobronchial GCTs, only one case (1/4,25%) exhibited focal and weakly positive TFE3 staining (Fig. 3A). In the control groups, subcutaneous tissue and the esophagus exhibited a ratio of (3/4, 75%) and (3/3, 100%) for TFE3 expression, respectively. It seems that GCTs had a lower ratio of TFE3 expression in the tracheobronchial tree than in other sites, but with no significant difference (P = 0.2).

Positive calretinin expression, ranging from focal weak to diffuse strong staining, was detected in six of eleven (55%) GCTs. Among the four tracheobronchial GCTs, only one case (1/4,25%) demonstrated focal and weakly positive calretinin staining (Fig. 3B). In the control group, calretinin-positive cases occurred in subcutaneous tissue (4/4, 100%) and the esophagus (1/3, 33%). The results demonstrated that GCTs in subcutaneous tissue exhibited a relatively higher ratio of calretinin expression than those in other sites, but no significant difference existed (P = 0.108).

Patient treatment and follow up

Treatment and follow-up information of all patients are shown in Table 1. Complete follow-up data (mean, 42 months; interval range, 24-68 months) were available for three patients.

Two patients received symptomatic therapies after endoscopic biopsies (Case 1 and Case 2). A bronchoscopy follow-up obtained in patient 1 showed that the bronchial lesion had no change one month later, while this patient lived asymptomatic for 2 years. The symptoms of patient 2 were significantly improved after anti-tuberculosis and antifungal treatment; however, the follow-up of this patient was lost after discharge from the hospital. Case 3 underwent excision of the tracheal mass via an endoscope. There was no evidence of the disease in this patient after a period of 5 years and 8 months. Tracheal resection was performed, followed by tracheoplasty with tracheal metallic tubes in patient 4. A 2-year follow-up revealed that this patient occasionally went to the hospital because of repeated cough, sputum and shortness of breath. Recently, the patient had her third annual follow-up tracheoscopy, which showed a tracheostenosis with no tumor recurrence.

Discussion

Squamous cell carcinoma and adenoid cystic carcinoma are the most common tumors of the tracheobronchial tree[14]. Granular cell tumors of the tracheobronchial tree are extremely rare, with an estimated population-based incidence of only 2:100,000[5]. Approximately, 5.3% of GCTs were in the tracheobronchial tree in our series, which is slightly lower than previous research results [5, 8]. The age

range was five to 84 years, and these tumors tended to occur classically in middle-aged patients, with a mean age of 42 years. Among the patients with tracheal GCTs (mean age 35 years; range 6-77), while among those with bronchial GCTs (mean age 51 years; range 5-84)[5, 14–17]. The mean age of the patients with tracheal GCTs was lower than the mean age of those with bronchial GCTs. Tracheobronchial GCT involvement in children is exceedingly rare [5, 14, 17]and a 15-year-old girl with a tracheal GCT was reported in our study. Tracheal tumors are more prevalent in women, and bronchial tumors are seen equally in males and females. The mean size of the neoplasm at the time of diagnosis was 2.0 cm, with a range from 0.05 to 6 cm in its large axis[5, 18, 19]. The mean size of tracheal tumors is twice as large as that in the bronchus, which may be related to their anatomical structure [5] Consistent with our cases, most of these cases were solitary but could be multiple in 7-25% of cases[20]. Regarding the site, tumors are more likely to occur in the bronchus. Bronchial GCTs were equally distributed over both lungs and showed a preference for the upper lobes [5]. In contrast, GCTS occurred more frequently in the trachea (75%) in the present study.

The clinical presentations of the patients vary depending upon the size and location of the tumor[16]. Most of the patients presented with cough, dyspnea, asthma, hemoptysis, and pneumonia, while others were asymptomatic and diagnosed incidentally. Patients in our studies often presented with cough. It is worth mentioning that three of four cases suffered from lung infection. Patients with cigarette smoking are frequently noted [5]. However, only one patient in our cases had a smoking history of at least 10 pack-years. The index case also had a history of cigarette smoking, but because of the small number of patients and insufficient database, the association between GCTs and smoking was not clearly established. Bronchoscopy showed that tracheal GCTs appear more frequently as pedunculated polypoid lesions with intact mucosa partially obstructing the tracheal lumen[21]. On imaging studies, these tumors can present as bronchial obstruction, coin lesion or hilar mass[22]. In our study, half of the cases were considered to be lung infections on chest CT examination, which were confirmed after bronchoscopy. Bronchoscopy is recommended as the diagnostic test of choice because it is particularly helpful in evaluating the presence of intraluminal tracheobronchial lesions and can facilitate diagnosis with biopsy[17].

The immunohistochemical profile of GCTs has undergone extensive analysis. It is well established that granular cell tumors are positive for S-100 protein[2]. In addition to the S-100 protein, positive expression of CD68, which is a histiocytic marker in GCTs, indicates intracytoplasmic lysosomes in this otherwise neural sheath-derived tumor, which is best regarded as a GCT[23, 24]. In the present study, S100 protein, CD68 and Nestin expressions were noted in all sites of cases where it was performed. In corroboration with a recent study by Parfitt et al. [12], we show that all GCTs were positive for Nestin. GCTs exhibited a relatively lower ratio of calretinin expression in both the tracheobronchial tree and esophagus, while positive calretinin expression was detected in 100% of GCTs originating from subcutaneous tissues in our study, which is similar to previous studies [11]. In contrast to the results of Brian et al. [25]and Murakata et al.[26], none of the GCTs in our study expressed α-inhibin. Although calretinin expression in a GCT has been attributed to a neural lineage, the reasons for α-inhibin positivity have yet to be clarified. It is known that tumors of the peripheral nerves are negative for inhibin-α [2]. Whereas most investigators have

identified that nearly 100% of GCTs are inhibin-α positive, others have reported variable cytoplasmic inhibin-α positivity[9, 24–27]. These discrepancies appear to be independent of the antibodies used and may be the result of other methodological differences between laboratories.

TFE3 is a member of the helix-loop-helix family of transcription factors and is considered a useful marker in alveolar soft part sarcoma (ASPS) and Xp11.2 translocation cancer diagnostics, including Xp11.2 translocation-associated renal cell carcinoma (RCC), Xp11 translocation perivascular epithelioid cell tumor and melanotic Xp11 translocation RCC[28]. Some previous studies have revealed that more than 90% of GCT cases have diffusive and marked positivity for TFE3 by Chamberlain et al. and Schoolmeester et al. [9, 10]. To the best of our knowledge, only one case of primary tracheal GCT with TFE3 expression was reported by a previous study[10] Recently, Yang Liu et al. demonstrated that only 11/45 (24%) cases with TFE3 overexpression and 13/45 (29%) cases with focal or weak TFE3 staining in Chinese patients were lower than those in occidental patients according to previous studies. They also identified that GCTs in subcutaneous tissue exhibited a relatively higher ratio of TFE3 expression than those in other sites [29]. In the present study, GCTs in the tracheobronchial tree, subcutaneous tissue and esophagus exhibited a ratio (1/4, 25%),(3/4，75%)and，3/3，100%， for TFE3 expression, respectively. In contrast to the results of Chamberlain and Schoolmeester, GCTs in the tracheobronchial tree exhibited a much lower ratio (1/4,25%) of TFE-3 expression, which showed only weak focal staining. Compared with these studies, positive TFE-3 expression was detected in 86% (6/7) of GCTs in the control group originating from the subcutaneous tissue and esophagus. This finding may reflect a site-specific phenomenon distinguishing GCTs of the tracheobronchial tree. However, no rearrangement or amplification of TFE3 was identified in these tumors according to FISH data [9, 29]. As a possible explanation, Chamberlain et al. proposed that aberrant nuclear TFE3 accumulation could be caused by organelle or intracellular metabolic signaling pathway dysfunctions, which could lead to the typical cytoplasmic accumulation of phagolysosomes in GCTs [9].

Microscopically, these tumors are unencapsulated, often infiltrating surrounding tissues. They are composed of cells with abundant eosinophilic granular cytoplasm with a small and uniform nucleus. Granular cell tumor cells were mainly round and polygonal; however, spindled and fascicular characteristics were also present in several tumors[12]. Fanburg-Smith et al. proposed six diagnostic criteria for malignant GCTs: (1) necrosis, (2) spindling, (3) brisk mitotic activity, (4) a high nuclear to cytoplasmic ratio, (5) vesicular nuclei with prominent nucleoli and (6) pleomorphism. The presence of three or more of the following features suggests malignant GCTs. If the specimen exhibits one or two of these features, it is classified as atypical GCT[30]. In the present study, one sample exhibited a fusiform or spindled morphology, which should be classified as atypical GCT. Some scholars believe that malignant GCTs can only be determined when metastasis occurs[31]. According to statistics, approximately 98% of GCTs are benign lesions[32], and tracheobronchial malignant GCTs are very rare. Although extremely rare, it is possible that pulmonary GCTs can be malignant; the first case of malignant pulmonary GCT was reported in 2003[31]. The differential diagnosis of GCT includes all subglottic masses. Benign and malignant tumors of the trachea, along with esophageal, thyroid, and mediastinal tumors, should be considered. The majority of tracheobronchial tumors in adults are malignant and

include squamous cell carcinoma, adenoid cystic carcinoma, neuroendocrine tumors (large cell neuroendocrine tumors and small cell carcinoma), alveolar soft tissue sarcoma and metastases. However, various benign tumors, such as neurilemmoma, leiomyoma, hemangioma, benign fibrous histiocytoma and carcinoid tumors, should also be considered.

In our series, retreatment with one patient was indicated, and the majority of the patients were in complete remission after the first treatment. Patients treated with surgery remained in remission for up to 10 years. Even patients with residual disease continued to live with stable disease, which indicates a very benign course. There is a high recurrence rate when these tumors are removed either endoscopically or by laser therapy. Incompletely excised lesions have a recurrence rate of 0–12%. It is therefore advocated that lesions should be completely excised when possible if morbidity is minimal. Close follow-up once a year for at least 5 years is recommended in GCTs, especially in lesions treated with biopsy or subtotal resection[33].

Conclusion

We have described the clinicopathological features of four tracheobronchial GCTs. Diagnosis of this tumor requires a high index of suspicion given a clinical presentation that often mimics pneumonia, so bronchoscopy is recommended as the diagnostic test of choice. Additionally, this study is complementary to previous studies that described GCTs overexpressing TFE-3 since tracheobronchial GCTs in our series appeared mostly negative for this marker. Further studies including more cases are required to determine the influence of TFE3 overexpression in GCTs.

Abbreviations

GCT granular cell tumors

IHC immunohistochemical

CT computed tomography

TTF-1 thyroid transcription factor-1

TFE3 transcription factor E3

ASPS alveolar soft part sarcoma

RCC renal cell carcinoma

Declarations

Acknowledgements

None.

Authors' contributions

LJ and YW designed the study. YZ performed ancillary studies. ZP and CL performed the histological examination. YW was a major contributor of manuscript writing. LJ revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Patient's consent for publication was obtained.

Competing interests

The authors declare that they have no competing interests.

Footnotes

Conflicts of interest: none.

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Tables

Due to technical limitations, tables 1 and 2 are only available as a download in the Supplemental Files section.

Figures

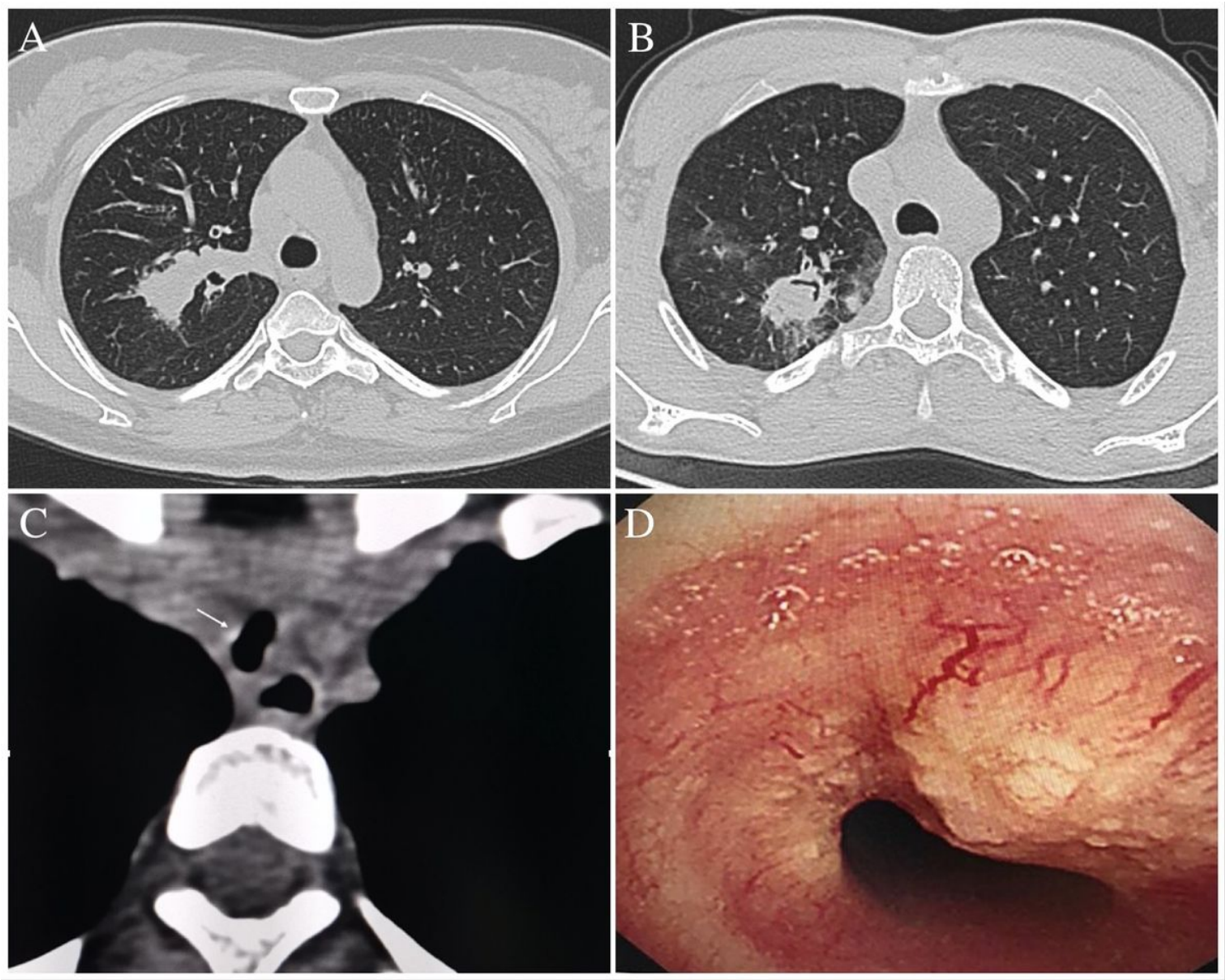

Figure 1

CT and Bronchoscopy characteristics of the primary tracheobronchial GCTs. Chest CT revealed a little soft tissue shadow in the upper lobe of the right lung(A). Chest CT revealed a soft tissue nodule was seen in a cavity lesion in the apex of the upper lobe of the right lung(B). Neck CT revealed the trachea was locally thickened and narrow at the level of the thoracic 2 vertebra, with a diameter of about 0.8cm(C). Bronchoscopy demonstrated a separate white-to-yellow apophysis lesion on the right wall of trachea(D).

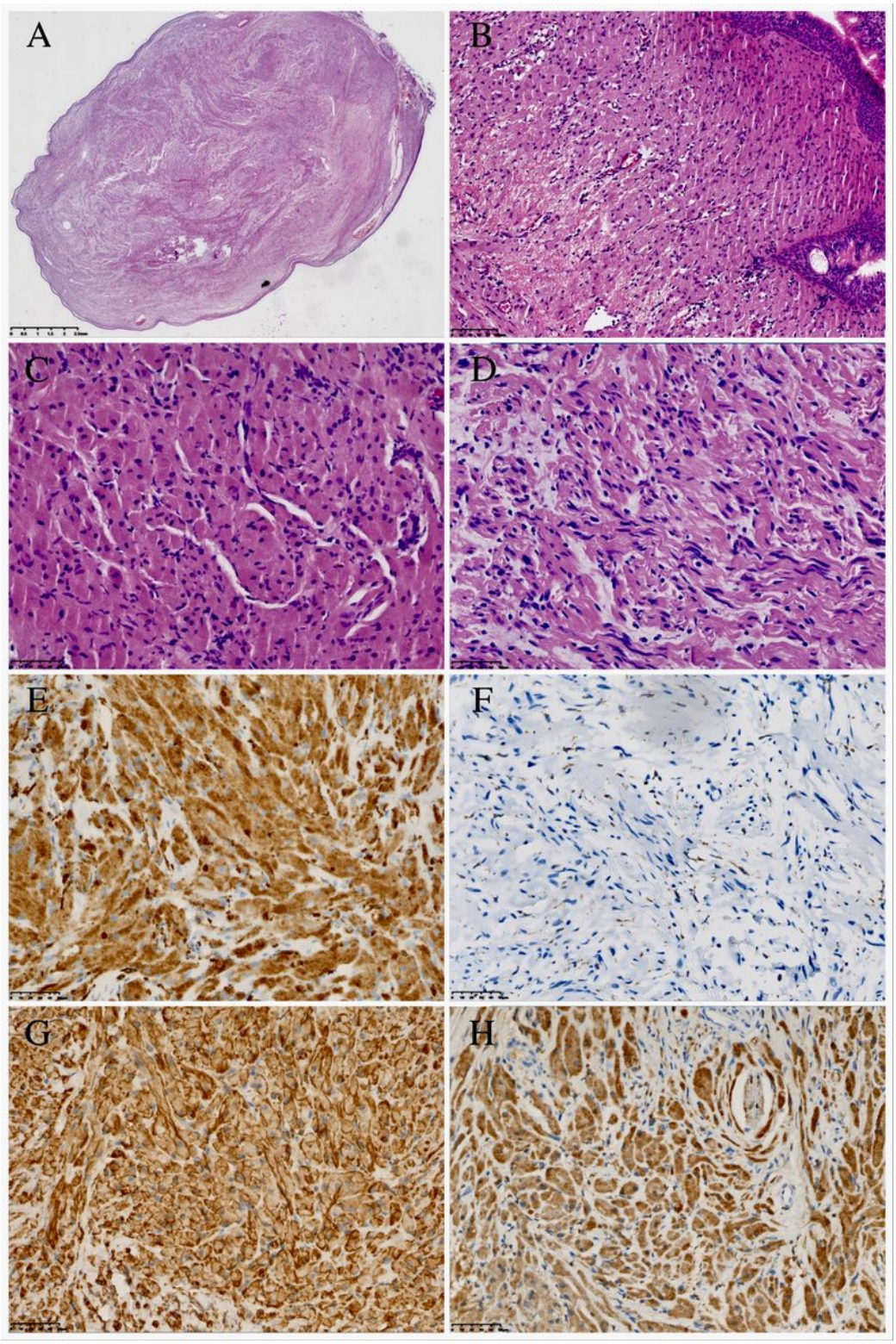

Figure 2

Histopathological and IHC stain of the primary tracheobronchial GCTs. The tumors had an indistinct border and grew as expansile submucosal nodules(A)or with an infiltrative pattern entrapping submucosal glands (B) (H&E stain, ×200). The neoplastic cells are comprised of polygonal or ovoid cells with abundant eosinophilic and granular cytoplasm(C); however, areas of spindling were also present (D)

(H&E stain, ×400). They are diffuse or focal positive for CD68 (E, F), Nestin (G) and S100 protein (H) (IHC stain, x400).

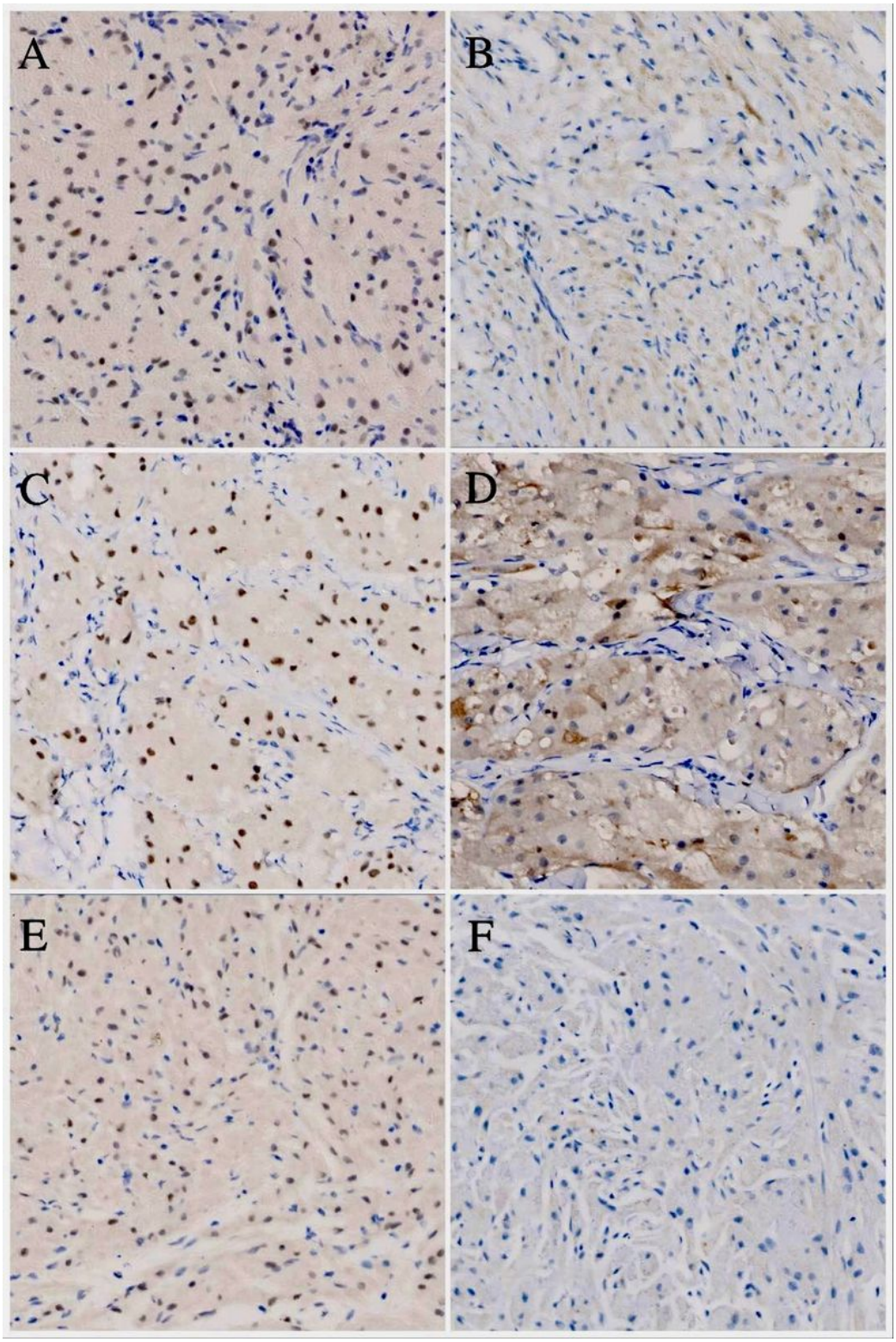

Figure 3

IHC stain of the tracheobronchial tree, subcutaneous tissue and esophagus of GCTs. Focal and weakly positive for TFE-3(A) and calretinin(B) of tracheobronchial GCT; Diffuse positive for TFE-3(C) and

calretinin(D) of subcutaneous tissue of GCT; Weakly positive for TFE-3(E) and negative for calretinin(F) of esophageal GCT.

Supplementary Files

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- Table1.xlsx
- Table2.xlsx