Case report

Pulmonary granular cell tumor coexisting with interstitial lung disease – a rare case report

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A granular cell tumor (GCT) is a soft tissue neoplasm of rare occurrence in the lung. A 44-year-old male asphalt worker had interstitial lung disease. Incidentally, a 7 mm polypoid nodule was observed at the entrance of the right upper lobe bronchus. Tumor cells were characterized by a large granular eosinophilic cytoplasm and small, uniform nuclei. The neoplastic cells were diffuse positive for S-100, CD-68, NSE, vimentin, and SOX-10, and focal positive for calretinin and inhibin A. This case is unique in its distinction as the second literature case of pulmonary GCT coexisting with interstitial lung disease.

Key words: granular cell tumor, interstitial lung disease, endobronchial tumor.

Introduction

Granular cell tumors (GCT) are a rare form of mesenchymal neoplasm that originates from Schwann cells. Although it was previously classified as myeloblastoma/myoblastoma, recent studies have reached a consensus that its origin is indeed neuronal [1, 2]. Granular cell tumors can occur at any site, but they are more commonly localized in the head and neck region, and most of them arise in the oral cavity (70%). This neoplasm most commonly occurs on the tongue, oral mucosa, and hard palate. Granular cell tumors are rarely found in the respiratory tracts. Pulmonary GCT is usually a benign, solitary, submucosal nodule. It is important to note that multiple lesions can occur infrequently and should be taken into consideration [3]. Histologically, there are three main forms: benign, atypical, and malignant. However, clinical behavior does not always align with histology. It is essential to clarify this discrepancy [1]. Granular cell tumors may be associated with various lesions and tumors [2, 3]. In this report, we present the case of a 44-year-old male patient who presented to the clinic with a suspicion of interstitial lung disease. During the evaluation, an endobronchial lesion was incidentally detected, and a diagnosis of GCT was made. To the best of our knowledge, this is the second case report describing GCT with interstitial lung disease.

Case report

A 44-year-old male asphalt worker was referred to our hospital's chest diseases outpatient clinic for evaluation of a persistent chest pain that had lasted for the past month. The patient had been experiencing additional complaints such as cough, white sputum, shortness of breath, night sweats, and occasional coughing up blood for one year. The patient had a 60-pack-year smoking history and had lost six kilo-

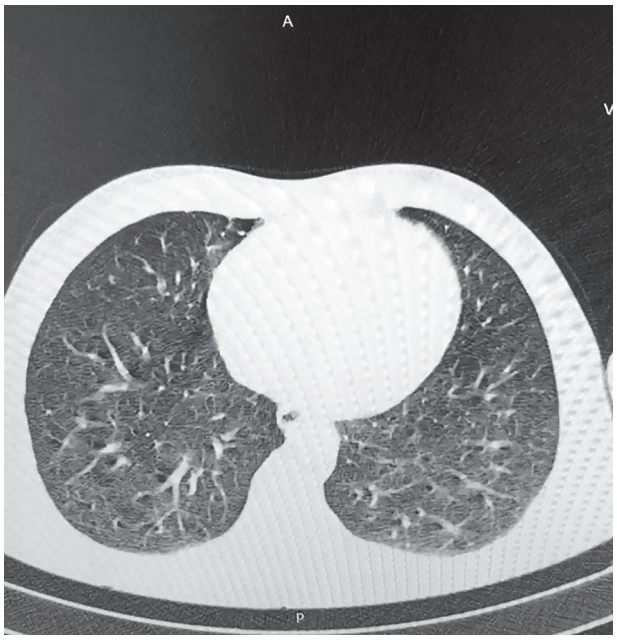

Figure 1. Thorax computed tomography showed bilateral diffuse ground-glass densities

Figure 2. Polypoid nodule at the entrance of the right upper lobe bronchus

grams in the last month. His respiratory system examination and pulmonary function test results were normal. Chest X-rays and thorax computed tomography (CT) scans revealed bilateral diffuse ground-glass opacities (Figure 1). According to the radiological and clinical findings, the diagnosis was interstitial lung disease. The results indicate that the blood, hematological, and serum biochemical values were within normal limits. The patient's biomarkers for vasculitis and collagen disease were negative. Bronchoscopy was performed because of the unexplained chest pain, hemoptysis and bilateral diffuse ground-glass opacities. The fiber optic bronchoscopy revealed a 7 mm polypoid nodule at the entrance of the right upper lobe bronchus (Figure 2). A forceps biopsy was performed with preliminary diagnoses of malignancy, diffuse interstitial lung disease, and lymphocytic interstitial pneumonia.

Microscopically, the neoplasm composed of solid nests and sheets of uniform cells exhibited abundant eosinophilic granular cytoplasm with small oval to round nuclei. There was also pseudoepitheliomatous hyperplasia of overlying squamous epithelium (Figures 3A, B). Mitotic figures, necrosis, and nuclear atypia were not present. Immunohistochemical analysis revealed diffuse positive staining for S-100, CD68, NSE, vimentin, and SOX-10 (Figures 3 C–G). Additionally, focal positive staining was observed for calretinin and inhibin A. PanCK, synaptophysin, and chromogranin-A staining were negative in the neoplasm. The Ki-67 proliferation index was less than 1%. The histopathological diagnosis was a benign GCT, based on the immunohistochemical and morphological findings.

Discussion

Granular cell tumors, also known as granular cell myeloblastomas/myoblastomas or Abrikossoff's tumors, were first described by Abrikossoff in 1926 [2, 3]. Abrikossoff reported that the origin of the neoplasm was muscle tissue. However, recent ultrastructural, immunohistochemical, and histological studies have indicated that the neoplasm actually originates from Schwann cells [4].

Granular cell tumors are most commonly seen in the head and neck region, accounting for approximately one-third to one-half of the cases. Most of them are located in the oral cavity, usually on the tongue [5]. This tumor is also frequently observed in the esophagus, colon, skin, and breast [6]. Pulmonary GCT is rare, with only 2–6% of GCTs occurring in the lung. The most common location for pulmonary GCT is the lung parenchyma, and of these, 90% are endobronchial. Additionally, these occurrences tend to occur at sites of bifurcation [2, 6, 7].

In 4–10% of cases, multiple endobronchial lesions were observed [2]. Grossly, GCT is characterized as small (0.3–5.0 cm), polypoid, solitary, and submucosal nodules [2, 3]. It is usually seen between the third and fifth decades [8]. Although it is observed with equal frequency in men and women, some studies have reported a higher prevalence in women [2, 9, 10].

The symptoms of GCT can vary depending on the size and location of the tumor. Common symptoms at presentation include chest pain, dyspnea, coughing, and hemoptysis [2]. The nodule may not cause any symptoms (8%). In 8% of the cases, a tumor was detected incidentally during a bronchoscopy [3].

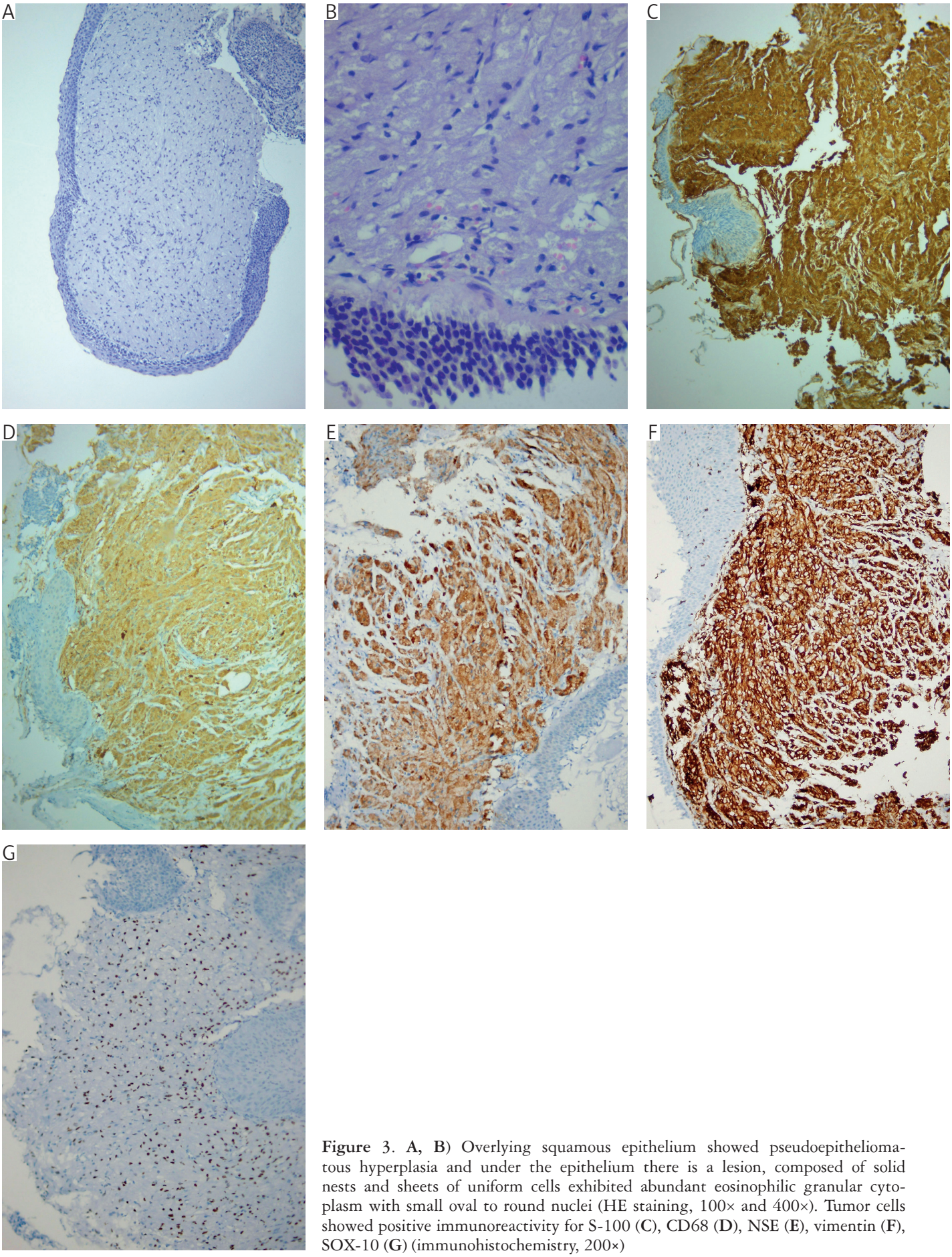

Figure 3. A, B) Overlying squamous epithelium showed pseudoepitheliomatous hyperplasia and under the epithelium there is a lesion, composed of solid nests and sheets of uniform cells exhibited abundant eosinophilic granular cytoplasm with small oval to round nuclei (HE staining, 100× and 400×). Tumor cells showed positive immunoreactivity for S-100 (**C**), CD68 (**D**), NSE (**E**), vimentin (**F**), SOX-10 (**G**) (immunohistochemistry, 200×)

In our case, the lesion was detected incidentally. Our patient presented with symptoms including chest pain, chronic cough, and hemoptysis. However, some of these symptoms may also be associated with interstitial lung disease. Granular cell tumor can be presented with asthma and post-obstructive pneumonia [3]. Approximately 13% of GCT cases occur in association with other neoplasms. Lung carcinoma is the most common neoplasm coexisting with pulmonary GCT. In addition, nonneoplastic diseases such as sarcoidosis and HIV infection were reported in GCT cases [3]. Benninger *et al*. [11] reported that the patient had an interstitial lung disease and GCT detected incidentally during the bronchoscopy, as in our case. In a series of 19 patients with pulmonary GCT, lesions were detected incidentally in 9 patients [7]. While no lesions were detected on the CT scan in our case, an endobronchial lesion was identified during the bronchoscopy performed to rule out other diseases. A definitive diagnosis was based on the histopathological examination of a biopsy specimen. Polygonal or ovoid tumor cells showed abundant eosinophilic and granular cytoplasm. Large lysozymes, which stained positively with periodic acid-Schiff staining and were resistant to diastase, were the reason for this granular appearance. The granular appearance of the cytoplasm and positive staining for the immunohistochemical histiocytic marker CD68 confirmed the existence of histiocytes. Immunohistochemically, these tumor cells were also positive for S-100, vimentin, NSE, calretinin, NK1-C3, inhibin A, and SOX-10 [2, 12, 13]. The neuronal origin of GCT was supported by S-100, NSE, NK1-C3, and SOX-10 immunopositivity in neoplastic cells [12]. Calretinin expression was associated with neural origin. Further investigation is necessary to determine the etiology of inhibin positivity [4]. Epithelial, endothelial and smooth-muscle markers were negative in tumor cells [2]. Pseudoepitheliomatous hyperplasia was detected in 50–65% of cases. This is a diagnostic feature of GCT [2, 3]. The current case demonstrated pseudoepitheliomatous hyperplasia on microscopic examination. In some cases, this feature can resemble squamous cell carcinoma, especially in superficial biopsies. Therefore, it is crucial for pathologists to accurately differentiate GCT [2, 14].

Granular cell tumors are a type of neoplasm that is often benign. These tumors may exhibit an infiltrative pattern, which can invade muscle fibers, fibrous septa, and nerve sheath bundles. Peribronchial tissue extension findings were observed in 40% of cases [3]. The malignant transformation of a GCT was a rare occurrence, affecting 1–2% of cases [6]. Fanburg-Smith *et al*. [15] identified six diagnostic histological criteria to categorize GCT into three subtypes: benign, atypical, and malignant. The histological criteria were as follows: tumor necrosis, spindle cells, vesicular nuclei with large nucleoli, increased mitotic activity (> 2 mitoses in 10 high-power fields at 200 × magnification), a high nuclear-to-cytoplasmic ratio, and pleomorphism. To make a diagnosis of malignancy, at least three of these criteria must be met. An atypical GTC is diagnosed when one or two of these criteria are present. If none of these criteria are found, the diagnosis should be a benign GCT [15]. In our case, none of the histological criteria for malignancy were observed. To date, seven cases of malignant GCT in the lung have been described [13]. Houcine *et al*. [1] reported an unusual metastasis in a patient with a GCT diagnosis who did not show any histologically malignant features. This finding suggests that metastasis may be the critical factor in determining the malignancy of a tumor. Further research is necessary to definitively differentiate among benign, atypical, and malignant forms of GCT [1].

Immunohistochemical p53 expression and Ki-67 proliferation index can predict aggressive and malignant clinical behavior. In our study, p53 expression was not detected, and the Ki-67 proliferation index was low (1%) [15]. An immunohistochemical study is an important tool in the differential diagnosis process. The differential diagnosis includes fibroxanthoma in benign cases and peripheral sheath tumor, histiocytosis and melanoma in malignant cases [1].

In genetic studies of malignant GCT, monosomy 22, trisomy 10, and loss of *CDKN2A* were frequently observed. This was consistent with findings in peripheral neural sheath tumors [14]. Researchers found that *ATM* mutations and mutations in *ASXL1-, NOTCH2-,* and *PARP4*-related pathways were associated with malignant GCT [16, 17]. Another study identified elevated expression levels of several genes (*WRN, KMT2A, RPA1, NSD1, DDR2, ZNRF3,* and *NOTCH4*) in GCT of malignant transformation. High tumor mutational burden and high microsatellite instability were also detected [13].

The treatment of pulmonary GCT has not been clearly defined. Treatment options include surgical resection, bronchoscopic removal, YAG laser, and fulguration. Surgical excision is the treatment with the highest cure rate [3]. According to the literature, surgical excision was recommended for tumors that are larger than 8 mm in diameter [11]. Tumors larger than 8 millimeters were more likely to infiltrate the peribronchial tissue [18]. However, most authors agreed that segmental or lobar resection was required when postobstructive parenchymal damage had occurred. If the distal lung parenchyma is preserved, bronchoscopic extirpation and laser treatment could be considered [3]. In our case, due to the small size of the tumor, it was removed using a rigid bronchoscope.

It was reported that granular tumor cells larger than 1 cm, removed by bronchoscopic resection, had a high recurrence rate. This may be explained by the fact that

large tumors often infiltrate the tracheal wall. Therefore, a surgical approach was preferred in such cases. While surgical resection was curative, there had been reported cases of tumor recurrence [19].

In 20 GCT cases, recurrence was detected in only one case, on average 3.3 years after surgical excision [3]. Therefore, annual follow-up was recommended for a minimum of five years [19]. Even with benign subtypes of GCT, it is important to monitor patients for possible recurrence. The follow-up process includes CT scans and endoscopic examinations [20]. In our case, there was no recurrence of GCT during the average four-year follow-up period.

Conclusions

Pulmonary GCT is a rare entity. Although this tumor is generally benign, it is crucial to be mindful of the criteria that would indicate malignancy. The clinical and radiological findings of our patient were considered to be interstitial lung disease, and pulmonary GCT was diagnosed incidentally. According to the current literature, this is the second documented case of pulmonary GCT with coexistent interstitial lung disease.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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