Title: Granular Cell Tumor of the Lung - Report of a Case

Running title: Granular Cell Tumor of the Lung

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ABSTRACT

A pulmonary granular cell tumor (GCT) was discovered on a chest radiograph for chronic cough in a 42-year-old Asian woman. A chest computed tomography (CT) scan subsequently showed a right middle lobe (RML) nodular lesion which exhibited intense fluorodeoxyglucose (FDG) uptake on Positron Emission (PET) scan. A thoracoscopic RML lobectomy was then performed and immunohistochemical study and Ki-67 proliferative index on the pathology sample demonstrated a benign GCT. 36 months after surgery, the patient remains symptom free and there has been no recurrence of the tumor on follow-up CT scan.
INTRODUCTION

Granular cell tumors (GCTs), or Abrikossoff tumors, are rare tumors that are usually benign(1). GCTs develop between the third and fourth decades of life. They occur in all parts of the body, but predominate in the head and neck region (2). They can, however, occur in the lung.. This case report describes a 42-year-old woman with a pulmonary GCT detected on chest radiograph..

CASE REPORT

A 42-year-old Asian woman suffered from chronic cough for several months. Chest radiograph (Figure 1) and subsequent chest computed tomography scan (Figure 2) demonstrated a nodular lesion in the medial segment of right middle lobe (RML). There was no enlargement of the tracheobronchial and mediastinal lymph nodes. The tumor appeared lobulated, and demonstrated heterogenous enhancement with intravenous contrast administration on CT. There was also a suggestion of possible mediastinal pleura involvement due to the “pleural tail sign” noted on chest CT. The tumor size was approximately 2.8 x 2.3 x 2.4 cm. Due to the close proximity of the tumor to the right atrium of the heart, CT guided biopsy was contraindicated. The nodular lesion exhibited intense fluorodeoxyglucose (FDG) uptake on whole body PET/CT scan with an maximum standardized uptake value (SUV) max of 4.6 (see Figure 2). No other focal abnormality was noted on CT in the chest, neck or upper abdomen. The bone scan and liver sonogram were
both negative.

A RML lobectomy was performed under video-assisted thorascopic control. Lymph node dissection, including interlobar, hilar and subcarinal nodes, was also performed. Grossly, a brown-white elastic tumor measuring 3.3 x 3 x 2.8 cm was located at 0.5 cm distal to the bronchial margin (Figure 2) without pulmonary vasculature invasion.

Microscopic sections through the tumor demonstrated a poorly circumscribed mass composed of plump eosinophilic cells with central small dark nuclei and abundant granular cytoplasm. The tumor cells were round to polygonal in shape and had indistinct cell membranes. Focal extension into the alveolar space with focal fibrosis and mild desmoplastic reaction were seen close to the sub-bronchial area. No necrosis, obvious pleomorphism or mitotic figures were seen in the sections. The immunohistochemical (IHC) study demonstrated the following: Vimentin(+)(Dako, USA), Cluster of differentiation 68(CD68)(+)(Novocastra, UK), S-100(+)(Novocastra, UK), Inhibin-alpha(+)(Dako, USA), Cytokeratin(-), Carcinoembryonic antigen (CEA)(-), Desmin(-), Synaptophysin(-), Human Melanoma Black-45 (HMB-45)(-)(Dako, USA), Thyroid transcription factor-1(TTF-1)(-) (Dako, USA), and Chromogranin(-)(Figure 3). The Periodic acid-Schiff (PAS)(Merck, ) stain and diastase-resistant PAS stain show the cytoplasmic granularity. The Ki-67 proliferative index was low (<1%). The surgical resection margins and all regional lymph nodes were tumor free. The overall picture is, therefore, compatible with a primary granular cell tumor.
36 months after surgery, the patient was remains symptom free and there has been no recurrence of the tumor on follow-up CT scan.

Immunohistochemistry was performed on 4μm thick formalin-fixed, paraffin-embedded tissue sample sections. These slides were placed in a 65°C oven for two hours and deparaffinized in xylene and absolute ethanol. The dewaxed slides were then treated with 3% H₂O₂ and 0.1% sodium azide to inactivate endogenous peroxidase. The slides were then incubated with antibody before incubation with peroxidase conjugated goat anti-mouse immunoglobulin. Diaminobenzidine was used as chromogenic substrate, and brown precipitate was identified as positive staining. The samples were counterstained with hematoxylin and the slides were mounted with glycerol gelatin. Each batch had a positive and a negative control for quality assurance purposes.

DISCUSSION

GCTs were first described by Abrikossoff in 1926 (4). They typically present on the tongue, hypopharynx, esophagus, colon, skin, or breast (5-7). It is rare for a GCT to present in the lung. In addition, most patients with pulmonary GCTs present with symptoms secondary to bronchial obstruction, hemoptysis, or weight loss.(8) Our patient presented only with chronic cough.

There is only one report in the current literature concerning FDG activity in a GCT. It concerns a GCT which occurred in the breast and demonstrated an average SUV of only 1.8
Since our patient’s PET scan showed intense uptake of FDG with an SUV max of 4.6 and since it exhibited a “pleural tail sign” on chest CT, it was suspicious for malignancy. Complete surgical resection of the tumor via a RML lobectomy was therefore performed in keeping with the current surgical treatment of pulmonary GCT (8). The RML lobectomy was performed before the tumor was pathologically proven as benign due to the close proximity of the tumor to the right atrium, the positive PET findings, the negative bronchoscopy results and the lack of a definitive diagnosis at frozen section.

Pulmonary GCTs are benign in nature, and no malignant changes in primary tracheo-bronchial GCTs have been described (10). Six histologic criteria determine malignancy including degree of necrosis, spindling of the tumor cells, vesicular nuclei with large nucleoli, increased mitotic rate (> 2 mitoses/10 high-power fields at 200× magnification), a high nuclear-to-cytoplasmic (N:C) ratio, and pleomorphism. (11). The proliferative index with Ki67 was below 1% in this patient supporting the benign diagnosis.

GCTs, by IHC, are strongly positive for S-100 protein and frequently express other nonspecific markers. In our patient, the IHC scan demonstrated Vimentin(+), CD68 (+), S-100(+), and Inhibin-alpha(+). On review of the literature, almost all GCTs were positive for S-100 protein and none of the tumors expressed HMB-45.

Although pulmonary GCTs are usually benign, malignant pulmonary GCTs have been reported in the literature (12). For this reason, even though the tissue biopsy demonstrates a
benign pattern before surgery, complete surgical excision is still necessary.

In conclusion, pulmonary GCTs are rare and usually benign tumors. However, when elevated FDG uptake on PET scan suggests malignancy, complete surgical resection of the tumor is the only treatment option.
REFERENCES


11. Fanburg-Smith JC, Meis-Kindblom JM, Fante R, Kindblom LG. Malignant granular cell

FIGURE LEGENDS

Figure 1: Chest radiograph demonstrates a nodular lesion in the medial segment of right middle lobe of the lung.

Figure 2: Chest computed tomography shows a lobulated, tumor with heterogenous enhancement and suspicious invasion of the mediastinal pleura. The whole body PET scan shows a nodule with markedly increased FDG uptake with an SUV max of 4.6. Grossly, the tumor is brown-white, elastic and measures 3.3 x 3 x 2.8 cm.

Figure 3: The immunohistochemical study demonstrate Vimentin(+), Cluster of differentiation 68 (CD68) (+), S-100(+), Inhibin-alpha(+), Cytokeratin(-), Carcinoembryonic antigen (CEA)(-), Desmin(-), and Synaptophysin(-). (X200)