

# Malignant Granular Cell Tumor at the Retrotracheal Space

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## Abstract

We report a case of an extremely rare neoplasm, malignant granular cell tumor (MGCT). The patient was a 21-year-old woman, who was 5 months pregnant. The tumor occurred in the retrotracheal space, extending from the level of the larynx to the thoracic inlet. In addition, there were multiple, variable-sized tumor nodules within both lung fields on chest CT scan. Histologically, tissue biopsied from the periphery of the tumor consisted of solid sheets of large ovoid cells with ample, eosinophilic cytoplasm, eccentric nuclei, and prominent nucleoli. Each cell showed slight atypism of the nuclei. There was a focal necrosis at the periphery of the lesion. These cells stained strongly for S-100 protein, neuron-specific enolase (NSE) and CD68. On electron microscopy, the tumor cells contained autophagic vacuoles. The patient refused further treatment and died 7 months later. The exact cause of death was not known. Until now, the diagnosis of MGCTs has been made only when metastasis and an aggressive clinical course are identified, although some observers advocate that some histologic features such as nuclear pleomorphism, necrosis, and the presence of any mitotic activity are indicative of malignancy. These histologic findings are not easily detectable in every case of MGCT, as in our case. So the diagnosis of a MGCT should be considered in cases with aggressive clinical findings and some histologic features, such as necrosis, nuclear atypism, and mitotic activities, which could suggest the malignant behavior of this neoplasm.

**Key Words:** Malignant granular cell tumor, retrotrachea

## INTRODUCTION

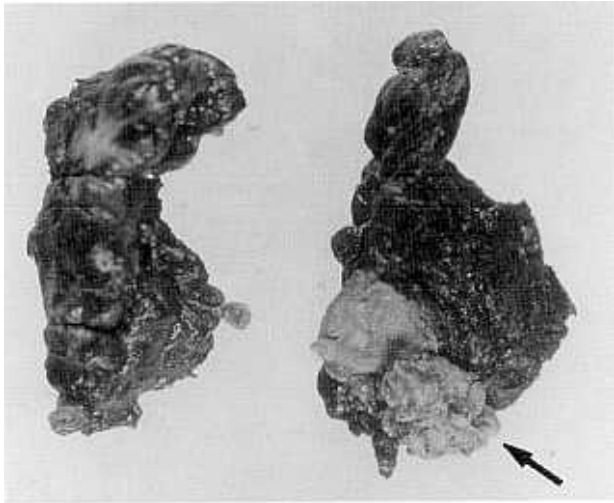
The granular cell tumor, first presented by Abrikossoff as "myoblastic myomata" in 1926, is not a rare soft tissue neoplasm, most likely of Schwann cell origin.<sup>1,2</sup> Since that time, approximately 1000 cases have been reported in the literature. The vast majority of granular cell tumors, also called granular cell myoblastomas, are benign, although they may be locally aggressive.<sup>3</sup> Malignant granular cell tumors were first described by Ravich et al. in 1945.<sup>4</sup> Since then, 35 additional cases have been reported in the English language literature. We describe a patient who presented with a malignant granular cell tumor of the retrotracheal space and discuss the criteria of malignancy by reviewing the recent literature.

## CASE REPORT

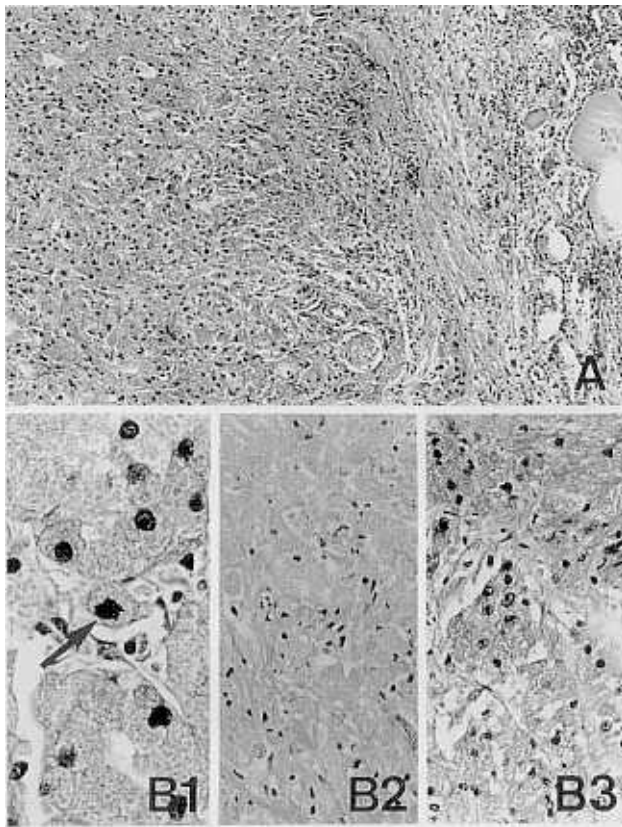
A 21-year-old woman, who was 5 months pregnant, was admitted to our hospital because of severe dyspnea and a palpable anterior neck mass. She

mentioned that she had a 10-year history of asthma, diagnosis of which at that time was made at a private clinic. In this regard, clinicians initially thought that the cause of dyspnea was a result of asthmatic attack. Empirical treatment for the asthma was applied. But there was no improvement. In addition, the severe dyspnea deteriorated. So the anterior neck mass was thought to be the most likely cause of dyspnea. An exploratory operation was done under the impression of a tumor of the thyroid gland. A preoperative radiologic study was not performed because of her pregnancy. During intubation, the tracheal lumen was so narrowed that the endotracheal tube could not be passed. After the open tracheotomy, an anterior midline neck incision was done. As soon as the anterior neck was opened, the underlying thyroid gland with an attached huge pale yellow mass bulged out, which was not resectable. A total thyroidectomy was done to relieve the compression effect on the trachea. Some portion of the thyroid abutted on the underlying huge mass without adhesion, so an incisional biopsy of the tumor was done in a small amount. The underlying huge mass was firmly attached to the surrounding soft tissues. The biopsied tumor tissue measured 2×2×2 cm, which was sent as attached to the left thyroid gland. It had some adhesion to the thyroid tissue. However, there was no definite infiltration and it was easily peeled away from the thyroid tissue (Fig. 1). Histologically, the tumor consisted of solid sheets of relatively uniform large tumor cells which had am-

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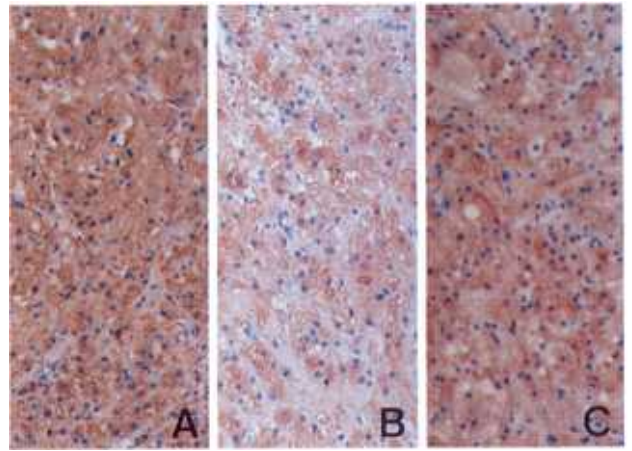


*Fig. 1. The left thyroid gland was attached with an irregular small fragment of infrathyroid soft pale-yellow tissue (arrow). This tissue was clearly separated from the thyroid tissue, but not encapsulated. The right thyroid gland was grossly unremarkable.*

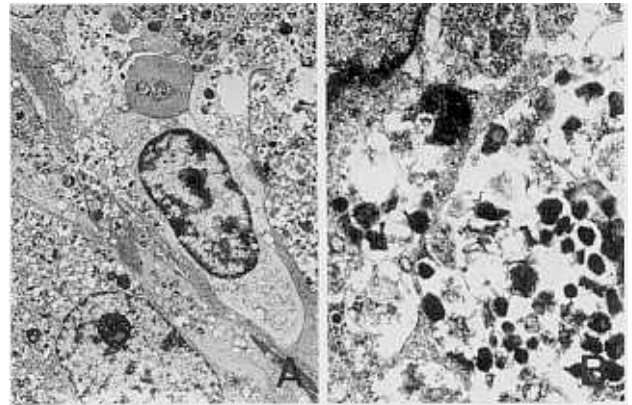


*Fig. 2. Histologically, the tumor was composed of large uniform cells having ample, eosinophilic, and granular cytoplasm (A). The nucleus was small and displaced to the periphery. There were few mitotic activities (arrow) (B-1,  $\times 400$ ), focal necrosis (B-2,  $\times 200$ ), and slight atypism of the nucleus (B-3,  $\times 200$ ).*

ple, eosinophilic, and granular cytoplasm, single eccentric and vesicular nuclei, and often prominent nucleoli. There was a focal necrosis at one portion of

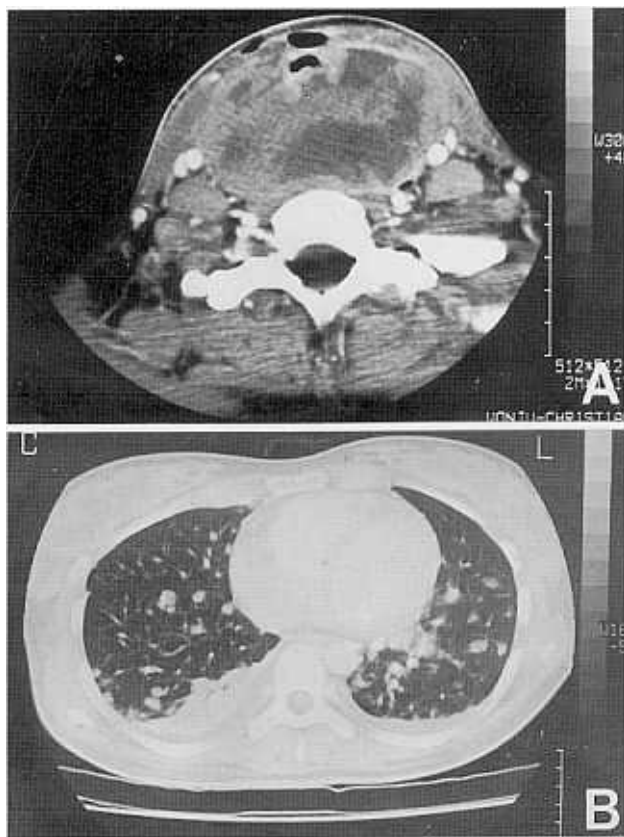


*Fig. 3. Immunohistochemical stains for S-100 protein (A), NSE (B), CD68 (C) revealed positivity in tumor cells ( $\times 200$ ).*



*Fig. 4. Ultrastructurally, the tumor cell cytoplasm was filled with many large autophagic granules and dilated mitochondria. The nucleus showed a heterochromatic pattern with prominent nucleoli ((A)  $\times 3000$ , (B)  $\times 15000$ ).*

the resected specimen. The tumor cells grew around the vessels, however, no vascular invasion was identified. Perineural invasion was present. Two mitotic figures per 50 high power fields were identified. Although slight nuclear atypism was present, the nuclei showed relative uniformity in size and shape (Fig. 2). It looked like the benign counterpart, generally. The tumor cells were immunoreactive with S-100 protein, NSE, CD68 and vimentin (Fig. 3). The results of immunostains of the desmin, estrogen receptor, HMB-45, CEA, lysozyme, and thyroglobulin were negative. Electron microscopic examination showed that the cytoplasm of the tumor cells was filled with variable-sized lysosomal autophagic vacuoles and dilated mitochondria (Fig. 4). So we made a diagnosis of granular cell tumor of uncertain malignant potential. The pregnancy was terminated and a postoperative lateral neck radiograph was done. It showed the mass was



*Fig. 5. On neck CT scan (A) a very large, heterogenous mass was noted at the retrotracheal area. Both carotid arteries were displaced laterally. The central portion of the mass showed multiple necrotic portions with low density. There was no evidence of bony destruction of the vertebra. On chest CT scan (B) there were multiple variable sized nodules in both lung fields.*

a retrotracheal tumor which had a relatively homogenous radiologic density and deviated the trachea anteriorly from the original prevertebral location. It extended from the level of the larynx to the thoracic inlet. There were centrally located multifocal necroses, but there was no definite invasion to the surrounding soft tissue and cervical vertebra (Fig. 5A). However, a chest radiograph and chest CT scan revealed multiple, variable-sized, tumor nodules that had similar radiologic densities to the neck mass (Fig. 5B).

After diagnosis, the patient refused further treatment and died 7 months later. The exact cause of death was not known.

## DISCUSSION

MGCT is a rare neoplasm with only 35 cases reported as of 1996.<sup>5</sup> The diagnosis of MGCT in this case is based primarily on the multiple bilateral pulmonary nodules and their aggressive clinical course.

The diagnostic criteria of MGCT have not yet been

clearly defined. Some observers advocate that MGCT should be reserved for cases in which lymph node and/or distant organ metastasis is evident.<sup>3</sup> However, GCTs with local recurrence but lacking metastasis have been reported as malignant.<sup>6,7</sup> So Simsir et al. maintained that MGCT ought to be considered in any GCT with an aggressive clinical course defined by persistent local recurrence and destruction of neighboring structures.<sup>5</sup>

Tumor location is an additional clinically helpful parameter to suggest malignancy. Simsir et al. reviewed reported MGCTs and suggested that MGCTs arose from deep soft tissue in nine of 12 cases, whereas BGCTs more often arose in superficial soft tissue.<sup>5</sup> Among these 12 new cases of MGCT, the most common location was the chest wall, followed by the thigh, whereas BGCTs occurred more frequently in the head and neck region, especially the tongue. In our case, the tumor arose in the retrotracheal space which has never been reported before.

Tumor size also has a close relationship with malignancy. MGCTs range in size from 0.5 cm to 15 cm in maximal dimension, 10 of 12 being larger than 5 cm, in contrast to BGCTs which are usually less than 3 cm.<sup>8</sup>

Microscopic criteria for malignancy are still debatable. Some reports described the microscopic features associated with malignancy.<sup>8-11</sup> These included the presence of necrosis, wide cellular sheets, tendency to a spindle-cell structure, vesicular nuclei with nucleoli, marked nuclear pleomorphism with hyperchromasia, anisonucleosis, and mitotic activity. The mitotic activities were variable from 0 to 27/10HPF.<sup>5</sup> However, these are not omnipresent findings in every case. For this reason, even though these microscopic features favor a diagnosis of malignancy, the absolute histologic criteria for malignancy have not yet been firmly established.

So only close correlation between clinical and histologic findings can lead to an accurate diagnosis of malignancy.

Histogenesis of GCT has been a subject of controversy. Most of the earlier accounts of granular cell tumor concurred with Abrikossoff's opinion of muscle differentiation.<sup>1</sup> More recently, Fisher and Wechsler maintained the concept of neural differentiation based on the presence of an incomplete basal lamina and numerous intracellular, membrane-bound autophagic vacuoles that contain myelin figures in addition to other cellular debris.<sup>2</sup> Garancis et al. also suggested that the granular cells are Schwann cells altered by a lysosomal defect.<sup>12</sup> Schwann cell origin is further supported by the positive staining of cytoplasm and

nuclei for S-100 protein.<sup>13-18</sup> Staining of the granular cells for myelin proteins (PO and P2) and myelin-associated glycoproteins suggests that the granules are myelin or myelin breakdown products as was originally suggested by Fisher and Wechsler.<sup>2,19</sup> Our case also stained for neuronal markers, NSE and S-100 protein. Positive staining of granular cell tumor for CD68 was reported to be caused by the glycoprotein of the lysosomal membrane,<sup>20</sup> and the abundant autophagic granules in our case support this theory.

In conclusion, MGCT should be considered when the tumor shows aggressive clinical findings, defined by metastasis and destructive growth and local recurrence, as well as the supportive histologic features defined by necrosis, atypism, and any mitotic activities.

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