Lung Metastases from Esophageal Granular Cell Tumor: An Undoubted Criterion for Malignancy

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A 56-year-old woman presented with a previous history of pharyngolaryngeal esophagectomy with a final histopathological diagnosis of malignant granular cell tumor (MGCT) from the cervical esophagus. The radiological and pathological findings of primary tumor have already been described.1 A close clinical and radiological follow-up, including endoscopy and computed tomography (CT) scan, was performed. Thirty months after the surgical procedure, a thoracic-abdominal-pelvic CT scan revealed three sub-centimeter pulmonary nodules involving the left lower lobe and lingula. Three months later, a new thoracic CT scan showed an increase in the size of the lung nodules that was very suggestive of metastases (Fig. 1A). A wedge resection (atypical segmentectomy) was performed for diagnostic and therapeutic purposes. Grossly, three lung nodules (10, 13, and 14 mm in diameter) were observed (Fig. 1B), and the surgical margin was free of tumor (Fig. 1C). The immunohistochemical (IHC) study revealed strong S100 cytoplasmic expression in the tumor cells (Fig. 1D), and the proliferation index (Ki-67) showed positive nuclear staining in 4% of neoplastic cells (Fig. 1E). The granular tumor cells did not stain for epithelial (cytokeratin and epithelial membrane antigen), muscular (smooth muscle actin and desmin), vascular (CD31 and CD34), or melanocytic (homatropine methylbromide 45, melan-A, melanogenesis-associated transcription factor, and SRY-box 10) markers. On histopathological examination, the larger nodule exhibited a predominant spindle cell formation with focal nuclear pleomorphism, mitoses, and fibrosis (Fig. 2A and B); however, the smaller nodule showed a conventional granular cell proliferation with abundant eosinophilic cytoplasm and small nuclei (Fig. 2C and D). A striking vascular invasion was observed (see Fig. 2C), and necrosis was not detected. The other nodule showed a combined pattern (conventional granular tumor cells and spindle cell formation), less fibrosis, focal nuclear pleomorphism, and mitosis (Fig. 2E and F). These findings highlight the morphological heterogeneity of metastases in MGCT.2–4

The present case, although not exceptional, provides radiological and pathological findings in MGCT with lung metastases detected during follow-up. According to the Nasser and Fanburg-Smith classification criteria, the primary tumor fulfilled the histological criteria for classification as granular cell tumor with increased risk for metastasis.2–5 The present histological evaluation confirmed the radiological suspicion of lung metastases and the malignant nature of the primary tumor. To the best of our knowledge, almost all MGCTs with lung metastases described in the English-language literature make reference only to the radiological findings or core biopsy or cytologic examination results and not to the pathological description of pulmonary surgical resections.2,5 In fact,
Figure 1. (A) Coronal maximum intensity projection computed tomography image obtained 33 months after surgery for primary esophageal tumor showing an increase in the size of both lung metastases (arrows). (B) A cut surface from the nodule involving the left lower lobe. (C) Histological image from the lung metastasis of a malignant granular cell tumor (larger nodule) and the normal lung parenchyma around the tumor, hematoxylin and eosin (hematoxylin and eosin staining; original magnification, ×10). (D) Strong cytoplasmic S100 expression in metastatic granular cell tumor (original magnification, ×20). (E) Low proliferation index (4%) (Ki-67 staining; original magnification, ×10).

Figure 2. (A and B) Histological examination of the larger nodule reveals fibrosis (asterisk), a predominant spindle cell formation (arrow) with nuclear pleomorphism, and nucleoli (arrowhead) (hematoxylin and eosin [HE] staining; original magnification, ×10 and ×100, respectively.) (C and D) The smaller nodule shows a granular cell proliferation with abundant eosinophilic cytoplasm, striking vascular invasion (arrow), and scant fibrosis (HE staining; original magnification, ×10 and ×40, respectively). (E and F) The intermediate-size nodule shows a combined pattern with conventional granular tumor cells, spindle cell formation, and mitosis (arrow) (HE staining; original magnification, ×10 and ×60).
many of the lung metastases from MGCT are unresectable (as reported by Aksoy et al.6) and only sporadic cases of MGCT with lung metastases with macroscopic and histological autopsy findings have been published.7,8 We cannot exclude the possibility of an alternative diagnosis in such cases (for instance, aggressive sarcomas [malignant peripheral nerve sheath tumor] with focal or diffuse granular cell change instead of a true MGCT), considering the location of the tumor associated with major nerve trunks and the lack of a detailed immunohistochemical tumor profile description.7,8

In the present clinical scenario of known primary esophageal MGCT, the diagnosis of the lung nodules is relatively straightforward. However, if this were the first presentation of the tumor, it would prove a diagnostic challenge between primary or metastatic MGCT. Indeed, metastatic MGCT to the lung typically presents with bilateral and/or multiple nodules instead of a single solitary tumor, as would be the case in primary lung MGCT. For example, Jiang M et al.,9 described a primary solitary tumor, as would be the case in primary lung bilateral and/or multiple nodules instead of a single metastatic MGCT to the lung typically presents with a small nodule centrally located within the left lower lobe. The possibility of this being a metastatic MGCT was excluded by the clinical and radiological preoperative evaluation.

On the basis of morphological features and strong S100 immunoreactivity, the most important differential diagnosis in the present case was a metastatic melanoma with granular cell change. The patient had no previous history of cutaneous or mucosal melanoma, which made a diagnosis of metastatic melanoma unlikely. In addition, in many cases granular cell tumor and melanoma can be differentiated on the basis of an IHC study. Homatropine methylbromide 45 and SRY-box 10 IHC expression favor a diagnosis of melanoma; however, melan-A and melanogenesis-associated transcription factor are not useful for such a distinction because both can be expressed in MGCT.10 BRAF mutation, BRAF IHC expression,11,12 or melanosomes in ultrastructural study would support a diagnosis of melanoma, although these ancillary methods are not always available.

The patient described herein is currently free of disease, and at present no chemotherapy or radiotherapy is indicated and close clinical and radiological follow-up are being maintained.

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References