

Case Report

Fatal multiple malignant glomus tumors of the lung with rapid metastasis to multiple organs after surgery: a case report and literature review

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Abstract: Glomus tumor of the lung is a benign, but occasionally malignant, mesenchymal neoplasm. Rapid spread and early death occur extremely rare. Here we report a fatal case of multiple malignant glomus tumors of the lung with rapid metastasis to multiple organs after surgery in a 41-year-old woman who was admitted due to progressive cough and hemoptysis. A computed tomography scan of the chest showed multiple circumscribed nodular lesions in the right lower lobe of the lung. Bronchoscopic examination revealed a polypoid mass in the basal segment of the right lower lobe. The patient underwent a right lower lobectomy, and postoperative histological and immunohistochemical analyses suggested the diagnosis of multiple malignant glomus tumors. She developed extensive multi-organ metastases ten months after surgery and died later. Positivity for EGFR and ERCC, unique sites of metastasis, rapid spread and early death are unusual features of our case. In addition, we performed a literature review focused on the reported metastatic cases, which revealed that female gender, hemoptysis, nuclear atypia with increased mitotic activity, spindling, necrosis, and early fatalness are common features of metastatic cases.

Keywords: Malignant glomus tumor, lung, metastasis, glomangiosarcoma

Introduction

Glomus tumor is a mesenchymal neoplasm consisting of cells derived from smooth muscle cells that surround blood vessels in the glomus body. It predominantly affects the subcutaneous tissue of the distal extremities and occasionally occurs in visceral organs, accounting for only 1.6% of soft tissue tumors [1]. Primary glomus tumors of the lung are rare, with no more than 50 cases having been documented in the English literature to date [2]. Despite the fact that the vast majority of pulmonary glomus tumors are benign, > 10 cases with malignancy (glomangiosarcomas) have been previously reported [2]. However, fatal cases with rapid metastasis are exceedingly rarely seen [3-6]. Herein we report a unique fatal case of multiple malignant glomus tumors of the lung with rapid metastasis to multiple organs after surgery. In addition, we performed a literature review focused on the reported metastatic cases to highlight their common features.

Case report

A 41-year-old woman presented with recurrent paroxysmal dry cough for half a year and aggravation of cough with hemoptysis (blood-streaked sputum) for a week, without symptoms of shortness of breath, chest distress, low-grade fever, night sweats, fatigue, or weight loss. She had ever visited a local hospital and was diagnosed with bronchitis, but did not receive any systemic therapy. She had a past history of surgical resection of breast fibroadenoma and hysteromyoma picking, but denied any history of smoking, drinking, or major diseases such as hypertension, heart disease, and diabetes, or family history of cancer, infectious disease, or genetic disease.

The physical examination was unremarkable except that the auscultation revealed harsh respiratory sound in bilateral lungs and slightly attenuated respiratory sound in the right lower lung. Routine hematological and biochemical

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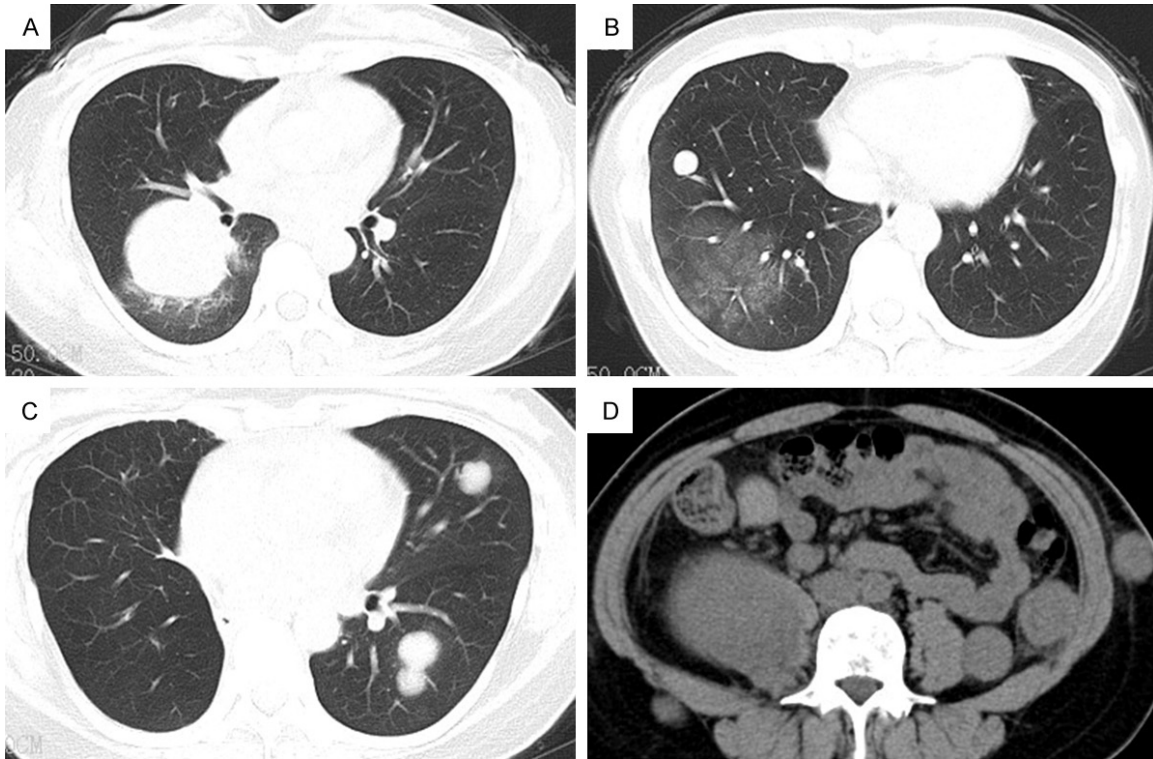


Figure 1. Chest and abdominal CT images. A and B. A CT scan of the chest before surgery showed multiple circumscribed nodular lesions in the right lower lobe of the lung; C. A CT scan of the chest after surgery showed metastases to the left lung; D. A CT scan of the abdomen after surgery showed multiple metastases to the abdominal cavity and pelvic cavity.

laboratory investigations revealed no significant findings. Ultrasound imaging of internal organs showed no abnormalities. Pulmonary function test indicated obstructive ventilatory disturbance and decreased diffusion capacity. A computed tomography (CT) scan of the chest showed multiple circumscribed nodular lesions in the right lower lobe of the lung, right lower lobe atelectasis, and local alveolar hemorrhage. The largest lesion measured $7.5 \times 5.0 \times 5.0$ cm (**Figure 1A, 1B**). The contrast-enhanced CT of the chest showed mild enhancement of the lesions, with blood vessels seen around the lesions (data not shown). A CT scan of the bones revealed no obvious active bone lesions. Upon bronchoscopic examination, a polypoid tumor was observed in the basal segment of the right lower lobe (data not shown). The patient was submitted to a right lower lobectomy with lymphadenectomy ($n = 36$) under general anesthesia. Grossly, the tumor was well-circumscribed and firm. Histologically, the tumor was rich in blood vessels, and the tumor tissue was composed of nested oval-shaped cells surrounding the blood vessels, with focal

spindle cell morphology visible (**Figure 2A, 2B**). The tumor cells had round nuclei and showed severe atypia with mitotic figures more than 5 per 50 high-power fields (HPFs). Despite the presence of enlarged lymph nodes, no lymph node involvement was detected histologically. No tumor embolus, pleura involvement, or nerve invasion was observed. The resection margin of the segmental bronchus was free of tumor. These histological findings were suggestive of high-grade soft tissue sarcoma. Immunohistochemically, the tumor cells were positive for actin, vimentin, desmin, EGFR, ERCC1, and calponin, but no immunoreactivity was found for TTF1, CK7, CK5/6, CHG, calretinin, CD34, EMA, HMB45, and S-100 (**Figure 2C-F** and data not shown). Of note, Ki-67 immunolabeling was detected in $> 30\%$ of tumor cell nuclei. Based on the combination of histological and immunohistochemical findings, a final diagnosis of multiple malignant glomus tumors of the lung was made.

Ten months after surgery, the patient was readmitted due to abdominal distention and

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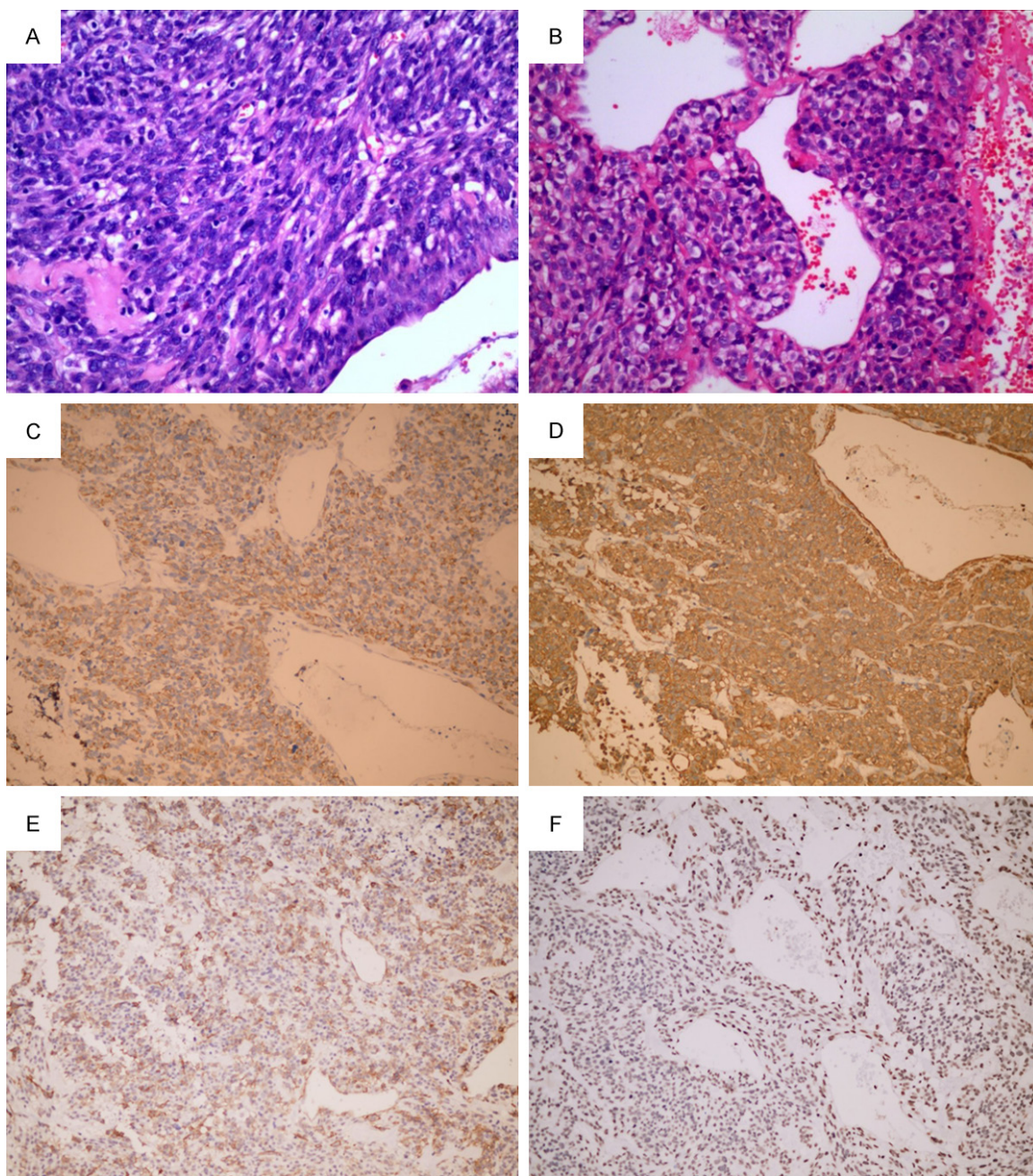


Figure 2. Histological and immunohistochemical staining. (A and B) Microscopic images showing nested oval-shaped cells surrounding the blood vessels, focal spindle cell morphology, and severe atypia with mitotic activity in the tumor tissue (H&E staining; magnification, $\times 200$); (C-E) Immunohistochemical images showing that the tumor cells were positive for actin (C), desmin (D), EGFR (E), and ERCC (F).

poor appetite for half a month. CT of the abdomen revealed extensive metastases to the left lung (**Figure 1C**), abdominal cavity, pelvic cavity, psoas major muscle, and subcutaneous soft tissue (**Figure 1D**), with ascites. After symptomatic treatment, the patient's symptoms did not improve. The patient requested to leave the hospital and died several days later.

Discussion

Malignant glomus tumor of the lung with metastasis is an extremely rare condition, and in addition to the present case, only six cases have been documented in the English literature [3-8]. Consistent with primary bronchopulmonary glomus tumors, metastatic cases occurred

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Table 1. Summary of reported cases of malignant primary pulmonary glomus tumors with metastasis

Ref.	Age (yrs)	Sex	Symptoms	Tumor location	Tumor size (cm)	Mitotic activity and atypia	Atypical mitotic figures	Spindling	Necrosis	Site of metastasis	Time to metastasis	Treatment	Outcome
[3]	69	M	Hemoptysis	Right upper lobe	9.5	Y	N/A	N	Y	Lung, mediastinum, brain, liver, subcutaneous tissue	4 months	Lobectomy, chemotherapy	Dead at 17 mo
[7]	9	F	N/A	Lung	4.5	Y	N	Y	Y	Small bowel	5 years	N/A	Alive
[4]	48	M	Fever, cough, hemoptysis	Left upper lobe and hilum	3.5	Y	N/A	Y	Y	Lung	At presentation	Lobectomy	Dead at 4 days
[8]	35	F	Hemoptysis	Left hilum	N/A	N/A	N/A	N/A	N/A	Lymph node, lung	16 years	Pneumonectomy with node dissection	N/A
[5]	60	F	Cough, hemoptysis	Left upper lobe, parahilar	2.5	Y	N/A	N/A	Y	Lymph node, GI tract, spleen, adrenal gland	At presentation	No treatment	Dead within a few months
[6]	59	F	Cough, hemoptysis	Multiple, bilateral	2.5	Y	N/A	Y	N/A	Lymph node, lung, GI tract, spleen	At presentation	Palliative therapy	Dead within 20 weeks
Our case	41	F	Cough, hemoptysis	Multiple, right lower lobe	7.5	Y	N	Y	N	Lung, abdominal cavity, pelvic cavity, psoas major muscle, subcutaneous soft tissue	11 months	Lobectomy	Dead at 11 months

F: Female; GI: Gastrointestinal; M: Male; N/A: Not known; N: No; Y: Yes.

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manly in adults (**Table 1**), with the exception of a 9-year old girl [7]. Intriguingly, unlike primary bronchopulmonary glomus tumors with a male predominance (male/female ratio, ~2.4:1), metastatic cases show an obvious female predominance (5 out of 7), which is similar to the striking female predominance (male/female ratio, 1:3) observed among patients with subungual lesions [2].

Primary bronchopulmonary glomus tumor often presents no specific clinical presentations that can distinguish it from other bronchopulmonary diseases. The patients frequently develop symptoms secondary to airway irritation and/or obstruction, such as cough and chest pain, while peripherally arising glomus tumors are usually asymptomatic [2]. Our case had a bronchial type disease and therefore developed obvious symptoms before presentation (cough and hemoptysis). Interestingly, hemoptysis was noted in the majority of metastatic cases (6 out of 7), but only in occasional cases of benign lesions [2]. Therefore, for suspected cases of bronchopulmonary glomus tumor with hemoptysis, the possibility of malignancy should be considered.

Although radiological modalities allow for the detection of bronchopulmonary glomus tumors, they cannot give a clear diagnosis due to the lack of specific manifestations, and the definite diagnosis relies primarily on pathological features and immunostaining [5]. Histologically, glomangiosarcomas can be divided into two categories based on the presence or absence of associated benign glomus tumor: glomangiosarcomas arising in a glomus tumor and *de novo* glomangiosarcomas [3]. The former is easier to recognize and often shows the feature of focal “spindling” of cells with cytological malignancy, as observed in the present case, while the latter is relatively difficult to diagnose and requires recognition of features suggestive of glomus tumors [3].

Immunohistochemically, glomus tumor cells are positive for cytoplasmic smooth muscle markers (e.g., actin and calponin) and pericellular basement membrane constituents (e.g., collagen IV and laminin), but generally negative for all neuroendocrine markers (e.g., S100) [9]. In addition, glomus tumor cells show reactivity for vimentin and variable staining for desmin and CD34 [9]. The combination of histology

and immunohistochemical staining pattern easily differentiates glomus tumor cells from other conditions that bear similarities to glomus tumor cells in clinical, imaging or histological findings, such as carcinoid tumors, hemangiopericytoma, and sclerosing hemangioma [3, 5, 9].

An interesting point of our case is that the tumor cells were positive for EGFR and ERCC (**Figure 2E, 2F**). Currently, the exact etiology of glomus tumors is unknown, and there have been few studies on the molecular genetics of glomus tumors. EGFR and ERCC as therapeutic targets have been well studied. The finding of increased EGFR and ERCC expression in glomus tumors, together with molecular abnormalities identified in previous studies, such as BRAF and KRAS mutations [9] and increased BCL-2 and p53 expression [10], may provide new clues to the etiology, malignant transformation, and treatment of glomus tumors.

Current diagnostic criteria for malignant glomus tumors are: (1) marked atypia and mitotic activity (> 5/50 HPFs); or (2) atypical mitotic figures [11]. In our case, the tumor cells showed nuclear atypia and increased mitotic activity. Consequently, the tumor was diagnosed as a malignancy. Folpe *et al* [7] identified that the 5-year cumulative metastatic risk of glomus tumors was significantly associated with deep location, size more than 2 cm, and atypical mitotic figures, while the combination of nuclear atypia and high mitotic activity showed a trend toward, but did not achieve, statistical significance possibly due to small sample size. Actually, nuclear atypia with increased mitotic activity was reported in nearly all ($n = 6$) and tumor size was greater than 2 cm in all the published metastatic cases, but atypical mitotic figures were rarely documented (**Table 1**). This finding suggests that nuclear atypia with increased mitotic activity might be a significant risk factor for metastasis in pulmonary glomus tumors. In addition, spindle cell morphology ($n = 4$) and necrosis ($n = 4$) were commonly seen in the reported metastatic cases (**Table 1**).

The sites of metastasis in malignant pulmonary glomus tumors are diverse. The lungs are the most commonly affected site ($n = 5$), followed by the gastrointestinal tract ($n = 4$) and lymph nodes ($n = 3$) (**Table 1**). In our case, the lung and gastrointestinal tract were also affected,

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although lymph node involvement was not detected. Other organs, such as the skin and spleen, may also be affected (**Table 1**). Of note, involvement of the pelvic cavity and psoas major muscle, as observed in the present case, has not been reported previously.

Rapid spread and early death are another striking feature of our case. Of the seven patients with metastatic disease, five died of the disease in less than one year (**Table 1**). Interestingly, the time from presentation to metastasis was short in all these five cases (< 1 year; **Table 1**), including three cases with metastasis at presentation. In contrast, two metastatic cases had a significantly longer latency period for the development of metastasis (5 and 16 years, respectively) [4, 8]. The long latency period may reflect the relatively low malignancy of the tumor. In addition, although glomus tumors may be multicentric, the rapid death of the three patients who underwent local excision before a metastatic disease was detected strongly suggests that metastasis might indeed occur at surgery (**Table 1**). This observation, together with the above finding that the lungs are the most commonly affected site, suggests that in patients with multiple pulmonary glomus tumors, the possibility of metastasis should be highly suspected.

Radical surgery is the only modality of curative treatment for malignant pulmonary glomus tumors without metastasis. However, for patients who have developed metastatic disease, no ideal therapy is currently available. Chemotherapy with doxorubicin has been reported to induce a complete response in a patient with metastatic disease, but disease progression appeared not to be delayed [3]. Palliative therapy may be considered for patients with wide metastases [6]. For patients suspected of having malignant pulmonary glomus tumor, early diagnosis should be made and aggressive surgery be performed before metastasis to achieve a good prognosis.

In conclusion, we document a fatal case of multiple malignant glomus tumors of the lung with rapid metastasis to multiple organs after surgery. Despite its rarity, malignant glomus tumors can be fatal within months of recognition if metastases develop. Our case stresses the importance of diagnosis and surgery before metastasis in patients with malignant

pulmonary glomus tumors. Especially, the possibility of metastasis should be highly suspected in patients with multiple pulmonary glomus tumors.

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Disclosure of conflict of interest

None.

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