Case report

Primary pulmonary glomus tumor of uncertain malignant potential: A case report with literature review focusing on current concepts of malignancy grade estimation

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ABSTRACT

We report a 38-year-old woman with a left lung tumor presenting as obstructive pneumonia. Bronchoscopic examination revealed a polypoid tumor filling the left main bronchus. The tumor was partially resected by a snaring procedure for diagnostic purposes. Microscopic examination revealed a submucosal tumor located underneath normal bronchial epithelium. The tumor was composed of sheets of uniform oval to cuboidal cells encompassing numerous blood vessels. Immunohistochemically, the tumor cells exhibited smooth muscle markers, but were negative for neuroendocrine markers. The diagnosis of primary pulmonary glomus tumor was therefore made. Subsequent bronchoscopic intervention allowed us to pin-point the origin of the tumor: superior segmental B 6a/b. She underwent a left lower lobe superior segmental resection successfully. Glomus tumors are relatively rare soft tissue tumors, and those of bronchopulmonary origin are exceedingly rare clinical condition. Among primary lung tumors, the carcinoid tumor is a mimic of the glomus tumor, and differentiating these tumors is known to be difficult, especially using small biopsy samples. In the present case, a large tissue sample obtained by bronchoscopic snaring was quite useful for the correct preoperative diagnosis. Because of the disease rarity, malignancy grade estimation of visceral glomus tumors has not been clearly addressed. Recently, the histopathological diagnostic criteria for malignant glomus tumors was defined in the WHO classification of soft tissue and bone tumors 4th edition. Here we also reviewed the literature on primary bronchopulmonary glomus tumors with special attention to the current concept of malignancy grade estimation.

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1. Introduction

Glomus tumors are relatively rare soft tissue tumors composed of cells that resemble the modified smooth muscle cells of the specialized form of arteriovenous anastomosis “glomus body” [1–4]. The most common site of the tumor is the subungual region; however, they occasionally occur in visceral organs such as airway tracts [1,2]. Primary glomus tumors of the lung are exceedingly rare, and the diagnostic and therapeutic strategies for this rare condition have not been well established. Here, we report a case of primary pulmonary glomus tumor that arose in a left segmental bronchus as a protruding polypoid mass with a clinical manifestation of obstructive pneumonia. In the present case, bronchoscopic intervention became a powerful tool not only for histological diagnosis but also for determining the proper operative procedure for the tumor. Ever since the criteria for the diagnosis of malignancy in glomus tumors was first established in 2001 [5], the malignancy estimation of visceral glomus tumors is a worrisome problem to be addressed because of the rarity of this condition. Recently, the criteria were modified and employed in the WHO classification of soft tissue and bone tumors 4th edition [4]. However, pulmonary glomus tumors diagnosed by the current WHO criteria have been scarcely reported. We also reviewed previous cases of primary bronchopulmonary glomus tumors in the literature, with special attention given to current diagnostic criteria.
2. Case presentation

A 38-year old woman visited a local hospital with the chief complaint of high fever and was diagnosed with pneumonia. She had no history of smoking. She had a past medical history of bronchial asthma, but asthmatic symptoms had ceased for a long time. Although antibiotic treatment was properly initiated, her symptoms persisted. Chest CT examination revealed a left lower lobe atelectasis with a water density mass in the left bronchus (Fig. 1a). Bronchoscopic examination revealed a polypoid mass in the left main bronchus. She was suspected of having a primary bronchial tumor and was referred to our hospital for further examination. Physical examination revealed decreased air entry in the left lower lung. Routine hematological and chemical laboratory results were normal, except for a slight increase in CRP (1.0 mg/dl).

Upon initial bronchoscopic examination, a polypoid tumor was observed that occluded nearly 90% of the lumen of the left main bronchus (Fig. 1b). For confirmation of the tumor type, a partial resection of the tumor was performed by bronchoscopic snaring. Postoperative chest X-ray revealed improvement of the atelectasis, and she was tentatively discharged. The partially resected surgical specimen consisted of tumor tissue that measured 1.5 cm in diameter (Fig. 1c). The tumor was well-circumscribed, firm, and tan in color (Fig. 1d). Microscopically, the tumor was located within the bronchial interstitial connective tissue covered by the bronchial epithelium with focal erosion. The tumor was composed of sheets of oval to cuboidal cells. Abundant vascular spaces were observed in the tumor, and some were surrounded by tumor cells (Fig. 2a). Blood vessels in the tumor were small to medium-sized, thin-walled, and some were dilated, resembling capillaries or venules. The tumor cells were uniformly monotonous with a centrally placed round nucleus and amphophilic to lightly eosinophilic cytoplasm (Fig. 2b). No necrosis, vascular invasion, obvious cellular atypia, or mitotic figures were observed. Immunohistochemically, the tumor cells exhibited cytoplasmic positivity for α-smooth muscle actin, calponin, and vimentin (Fig. 2c and d). Immunostaining was negative for desmin. The individual tumor cells were surrounded by positive staining for silver impregnation and anti-type IV collagen antibody, which showed an intricate chicken-wire pattern representing basement membrane material (Fig. 2e and f). No immunoreactivity was found for cytokeratin, CD34, CD31, S-100, CD56, chromogranin A, or synaptophysin (data not shown). Ki-67 immunolabeling was detected in approximately 3% of tumor cell nuclei. Histopathologically, the tumor was diagnosed as a...
classical glomus tumor. Two weeks later, she was re-admitted to our hospital because of total collapse of the left lung. A repeat bronchoscopic examination revealed total obstruction of the left main bronchus with bloody and fibrinous coagulation. After removal of the coagulative materials with biopsy forceps, the bronchial tumor was resected by a snaring procedure. Then, the origin of the tumor was confined to the bronchial mucosa of the left lower lobe superior segmental bronchus. One month later, she underwent a left lower lobe superior segmental resection. Grossly, the tumor was a firm cylindrical mass measuring 2.6 cm in length and 1.4 cm in diameter, which arose from the superior segmental B6a/b crista and filled and enlarged the lumen of B6a, B6b, and B6c (Fig. 1 e–g). The proximal resection margin of the superior segmental bronchus was free of tumor. Histopathological examination of the resected specimen confirmed the preoperative diagnosis of a classical glomus tumor. In all sections, no necrosis, infiltrative growth, vascular invasion, conspicuous cellular atypia, increased mitotic activity, or atypical mitotic figures were observed. The patient had an uneventful postoperative course. She had no respiratory complaints and no recurrence of the tumor two years following tumor resection, and then she was lost to follow-up.

3. Discussion

Glomus tumors are distinctive mesenchymal neoplasms composed of cells that closely resemble the normal glomus body [1–4]. Glomus tumors are uncommon, with an estimated incidence of 1.6% in 500 consecutive soft tissue tumors [6]. The vast majority of glomus tumors occur in the dermis and subcutis of the extremities, with the single most common site of the subungual region of the finger; however, rare tumors have been reported in visceral organs [1,2]. Primary glomus tumors of the lung are exceedingly rare, with only 36 previously reported cases in the English literature (Table 1) [5,7–36]. Almost the same number of cases with primary tracheal glomus tumors have also been reported to date [37]. A survey of the literature shows that the primary bronchopulmonary glomus tumor usually occurred in adults, with the exception of a 9-year old female patient [5]. There is an obvious male predominance (26 out of 37), in sharp contrast with a striking female predominance (male to female ratio of 1:3) among patients with subungual lesions [1,2]. No causative relationship has yet been reported between smoking and tumorigenesis of glomus tumors. Primary pulmonary glomus tumors affected both bronchi and peripheral lung tissues including subpleural regions. In the bronchi, the tumor appeared as protruding polypoid masses, whereas it appeared as nodular lesions in the peripheral lung. The sizes of pulmonary glomus tumors tend to be larger than those of cutaneous glomus tumors with a typical tumor size of <1 cm [3,4]. Symptoms due to airway irritation and/or obstruction are common in bronchial glomus tumors, whereas peripherally arising glomus tumors are usually asymptomatic and found incidentally. The present case is a central (bronchial) type of glomus tumor of the lung presenting as pneumonia due to airway obstruction.

Histopathologically, there are two major diagnostic problems of primary pulmonary glomus tumors: first, the differential diagnosis of glomus tumors from other pulmonary tumors, and the second is the estimation of the malignant potential of this quite rare clinicopathological condition. In general, the items of differential diagnosis of cutaneous glomus tumors include adnexal tumors (especially hidradenoma) and less frequently intradermal nevi.
| Ref. | Age/sex | Presenting symptoms | Side Location | Size (cm) | Biopsy diagnosis | Postoperative histological diagnosis | Metastasis; site | Treatment | Clinical outcome | Classification according to the WHO 3rd/4th ed. |
|------|---------|---------------------|---------------|-----------|-----------------|------------------------------------|-----------------|-----------|----------------|-----------------------------------------------|
| [7]  | 67/M    | Epigastralgia       | L Lower lobe, subpleural | 6.5       | N/A             | GT                                 | No              | Lobectomy | FOD at 9 months | MGT/GTUMP                                    |
| [8]  | 34/M    | ASX                 | R Upper lobe       | 2.0       | N/A             | GT                                 | No              | Lobectomy | FOD at 9 months | GTUMP/ GTUMP                                |
| [9]  | 50/M    | ASX                 | R Subpleural       | 1.1       | Not performed   | GT                                 | No              | Wedge resection | FOD at 3 months | GTUMP/ GTUMP                                |
| [9]  | 41/M    | ASX                 | R Lower lobe, peripheral | 1.5       | Not performed   | GT                                 | No              | Wedge resection | FOD at 9 months | GTUMP/ GTUMP                                |
| [10] | 20/M    | Pneumothorax        | L Main bronchus     | 1.4       | Carcinoid       | GT                                 | No              | Sleeve resection | FOD at 6 months | GTUMP/ GTUMP                                |
| [10] | 65/F    | ASX                 | R Infralobar       | 3.0       | Not performed   | GT                                 | No              | Wedge resection | FOD at 6 months | GTUMP/ GTUMP                                |
| [10] | 40/M    | ASX                 | R Upper lobe, subpleural | 1.1       | Not performed   | GT                                 | No              | Lobectomy | FOD at 6 months | GTUMP/ GTUMP                                |
| [10] | 69/M    | Hemoptysis          | R Upper lobe       | 9.5       | Not performed   | Glomangiosarcoma                    | Lung, Mediastinum, Brain, Liver, Skin | Lobectomy; chemotherapy | DOD at 17 months | MGT/MGT                                     |
| [5]  | 38/M    | N/A                 | L Lung       | 3.8       | N/A             | Glomangiosarcoma                    | N/A             | N/A       | N/A            | MGT/MGT                                      |
| [5]  | 9/F     | ASX                 | N/A Lung | 4.5       | N/A             | Glomangiosarcoma                    | GT tract        | N/A       | AWD at 60 months | MGMT/GMT                                    |
| [11] | 48/M    | Hemoptysis          | L Main bronchus     | 0.7       | GT               | GT                                 | No              | Wedge resection | FOD at 3 months | GTUMP/ GTUMP                                |
| [12] | 29/F    | Cough, dyspnea, chest pain | L Main bronchus | 1.5       | Carcinoid tumor | GT                                 | No              | Bronchotomy plus mass extirpation | FOD at 17 months | GTUMP/ GTUMP                                |
| [13] | 53/M    | Cough               | R Basal bronchus   | 2.5       | Degenerated atypical cells | Glomangiosarcoma | No           | Lobectomy | FOD at 23 months | MGT/MGT                                      |
| [14] | 29/M    | Chest discomfort    | R Main bronchus    | 3.0       | Adenoma          | GT of undetermined malignant potential | No           | Sleeve upper lobectomy with node dissection | N/A            | MGT/GTUMP                                    |
| [15] | 40/M    | Fever, cough, chest pain | L Main bronchus     | 0.9       | Not performed   | GT                                 | No              | Endoscopic removal | FOD at 1 month | GTUMP/ GTUMP                                |
| [16] | 50/M    | ASX                 | R Upper lobe, bronchus intermedius | 4.0       | N/A             | GT                                 | Not obtained | Lobectomy | Laser coagulation followed by cryotherapy Segmental resection | FOD at 3 months | GTUMP/GTUMP |
| [17] | 37/M    | Cough               | R Bronchus intermedius | 0.8       | Typical carcinoid | GT                                 | No              | N/A       | N/A            | MGT/MGT                                      |
| [18] | 67/M    | Cough               | R Superior bronchial trunk | 0.8       | Typical carcinoid | GT                                 | No              | N/A       | N/A            | MGT/MGT                                      |
| [19] | 64/M    | ASX                 | L Lower lobe, bronchus intermedius | 3.5       | Not performed   | Glomangiona                         | No              | Tumor removal | N/A            | MGT/GTUMP                                    |
| [20] | 56/F    | Hemoptysis          | R Lower lobe, bronchus intermedius | 5.5       | Not diagnostic | Glomangionioma                       | No              | N/A       | N/A            | MGT/GTUMP                                    |
| [21] | 54/M    | Cough               | R Lower lobe, bronchus intermedius | 2.3       | Typical carcinoid | GT                                 | No              | N/A       | N/A            | MGT/GTUMP                                    |
| [22] | 55/M    | ASX                 | R Upper lobe       | 1.1       | N/A             | GT                                 | No              | Lobectomy | N/A            | GTUMP/ GTUMP                                |
| [23] | 69/M    | Hemoptysis          | R Main bronchus    | 2.0       | Angiomous lesion | GT                                 | No              | Lobectomy | N/A            | GTUMP/ GTUMP                                |
| [24] | 21/F    | ASX                 | L Upper lobe, parahilar bronchus | 2.5       | N/A             | GT                                 | No              | Lobectomy | N/A            | GTUMP/ GTUMP                                |
| [25] | 39/M    | Cough               | R Main bronchus    | 2.5       | GT               | GT                                 | No              | Endoscopic resection | FOD at 72 months | GTUMP/GTUMP                                |
| [26] | 74/M    | Cough, dyspnea, chest pain | R Upper lobe, parahilar bronchus | 3.4       | GT               | Glomangiosarcoma                    | No              | Lobectomy with node dissection | FOD at 12 months | MGT/MGT                                      |
| [27] | late 30s/M | Hemoptysis      | R Bronchus intermedius | 1.5       | Carcinoid, suspected | GT                                 | No              | Sleeve lobectomy | FOD at 10 months | GTUMP/ GTUMP                                |
| [28] | 39/M    | ASX                 | L Upper lobe       | 2.0       | Sclerosing hemangioma | GT                                 | No              | Lobectomy with node dissection | N/D            | GTUMP/ GTUMP                                |
| [29] | 62/M    | Hemoptysis          | L Main bronchus    | 1.6       | Neuroendocrine tumor | GT                                 | GT              | Lobectomy | N/A            | GTUMP/ GTUMP                                |
| [30] | 35/F    | Hemoptysis          | L Hilum           | 1.6       | Glomangiosarcoma | Glomangiosarcoma                    | Lymph node, Lung | Pneumonectomy with node dissection | N/A            | GTUMP/ GTUMP                                |
| [31] | 43/F    | ASX                 | R Upper lobe, peripheral bronchus | 2.0       | Not performed   | Glomangiosarcoma                    | Lung           | Thoracoscopic lung resection | FOD at 6 months | GTUMP/ GTUMP |
| [32] | 28/M    | Hyperpyrexia, anemia | R Upper lobe       | 3.0       | Low-grade MGT   | Low-grade MGT                       | No              | Lobectomy | FOD at 12 months | GTUMP/ GTUMP |
| [33] | 60/F    | L                   | 2.5       | MGT             | Not obtained | Not performed | Not performed | Not performed | Not performed | MGT/MGT                                      |
Criteria for the diagnosis of malignancy

10 cases with malignancy have been previously reported by Enzinger and Weiss [1] and employed in the WHO classification of soft tissue and bone tumors, 3rd edition [3]. In the criteria, the diagnosis of “malignant glomus tumor” should be reserved for tumors showing the following: 1) large size (>2 cm) and deep location; 2) atypical mitotic figures; or 3) marked atypia with mitotic activity. According to the criteria, the majority of visceral glomus tumors could be diagnosed as “malignant” because of their consistent “deep” location and relatively large sizes. In the literature, however, 10 out of 19 cases of bronchopulmonary glomus tumors with sizes of >2.0 cm did not show histologically atypical features or clinically malignant behavior. Because the first criterion was elaborated mainly based on a large number of atypical glomus tumors of the skin, whether this criterion was applicable to visceral glomus tumors remained uncertain [14]. Currently, growing evidence has shown that most of the large and deeply located glomus tumors behave in a clinically benign fashion; therefore, the first diagnostic criterion was modified, and these lesions are now considered glomus tumors of uncertain malignant potential [2,4]. Previous and current diagnostic criteria of glomus tumors with atypical features proposed by Folpe et al. are comparatively shown in Tables 2 and 3. Briefly, glomus tumors of >2 cm in size with a deep location were previously diagnosed as malignant but are now categorized as having uncertain malignant potential. Visceral glomus tumors are essentially considered bearing uncertain malignant potential because of their deep location. However, malignancies are defined solely by histological findings in the current criteria. In our case, the tumor is 2.6 cm in maximal diameter, but neither mitotic figures nor an obvious nuclear atypia was observed. Our case is therefore defined as a glomus tumor of uncertain malignant potential, according to the current diagnostic criteria [2,4]. The tumor grew cylindrically in the bronchial lumen with no infiltrative growth. There was no necrosis. Ki-67 immunolabeling was found in only approximately 3% of tumor cells. All of these findings suggested the probable benign nature of the tumor. A conservative surgery was therefore considered feasible. Our repeated bronchoscopic intervention allowed us to identify the origin of the tumor, thus opening a door for limited resection. Without the repeated interventions, the patient would have required at least a lobectomy. To date, the follow-up of glomus tumors of uncertain malignant potential has been good, but the number of cases is small and the follow-up period is short. Because it is still unclear whether large visceral glomus tumors are truly benign or potentially malignant indolent tumors, close post-operative follow-up is warranted. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Table 1 (continued)

| Ref. | Age | Sex | Presenting symptoms | Side | Location | Size (cm) | Biopsy diagnosis | Postoperative histological diagnosis | Metastasis; site | Treatment | Clinical outcome | Classification according to the WHO 3rd/4th ed. |
|------|-----|-----|---------------------|------|----------|-----------|-----------------|--------------------------------------|-----------------|------------|----------------|---------------------------------------------|
| [34] | 49/M | Cough, hemoptysis | R | Lower lobe | 3.0 | Not performed | GTUMP | Lymph node, GI tract, Splenic Adrenal gland | Wedge resection | N/A | MGT/GTUMP | DOD within a few months |
| [35] | 59/F | Cough, dyspnea, chest pain | L&R | Multiple | 2.5 | MGT | Not obtained | Lymph node, Lung, GI tract, Splenic No | Not performed | DOD within 20 weeks | MGT/MGT | |
| [36] | 66/F | ASX | R | Middle lobe | 4.5 | Not performed | MGT | Lobectomy | FOD at 13 months | MGT/ | Suspicion of GTUMP | |
| * | 38/F | Fever | L | Lower lobe, B³ 2.6 | GT | GTUMP | No | Segmentectomy | FOD at 24 months | MGT/GTUMP | |

AWD, alive with disease; ASX, asymptomatic; DOD, died of disease; DOOD, died of other disease; F, female; FOD, free of disease; GI, gastrointestinal; GT, glomus tumor; GTUMP, glomus tumor of uncertain malignant potential; L, left; M, male; MGT, malignant glomus tumor; N/A, not available; N/D, not determinable because of undetailed histological information; R, right; *, our case.
Table 2
WHO classification of glomus tumors with atypical features.

| WHO 3rd edition (2002) | WHO 4th edition (2013) |
|------------------------|------------------------|
| **Malignant glomus tumors** | |
| 1) Size >2 cm and subfascial or visceral location or | 1) Marked nuclear atypia and any level of mitotic activity or |
| 2) Marked nuclear atypia and any level of mitotic activity or | 2) Atypical mitotic figures |
| 3) Atypical mitotic figures | |
| Glomus tumors of uncertain malignant potential | |
| Not fulfilling criteria for malignancy, but having at least one atypical feature | |
| other than nuclear pleomorphism | |
| **Sympathetic glomus tumors** | |
| Striking nuclear atypia in the absence of any other worrisome feature (e.g., large size, deep location, mitotic activity, necrosis) | |

Table 3
Classification of glomus tumors with atypical features in Enzinger and Weiss's Soft Tissue Tumors.

| 5th edition (2008) | 6th edition (2014) |
|-------------------|-------------------|
| **Malignant glomus tumors** | |
| 1) Marked atypia + mitotic activity (≥50 HPF) or | 1) Marked atypia + mitotic activity (≥50 HPF) or |
| 2) Atypical mitotic figures or | 2) Atypical mitotic figures |
| 3) Large size (>2 cm) + deep location | |
| Glomus tumors of uncertain malignant potential | |
| 1) Superficial location + high mitotic activity (≥5/50 HPF) or | |
| 2) Large size only or | |
| 3) Deep location only | |
| **Sympathetic glomus tumors** | |
| Lacks criteria for malignant glomus tumor and marked nuclear atypia only | |

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