Case Report
Histologic characteristics and prognosis of lung mixed squamous cell and glandular papilloma: six case reports

Fei Li¹, Ming He¹, Fang Li², Yong Li¹, Yuan Song³

Departments of ¹Thoracic Surgery, ²Pathology, ³Clinical Laboratory, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China

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Abstract: Lung mixed squamous cell and glandular papilloma (LMSCGP) has no clear signs, clinical symptoms, or imaging features; thus, its diagnosis primarily relies on post-resection histology and immunohistochemistry. Therefore, in this work six case reports are described to review the clinicopathologic characteristics, diagnosis, treatment, and prognosis. Here, we report the clinical symptoms, imaging features, pathologic characteristics, and follow-up data of six LMSCGP patients. Among the 6 patients, 4 were males and 2 were females, with a mean age of 52.7 years (39-67 years). These patients accounted for 0.0827% of patients who underwent thoracic surgery in the same period (6/7357). Preoperative diagnosis indicated cancer or most likely cancer in 3 patients, benign lesions in 3 patients, and bronchial adenoma in 1 patient. All 6 patients underwent surgery, consisting of wedge resection in 3 patients and lobectomy in the other 3 patients. Hilar lymph node metastasis was not identified during postoperative pathologic diagnosis. Conclusion: LMSCGP is a rare lung tumor with a certain heterogeneity that makes definite preoperative diagnosis difficult. Complete surgical resection is the preferred treatment choice and results in a good prognosis in most cases.

Keywords: Mixed squamous cell glandular papilloma, lung tumor, prognosis, surgery

Introduction
Papilloma is a rare solid tumor that can be histologically divided into squamous cell papilloma, glandular papilloma, and mixed squamous cell and glandular papilloma (MSCGP). MSCGP is a benign mixed papilloma composed of bidirectionally differentiated squamous and glandular epithelial cells. MSCGP is clinically rare, and lung MSCGP (LMSCGP) is even rarer [1]. Most patients with LMSCGP lack typical clinical manifestations have lesions that occur in the peripheral regions of the lung, and imaging characteristics that are indistinguishable from intrapulmonary nodules. Therefore, LMSCGP is primarily differentially diagnosed from pulmonary hamartoma, peripheral lung adenocarcinoma, and pulmonary sclerosing hemangioma [2]. There are currently fewer than 30 reports describing LMSCGP, and knowledge on this disease is lacking. Therefore, in this report, the clinical and pathological characteristics of seven LMSCGP patients were reviewed and their treatment and prognosis were evaluated in order to provide insight into subsequent diagnosis and treatment.

Case presentation
Six LMSCGP patients were treated at the Department of Thoracic Surgery at The Fourth Hospital of Hebei Medical University between June 30, 2008 and June 30, 2018. The patients accounted for 0.0827% (6/7357) of patients who underwent thoracic surgery in the same period. The basic information of the patients is shown in Table 1. Among the 6 patients, 4 were males and 2 were females, and the mean age was 45 years (36-72 years). Two patients had 30 years of long-term regular smoking (20 cigarettes/day) but no history of drinking. Four patients had a history of hypertension, two patients had uterine myomectomy, two patients had coronary heart disease, one patient had...
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Table 1. The information of the six LMSCGP patients

<table>
<thead>
<tr>
<th>Site number</th>
<th>Sex/Age</th>
<th>Symptoms</th>
<th>Gross</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female/57</td>
<td>Asymptomatic</td>
<td>Solid, 2.5 × 1.8 × 1.2 cm, dirty pleura 0.1 cm, Located in the bronchi</td>
<td>Right upper lobe resection</td>
<td>25 months, A&amp;W</td>
</tr>
<tr>
<td>2</td>
<td>Male/49</td>
<td>Asymptomatic</td>
<td>Solid, 3.8 × 2.5 × 2.2 cm, dirty pleura 1.2 cm</td>
<td>Right upper lobe resection</td>
<td>24 months, A&amp;W</td>
</tr>
<tr>
<td>3</td>
<td>Male/48</td>
<td>Bloating, loss of appetite</td>
<td>Solid, 1.8 × 1.5 × 0.8 cm, invading pleura</td>
<td>Left lower lobe wedge resection</td>
<td>21 months, A&amp;W</td>
</tr>
<tr>
<td>4</td>
<td>Male/39</td>
<td>Asymptomatic</td>
<td>Solid, 4.2 × 2.7 × 1.5 cm, dirty pleura 0.4 cm</td>
<td>Right upper lobe resection</td>
<td>78 months, A&amp;W</td>
</tr>
<tr>
<td>5</td>
<td>Female/67</td>
<td>Chest pain</td>
<td>Solid, Partial Cystic, 2.0 × 2.0 × 1.7 cm</td>
<td>Right upper lobe wedge resection</td>
<td>35 months, A&amp;W</td>
</tr>
<tr>
<td>6</td>
<td>Male/59</td>
<td>Asymptomatic</td>
<td>Solid, 3.0 × 2.7 × 1.5 cm, invading pleura</td>
<td>Right lower lobe wedge resection</td>
<td>11 months, double lung metastasis</td>
</tr>
</tbody>
</table>

NED, no evidence of disease; LFU, lost to follow-up; DOD, dead of disease; A&W, alive and well.
left inguinal hernia, and one patient had hepatic cystectomy. None of the 6 patients had a history of cancer and related familial diseases. The main complaint was identified during the physical examination in 4 patients. One patient presented with bloating and loss of appetite, while another one had cough and sputum production. Lesions were located in the right upper lobe in 4 patients, right lower lobe in 1 patient, left lower lobe in 1 patient, and right middle lobe in 1 patient.

All six patients were preoperatively diagnosed with LMSCGP by enhanced thoracic CT (Figure 1). All patients had a single lesion and among them, 5 had the peripheral type and 1 had the central type. The tumor diameter was > 3 cm in 3 patients, < 3 cm in 4 patients, and < 2 cm in 1 patient. The thoracic CT showed that the peripheral tumors were mostly rounded with a distinct boundary, no lobes and spicules, and with a consistent tissue density. The pleural region near the tumor showed a depression or long protrusion, and the mean CT value of the tumor was 35 Hz-67 Hz. Intratumoral calcification spots were observed in only 1 patient. In the patient with the central type tumor, the tumor was located near the anterior segment of the bronchus in the right upper lobe.

All patients underwent video-assisted thoracoscopic surgery (VATS), and among them, 3 underwent triportal VATS, 2 underwent single utility port VATS, and 1 underwent uniportal VATS. After the surgery, two thoracic drainage tubes (one to drain fluid and one to drain gas) were placed in the right upper lobe of 4 patients, and one thoracic drainage tube was placed in the lower lobe of the other 2 patients. Postoperative thoracic CT (200 ml/d) indicated good recruitment maneuvering and thoracic drainage tubes were removed. The mean length of postoperative hospital stay was 4.8 days.

The macroscopic features of the tumor are shown in Table 1. The six patients had similar histologic features (Table 2 and Figure 2), including a clear boundary between the tumor tissue and adjacent normal tissues and papillary-like tumor covered by squamous and glandular epithelial cells. The tumor was primarily composed of glandular epithelial cells (66%) and ciliated columnar cells, non-ciliated epithelial cells, and mucinous columnar cells. Immunohistochemistry indicated that the tumor was mostly positive for villin, CK20 and TTF-1, and a high proportion of tumors was also positive for CK7, Ki67 and Napsin A (Figures 3 and 4). Lymph node metastasis and bronchial stump positivity were not observed in the 6 patients.

All patients underwent follow-up once at 1, 3, 6 and 12 months post-surgery and then once per year thereafter. Forms of follow-up include telephone, mail and Wechat. Patients were followed up for a mean time of 31 months (12-52 months). The follow-up include routine blood test, color doppler ultrasound of both supraclavicular lymph nodes and thoracic CT. Routine follow-up was conducted in all 6 patients after the surgery. Recurrence and metastasis were not observed in 6 patients, and none of the patients received adjuvant therapy. Multiple nodules were identified in both lungs of one patient by thoracic CT at 11 months post-surgery and metastasis was considered. However,
the patient had no signs of discomfort and refused to receive further diagnosis and treatment. This patient is still alive and underwent 12 months’ follow-up.

Discussion

Lung papilloma was first reported by Spencer et al. in 1980 [3]. This tumor usually develops in the peripheral region of the lung and, in most cases, it is identified during physical examination. Patients with lung papilloma have no specific clinical symptoms [4]. Flieder classified lung papilloma into squamous cell papilloma, glandular papilloma and MSCP based on its histologic features, and MSCP is the rarest form of lung papilloma. LMSCGP is a benign lung carcinoma composed of bidirectionally differentiated squamous and glandular epithelial cells, and was previously known as mixed papilloma and transitional cell papilloma [5]. LMSCGP is commonly found in males, and 4 of the 6 patients in this study were males. LMSCGP can be classified as central type or peripheral type based on its site of development. The central type is the one most commonly reported in the literature. Central type LMSCGP lesion is found close to the bronchus, and some patients can present with respiratory symptoms such as cough and phlegm production. However, central type LMSCGP was identified in only 2 of the 6 patients. One patient was diagnosed with LMSCGP due to respiratory symptoms, which was inconsistent with previous studies [6, 7]. Since the number of reported cases is low, a further follow-up of new cases with this lesion is needed.

In terms of pathogenesis and mechanism, the pathogenesis of squamous cell papilloma is associated with long-term smoking and HPV infection [8], whereas the pathogenesis of glandular papilloma is associated with direct stimulation by inflammatory factors. However, the pathogenesis of LMSCGP still needs further

Table 2. The histologic features of six LMSCGP patients

<table>
<thead>
<tr>
<th>Site number</th>
<th>Villin</th>
<th>CK20</th>
<th>TTF-1</th>
<th>CK7</th>
<th>Ki67</th>
<th>Napsin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>positive cells 3%</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>positive cells over 40%</td>
<td>positive cells over 40%</td>
<td>+</td>
<td>high expression of basal cells</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>positive cells 3%</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>positive cells over 40%</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>positive cells 3%</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>positive cells over 40%</td>
<td>-</td>
<td>+</td>
<td>positive cells 3%</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Figure 2. Histopathologic features of LMSCGP are shown. A. Squamous epithelial cells and glandular epithelial cells (H&E 200 ×). B. The tumor tissue and the surrounding normal lung tissue have clear boundaries, and the tumor is papillary, with squamous epithelial cells and glandular epithelial cells (66%), composed of ciliated columnar cells, non-ciliated epithelial cells, and mucous columnar cells. (H&E 400 ×).

Figure 3. Immunohistochemical staining of the LMSCGP is shown with CK7 (A) positive (Envision 100 ×), and CK20 (B) positive (Envision 100 ×).
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studies. There is no significant trend in the age of LMSCGP onset, but the disease is primarily found in middle aged individuals and more in men than women. The male to female ratio of patients in this study was 2:1. Most peripheral LMSCGP types are clinically characterized by slow growth and lack of typical clinical manifestations. Central type tumors are close to the bronchus and their enlargement can directly result in respiratory symptoms, such as cough, sputum production, or thoracic pain. One of the patients in this study had indeed respiratory symptoms [4, 9].

LMSCGP is differentially diagnosed from lung tumors such as pulmonary hamartoma, peripheral lung adenocarcinoma, and pulmonary sclerosing hemangioma. Thoracic CT is the primary method for a differential diagnosis [10]. LMSCGP appears as intrapulmonary soft tissue-like nodules with consistent density by thoracic CT but has no significant changes in enhanced CT value. The thoracic CT characteristics of pulmonary hamartoma are popcorn-like calcification and consistent soft tissue density shadows in other parts of the tumor. Pulmonary sclerosing hemangioma and peripheral lung adenocarcinoma display enhancing lesions following enhanced CT scan. However, unique features of peripheral lung adenocarcinoma also include being "lobulated" or "spiculated". Our results demonstrated that in the 4 patients with peripheral type LMSCPG, the tumors appear round with a clear boundary, single lesion, consistent intratumor density, and lack of lung cancer-associated imaging features such as lobulation and speculation. Tumors that develop near the pleura can lead to pleural depression or bulging, and these features can be easily confused with those of peripheral lung adenocarcinoma [5, 6]. Intratumoral calcification spots were identified in only 1 patient who was diagnosed with pulmonary hamartoma. For patients whose pathology cannot be confirmed by preoperative bronchoscopy or CT-assisted lung puncture, PET-CT can be used to assist diagnosis in addition to traditional thoracic CT examination. However, PET-CT is not a routine test for LMSCGP due to its high false positive rate and cost. A study reported that PET-CT results in LMSCGP patients results in mild to high FDG intake and SUV values up to over 100 [11].

Histopathology is still the method for a definitive LMSCGP diagnosis. The pathology of the 6 patients was confirmed after surgical resection. All 6 patients had similar histologic features, including a clear boundary between tumor tissues and adjacent normal tissues and papillary-like tumors composed of squamous and glandular epithelial cells. Glandular epithelial cells were more abundant than squamous epithelial cells, and these cells were composed of ciliated columnar cells, non-ciliated epithelial cells and mucinous columnar cells (Table 1). During LMSCGP progression, the tumor had a similar biological behavior as that of esophageal and colonic papilloma with exogenous growth [12]. LMSCGP has a similar growth pattern as peripheral lung cancer and is usually found along the alveolar wall [1]. Immunohistochemistry showed that all 6 patients were positive for CK5/6, P40, and TTF-1, 5 patients

Figure 4. Immunohistochemical staining of the LMSCGP is shown with (A) Ki-67 positive (Envision 100 ×), (B) Napsin A positive (Envision 100 ×), (C) TTF-1 positive (Envision 100 ×), and (D) villin positive (Envision 100 ×).
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were positive for Napsin A and CK, 5 patients were positive for Ki67, and 1 patient had high expression in basilar cells. Glandular epithelial cells are only positive for CK7 but negative for CK5/6, whereas squamous epithelial cells are only positive for CK5/6 and negative for CK7 (Table 2). Previous immunohistochemistry of the two types of tumor cells indicated negative expression of CK5/6, CK7, CAM5.2, and 34BE12 [13].

In terms of treatment, most LMSCGP patients were without pathologic diagnosis before surgery and were definitively diagnosed with the lesion from frozen sections obtained by wedge resection. Since the lesion was near the bronchus in 3 patients and wedge resection was difficult, post-lobectomy frozen section pathology was performed. All patients in this study underwent VATS due to the increased application of VATS in the Department of Thoracic Surgery. Since this surgical method is minimally invasive, painless and has a quick recovery, all patients had no postoperative respiratory complications such as atelectasis and pneumonia. Therefore, VATS is worthy of wide application in the treatment of LMSCGP. As regard LMSCGP prognosis, it is widely agreed that this disease is a benign lung tumor, and adjuvant therapy is usually not required following surgical resection. However, it was previously reported [14, 15] that a few patients may exhibit malignant changes before the surgery, which were mostly reported as squamous cell carcinoma [16]. Nevertheless, currently no reports of postoperative recurrence and metastasis are available. In this study, thoracic CT re-examination of 1 patient revealed multiple scattered and non-uniform nodules with a clear boundary in both lungs at 11 months post-surgery, and this patient was considered as carrying metastatic tumors. CT-guided lung biopsy indicated squamous cell carcinoma, which suggests that the patient may already have intrapulmonary micrometastasis before the surgery.

In conclusion, LMSCGP has no clear characteristics regarding vital signs, clinical symptoms, and imaging features; thus, its definitive diagnosis primarily relies on post-resection histology and immunohistochemistry. Surgical resection is the main treatment method for this disease and generally results in a good prognosis. Although postoperative recurrence and metastasis were not previously reported, multiple postoperative metastases in both lungs were observed in one patient, which may be due to metastasis of tumor from other sites. Therefore, further case reports are required for this disease to find more specific features for its identification.

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Disclosure of conflict of interest

None.

Address correspondence to: Yuan Song, Department of Clinical Laboratory, The Fourth Hospital of Hebei Medical University, No. 12 Jiankang Road, Shijiazhuang 050011, China. Tel: +8613613307299; E-mail: songyuan1107@163.com

References


