Original Article
Massive cryptogenic hemoptysis undergoing pulmonary resection: clinical and pathological characteristics and management

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Abstract: Massive cryptogenic hemoptysis is a common presenting symptom and cause of hospitalization for respiratory diseases, and represents a challenging condition in the clinical. This study aimed to analyze the clinical and pathologic data and management of patients with massive cryptogenic hemoptysis. We retrospectively reviewed 12 patients with massive cryptogenic hemoptysis in our hospital between January 2003 and December 2012. Bronchoscopy showed submucosal vascular abnormalities in 4 patients. Of 6 patients managed with conservative measures, bleeding was completely controlled in 2 patients. Of 10 hemoptysis patients, three were controlled by bronchial arterial embolization, and seven by surgery. Pathological examination showed a superficial dysplastic, tortuous and dilated bronchial artery under the bronchial epithelium in 4 patients, and bronchiole dilation in 2 patients, indicating Dieulafoy’s disease of the bronchus and bronchiectasis. No malignance developed within the follow-up. In conclusion, Dieulafoy’s disease of the bronchus and bronchiectasis should be suspected in patients with massive cryptogenic hemoptysis. BAE and surgical treatment should be considered in case that massive hemoptysis could not be controlled by conservative management.

Keywords: Cryptogenic hemoptysis, Dieulafoy’s disease, bronchus, outcome

Introduction
Massive hemoptysis is a life-threatening condition that can lead to airway compromise and death [1, 2]. Commonly, the etiology of hemoptysis is related to lung neoplasm, bronchiectasis, and tuberculosis [3]. While hemoptysis is usually identified with the currently available diagnostic tools such as computed tomography (CT) scan and fibroptic bronchoscopy, 5-20% of cases remain classified as cryptogenic [4]. It represents a challenge to identify the etiology of cryptogenic hemoptysis and manage the patient with massive cryptogenic hemoptysis in emergency. Up to now, multidisciplinary approach, such as medical management especially together with bronchial artery embolization, has been effectively applied to the treatment of massive hemoptysis, and surgical treatment has seldom been employed [5].

In this study, we retrospectively reviewed patients with massive cryptogenic hemoptysis who underwent pulmonary resection in the past 10 years, to analyze their clinical and pathologic aspects and evaluate the management of these patients.

Materials and methods
Subjects

This study was conducted between January 2003 and December 2012 in a tertiary university hospital in Wenzhou, China. The study protocols were approved by Ethics Committee of Wenzhou Medical College (Wenzhou, China), and all participants gave signed consent. All consecutive patients presenting with massive hemoptysis were included. Hemoptysis was considered as massive for bleeding of 200 ml or more per 24 h, or bronchial blood loss caus-
Massive cryptogenic hemoptysis

**Table 1.** Bleeding sites in lung area in 12 patients with massive cryptogenic hemoptysis

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper</td>
<td>2</td>
</tr>
<tr>
<td>Right middle</td>
<td>2</td>
</tr>
<tr>
<td>Right lower</td>
<td>3</td>
</tr>
<tr>
<td>Left upper</td>
<td>2</td>
</tr>
<tr>
<td>Lingula</td>
<td>1</td>
</tr>
<tr>
<td>Left lower</td>
<td>2</td>
</tr>
</tbody>
</table>

**Management of hemoptysis**

All patients received conservative management initially in a uniform manner as follows. Strict bed rest and lateral decubitus toward the site of bleeding were maintained. Controlled humidified oxygen-air mixture therapy was administered. Antibiotics were prescribed in patients with suspected bacterial infections. Agents including vasoconstrictive drug vasopressin, antifibrinolytic drug tranexamic acid and reptilase were administered intravenously. Blood count, biochemistry, clotting test and arterial blood gas analysis were performed. Sputum specimens were submitted for microscopic study and culture of bacteria, acid-fast bacilli and fungi examination. Chest X-ray and CT-scan were performed as soon as possible. Fiberoptic bronchoscopy was performed to identify the location of the bleeding and a possible etiology in 10/12 patients for failure of hemorrhage control or as an emergency. In case of recurrent hemoptysis, bronchial arteriography associated with bronchial arterial embolization was performed with a Seldinger technique. If all the means of treatment described above failed or airway compromise might happen, an emergency surgical treatment was applied when the site of bleeding was localized. After surgery, the lung samples were handled by the same pathologist.

**Data collection**

Demographic data and information concerning age, sex, smoking status, risk factors for hemorrhage, comorbid condition, hospital outcome and prognosis were collected from the patients.

**Analysis of outcome**

Immediate control of bleeding, recurrences, and results of management were analyzed.

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**Figure 1.** CT scans showing the alveolar infiltrate and ground glass opacity in right upper lobe.

**Figure 2.** Bronchoscopic image showing a small, sessile, non pulsating nodular lesion about 7 mm in diameter and 1 mm high at the beginning of right upper anterior bronchus.
After discharge, the follow-up were conducted in the outpatient department or by direct phone contact until December 2012 at intervals of 2 week, 3 month and every year.

Statistical analysis

Data were analyzed using the SPSS version 12 statistical analysis package (SPSS Inc., Chicago, IL, USA). Examined data were expressed as the mean ± SD and assessed using the t-test if appropriate. P < 0.05 was accepted as statistically significant.

Results

Demographic and clinical presentation

During the 10-year study period, 112 patients were referred to our hospital for massive hemoptysis. In these patients, the most commonly identifiable etiology for hemoptysis included brochiectasis in 50 patients (44.6%), tuberculosis in 16 patients (14.3%), lung cancer in 5 patients (4.5%), bacterial pneumonia in 25 patients (22.3%), and aspergilosis in 4 patients, (3.6%). In 12 of 112 patients, the etiology remained cryptogenic, including 11 male and 1 female. The mean age was 44.67 ± 17.70 years (range 21-85 years) with a mean smoking consumption of 18.50 ± 11.15 pack-years (range 5-40 years). The volume of bleeding was estimated at 446.67 ± 177.73 mL per day (range 230-800 mL) upon admission to our unit.

Chest X-ray, CT-scan, fiberoptic bronchoscopy and angiographic findings

In all 12 patients with cryptogenic hemoptysis, chest X-ray and CT-scan showed a single lobar alveolar infiltrate and ground glass opacities (Figure 1). Fibrotic bronchoscopy showed submucosal vascular abnormalities, dilated submucosal vessel, or nodules about 5 mm in diameter and 1 mm high above the surface in 4 patients (Figure 2). The site of bronchial bleeding was located to left side in 5 patients, right side in 7 patients. The upper lobes were involved in 4 patients, middle lobe and lingula in 3 patients, and lower lobes in 5 patients (Table 1).

Outcomes

Conservative measures were used in 6 patients with massive cryptogenic hemoptysis, but complete control of bleeding was obtained in 2 patients. Hemoptyasis was uncontrolled in 4 patients treated with terlipressin, 1 of them had respiratory compromise immediately and 3 of them received BAE secondarily. A first-line bronchial arteriography was attempted in 6 patients, with 3 patients receiving several embolizations. Hypervascularisation of bronchial arteries was found with the presence of bronchial artery tortuosity in 7 patients, and retrograde of bronchial-to-pulmonary artery shunting in 2 patients. BAE was performed in 9 patients, leading to cession of bleeding in 3 patients but not in other 6 patients (Table 2; Figure 3).

A total of 7 patients received surgery during hospitalization because of persistent hemoptysis despite the conservative treatment or BAE. The type of pulmonary resection was performed after confirmation of a localized lesion (Table 3). All these 7 patients undergoing emergency resection survived in long term and had no obvious complications.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/age</th>
<th>Smoke (No. of pack-years)</th>
<th>Localization of hemoptysis lobe</th>
<th>BAE</th>
<th>Type of pulmonary resection</th>
<th>Outcome</th>
<th>Pathological findings</th>
<th>Follow-up</th>
</tr>
</thead>
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<td>M/31</td>
<td>Yes (15)</td>
<td>RML</td>
<td>Yes</td>
<td>lobectomy</td>
<td>Lived</td>
<td>Dieulafoy</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>F/34</td>
<td>No (0)</td>
<td>RLL</td>
<td>No</td>
<td>lobectomy</td>
<td>Live</td>
<td>Bronchiectasis</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>M/21</td>
<td>Yes (5)</td>
<td>RML</td>
<td>Yes</td>
<td>lobectomy</td>
<td>Lived</td>
<td>Dieulafoy</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>M/44</td>
<td>Yes (20)</td>
<td>LLL</td>
<td>No</td>
<td>lobectomy</td>
<td>Lived</td>
<td>Unidentified</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>M/85</td>
<td>Yes (40)</td>
<td>LUL+</td>
<td>Yes</td>
<td>lobectomy</td>
<td>Lived</td>
<td>Dieulafoy</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>M/63</td>
<td>Yes (10)</td>
<td>Lingula</td>
<td>No</td>
<td>pneumonectomy</td>
<td>Lived</td>
<td>Dieulafoy</td>
<td>70</td>
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<tr>
<td>7</td>
<td>M/56</td>
<td>Yes (30)</td>
<td>RUL RUL</td>
<td>Yes</td>
<td>lobectomy</td>
<td>Lived</td>
<td>Bronchiectasis</td>
<td>34</td>
</tr>
</tbody>
</table>

RUL, right upper lobe; RML, right middle lobe; RLL, right upper lobe; LUL, left upper lobe; LLL, left lower lobe.

Table 2. Demography of massive cryptogenic hemoptysis patients operated
Massive cryptogenic hemoptysis

For 7 patients with persistent hemoptysis, pathological examination showed a superficial dysplastic bronchial artery in the submucosa and a tortuous and dilated bronchial artery under the bronchial epithelium (Figure 4). Four patients were diagnosed as Dieulafoy’s disease, and 2 patients as brochiectasis. No evidence for chronic bronchial or other vascular disease was observed in 1 patient. No microorganisms such as bacteria, mycobacteria and fungi were identified in all 7 patients.

Discussion

This study aimed at characterizing the clinical spectrum and the management in patients with massive cryptogenic hemoptysis. In a case series of Chinese patients with massive hemoptysis, the most frequent causes were tuberculosis, brochiectasis, lung cancer, necrotizing pne-
umonia and arteriovenous malformation [7]. Most of these conditions could be diagnosed by the combined use of a chest computed tomography (CT) scan, fiberoptic bronchoscope and bronchial artery embolization (BAE). Although CT scan is the efficient approach to identify the cause and localization of hemoptysis, this imaging technique has several limitations [6]. In patients with pulmonary parenchymal diffused with bleeding and bronchial mucosal abnormalities, it might become difficult for CT scan, and fiberscopy appears to be the complementary approach. However, the timing of a diagnostic bronchoscopy in massive hemoptysis remains controversial, because the presence of large mount of blood in bronchial tree makes the optical exploration hard. In this case series, despite extensive diagnostic tools, no precise cause was found in 12 out of 112 patients (10.7%) with massive hemoptysis and they were considered as massive cryptogenic hemoptysis. Recent studies showed that up to 25% of patients presenting with hemoptysis are classified as cryptogenic [8-10].

In our study, 11 out of 12 patients with massive cryptogenic hemoptysis were males, in a high proportion of smokers. These data are consistent with the results of previous studies showing that patients with cryptogenic hemoptysis had a high proportion of smoking, varying between 42% and 72% of the studied population [11, 12]. Smoking-induced inflammatory changes and a remarkable proliferation capacity of the bronchial vessels may be responsible for the hemoptysis [13-15].

Hemoptysis is a common symptom for referral to pulmonologist. Although massive hemoptysis is considered a life threatening condition that requires urgent and effective management, there is no definitely consensus on the cutoff volume for the expectorated blood [6]. While it was recommended that massive hemoptysis should be defined as any hemoptysis that is more than 100 ml per day or causes airway compromise, the volume of > 200 ml per day was proposed as the better predictor for massive hemoptysis [8, 16, 17].

Massive hemoptysis is associated with a high mortality of 10-15% in spite of intensive care [10, 18]. An integrated approach for the management of massive hemoptysis including conservative measures, BAE and surgery is suggested [9]. Vasopressin is one of the extensively drugs in patients with moderate and massive hemoptysis. Previous studies reported that the efficacy of vasopressin to stop bleeding ranged from 27% to 60% [19]. In our case series, we used this drug to control bleeding as the main conservative measure, we achieved poor success rate in our cohort, and similar to the previous results that only 2 out of 12 patients of cryptogenic hemoptysis were controlled [20].

Recently, BAE is regarded as the first-line non-surgical treatment of massive hemoptysis [9]. Although the efficacy and safety of BAE has been established in massive hemoptysis, recurrence of hemoptysis after BAE occurred in 5-30% of patients [21]. Failure of BAE may be due to incomplete embolization, recanalization of the embolized vessels, technique skill, revas-
Massive cryptogenic hemoptysis

cularisation of underlying inflammation and disease progression. Furthermore, less information was reported for BAE in cryptogenic hemoptysis. In case that life-threatening hemoptysis continues to occur despite BAE, emergency surgery should be attempted [22]. Our series showed that 7 of 12 patients with massive cryptogenic hemoptysis received surgery.

In this series of case, our study demonstrated that Dieulafoy’s disease of the bronchus and bronchiectasis were the main pathological abnormality for massive cryptogenic hemoptysis. Dieulafoy’s disease of the bronchus is a vascular anomaly characterized by the presence of a dysplastic artery in the submucosa [23]. It was reported that the disease accounted for up to 55% of cryptogenic massive hemoptysis [22]. However, Dieulafoy disease of bronchus is under diagnosed for lack of pathological procedure. If bronchoscopy showed a nodule with a small, sessile, non pulsating nodular lesion, often with a white cap and apparently normal mucosa, Dieulafoy’s disease of the bronchus should be taken into account [23]. Nevertheless, it is difficult to diagnose this condition because bleeding in the bronchial tree makes the image obscure. At present, the pathogenesis of Dieulafoy’s disease of the bronchus remains unclear. In our series of case, we described the pathologic investigation of this lesion after a surgical lung resection. The pathological examination of a part of the resected lung lobe revealed a dilated, hypertrophic and tortuous bronchial artery coiling around the bronchus and reaching to the submucosa, consistent with previous report [24].

Interestingly, two cases with bronchiectasis were confirmed in patients with massive cryptogenic hemoptysis after surgical pathology. Although high-resolution computed tomography (HRCT) has been regarded as the gold standard for the diagnosis of bronchiectasis, there was no evidence of bronchiectasis on HRCT using 1 mm slices at 5 mm intervals in all our cases. It is well known that conventional HRCT can miss small areas of bronchiectasis. Multidetector CT (MDCT) using 1 mm contiguous slices could improve diagnostic accuracy of bronchiectasis compared with conventional HRCT [25]. Therefore, MDCT is recommended for the identification of the cause of cryptogenic hemoptysis.

Several limitations should be acknowledged in our study. First, although it was conducted in a referral centre with an extensive medical experience of massive hemoptysis, our experiences with BAE and surgery is limited. Next, no data on BAE and surgical treatment for mild or moderate cryptogenic hemoptysis were collected and analyzed.

In summary, we analyzed the etiologies of massive cryptogenic hemoptysis and found that Dieulafoy’s disease of the bronchus and bronchiectasis are the main pathological abnormality. Multidisciplinary approach remains as the cornerstone for the management and exploration of massive cryptogenic hemoptysis. BAE and surgical treatment should be considered in case that massive hemoptysis could not be controlled by conservative management.

Disclosure of conflict of interest

None.

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References

Massive cryptogenic hemoptysis


