Cryptogenic Hemoptysis in Chronic Obstructive Pulmonary Disease: Characteristics and Outcome

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Key Words

Chronic obstructive pulmonary disease • Hemoptysis

Abstract

Background: Hemoptysis is a common presenting symptom and cause of hospitalization in the department of respiratory diseases. In a number of patients with chronic obstructive pulmonary disease (COPD) presenting with this symptom, investigations fail to reveal a precise etiology. Little data are available regarding characteristics and outcome of COPD patients presenting with cryptogenic hemoptysis (CH). **Objectives:** Our study goal was to assess the functional characteristics of these subjects, the risk factors for CH and the severity of hemoptysis, as well as long-term outcome. **Methods:** For more than 1 year, we enrolled and followed a group of 39 consecutive COPD patients admitted to our center with CH. **Results:** Between 1988 and 2003, 39 patients with COPD were admitted for CH in which investigation failed to reveal an etiology. The mean age was 51.3 years. All subjects were active smokers. Twenty-one patients (54%) had at least 1 risk factor for prolonged bleeding. Patients with more severe airflow obstruction tended to have more severe bleeding. Bronchoscopy appeared as useful as a computed tomography in locating the bleeding site. Arterial em-

bolization succeeded in controlling bleeding in all patients who underwent angiography. One patient experienced a relapse in bleeding at 2 months. One developed lung cancer after 1 year. Thirty-four patients were followed for an average of 5 years. Only 2 subjects experienced recurrent hemoptysis. None died. **Conclusions:** CH in patients with COPD is associated with a favorable short- and long-term outcome when managed with timely angiographic embolization. Long-term incidence of lung cancer was uncommon after an episode of CH, and recurrences of hemoptysis were rare.

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Introduction

Hemoptysis is a frequent presenting symptom and cause for hospital admission. It can range from a benign self-limited bleeding event to a life-threatening condition, leading to airway compromise and death. Causes of hemoptysis are various but most commonly include bronchiectasis, bronchopulmonary neoplasm and tuberculosis [1]. Hence, it represents a challenge for the caring physician who has to assess the severity and identify the etiology in order to properly manage the patient presenting with hemoptysis. Despite the use of modern diagnos-

tic tools such as fiberoptic bronchoscopy and computed tomography (CT) of the thorax, some 7–22% remain without a precise etiology and are termed ‘cryptogenic hemoptysis’ (CH) [1–8]. In a recent study, Herth and colleagues [3] reported an important incidence (6% at 3 years) of bronchopulmonary carcinoma developing in patients who had an episode of CH. On the other hand, other studies have suggested a more favorable outcome. Savale and colleagues [9] recently suggested Dieulafoy’s disease of the bronchus as a potential cause for CH in a subset of patients that is yet to be determined.

However, data are scarce in the literature concerning the outcome of patients with coexisting chronic obstructive pulmonary disease (COPD) experiencing an episode of CH. Thus, we aimed to determine the short- and long-term outcome of a cohort of consecutive patients with COPD presenting at our center with CH.

Materials and Methods

Population Selection

The study was conducted between 1988 and 2003 in Calmette hospital, Lille, France, a tertiary university hospital and referral center. All consecutive patients presenting with a diagnosis of COPD and hospitalized for CH were included in the study (39 patients, 36 males and 3 females). During the same period, approximately 5,800 patients with COPD were hospitalized, and 320 patients with COPD were admitted because of hemoptysis. CH represented approximately 12% of all cases of hemoptysis seen in patients with COPD. COPD was defined and classified according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria (history of significant past tobacco exposure with an associated obstructive ventilatory defect on spirometry). Hemoptysis was classified according to the amount of blood expectorated at initial presentation and daily: mild (blood-tinged sputum or <30 ml/24 h), moderate (30–100 ml/24 h) and severe (>100 ml/24 h). The study was approved by the local institutional review board, and consent was obtained from patients prior to enrolment.

In-Hospital Management of Hemoptysis

All patients were initially monitored with expectant care. Patients hospitalized with hemoptysis had an initial blood work (including arterial blood gas measurements, complete blood count, coagulation studies and serum electrolyte and creatinine measurements) and plain chest radiograph. Demographic data and information concerning comorbidities, smoking status and risk factors for hemorrhage was obtained from patients. Within the first 24 h after admission, fiberoptic bronchoscopy under local anesthesia was performed in a standard fashion in all patients to look for the location of the bleeding and for a possible etiology. When active bleeding was found, local instillations of ice-cold saline and topical adrenaline were given in an attempt to control it. Patients with a precise etiology of bleeding were thus excluded from the study. High-resolution CT of the thorax with contrast injection (when not contraindicated by renal insufficiency or con-

trast media allergy) was then performed in all patients to further investigate the etiology of hemoptysis. CH was defined as endoscopic examination and imaging studies showing no significant abnormalities that could account for a precise etiology of the bleeding (e.g., tumor, bronchiectasis).

Patients presenting with severe active bleeding and those who experienced recurrent bleeding during hospitalization ($n = 29$) were treated initially with intravenous terlipressin acetate at a dosage of 4–6 mg per day given in slow infusion unless contraindicated. Terlipressin is a vasoconstrictor used in France for the treatment of hemoptysis [10]. Usual dosage starts with 0.5 mg as slow infusion (over 15 min) every 6 h and can be increased up to 1 mg every 4 h, depending on evolution of hemoptysis and secondary effects of terlipressin (bradycardia, chest pain, abdominal pain, distal ischemia of the limbs, electrocardiogram abnormalities). Patients with severe or recurrent hemoptysis uncontrolled with terlipressin underwent bronchial arteriography ($n = 21$) in order to attempt bronchial artery embolization. Embolization was considered successful when bleeding stopped immediately and no recurrence was observed within the following 24 h.

Upon discharge from the hospital, patients underwent pulmonary function testing, and follow-up as outpatient was scheduled for the following year to insure there were no recurrences and no development of neoplasm.

Analysis of Outcome

Patient demographics and clinical variables were analyzed using standard statistical analysis software (Statview 5.0, SAS Institute, USA). Results were expressed as mean $\pm$ SD and range, unless otherwise stated. Comparisons used Student’s t test for continuous variables and χ^2 tests for categorical variables. A p value <0.05 was considered statistically significant.

Results

Demographics and Clinical Characteristics on Admission

During the study period, 39 patients (36 males, 3 females) with COPD were hospitalized and investigated for hemoptysis which was categorized as cryptogenic. The mean age was 51.3 years (range 24–80). All patients were active smokers on admission with a mean smoking duration of 17.2 ± 4 years and a mean total of 31.7 ± 15 pack-years. Previous history of hemoptysis was present in 11 patients. The average time between COPD diagnosis and hemoptysis episode was 4.7 ± 5.4 years. Fifteen patients (38%) had a cardiovascular condition and 21 patients (54%) had a predisposing risk factor for bleeding: 10 patients had an abnormal coagulation study result (5 with thrombopenia and 5 with prolonged partial thromboplastin and/or prothrombin time) and 11 were taking medication known to increase bleeding (listed in table 1). The average amount of expectorated blood was estimated at 76 ± 84 ml, then 70 ± 100 ml per day subsequently.

Table 1. Clinical characteristics on admission

Characteristics	Patients
Active smoker	39 (100)
Male gender	36 (92)
History of previous hemoptysis	11 (28)
History of previous tuberculosis	2 (5)
COPD GOLD stage	
I	26 (67)
II	10 (26)
III	2 (5)
IV	1 (3)
Cardiovascular comorbid condition	15 (38)
Coronary artery disease	6 (15)
Systemic arterial hypertension	7 (18)
Atrial fibrillation	3 (8)
Associated risk factor for bleeding	21 (54)
Thrombopenia	5 (13)
Abnormal coagulation study result	5 (13)
Drugs predisposing to hemorrhage ¹	11 (28)

Figures in parentheses are percentages.

¹ Nonsteroidal anti-inflammatory drug or acetylsalicylic acid (n = 7), clopidogrel (n = 1), vitamin K antagonist (n = 2) and low-molecular-weight heparin (n = 1).

Patients were classified as having mild (n = 14, 36%), moderate (n = 7, 18%) and severe hemoptysis (n = 18, 46%). No patient expectorated more than 500 ml of blood.

Pulmonary function testing was done in all subjects upon discharge from the hospital. All patients had airflow obstruction, which was not reversible using β_2 -agonists, with a mean forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) ratio of $63 \pm 22\%$. Mean FEV₁ was 2.62 ± 1.1 liters ($76.4 \pm 28\%$ of the predicted value). The severity of airflow obstruction was quantified according to the GOLD classification for COPD [11], and the number of patients with each degree of severity is shown in table 1. Thirty-six patients were classified as having mild to moderate COPD (GOLD stage 1 and 2), 2 patients had severe (GOLD stage 3) and 1 patient had very severe (GOLD stage 4) airflow obstruction. The comparison of pulmonary function testing and severity of hemoptysis is shown in table 2. When compared with those with mild hemoptysis, patients with severe hemoptysis had a significantly lower mean FEV₁ (86.2 ± 24.7 vs. $65 \pm 27\%$ predicted, respectively; $p = 0.02$). The FEV₁/FVC ratio was also significantly higher in the mild hemoptysis group when compared with the severe group (68 ± 13 vs. $60 \pm 18.7\%$, respec-

Table 2. Results of pulmonary function study in relation with severity of hemoptysis

	Severity of bleeding			p value
	Mild (n = 14)	Moderate (n = 7)	Severe (n = 18)	
FEV ₁ , liters	2.54 ± 0.84	3.5 ± 1.87	2.42 ± 1.12	NS
FEV ₁ , %	86.2 ± 24.7	87.7 ± 34.9	65 ± 27	0.02 ¹
FVC, liters	3.83 ± 0.82	4.27 ± 1.85	3.6 ± 0.96	NS
FVC, %	97.8 ± 18.24	89.3 ± 28.1	86.6 ± 16.2	NS
FEV ₁ /FVC	0.68 ± 0.13	0.66 ± 0.45	0.6 ± 0.187	0.02 ¹
RV, liters	2.46 ± 0.58	2.44 ± 0.01	3.23 ± 0.67	NS
RV, %	109 ± 22.5	121 ± 9.9	142 ± 33	NS
TLC, liters	6.21 ± 0.99	6.29 ± 1.66	6.66 ± 1.37	NS
TLC, %	100 ± 8.1	88.7 ± 18	105.3 ± 15.7	NS

Results are expressed as the mean value $\pm$ SD. NS = Not significant; RV = residual volume; TLC = total lung capacity.

¹ Comparing groups of patients with mild versus severe hemoptysis.

tively; $p = 0.02$). The mean hemoglobin level on admission was 14.0 ± 1.7 and 12.3 ± 2.2 g/dl on discharge. The mean hemoglobin level on discharge was significantly lower in patients with severe hemoptysis when compared with those with moderate hemoptysis (11.5 vs. 13.6 g/dl; $p = 0.003$).

Bronchoscopy and CT Findings

CT of the chest was done in all patients. Emphysematous lesions were found in 44% of patients (n = 17). An alveolar infiltrate was present in 20 patients (51%) and useful in localizing the source of bleeding in 18 patients (46%). Flexible bronchoscopy was performed in all patients and findings are outlined in table 3. It was useful in localizing bleeding in 25 patients (64%). Bronchoscopy seemed more useful than CT in localizing the bleeding source but the difference did not reach statistical significance (64 vs. 46% of cases; $p =$ not significant). There was no discordance between these 2 modalities when results were positive in localizing the origin of bleeding.

Management of Hemoptysis

Conservative measures alone were used in 10 patients (26%), having mild hemoptysis and no recurrence. Twenty-nine patients (74%) received intravenous terlipressin acetate which seemed to control bleeding in 8 cases (21%). Mild complications were seen in 11 patients treated with

Table 3. Findings and localization during flexible bronchoscopy

Finding and localization	Patients
No blood visible	6 (15)
Diffuse blood in bronchial tree	8 (21)
Left-sided bleeding	8 (21)
Diffuse	1 (3)
Lower lobe	4 (10)
Upper lobe	3 (8)
Right-sided bleeding	17 (44)
Diffuse	3 (8)
Upper lobe	5 (13)
Middle lobe	5 (13)
Lower lobe	4 (10)
Hypervascularized mucosa ¹	4 (10)

Figures in parentheses are percentages.

¹ In addition to the above stated findings.

terlipressin: 9 cases of hyponatremia which resolved with fluid restriction, 1 case of increased systemic arterial blood pressure and 1 bradycardia responsive to atropine treatment. Hemoptysis was uncontrolled in 21 patients treated with terlipressin (72%) and all underwent bronchial arteriography to attempt bronchial artery embolization. Bronchial hypervascularization was seen in 20/29 patients: bilateral in 7 patients, right-sided in 6 and left-sided in 7 patients. Active bleeding with contrast extravasation into the bronchial lumen was seen in 2 patients. Embolization was not done in 1 case because of failure to catheterize the artery, which hemoptysis subsequently resolved with terlipressin therapy. Two patients experienced complications from embolization: 1 subintimal ostium dissection and 1 transient posterior cord ischemic lesion. No patient died from complications linked to the procedure. At 24 h and in all patients with findings of bronchial hypervascularization, hemoptysis was controlled by embolization (n = 20).

Follow-Up and Outcome

No patient died during hospitalization. One relapse of hemoptysis was seen at 2 months, and embolization was done in the same territory as during his previous episode. One case of bronchopulmonary cancer was diagnosed at 1 year. Two patients were lost to follow-up: 1 patient did not show up at his 1-month appointment, the other at 1 year. The remaining 34 patients were followed for an average of 5 ± 3.4 years after hospitalization, and 2 relapses of CH were seen: 1 relapse after 5 years and the other after 7 years.

Discussion

Hemoptysis is a frequent cause for referral and admission in pulmonary practice accounting for up to 9% of admissions to a respiratory service [8]. It is most commonly caused by bronchiectasis, bronchopulmonary cancer and tuberculosis with its causes varying with geographical location. Even with the advent of modern, more precise diagnostic tools such as CT and flexible bronchoscopy, up to 25% of patients presenting with hemoptysis remain without a precise etiology and are classified as having CH [2–7]. Although usually following a self-limited benign course, CH can present as a life-threatening condition which requires timely management to control bleeding [9]. COPD is also very commonly encountered in pulmonology practice, and patients suffering from COPD often present with hemoptysis, a significant percentage of which will be cryptogenic. At present, there are very few series that have looked at the outcome of patients with CH, the largest ones (n = 135) being those by Herth et al. [3] and Savale et al. [9] (n = 81). Also, these looked at a general population of patients with CH, not specifically those with concurrent COPD, which can account for a significant number of patients with CH. Thus, there is no literature concerning the outcome and optimal management of COPD patients presenting with CH.

Our study aimed at characterizing a group of 39 consecutive COPD patients who presented at our center with CH and to evaluate their outcome, both short and long term. Patients in our study were mostly males (92%), in a proportion higher than previously reported in other series of CH cases in which a majority of patients were also of male gender but in proportions around 70% [3, 9, 12]. Also, all patients in our cohort were active smokers upon admission, a proportion higher than in other series, reflecting the fact that all had COPD, a disease for which tobacco smoking is the main etiology.

Airflow obstruction was mild or moderate in a majority of patients in our group, but patients with lower FEV₁ and FEV₁/FVC ratio, hence with more severe COPD, had a tendency to present with more severe bleeding. No data on pulmonary function testing of patients with CH were previously reported in the medical literature. Whether this could be caused by increased airway inflammation and consequent mucosal hypervascularization remains unclear. We did not find any statistically significant relationship between the presence of arterial bronchial hypervascularization and CT findings of emphysema or more severe airflow obstruction in our group. Another

hypothesis would be a more frequent prevalence of secondary pulmonary arterial hypertension in patients with more severe COPD, leading to increased bleeding, although the bronchial circulation is generally believed to be the main source of hemoptysis in cryptogenic cases. Measurements of pulmonary artery pressures would be necessary to verify this hypothesis.

Management of hemoptysis has evolved to a more minimally invasive approach in the past 2 decades. In our cohort, intravenous terlipressin acetate was used in 29 patients with hemoptysis of at least moderate severity and in patients showing recurrences during admission. Few studies have evaluated the efficacy of this molecule in patients with hemoptysis. Using this treatment, Ramon and colleagues [10] showed a 60% success rate (12/20 patients) in stopping bleeding at 48 h in a series of 20 patients with hemoptysis. However, results in our cohort were not as encouraging, with only 8 patients (27%) being controlled by terlipressin acetate. However, we also had fewer side effects than previously reported with this molecule, all of which were without significant clinical consequences.

The role of flexible bronchoscopy in the management of severe hemoptysis has recently been questioned [13, 14]. Hsiao and colleagues [13] suggest that attempting flexible bronchoscopy in a context where bronchial artery embolization will surely be attempted does not add significant clinical information. Revel et al. [14] also showed that CT was as sensitive as bronchoscopy in localizing the source of bleeding in patients with hemoptysis. In our cohort, bronchoscopy appeared as useful as CT in localizing the origin of the bleed and even seemed better in doing so (64 vs. 46% of patients), although these numbers did not reach statistical significance. Both modalities should be viewed as complementary tests since they can provide different information which can be crucial in the diagnosis and management of the episode of hemoptysis.

Bronchial artery embolization recently emerged as a cornerstone in the treatment of hemoptysis. Its short- and long-term safety and efficacy have been established in treating hemoptysis of various causes, including CH [9, 15–18]. In our group, bronchial artery embolization was efficient in immediately controlling hemoptysis in 95% of cases, a number which is similar to that previously reported in the literature, with the only failure of therapy being secondary to technical inability to embolize the culprit artery. The complication rate was also low, similar to previously available data [17, 19]. The main arteriographic finding in our group was bronchial hypervascularization. Although we did have cases of severe hemop-

tysis in our cohort, no patient had to undergo surgery due to unsuccessful therapy with terlipressin and embolization. In their study of 81 patients with CH, Savale and colleagues [9] had a surgery rate of 7% after unsuccessful bronchial artery embolization. They also suggested Dieulafoy's disease of the bronchus, a vascular mucosal anomaly, as a possibly under-recognized cause of severe life-threatening hemoptysis, given this lesion was found on pathological specimens in 5 of their patients who had undergone surgical resection due to uncontrolled hemoptysis. We did not encounter such a lesion, but no surgery was performed in our group of patients.

Long-term follow-up data were available in an important number of our patients for a period of 1 year after the initial event. Recurrence of hemoptysis occurred in 1 patient at 2 months, which was again cryptogenic. Embolization of the left bronchial artery had initially been done in this patient and was performed again successfully in the same territory, with control of the bleeding. Herth et al. [3] had reported an incidence of 6% of lung cancer at 3 years in their cohort of 135 patients. Moreover, only 59% of patients in their cohort were active smokers and 42% had COPD, making these numbers seem even higher than expected. This was higher than previously reported rates, although some of these studies had been done before the lung cancer epidemic [7, 20, 21]. Only 1 case (2.6%) of bronchopulmonary cancer was diagnosed after 1 year in our group of patients. This is surprising given a higher proportion of our patients were active smokers and their mean age was slightly higher (51.3 vs. 46.7 years) than in patients in the cohort studied by Herth and colleagues [3]. However, most of our patients had mild to moderate COPD, and previous results have suggested that lung cancer incidence increases with more severe degree of airflow obstruction [22]. Also, the small number of patients in both cohorts could account for this difference alone since it is not statistically significant, and a larger study group would be needed to confirm this hypothesis. Whether or not CH is associated with a higher risk for development of lung carcinoma thus remains a question.

In summary, in patients with COPD presenting with CH, there seemed to be a relationship between the severity of hemoptysis and that of airflow obstruction although the explanation for this remains unclear. All were active smokers and more than 50% had a predisposing risk factor for bleeding. CT and bronchoscopy are at least as sensitive in localizing the origin of the bleed although the latter appeared slightly more efficient at doing so in our cohort. However, they should be viewed as complemen-

tary tests in our opinion. Both short- and long-term prognosis appear excellent with appropriate, timely management, and bronchial artery embolization is efficient and safe in controlling hemoptysis in those patients presenting more profuse or recurrent bleeding. In the long term, recurrences of CH were uncommon after the first episode, and the prognosis appeared to be excellent. Al-

though it has been suggested that these patients are at risk for bronchopulmonary carcinoma, only 1 case was seen in long-term follow-up, suggesting its incidence after an episode of CH may not be as elevated as previously reported. Larger studies would be needed in order to confirm this hypothesis.

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