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BRIEF REPORT
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Short- and long-term efficacy of bronchial artery embolization using a gelatin sponge for the treatment of cryptogenic hemoptysis

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Abstract: Bronchial artery embolization (BAE) is the first choice treatment for hemoptysis. With advances in endovascular treatment, various embolic materials have become available. However, the optimal embolic material for the treatment of cryptogenic hemoptysis has not been determined. This study aimed to investigate the short- and long-term efficacy of BAE using a gelatin sponge in the treatment of patients with cryptogenic hemoptysis. The clinical characteristics, angiographic findings, and short- and long-term outcomes of BAE were retrospectively analyzed in 22 consecutive patients who underwent BAE for control of cryptogenic hemoptysis between January 2010 and September 2018. Selective angiography and super-selective BAE were successfully performed for all patients. A gelatin sponge was used in all patients. Further, polyvinyl alcohol was mixed with the gelatin sponge in 11 patients (50%). Angiography showed that the bronchial artery was responsible for hemoptysis in all patients, along with the intercostal artery in one patient (4.5%) and the inferior phrenic artery in one patient (4.5%). Immediate hemostasis was achieved in all patients. The recurrence-free rate was 100% for 1 month, 94.1% for 3 months, 94.1% for 12 months, and 87.4% for 24 months. Of two patients with recurrent hemoptysis, one underwent bronchoscopic hemoptysis and the other received intravenous hemostatic agents. No patient underwent BAE for recurrence. No severe complications occurred. In conclusion, BAE using a gelatin sponge has short- and long-term hemostatic efficacy for treating cryptogenic hemoptysis without any severe complications. A gelatin sponge is a suitable embolic material for patients with cryptogenic hemoptysis.

***Keywords*:** angiography, bronchial arterial embolization, emergency treatment, treatment outcome

Introduction

Hemoptysis is a common but occasionally life-threatening symptom in a wide variety of diseases such as lung cancer, tuberculosis, and aspergillosis. However, a small number of patients presenting with this symptom have no specific causative disease; this presentation is known as "cryptogenic hemoptysis". This group accounts for 7–22% of all hemoptysis cases (*1-4*).

Since its initial application in 1973 (*5*), bronchial artery embolization (BAE) has been the mainstay treatment for hemoptysis. BAE is less invasive than other treatments, and is applicable to patients who are ineligible for surgery or those with bilateral lung disease (*6-8*). Contrast-enhanced chest computed tomography (CT) and subsequent BAE are recommended for massive or life-threatening hemoptysis (*9*). The utilization of BAE for non-massive hemoptysis is also increasing (*9*). As endovascular treatment has achieved popularity for control of bleeding, various embolic materials have been developed. In general, coils and polyvinyl alcohol (PVA) permanently embolize target vessels, while embolization with a gelatin sponge (GS) is essentially temporary (*10,11*). Embolization with a GS can result in recanalization within several weeks to months (*12*). Although many retrospective studies have compared the efficacy of individual embolic materials, the optimal embolic material for BAE has not been fully elucidated. Moreover, as mentioned above, because hemoptysis incorporates various causative diseases, the optimal material may differ according to the underlying disease. Under these circumstances, the embolic materials for BAE are selected based on their characteristics and local availability.

Few studies have investigated the efficacy of BAE for cryptogenic hemoptysis to date (*4,9-15*). The prognosis for cryptogenic hemoptysis after BAE

is thought to be favorable (*9-15*), but the optimal embolizing material for cryptogenic hemoptysis remains unclear. Assuming that the rebleeding rate of cryptogenic hemoptysis is relatively low (*13*,*15*), BAE with transient embolic materials, but not with permanent materials, may be sufficient and suitable for these patients. Further, we previously reported favorable outcomes in patients who underwent BAE with a GS (*16*). In the current study, we aimed to investigate the short- and long-term efficacy of BAE using a GS in the treatment of patients with cryptogenic hemoptysis.

Materials and Methods

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board for clinical research of National Center for Global Health and Medicine (NCMG-G-003639-00) and registered on the UMIN Clinical Trials Registry (UMIN000042050). Informed consent was obtained from patients.

Study population

We retrospectively reviewed the medical records of 120 consecutive patients who underwent BAE for hemoptysis between January 2010 and September 2018 at the National Center for Global Health and Medicine, Department of Respiratory Medicine, and identified patients with cryptogenic hemoptysis. Cryptogenic hemoptysis was defined as follows: *i*) no history of respiratory comorbidities causing hemoptysis and *ii*) no indications of the etiological cause based on laboratory and radiological results. Whether these inclusion criteria were met was independently confirmed by at least one young pulmonary physician and one well-experienced pulmonary physician. All patients underwent BAE during hospitalization and received standard therapy, such as the administration of oxygen and homeostatic materials, including tranexamic acid and/or carbazochrome sodium sulfonate hydrate. The degree of hemoptysis was defined as follows: massive, > 400 mL/24 h; moderate, 30–400 mL/24 h; and mild, < 30 mL/24 h (*17*).

Imaging studies and analysis

All patients underwent contrast-enhanced CT of the chest before BAE to determine the responsible arteries, diameter of the bronchial artery on the lesion side, and presence or absence of bronchial arterial dilatation. Bronchial arterial dilatation was defined as a bronchial artery diameter of > 2 mm (*18*) or when the bronchial artery was traceable from its origin to the ipsilateral hilum (*19*). The imaging studies were independently reviewed by at least one diagnostic radiologist and at least two pulmonary physicians.

Angiography and embolization

All BAE procedures were performed by radiologists or with the collaboration of radiologists and respiratory physicians. We performed BAE *via* a transfemoral approach with the placement of a long vascular sheath (25 cm). All possible responsible arteries identified by CT were super-selectively evaluated using arteriography with 4-Fr guiding catheter and 2.8-Fr microcatheter systems with 0.014-inch guide wires during the session. When vascular abnormalities such as bronchial arterial hypertrophy, aneurysms, hypervascularity, and systemic-pulmonary shunting were observed, the arteries were super-selectively embolized using the 2.8-Fr microcatheter system. Embolization was performed on the responsible arteries with a GS or a combination of a GS and PVA particle. The GS was cut into 1 × 1 to 2 × 2 mm pieces in advance and was prepared as a slurry by mixing with contrast medium. We injected the embolic materials into the responsible arteries until the proliferation of peripheral blood vessels had disappeared on angiography. Bronchial aneurysm was defined as localized arterial dilation ≥ 1.3-fold larger than the proximal and distal vessels on CT or angiography. The bleeding site was identified by the greatest degree of diffuse ground-glass opacities on CT and/or coagulation on bronchoscopy. The angiography findings were retrospectively reviewed by at least one radiologist and one well-experienced pulmonary physician.

Outcome analysis

Technical success was defined as the successful embolization of responsible arteries. Short-term efficacy was defined as the cessation of hemoptysis associated with an improved clinical course during hospitalization (*13*). Long-term efficacy was defined as the absence of rebleeding for more than three months from the day of BAE. Recurrence was defined as either a new episode of hemoptysis of > 200 mL/24 h or the need for interventional therapies such as intravenous administration of hemostatic agents, bronchoscopy, or BAE. Complications resulting from additional treatment, permanent or significant disability, or death, were retrospectively reviewed.

Statistical analysis

Continuous variables were expressed as median and range. The bleeding recurrence-free rate was analyzed using the Kaplan–Meier method and was presented in a Kaplan–Meier curve. Statistical analyses were preformed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results and Discussion

Of the 120 patients who underwent BAE for hemoptysis during the study period, 22 patients with cryptogenic hemoptysis were identified. The clinical characteristics of the subjects are summarized in Table 1.

Of the 22 patients who underwent BAE for cryptogenic hemoptysis, 4 (18.2%) presented with massive hemoptysis, 15 (68.2%) with moderate hemoptysis, and 1 (4.5%) with mild hemoptysis. The degree of bleeding was not available in two (9.1%) patients because the data were missing. The bleeding region determined by CT and bronchoscopy was as follows: nine (40.9%) in the right upper lobe, two (9.1%) in the right middle lobe, three (13.6%) in the right lower lobe, seven (31.8%) in the left upper lobe, and one (4.5%) in the left lower lobe. All patients exhibited bronchial arterial dilatation on chest CT, and the median diameter was 2.4 mm (range 1.1–4.8 mm) at the origin of the bronchial artery on the affected side.

Technical success was achieved in all patients. All 22 patients exhibited hypervascularity and bronchial arterial hypertrophy on angiography. Four patients (18.2%) experienced aneurysms and six (27.2%) experienced systemic-pulmonary shunting. The number of embolized arteries was one in eight patients (36.4%), two in eight patients (36.4%), three in five patients (22.7%), and four in one patient (4.5%). The bronchial artery was responsible in all patients. The intercostal artery and inferior phrenic artery were also targeted in one patient each (each 4.5%). The intercostobronchial trunk (ICBT) was found in 12 patients (54.5%). In such patients, BAE was performed on the distal side to the branch of the intercostal arteries (Figure 1). The angiographic findings are summarized in Table 2. The median procedure time was 86 min (range 40–142 min). A GS was used as the embolic material in all patients (100%). The GS and PVA combination was used in 11 patients (50.0%).

Short-term efficacy was achieved in all patients after BAE. Nineteen patients were followed-up for

Table 1. Clinical characteristics of patients with cryptogenic hemoptysis (*n* = 22)

Clinical characteristics	Patients, *n* (%)
Male	14 (63.6)
Ever-smokers	16 (72.7)
Current smokers	9 (40.9)
Respiratory comorbidity	7 (31.7)
COPD	5 (22.7)
Asthma	1 (4.5)
Interstitial pneumonia	1 (4.5)
Cardiovascular comorbidity	13 (59.1)
Hypertension	6 (27.2)
Atrial fibrillation	3 (13.6)
Valvuloplasty	3 (13.6)
Deep venous thrombosis	1 (4.5)
Liver cirrhosis	1 (4.5)
Chronic renal failure	2 (9.1)
Use of antiplatelet/anticoagulant medications	5 (22.7)

COPD, chronic obstructive pulmonary disease

Table 2. Summary of angiographic findings (*n* = 22)

Angiographic findings	Patients, *n* (%)
Bronchial artery hypertrophy	22 (100)
Hypervascularity	22 (100)
Bronchial aneurysm	4 (18.2)
Systemic-pulmonary shunting	6 (27.2)
No. of embolized arteries	
1	8 (36.4)
2	8 (36.4)
3	5 (22.7)
4	1 (4.5)
Responsible artery	
Bronchial artery	22 (100)
Intercostal artery	1 (4.5)
Inferior phrenic artery	1 (4.5)
Intercostobronchial trunk	12 (54.5)

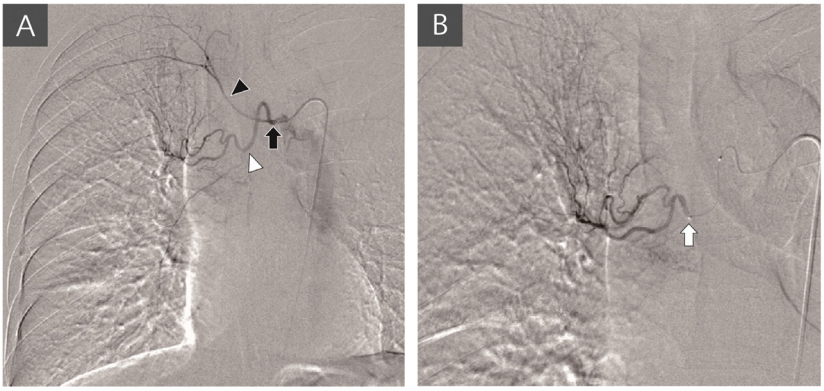

Figure 1. Selective angiography and super-selective bronchial artery embolization in a 68-year-old male patient. (A) Hypervascularity was observed during selective angiography of the intercostobronchial trunk (black arrow) with the right third and fourth intercostal arteries (black arrowhead) and a right bronchial artery (white arrowhead). The bronchial artery diameter was 1.2 mm. **(B)** Super-selective bronchial artery embolization performed on a right bronchial artery. The embolization was performed on a right bronchial artery after placing the microcatheter (white arrow) distal to the bronchial artery branch.

> 1 month, and the median follow-up period was 17 months (range 1–69 months). The recurrence-free rate was 100% for 1 month, 94.1% for 3 months, 94.1% for 12 months, 87.4% for 24 months, and 87.4% for >24 months (Figure 2). Rebleeding was observed in two patients, and only one patient required a bronchoscopic hemostasis procedure in addition to the administration of homeostatic materials. No patient underwent BAE for rebleeding. Table 3 summarizes the characteristics of patients who experienced rebleeding. No patient experienced severe complications such as spinal cord ischemia that resulted in prolonged hospitalization for additional treatment, permanent or significant disability, or death.

This study aimed to investigate the short- and long-term efficacy of BAE using a GS in the treatment of patients with cryptogenic hemoptysis. We found that BAE with a GS can terminate bleeding and suppress severe rebleeding with minimal complications in patients with cryptogenic hemoptysis. After conducting a literature research in PubMed and Ichushi-Web, we believe that this is the first study to investigate the efficacy of BAE with a GS in the treatment of cryptogenic hemoptysis in > 20 patients.

A GS is a widely used BAE material. In Japan, a national database study showed that 79% of BAE for cryptogenic hemoptysis used a GS (*20*). The advantages include its low cost; wide availability; and accumulated years of clinical use, which indicates its safety (*10,11*). In addition, as it is absorbed within several weeks after embolization (*12*), a second BAE procedure can target the same artery in case of rebleeding. One of the concerns regarding BAE with

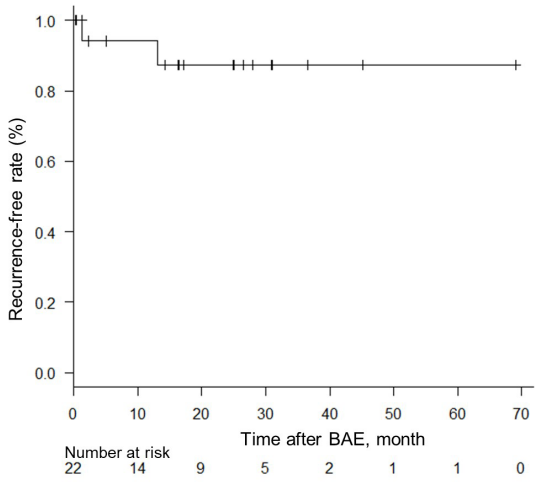

Figure 2. Cumulative recurrence-free rate curve of patients who underwent bronchial artery embolization (BAE). The recurrence-free rate was 100% for 1 month, 94.1% for 3 months, 94.1% for 12 months, 87.4% for 24 months, and 87.4% for > 24 months.

Table 3. Summary of patients with recurrent bleeding (n = 2)

Case no.	Recurrence-free duration	Age (years)	Sex	Smoking	Bronchial artery dilation	Hypervascularity	Aneurysm	Shunting	Bleeding site at time of BAE	Bleeding site at time of recurrence	Treatment for rebleeding	Recanalization on CT
1	15	67	M	Ex	Yes	Yes	No	No	RML	RLL	Bronchoscopic hemostasis, hemostatic materials	Yes
2	1	78	M	Ex	Yes	Yes	No	No	RUL	RUL	Hemostatic materials	No

M, male; BAE, bronchial artery embolization; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe; CT, computed tomography

a GS is recanalization that leads to another episode of hemoptysis. A previous study found that the recurrence rate was higher in a group of patients treated with gelfoam particle than in those treated with PVA (*21*). However, in light of its low risk of rebleeding (*13*,*15*), we hypothesized that BAE with a GS, a transient but inexpensive and widely used embolic material, is as effective as other permanent embolic materials for cryptogenic hemoptysis. Our results showed that BAE with a GS was sufficient and effective for treating cryptogenic hemoptysis. The recurrence-free rate remained as high as 87.4% during the 2-year follow-up period, and no life-threatening hemoptysis occurred at recurrence. Previous studies on cryptogenic hemoptysis also reported favorable prognoses after BAE (*13,22-25*). These studies used detachable coils (*13*), N-butyl cyanoacrylate (*22*), or PVA (*24*) as permanent embolic materials. Our outcome was comparable to these previous findings. Notably, no patients required a second BAE procedure for recurrence. Based on our results, we consider that the temporary effect of GS embolization is sufficient for treating cryptogenic hemoptysis, which has no underlying abnormality that can cause repetitive hemoptysis. The low cost, wide availability, and abundant clinical use are additional major advantages of the GS. Therefore, the GS should be considered an appropriate embolic material for the treatment of cryptogenic hemoptysis.

The representative complications associated with BAE include fever, local chest pain and allergic reaction to gelatin. Among such complications, the most severe complication is spinal cord ischemia caused by occlusion of the spinal artery, particularly of the great anterior radiculomedullary artery (the artery of Adamkiewicz, AKA). In this study, no cases of spinal cord ischemia were observed. To avoid AKA occlusion, BAE should be selectively performed on the exact responsible artery through precise angiography. Super-selective BAE has decreased the occurrence of spinal cord ischemia. The prevalence of spinal cord ischemia was reported to be as low as 0.19% in a recent report from Japan (*20*). This occurrence rate was quite low compared to previous studies, who reported rates between 1.4% and 6.5% (*26*). In addition, the accurate anatomical analysis of the AKA and bronchial artery has contributed to the decrease in spinal cord ischemia. The bronchial artery is the responsible artery in cryptogenic hemoptysis in most cases. In this study, 20 (90.9%) patients underwent BAE only in the bronchial artery. This finding is in line with previous studies (*13,22-24*). Uotani *et al.* (*27*) reported that the AKA originated from the intercostal or lumber artery at the Th7–12 or L1–3 level. Another study demonstrated that the spinal arterial supply directly from the bronchial artery was absent (*28*). Based on these data, BAE with a GS for cryptogenic hemoptysis targeting the bronchial artery can be performed safely without any concern for spinal cord ischemia. Moreover, the one concern regarding embolization of the bronchial artery is the presence of an ICBT. The intercostal artery can be a culprit in cryptogenic hemoptysis in a small population of patients. Due to the continuity between the intercostal arteries and the AKAs, extra attention should be paid to neurological complications in such cases. In our cohort, 12 patients (54.5%) had an ICBT. In such cases, GS embolization should be performed in the distal area posterior to the branching intercostal artery. One patient with intercostal artery embolization in this study underwent embolization after confirming no depiction of the AKAs by super-selective angiography for the intercostal artery.

Angiographic findings revealed the hypervascularity and hypertrophy of the bronchial artery in patients with cryptogenic hemoptysis, which is comparable with the findings of previous studies (*4,13,22-25*). In contrast, the prevalence of systemic-pulmonary shunting differs among studies. Most previous studies reported a low frequency of shunting in cryptogenic patients (*4,13,24,29*), but one study investigating cryptogenic hemoptysis in smokers noted shunting in 80% of patients (*23*). In the current study, systemic-pulmonary shunting was found in 27.2% of patients. This relatively high rate of shunting can be explained by the fact that our cohort included patients with a history of thoracic surgery such as cardiac valve replacement and mediastinal tumor resection. Inflammatory adhesion after surgery could induce shunting (*30*).

This study has several limitations. First, this was a single-arm retrospective analysis conducted in a single hospital. To generalize the results, we have begun a new prospective study regarding GS BAE. The results of the present study will aid the interpretation of more generalized studies in the future. Second, cryptogenic hemoptysis is essentially a diagnosis by exclusion and is thus heterogenous. Previous studies defined cryptogenic hemoptysis as no signs of underlying diseases on clinical investigation. As the precise definition differs slightly among studies, the validity of study comparisons is questionable. Finally, screening for asymptomatic cerebral infarction after BAE was not performed in this study.

In conclusion, GS BAE for cryptogenic hemoptysis yields short- and long-term hemostatic efficacy without severe complications. GS is a leading candidate for the optimal embolic material for patients with cryptogenic hemoptysis.

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