



Selective bronchial occlusion for acquired bronchobiliary fistula caused by treatment of hepatocellular carcinoma: A case series

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Abstract

Acquired bronchobiliary fistula (ABBF) is very rare among the complications that occur in patients with hepatocellular carcinoma (HCC) after treatment. Although surgery and drainage have been the main methods for treating ABBF for a long time, they are not entirely suitable for patients with refractory ABBF resulting from HCC therapy. In this study, we present four cases of ABBF caused by HCC treatment, who were treated using selective bronchial occlusion (SBO). Among the 4 patients with ABBF treated with SBO, 3 cases successfully blocked ABBF with SBO, and the treatment success rate was 75%. All successfully treated patients reported disappearance of symptoms of biliptysis and cough was alleviated. No life-threatening adverse reactions were reported following SBO intervention, and no deaths occurred. We believe that the use of video bronchoscopy to place a self-made silicone plug in the bronchus to treat refractory ABBF is a feasible palliative treatment, which can significantly improve the condition of ABBF patients.

KEYWORDS

acquired bronchobiliary fistula, biliptysis, hepatocellular carcinoma, interventional respiratory disease, occlusion therapy, silicone plug

INTRODUCTION

Acquired bronchobiliary fistula (ABBF) refers to the abnormal communication between bile duct and bronchus under the influence of various pathogenic factors. Its characteristic manifestations are persistent cough and repeated refractory pneumonia. Traditional views held that hepatic hydatid disease is the main cause of ABBF.^{1,2} In recent years, an increased number of ABBF cases have been reported in patients receiving hepatocellular carcinoma (HCC) treatment. However, there is still no consensus on the standard treatment of ABBF in HCC patients. Selective bronchial occlusion (SBO), involving the placement of occluders through bronchoscopy to seal the bronchus where the fistula is located, has emerged as an alternative approach. This technique has found widespread application in managing conditions such as massive hemoptysis and bronchopleural fistula (BPF).^{3,4} SBO can prevent bile from entering the bronchi, effectively reduce

further damage of bile to the lungs and bronchi, manage patient's symptoms and can also serve as a preparation for other treatments such as drainage or surgery. Our study represents the first attempt to employ SBO as a treatment regimen for patients with ABBF resulting from HCC treatment.

CASE SERIES

Patient data collection and SBO treatment procedure

This is a retrospective, observational, open-label, single-arm case series. We reviewed a case series of four patients with ABBF who underwent SBO at the Department of Respiratory and Intensive Care Medicine, First Affiliated Hospital of Second Military Medical University, between January 1, 2015, and December 31, 2022. The cases are summarized in Table 1.

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TABLE 1 Clinical characteristics and treatment of four patients with bronchobiliary fistula.

NO	Age	Gender	Initial diagnosis	Initial therapy	Period (year)	Symptoms	CT image feature	Management	Fistula location	Plugging range(lung)	Insert silicone plug (pieces)	Operation times	Silicone plug specification (mm)	Efficacy	Complication
1	54	M	Hepatoma	Surgery+ Intra-arterial therapies (TACE)+Radiotherapy+ Systemic therapies (Sorafenib)	1.5	Cough, bilioptysis, Purulent sputum, Chest pain, Fever, Dyspnea	Obstructive pneumonia of right lower lobe; pleural effusion	Thoracic drainage; Anti-infective therapy	B4-10(I-II)	Right inferior lobe; Right middle lobe	2 + 1*single plugged airway covered stent	3	4*6*10	Improve	Cough, Fever
2	53	M	Hepatoma	Surgery+ Intra-arterial therapies (TACE)+ Systemic therapies (Lenvatinib)	1	Cough, Bilioptysis, Hoarseness	Multiple flocculent shadows in both lungs	Biliary drainage (ENBD)	B9a(III)	Right inferior lobe;	8	6	8*6*10/5*5* 12/10*10* 21/3.5*5* 15/8*8*15	Improve	Cough, Fever
3	53	M	Hepatoma	Intra-arterial therapies (TACE)+ Systemic therapies (Chemotherapy +Immunotherapy+ Lenvatinib)	5	Cough, Bilioptysis, Hemoptysis	Right middle and lower lobe pneumonia	None	B5(II)	Right middle lobe	1	2	8*8*10	Improve	Fever
4	66	M	Hepatoma	Surgery+ Intra-arterial therapies (TACE)+ Ablation (MWA)	5	Cough, Chest discomfort, Bilioptysis	Pleural effusion	Biliary drainage (PTCD); Thoracic drainage	B8,B10(II)	Right inferior lobe	2	1	6*6*10/3*4*7	Unimproved	Dyspnea

Abbreviations: ERBD, endoscopic retrograde biliary drainage; M, male; MWA, microwave ablation; PTCD, percutaneous transhepatic cholangial drainage; TACE, trans-arterial chemoembolization.

Patients who met the indications of occlusion treatment according to abdominal B-scan ultrasonography, Magnetic Resonance Cholangiopancreatography (MRCP) and other necessary examinations were treated after signing the Informed Consent Form (ICF). The specific operation procedures are as follows: (a) Localization: Following intravenous anaesthesia, an 8# orotracheal tube is inserted to establish an artificial airway. Bronchoscopic irrigation with saline is applied to identify the site of the bronchial fistula and clear any yellow-green secretions. (b) Measurement and material preparation: The diameters of the proximal and distal airways where the fistula is located are evaluated using bronchoscope. Customized bronchial silicone plugs are prepared on-site, and adjusted to match the size of the bronchial lumen where the fistula is located. (c) Placement: The bronchoscope is passed through 8# orotracheal tube, and the silicone plug is pushed to the target bronchus with foreign body forceps and alligator forceps. We adjust position and angle of the silicone plug under the direct bronchoscopic control until the target bronchus is completely occluded. (d) Confirmation of effectiveness: After the above interventions are completed, the bronchoscope is withdrawn and we waited for 15 min before re-entering the airway to confirm the sealing effect of the silicone plugs. After confirming that no yellow green secretion overflows around the target bronchus, bronchoscope is removed and all the occlusion operations are completed. The personalized silicone plugs material utilized in the SBO treatment are manufactured by Wanhe Plastic Materials Company in Guangzhou, China (Figure 1).

Description of cases

The four ABBF patients in this series who received SBO treatment were all male, with an average age of 56.5 years (range: 55–66 years old). Prior to developing ABBF symptoms, all patients had undergone 2–3 different physical (surgery, Transarterial chemoembolization (TACE),

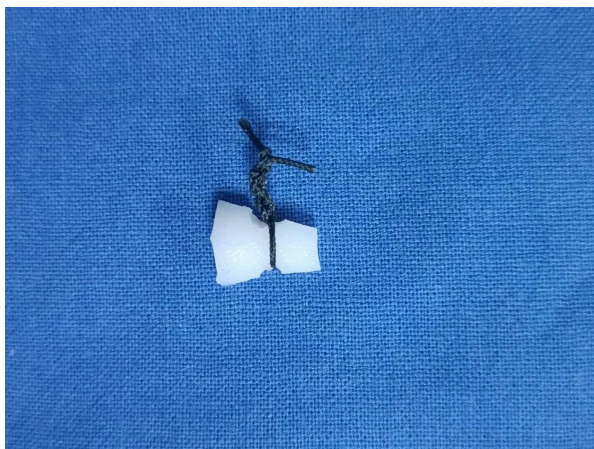


FIGURE 1 The silicone plug is cut into a pear shape, with a pull line attached to the middle part for easy grasping by foreign object forceps.

Microwaveablation (MWA), immunotherapy, etc.) or chemical (sorafenib, Lenvatinib, cisplatin) treatments that may have damaged the liver. The primary reported symptoms included biliptysis (bile in the sputum), cough, bronchoobstruction, chest pain, fever, hemoptysis, and so on. Diagnosis of ABBF was confirmed in all patients using bronchoscopy, which revealed that the fistulas in this series were located in the right lower lobe (3/4) and middle lobe (2/4), with a distribution between B4 and B10. It is worth mentioning that two patients were confirmed by bronchoscopy to have two or more fistulas in the lung. Before receiving SBO treatment, three patients underwent drainage procedures, and one patient received anti-infective conservative management. Among those who received drainage treatment, one patient underwent both chest drainage and Percutaneous Transhepatic Biliary Drainage (PTBD), while another patient received chest drainage alone and the third one only underwent Endoscopic Nasobiliary Drainage (ENBD). However, neither the drainage nor conservative management of patients in this series was effective.

Among the four ABBF patients, three were successfully treated with SBO, while, due to personal reasons, one declined the suggestion of using bronchoscopy for further exploration after the initial unsuccessful SBO attempt. On average, each patient required three SBO treatments (range: 1–6 times), and an average of 3.25 silicone plugs were inserted (range: 1–8 pieces) to achieve satisfactory outcomes. Throughout the 2-month observation period, occlusive therapy demonstrated stable response and effectiveness. A follow-up bronchoscopy performed on one patient after 2 months confirmed this conclusion. All successfully treated patients (3/4) reported immediate disappearance of symptoms of biliptysis. Although all patients in the series reported transient fever (range: 37.8–39.0°C) and cough within 1 day after operation, such symptoms were effectively managed with antitussive and anti-infection measures. In the long term follow-up (longer than 2 months), the patients' cough symptoms were alleviated. No life-threatening adverse reactions were reported following SBO surgery, and no deaths occurred among the patients. The post-intervention images of all patients undergoing SBO are shown in Figure 2.

DISCUSSION

The treatment of ABBF comprises surgical and non-surgical approaches. A comprehensive overview of existing ABBF treatment strategies is provided in Table 2. The effectiveness of bile drainage may be limited in cases caused by HCC treatment. Previous reports indicate that ABBF resulting from HCC treatment often requires prolonged drainage, suggesting that drainage alone may not lead to natural healing, particularly in cases of iatrogenic ABBF.⁵ In our study, only one of four patients showing significant biliary hypertension in imageology during preoperative evaluation. Neither the drainage nor conservative management of patients in this series were effective. SBO have been developed as an

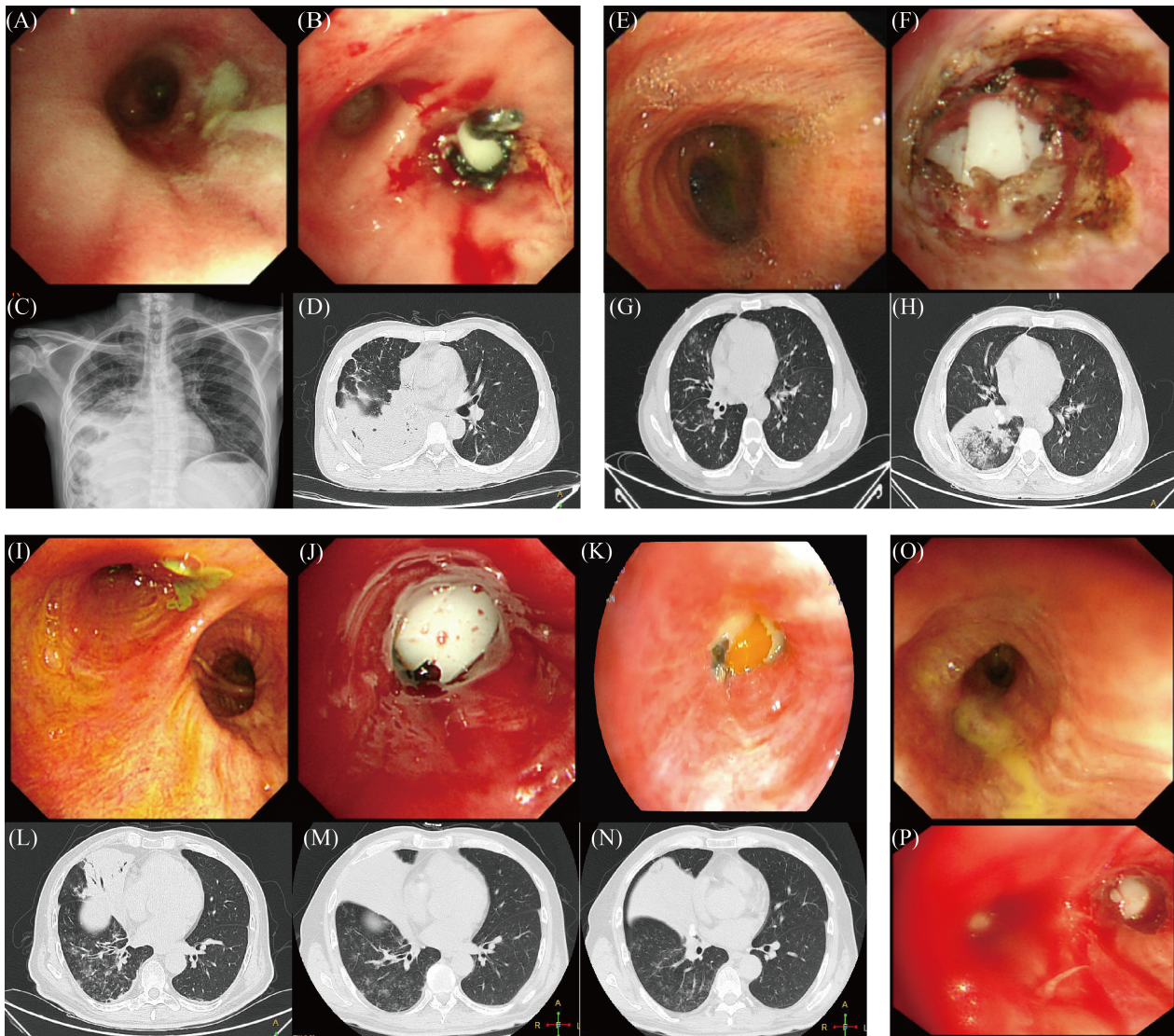


FIGURE 2 (A)–(D) is the imaging data of patient 1. (A) Bronchoscopy revealed that the pus mainly came from the basal segment of the right lower lobe and the dorsal segment of the right lower lung. (B) Use 2 self-made silicone plugs to block the basal segment of the right lower lobe bronchus (B6–B10). (C) x-ray shows incomplete expansion of the patient's right lower lung with pleural effusion before operation. (D) Postoperative CT showed the position of the metal stent. (E)–(H) is the imaging data of patient 2. (E) Bronchoscopy showed that the yellow green secretion mainly came from the distal end of the right lower lobe outer basal segment of the bronchus (B9). (F) Insert a silicone plug into the proximal end of the right lower lobe posterior basal segment bronchus (B10) and completely block the right lower lobe anterior, lateral, and posterior common trunk bronchus (B8–B10). Finally, burn with an argon knife (40 W). (G)–(H) Comparison of preoperative (left) and postoperative (right) CT shows that the silicone plugs successfully occluded the target bronchus. (I)–(N) is the imaging data of patient 3. (I) Bronchoscopy revealed fresh bile overflow in the medial segment of the right middle lobe bronchus (B5). (J) An 8 * 8 * 10 mm silicone plug was inserted to block the target bronchus in the right middle lobe. (K) Two months later, the bronchoscopy revealed that the silicone plug was successfully sealed, showing a light-yellow colour and no surrounding secretions overflowing. (L)–(N) CT showed inflammation in the lower lobe of the patient's right lung (left), with improvement after SBO (middle). Silicone plug was used to occluded the target bronchus (B5). (O)–(P) is the imaging data of patient 4. Bronchoscopy revealed that light yellow secretions originate from the right lower lobe anterior basal segment bronchus (B8) and the right lower lobe posterior basal segment bronchus (B10). And two silicone plugs were inserted after SB.

alternative solution for patients after failed endoscopic drainage. Previous studies by Kostopanagiotou and Ozdemir et al. demonstrated the feasibility of inserting silicone spigots (Watanabe spigot) into the affected bronchi of patients with ABBF caused by liver metastases and Cholangiocarcinoma, respectively, using bronchoscopy.^{6,7} Compared with PTBD and surgery, the potential advantages

of SBO include: SBO can have minimal trauma, high safety, short operation time, and can be attempted multiple times for patients, and so on.

In this case series, we successfully determined the location of the bronchial fistula in all patients using bronchoscopy. In principle, the occlusion should target the smallest subsegmental bronchus where the fistula is located.

TABLE 2 Summary of existing ABBF treatment.

	Treatment strategy	Mechanism	Path	Technology	Auxiliary materials/operations
Single therapy strategy	Embolization	Seal fistula tract	Abdomen	Laparoscopic endoscopy	Cyanoacrylate polyvinyl alcohol absorbent cotton
			Bile duct	PTBD/ERBD/ERCP	N-butyl 2-cyanoacrylate (NBCA); Micro-coils; Stent; Repetitive fibrin
		Bronchus	Bronchoscope	N-butyl 2-cyanoacrylate(NBCA)	
		Seal bile inflow or outflow tract	Bile duct	PTBD/ERBD/ERCP	N-butyl 2-cyanoacrylate(NBCA)
	Bronchus		SBO	Nickel-titanium alloy dumbbell-shaped implant device; Silicone spigots	
	Drainage	Drainage of accumulated bile, fistula closed spontaneously	Abdomen Bile duct	PTBD/ PAD ERBD/ERCP	Micro-coils; Stent; Sphincterotomy; Balloon dilatation
	Surgery	Excision fistula	Via thorax Via thorax /abdomen	Thoracoscope Thoracotomy, Laparotomy or Thoraco-phrenolaparotomy	Broad dorsal muscle flap; Greater omentum
Supportive Care	Improve patient status	Oral-	Drug	Somatostatin; Antibiotics	
Combined therapy strategy	Embolization+ Drainage	Seal fistula tract + drainage of accumulated bile	Bile duct /Bile duct+ bronchus	PTBD+ERBD/ERCP	Two or more materials combination

However, limited by the size of the bronchoscope, we currently only determine the location of the bronchial subsegment where the fistula is located, but not the specific opening and number of the fistula below subsegmental level, which is technically difficult to determine. Ultrathin bronchoscopy may solve this problem. In our experience, it is challenging to completely seal all fistulas at one time, so caution is advised when confirming the sealing effect. A recommended approach is to observe any secretion overflow in the sealing area through bronchoscopy for a certain period (About 15 min, empirical). It is worth mentioning that we innovatively used self-made pear-shaped silicone plugs to improve the success rate of sealing. The design of pear-shaped silicone plug helps to fix it in the bronchial lumen. The middle part of the silicone plug is attached with a pull line for easy grasping by foreign object forceps. As our previous research has shown, severe postoperative coughing is a common cause of ABBF occlusion failure.⁸ In this study, three patients reported coughing up silicone plugs after operation due to severe cough. Appropriate use of postoperative cough suppressants and effective control of cough severity can help reduce the likelihood of silicone plug expulsion and improve the success rate of SBO. In cases where the silicone plug cannot be stabilized after adjustment, combining silicone plugs with other auxiliary materials or methods such as covered stents or Argon Plasma coagulation (APC) is recommended for reinforcement.

In conclusion, our research validates the safety and feasibility of this treatment modality. To our knowledge, this is the first and the largest series report on the therapeutic effect of SBO on patients with ABBF caused by HCC treatment to date. Given that BBF is a rare disease, this conclusion is still limited by the number of cases. In addition, sealing the fistula alone does not address the underlying pathogenic factors of ABBF, thus also limiting the application of this treatment approach, which justifies further research and clinical attempts.

AUTHOR CONTRIBUTIONS

Bi Zhao designed the study, enrolled the patients, analysed the data, and wrote the paper and should be considered as first authors. Yuchao Dong and Haidong Huang made substantial contributions to the literature review, data collection, and paper writing. Bi Zhao, Rui Chen Huang and Yang Xia reviewed the literature, wrote the manuscript and produced the figures. Lijun Zhao and Wei Zhang designed the study, wrote, reviewed and edited the manuscript and share senior authorship. All authors have read and approved the final version of the manuscript. Bi Zhao, Rui Chen Huang and Yang Xia have contributed equally to this work and shared co-first authorship.

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The manuscript has been read and approved by all the authors, and each author believes that the manuscript represents honest work.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from The Shanghai Changhai Hospital. Restrictions apply to the availability of these data, which were used under license for this study.

ETHICS STATEMENT

This study has been approved by the Ethics Committee of Shanghai Changhai Hospital. Ethics approval number: CHEC2022-137. As this is a retrospective study and it does not include a description of individuals, authors do not need to obtain individual patient consent.

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