Original Article

Bronchopleural fistula after lung ablation: Experience in two cases and literature review

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Abstract

BACKGROUND: Bronchopleural fistula (BPF) complicating lung tumor ablation is rare but severe. The purpose of this article was to study its characteristics and treatments. **MATERIALS AND METHODS:** Two of 682 (0.3%) sessions of lung microwave ablation (MWA) were complicated with BPF and documented. Two electronic databases were searched for reported cases of BPF after lung tumor ablation. Case selection and data collection were done by 3 independent reviewers. **RESULTS:** A 56-year-old man and a 61-year-old woman developed BPF after MWA and died. Thirteen cases (mean age 63.8, 61.5% male) of BPF with adequate information were identified from 8 articles. Of the 13 cases, 5 (38.5%) had pulmonary co-morbidity, 3 (23.1%) had a history of pulmonary surgery, 7 (53.8%) had a target tumor adjacent or abutting pulmonary pleura, and 6 (46.2%) developed severe infections. After chest tube placement, pleurodesis, endoscopic therapy, surgery, and other treatments, 12 were cured and 1 died of BPF and pneumonia. **CONCLUSION:** BPF is a rare but severe complication of lung ablation, and the management needs a multidisciplinary and individualized treatment strategy.

Key Words: Ablation, bronchopleural fistula, malignancy, pulmonary

Introduction

The past 15 years witnessed the development of lung ablation techniques, including radiofrequency ablation (RFA) and microwave ablation (MWA),[1] to enable local control of lung tumors in poor surgical candidates. In general, lung ablation is a safe and minimally invasive procedure, but its use can be associated with various common complications including pneumothorax, pleural effusion, pneumonia, and hemorrhage,[2] and some rare but severe complications such as bronchopleural fistula (BPF). BPF is a sinus tract between the bronchus and the pleural space that may result in intractable pneumothorax, severe infection, respiratory failure, physical weakness, and even death. A greater understanding of BPF after MWA is important. Herein, we report two cases of BPF after lung MWA and a systematic review to initially study the pathogenesis, clinic features, and treatments of BPF after lung ablation.

Materials and Methods

Case reports

Informed consent was obtained from each patient to perform percutaneous MWA of lung tumors with the guidance of computed tomographic fluoroscopy (CT). Informed consent was obtained from each patient for the BPF treatment. Our Institutional Review Board gave us further approval to conduct and report this retrospective study. Of 682 consecutive sessions of lung MWA from January 2011 to January 2015 in our center, 2 (0.3%) was complicated with BPF and documented.

Case 1

The first patient was a 56-year-old man. He presented at our hospital for the treatment of recurrent lung cancer in November 2011. Six years ago, he had underwent radical resection of right lower lobe for a moderately differentiated adenocarcinoma with carinal lymph metastasis (T2N2M0), followed by mediastinal radiotherapy and three cycles of adjuvant chemotherapy with vinorelbine and cisplatin. Pretreatment CT image shows a 4.5 cm recurrent mass in the right lung with chest wall invasion but without regional lymph node metastasis or distant metastasis (T3N0M0) [Figure 1a]. CT-guided percutaneous lung biopsy of the lesion confirmed it as being a poorly differentiated adenocarcinoma. The patient refused a second radical resection, and CT-guided MWA procedure was performed with two microwave antennae [Figure 1b]. Postablation CT images showed a close contact of the ground-glass opacity (GGO) with the chest wall [Figure 1c].

Case 2

The second patient was a 61-year-old woman with a chronic hepatitis B infection. In March 2013, she presented to our hospital for treatment of active chronic icteric hepatitis B. Abdominal magnetic resonance imaging detected a mass in lung and the following chest CT revealed a peripheral 3.5 cm neoplasm adjacent to the oblique fissure in the left lower lobe without regional lymph node metastasis or distant metastasis (T2N0M0) [Figure 2a]. After consultations with a thoracic surgeon, the patient was not suitable for surgery because active hepatitis. The patient underwent a percutaneous lung biopsy, and the lesion was histopathologically confirmed as an adenocarcinoma. CT-guided MWA was simultaneously performed with two antennae [Figure 2b]. Postablation CT showed small pneumothorax and a close contact of GGO with the chest wall [Figure 2c].

Literature review

To identify BPFs after lung ablation in literature, system literature review was performed. With the help of a medical literature retrieval expert, using Reference Aid for Medicine, version 4.0 software (Beijing Kingyee, China), electronic searches were conducted in MEDLINE (PubMed) and China Knowledge Resource Integrated Database (CNKI) from January 2000 to January 2015. The searching key words were "lung" in title/abstract and "ablation" in title/abstract and "fistula" in title.

Twenty-five abstracts were identified from MEDLINE and 6 from CNKI. The 31 abstracts were assessed independently by 3 reviewers, and 16 abstracts were selected for full-text review. Of the 16 articles, 2 reported bronchocutaneous fistula

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DOI: 10.4103/0019-509X.172512

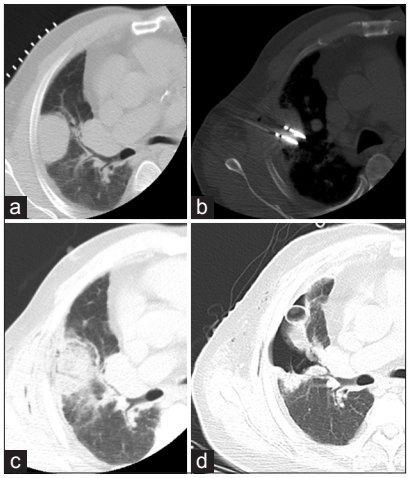

Figure 1: Bronchopleural fistula after a lung microwave ablation in a 56-year-old man with recurrent lung cancer after lung resection. (a) Pretreatment axial computed tomography image in lung window shows a 4.5 cm recurrent mass in the right lung. (b) Computed tomography image shows 2 antennae positioned in the tumor for ablation. (c) Postablation computed tomography image shows a close contact of ground-glass opacity with chest wall. (d) Computed tomography image obtained 32 days after ablation shows residual subcutaneous emphysema, pneumothorax, and multiple bronchopleural fistulae with persistent communication of bronchi with right thoracic cavity

without evidence of pneumothorax[3,4] and 1 mentioned an unconfirmed BPF with a large pneumothorax relieved several days later.[5] The three articles were removed. Two of the remaining 13 articles[6,7] were identified to have overlapping patients, and the more recent of these results was included where overlap occurred.[7] Another pair came from the same center but without overlapping patients.[2,8] The third pair[9,10] came from the same center with one overlapping patient; more detailed part of the 2 articles was analyzed. One case in a study[11] developed intraoperative pneumothorax not requiring postoperative drainage and returned home shortly after the ablation, but our reviewers considered this diagnosis of BPF owned inadequate evidence and precluded the case. So far, there were 19 cases from 12 articles identified.[2,7-17]

Of the 19 cases, 6 were mentioned in 3 series study[9,15,17] and 1 review[2] with inadequate information and were precluded after reviewers' study. Finally, there were 13 cases extracted from 8 case reports[7,8,10-14,16] with adequate information. Using a data extraction form developed apriori, three reviewers independently extracted the following information from included studies: Ablation modality; patient character including gender, age, pulmonary co-morbidities, and history of pulmonary surgery; target tumor characteristics including lobe, maximum diameter, histologic origin, and presence or absence of pleural contact; and complication characteristics including time between ablation and massive pneumothorax induced by BPF, infection in lung and pleural cavity, hospitalization time for BPF, treatments of BPF besides chest tube placement, and outcome of BPF.

Results

Case reports

Case 1

The day after the procedure, the patient began to complain of a cough, chest pain, and some dyspnea. Chest radiograph showed small pneumothorax and subcutaneous emphysema.

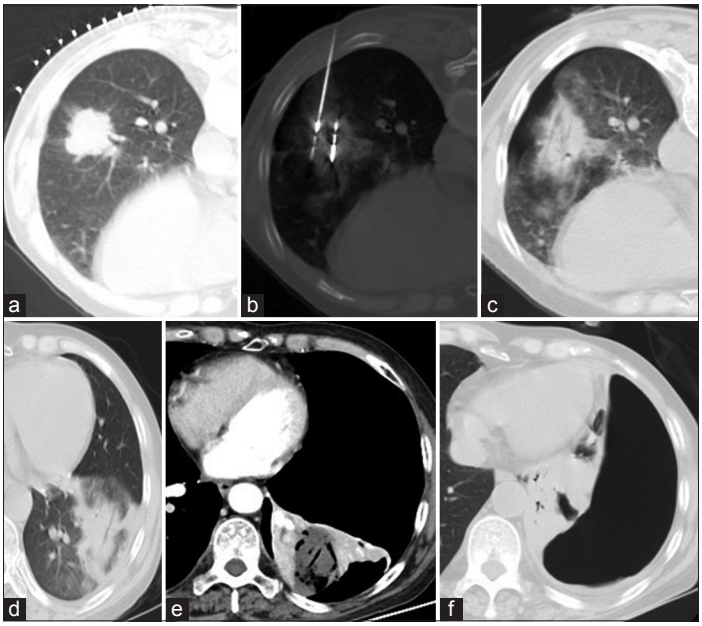

Figure 2: Bronchopleural fistula developed after lung microwave ablation in a 61-year-old woman with an adenocarcinoma lesion. (a) Pretreatment axial computed tomography image in lung window shows a 3.5 cm lesion in the left lower lobe. (b) Computed tomography image shows 2 antennae positioned in the tumor for ablation. (c) Postablation computed tomography image shows a close contact of ground-glass opacity with pleural. (d) A computed tomography follow-up scan at 48 h after microwave ablation shows a ground-glass opacity-like reaction band around the lesion, encompassing the entire tumor and involving a large-area pleural. (e) Enhanced computed tomography scan at 34 days after microwave ablation shows a larger pneumothorax, compression atelectasis, and a pleural ulcer. (f) Computed tomography image obtained 80 days after microwave ablation show longstanding bronchopleural fistula and large pneumothorax

No particular treatment was adopted. The above-mentioned symptom significantly deteriorated 3 days later and severe subcutaneous emphysema involved extensive area in chest and neck. A chest radiograph obtained 4 days after ablation shows extensive and severe subcutaneous emphysema. After consultation with a thoracic surgeon, skin incision, and chest tube placement were performed. Above-mentioned symptom relieved gradually, but pneumothorax became intractable. CT image obtained 32 days after ablation showed residual subcutaneous emphysema, pneumothorax, and multiple BPF with persistent communication of several bronchi to the right thoracic cavity [Figure 1d]. Pleurodesis with video-assisted thoracoscope was performed, but air leakage persisted till he died of brain metastasis and physical weakness 7 months later.

Case 2

CT follow-up scan at 48 h after MWA showed GGO-like reaction band around the lesion, encompassing the entire tumor and involving a large-area pleural [Figure 2d]. The patient suffered from intermittent fever after MWA. At 15 days after MWA, the patient's temperature had risen to 39.4°C despite broad-spectrum antibiotics. A sudden sharp chest pain, leading to feelings of tightness in the chest, occurred at 32 days after MWA, accompanied with shortness of breath, tachypnea, tachycardia, cough, and fatigue. A subsequent enhanced CT scan verified a massive pneumothorax, compression atelectasis, and a pleural ulcer [Figure 2e]. A chest tube was positioned to evacuate the air and repeat CT on day 38 after MWA showed elimination of pneumothorax and development of pleural

effusion. The positive results obtained from serial aspergillus antigen, smear, and culturing of the greyish-yellow phlegm revealed an aspergillus fumigatus infection. Intravenous voriconazole, nutritional support, and symptomatic treatment were all presented with poor efficacy. Repeat CT scans obtained 54, 66, and 80 days after MWA all showed large pneumothorax and longstanding BPF within the MWA cavitation that abutted the visceral pleura [Figure 2f]. Because of the uncontrollable aspergillus fumigatus infection, subsequent critical multiple infections, and intolerance to surgery, the patient died of secondary multiple organ function failure at 95 days after MWA.

Literature review

The baseline characteristics of the 13 included cases are presented in Table 1. In the 13 cases, there were 5 (38.5%) women and 8 (61.5%) men with an average age of 63.8 (48–81). Five (38.5%) patients had pulmonary co-morbidities including emphysema, chronic obstructive pulmonary disease (COPD), and bullae, and one patient receiving bilevel positive airway pressure therapy (BiPAP). Three (23.7%) patients had a history of pulmonary surgery. Five (38.5%) patients had pulmonary metastasis, and 8 (61.5%) had nonsmall cell lung cancer. There were 10 (76.9%) sessions of lung RFA and 3 (23.1%) of MWA. The average maximum diameter of the 13 target tumors inducing BPF was 2.75 cm (0.8–6.2 cm). Seven (53.8%) of the 13 tumors were adjacent or abutting pulmonary pleura.

Of the 13 cases, 6 (46.2%) developed massive pneumothorax intraoperatively or shortly after ablation, 7 (53.8%) developed 3–47 days later. Six (46.1%) cases of postablation severe infections were documented, including empyema in 5 and pneumonia in 2. Massive subcutaneous emphysemas were documented in 2 (15.4%) cases (case 7 and 11). Two cases (case 3 and 12) underwent surgery therapy shortly after ablation and were discharged soon, but the other 11 cases had been hospitalized for about 11 days to 12 weeks (averagely about 47 days) after the happening of massive pneumothorax induced by BPF. The treatment for BPF included chest tube placement, pleurodesis, endoscopic therapy, and surgery. On a special condition, stopping the use of BiPAP (case 6) or closure of cavity using autologous platelet gel (case 13) took effects.

Of the 13 BPFs, 12 (92.3%) were cured. One case (7.7%) was not cured till his death (case 1). The other death (case 11) happened 97 days after the resolving of air leak because of persistent empyema, multiple pneumonias and small bowel obstruction. Hence, the mortality of BPF after lung ablation in reviewed literature was 15.4% (2/13).

Discussion

BPF is a sinus tract between bronchus and pleural space that may result from necrotising pneumonia/empyema (anaerobic, pyogenic, tuberculous, and fungal), lung neoplasms, lung injuries, and complications of medical procedures such as lung biopsy, chest tube drainage, thoracocentesis, or radiotherapy.[19] More commonly, it arises as a complication of lung surgery following failure of the bronchial stump to heal.[18] With the development of thermal ablation of lung tumor, BPF after lung RFA has been reported occasionally, but BPF after lung MWA has rarely been reported. The incidence of BPF after lung ablation is 0.4% (4/1000)[9] to 0.6% (2/334).[8] In our experience of 682 procedures of lung MWA, the incidence was 0.3% (2/682), which is close to the rate in literature. Although the incidence is low, the mortality rate is high. One (50%) of 2 died of BPF in our center, and 2 (15.4%) of 13 died in reviewed literatures.

Multifactorial etiology may be assumed for the occurrence of lung-ablation-induced BPF. The formation of a sinus tract between bronchus and pleural cavity may be through the following ways. (1) Penetrating and ablating lung injuries in procedure involving bronchus may induce BPF. Ablation of the visceral pleura and adjacent lung tissue leads to dehydration and may reduce the elastic properties of the lung tissue to close up the puncture. An active repair process to seal the puncture may be impaired in the nonliving tissue surrounding the entry point and needle track. In this case, massive pneumothorax may develop intraoperatively or shortly after ablation, such as case 1 in our center and the 6 cases in literature mentioned above. (2) After necrotic tissue between pleural space and bronchus was sloughed but not infected, a BPF may form and a delayed pneumothorax may appear. The formation of BPF might be facilitated in this way in case 1 in our center and 3 cases in literature (case 4, 5, and 7). (3) The ablated and necrotic zone is infected or complicated with necrotizing pneumonia, and the disintegrated zone communicates both with bronchus and with the visceral pleura. When the necrotic and/or infected tissue is expectorated out or excreted into pleural cavity, a BPF may form. BPFs of case 2 in our center and case 11, 12, and 13 in reviewed literature might form in this way because BPF attacked many days after ablation and followed infection in the 4 cases.

Our[20] and other[9,21-23] articles had reported that emphysema was a risk factor for pneumothorax after lung ablation. Five (38%) of the 13 reported BPF cases had pulmonary co-morbidities including emphysema, COPD, and bullae. The BPF characteristics of case 6 in reviewed literature hinted that high pressure in the lung may facilitate the formation of BPF. In addition, it was reported that the presence of emphysema significantly increased the risk of lung abscess,[9] which may facilitate the formation of BPF. However, 2 cases in our center presented without chronic pulmonary co-morbidity. Consequently, emphysema may be a potential risk factor for BPF, but this need confirmation.

Yoshimatsu *et al*. had discovered that the contact of the GGO that emerged around the ablated lesion with the pleura significantly correlated with the frequency of delayed or recurrent pneumothorax.[21] It had been confirmed that GGO corresponds histopathologically to coagulation necrosis.[24] Thus, this could be explained by necrotic changes and rupture of the pleura and lung tissue around the site of needle insertion. Seven (54%) of the 13 tumors in the literature review and the tumor of case 1 in our center were adjacent or abutting pulmonary pleura. The target tumor of case 2 in our center didn't contact with

Table 1: Summary of 13 cases of BPF after ablation in 8 reviewed articles

Study	Patient number	Ablation modality	Patient character				Target tumor character				Complication character		Hospitalization※	Treatments of BPF besides chest tube placement	Outcome of BPF
			Sex	Age (year)	Co-morbidity	Surgery*	Location	MaxΦ (cm)	Origin	Pleural contact	Pneumothorax#	Infection			
Sakurai 2007[8]	1	RFA	Male	76	Emphysema	Yes	LLL	2.4	MC	Yes	8 h	Pneumonia	52 days	Endoscopy Pleurodesis	Death
	2	RFA	Male	81	Emphysema	No	RUL	6.2	PC	No	Intraoperative	Empyema	97 days	Pleurodesis Surgery Endoscopy	Cure
Clasen 2009[12]	3	RFA	Female	48	NR	No	LLL	2.1	MC	No	32 h	No	NR	Resection	Cure
	4	RFA	Male	61	NR	No	RLL	1.4	MC	No	5 days	No	11 days	No	Cure
Kodama 2009[10]	5	RFA	Male	58	Bullae	No	RLL	3.4	PC	Yes	12 days	No	6 weeks	Endoscopy	Cure
Nachiappan 2010[13]	6	RFA	Male	61	BiPAP	Yes	RUL	4.3	MC	Yes	>3 days	Empyema	12 weeks	Surgery Stop BiPAP	Cure
Cannella 2011[11]	7	RFA	Female	53	NR	No	LUL	2.4	MC	Yes	6 weeks	NR	5 weeks	No	Cure
Alexander 2012[7]	8	MWA	Female	71	NR	No	LUL	3.6	PC	Yes	Intraoperative	No	15 days	Pleurodesis Endoscopy	Cure
	9	MWA	Female	58	Emphysema	No	RUL	1.5	PC	Yes	2 h	NR	30 days	Pleurodesis Endoscopy	Cure
	10	MWA	Male	63	NR	No	RUL	0.8	PC	NR	Intraoperative	NR	31 days	Endoscopy Pleurodesis	Cure
	11	RFA	Female	63	NR	Yes	LUL	2.4	PC	NR	47 days	Empyema Pneumonias	51 days	Endoscopy	Cure, death
Li 2013[14]	12	RFA	Male	63	NR	No	RML	2.5	PC	Yes	28 days	Empyema	NR	Surgery	Cure
Andreetti 2014[16]	13	RFA	Male	73	COPD	No	RUL	2.7	PC	NR	8 days	Empyema	74 days	Endoscopy Cavity closure	Cure

*History of lung surgery; #Time between ablation and massive pneumothorax induced by BPF; ※Hospitalization time for BPF; MaxΦ=Maximum diameter; MC=Metastatic lung cancer; PC=Primary lung cancer; NR=Not reported; RUL=Right lower lobe; RML=Right middle lobe; RLL=Right lower lobe; LUL=Left upper lobe; LLL=Left lower lobe; BPF=Bronchopleural fistula; RFA=Radiofrequency ablation; MWA=Microwave ablation; BiPAP=Bilevel positive airway pressure; COPD=Chronic obstructive pulmonary disease

pleura, but the GGO did. Therefore, the contact of GGO with pleura may correlate with the formation of BPF, and the possibility to induce BPF may be reduced if an extensive ablation involving pleura is avoided.

Three (23%) of the 13 cases in literature and case 1 in our center had a history of pulmonary surgery. Although the target lesion of case 1 in our center was peripheral, it was relatively close to the right hilum, secondary to postsurgical change. This facilitated the communication of GGO with both pleura and bronchus. Hence, a history of pulmonary surgery may be another risk factor for BPF, though confirmation is needed.

Infection in ablated zone and surrounding tissue may promote the disintegration of the tissue between pleura and bronchus and thus bring about a BPF. The infection and BPF may occur weeks even months after ablation, just like those of case 2 in our center and case 11, 12, and 13 in reviewed literature. Of the 13 cases in literature, 6 (46%) were documented severe postablation infections, including empyema in 5 and pneumonia in 2. Infection may facilitate formation of BPF and BPF may bring about or aggravate infection. One death in our center and 2 deaths[7,8] in reviewed studies all resulted from severe infection in lung or pleura cavity.

However, the exact causes for this complication cannot be determined in these cases. Further accumulation of similar cases and analysis of the risk factors will be necessary to clarify its exact causes and modify ablation techniques to prevent BPF.

Through the characteristics of pneumothorax in the 15 cases of this and reported articles, we found that the diagnosis of BPF is often obvious from the clinical presentation, particularly in the presence of a chest tube. Clinical features suggestive of a postablation BPF include delayed or recurrent massive pneumothorax, steady increase in intrapleural air space, and persistent air leakage. Using standard and thin section noncontrast CT scans, most fistulae could be demonstrated actually. Seven (54%) of the 13 reviewed BPFs and both of the two BPFs in our center were documented with actual fistulae in CT image. Furthermore, bronchoscopy and associated procedures can be used to localize/confirm BPF.[7]

As shown in the current 2 and reported 13 cases, most BPF is associated with significant morbidity and mortality, but the management of BPF remains a major therapeutic challenge for clinicians, requiring frequent treatments including pleurodesis, endobronchial management, and/or surgical therapy.[19] Large symptomatic pneumothorax due to BPF necessitates immediate chest tube placement to expand the lung in all of the 15 case, and 2 of the 15 cases were successfully treated with chest tubes alone.

Surgery is a positive and traditional treatment for BPF. Successful management of a fistula is combined with treatment of the associated empyema cavity. Surgery was a good option for BPF especially when empyema occurred. When deemed required, surgical debridement, repair, and/or resection should be accomplished expeditiously. When treatment is protracted, secondary complications are more likely, and survival is adversely affected.[19] Surgical treatments were adopted in 4 of the 15 cases. Of the 4 cases, 2 (case 3 and 12 in literature) underwent surgery shortly after the attack of BPF and were cured, whereas the other 2 surgery performed 2 weeks (case 6) and 60 days (case 2 in literature) after the attack failed.

In a patient population with poor cardiopulmonary reserve, as seen in many patients presenting for lung ablation, the risks of general anesthesia and surgical intervention pose a challenge. Some cases were poor surgery candidates, like the two cases in our center. Cannella *et al*., suggested that minimally invasive treatment, chest tubes alone for example, was sufficient to cure BPF,[11] but air leakage persisted after chest tube placement in 13 of the 15 cases.

Pleurodesis is a minimally invasive treatment for BPF. The cheat tube can act as a conduit for exposure to various sclerosing agents, such as bacterial components, antibiotics, and fibrin glue to promote pleurodesis. Six of the 15 cases underwent chemical pleurodesis, but only 1 pleurodesis followed endobronchial occlusion (case 10 in literature) was successful. Large pneumothorax and persistent air leakage made the other 5 cases of pleurodesis failed. It seems that pleurodesis is apt to take effect when bronchial occlusion relieves air leakage partially.

Endobronchial management is another minimally invasive treatment for BPF.[25] Eight of the 15 cases underwent bronchial occlusion and air leakage stopped in 7 (87.5%), including case 10 mentioned above. Bronchial occlusion can be performed with coils, fibrin glue, oxycel cotton, cyanoacrylate, zelacin glue, autologous clot, and silicone embolic materials.[25] Alexander *et al*. reported 4 cases of BPFs following ablation and treated with one-way endobronchial valve, with 3 of the 4 pneumothoraces resolved after valve placement.[7] The valve prevents air from entering the excluded portion of the lung but allows normal clearance of mucus and debris, even allows drainage of pneumothorax.[7]

Conclusion

BPF is a rare, severe, and challenging complication after lung ablation. The formation of the sinus between bronchus and pleural cavity may be correlated with penetrating and ablating injuries of pleura and bronchus, sloughing of necrotic tissue, and disintegration of infected tissue. The high-risk factors of BPF may include emphysema, contact of GGO with visceral pleura, history of pulmonary surgery, and infection in ablated zone. All these need confirmation by systemic study, which is difficult because BPFs after lung ablation are rare. The management of BPF needs a multidisciplinary treatment strategy and should be individualized.

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How to cite this article: Zheng A, Yang X, Ye X, Huang G, Wei Z, Wang J, *et al*. Bronchopleural fistula after lung ablation: Experience in two cases and literature review. Indian J Cancer 2015;52:41-6.
Source of Support: Nil. **Conflict of Interest:** None declared.