Central Bronchopleural Fistulas Closed by Bronchoscopic Injection of Absolute Ethanol*

Kazuo Takaoka, MD; Shoichi Inoue, MD; and Seiji Ohira, MD

Five consecutive bronchopleural fistulas (BPFs) were successfully treated by injecting absolute ethanol directly into the submucosal layer of the fistula under flexible bronchoscopic observation. No complications occurred as a result of this treatment. Our nonsurgical treatment may be very useful to reduce the costs of and duration of hospitalization and to improve the patient’s quality of life. This is the first report of the bronchoscopic closure of BPFs by injecting absolute ethanol, and we would recommend this treatment as a first-line therapy for patients with a postoperative central BPF with an orifice that is <3 mm in diameter.

(CHEST 2002; 122:374–378)

Key words: bronchopleural fistula; bronchoscopic closure; ethanol

Abbreviation: BPF = bronchopleural fistula

Bronchopleural fistulas (BPFs) communicate between the lung parenchyma or clearly identifiable airways and the pleural space, and can be divided into central and peripheral types. Peripheral BPFs may be identified by CT scanning. On the other hand, central BPFs usually result from pulmonary resection procedures such as pneumonectomy or lobectomy and are diagnosed by bronchoscopy. Although the incidence of BPFs after pulmonary resection for the treatment of lung cancer is generally reported to range between 4.5% and 20% after pneumonectomy and 0.5% after lobectomy, modern stapling techniques have succeeded in reducing the incidence of BPF to 1%, indicating that pulmonary resection still has a high incidence of this life-threatening complication.

Treatment strategies include standard tube thoracostomy, image-guided percutaneous tube thoracostomy, open drainage, decortication, thoracoplasty, and muscle pedicle closure. However, these procedures often turn out to be unsatisfactory because of thoracic empyema, which hinders any surgical intervention. The development of flexible bronchoscopy has allowed us to close the fistula using tissue glues, fibrin glue, fibrin sealant, sclerosing agents, gelatin-sponge particles, lead plugs, balloons, coils, or autologous blood patches. However, these methods need particular materials. Therefore, we planned to develop a simplified method to treat BPF bronchoscopically.

We report the successful management of central BPF after pulmonary resection by the submucosal injection of absolute ethanol, which was applied directly to the fistula guided by flexible bronchoscopic observation. This procedure may reduce medical costs and the duration of hospitalization and may improve the patient’s quality of life. Bronchoscopic closure of BPF by injecting absolute ethanol, therefore, could be recommended as a first-line therapy for postoperative central BPF.

Materials and Methods

Patients

Five patients (two men and three women), with a mean age of 69 years (age range, 66 to 73 years), received diagnoses of central BPF after pneumonectomy (two patients) and lobectomy (three patients) of the right lung from 1988 to 1995 at Nikko Memorial Hospital (Table 1). BPFs developed within 1 week in two patients, 3 months in two patients, and 9 months in one patient after pulmonary surgery. The chief complaints at the onset were fever (three patients), bloody sputum (one patient), and air leakage (one patient).

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Bronchoscopy

Each patient received premedication with 0.5 mg atropine sulfate (Tanabe Pharmaceutical; Osaka, Japan) and 35 mg pethidine hydrochloride (Tanabe Pharmaceutical) IM, and the oropharynx was locally anesthetized by spraying with 10 mL 2% lidocaine hydrochloride (Xylocaine; Fujisawa Pharmaceutical; Osaka, Japan). An 8F endotracheal tube without a cuff (Portex; Kent, UK) was placed over a fiberoptic bronchoscope (2T20; Olympus; Tokyo, Japan), which then was inserted into the trachea in all patients. The endotracheal tube was kept in the trachea to allow easy insertion and extraction of a bronchofiberscope in spontaneously breathing patients so that we could easily repeat an injection of absolute ethanol and treat unexpected massive bleeding. All orifices of the BPFs could be visualized bronchoscopically.

The bronchoscopic treatment was repeated until the orifice of the BPF was closed. We expected that fibrin nets produced to repair the mucosa, which was damaged superficially by scratching, might result in a narrowing of the fistula. Therefore, the treatment procedure was initiated by scratching the intramural mucosa of the fistula using a brush or curette under bronchoscopic observation, after which 0.1-mL aliquots of absolute ethanol were injected into the mucosa around the fistula 6 to 41 times using an injection needle (NM-21 L; Olympus) through a fiberoptic bronchoscope. Ethanol overflowing the injected area was bronchoscopically aspirated. Ethanol injection was stopped when it was confirmed that the surrounding mucosa closed the orifice of the fistula. We checked the outcome of the treatment once every 2 weeks, even if the patient had no complaints, and performed the treatment again as soon as the patient had any subjective symptoms suggesting the existence of the fistula or if we found any orifices of the fistula still in place.

Table 1—Patients Characteristics and Outcomes*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, yr</td>
<td>73</td>
<td>67</td>
<td>68</td>
<td>73</td>
<td>66</td>
</tr>
<tr>
<td>Gender</td>
<td>Woman</td>
<td>Man</td>
<td>Woman</td>
<td>Woman</td>
<td>Man</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>Right middle and lower lobectomy</td>
<td>Right pneumonectomy</td>
<td>Right pneumonectomy</td>
<td>Right pneumonectomy</td>
<td>Right pneumonectomy</td>
</tr>
<tr>
<td>Time from surgery to onset</td>
<td>1 d</td>
<td>5 d</td>
<td>0 d</td>
<td>4 d</td>
<td>4 d</td>
</tr>
<tr>
<td>Initial symptom/sign</td>
<td>Fever</td>
<td>Fever</td>
<td>Fever</td>
<td>Fever</td>
<td>Fever</td>
</tr>
<tr>
<td>Initial bronchoscopy</td>
<td>Endobronchial injection</td>
<td>Endobronchial injection</td>
<td>Endobronchial injection</td>
<td>Endobronchial injection</td>
<td>Endobronchial injection</td>
</tr>
<tr>
<td>Frequency of 0.1 mL ETOH injection</td>
<td>Twice</td>
<td>Twice</td>
<td>Twice</td>
<td>Twice</td>
<td>Twice</td>
</tr>
<tr>
<td>Time from onset to cure</td>
<td>21 d</td>
<td>29 d</td>
<td>15 d</td>
<td>104 d</td>
<td>16 d</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Metastatic lung cancer (rectum)</td>
<td>Stomach cancer</td>
<td>Unknown</td>
<td>Interstitial pneumonia</td>
<td>Intestinal pneumonia</td>
</tr>
<tr>
<td>Tx/EOT = treatment; ETOH = ethanol; CT = chest radiograph; MRSA = methicillin-resistant Staphylococcus aureus.</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

CASE REPORTS

Each patient was treated one to four times until all orifices of the BPFs were closed. Characteristics for all patients treated by the bronchoscopic injection of absolute ethanol are summarized in Table 1.

Case 1

A 73-year-old woman complained of fever and air leakage through the intercostal drain on the day subsequent to middle and right lower lobe resection for single pulmonary metastasis of rectal cancer. As initial autologous blood and thrombin injection into the fistula was not effective, OK-432 (Picibanil; Chugai Pharmaceutical; Tokyo, Japan) was injected 2 weeks later, but the fistula was not obliterated. Therefore, 0.1-mL aliquots of absolute ethanol were bronchoscopically injected into 21 various points surrounding the small fistula of the bronchial stump. The patient was treated twice. The fistula was completely closed with scar formation, and the treated area was covered with scar tissue (Fig 1). Although an associated empyema was cured after the ethanol injection, the patient finally died 13 months later of metastases from recurrent rectal cancer.

Case 2

A 67-year-old man complained of fever, and BPF was diagnosed 9 months after pneumonectomy for squamous cell carcinoma of the lung. This patient was treated, from the beginning with absolute ethanol injections into 29 points surrounding the fistula after scratching of the inside wall, resulting in healing of the fistula. Bronchoscopic findings showed that scar tissue compressed the fistula to close it 1 month after the patient underwent the treatment (Fig 2). However, it took a further 14 months for...
Case 1
A 68-year-old woman complained of fever and received a diagnosis of methicillin-resistant Staphylococcus aureus empyema 2 months after right lower lobectomy for adenocarcinoma of the lung. Purulent fluid was observed to spring up from the pinhole fistula during expiration (Fig 3). Twenty-eight days later, 0.1-mL aliquots of absolute ethanol were injected into 21 points surrounding the small fistula of the bronchial stump. Both the fistula and the purulent fluid disappeared after the injections, and edematous bronchial mucosa was observed (Fig 3). The patient was treated for empyema with antibiotics 1 week later. The patient has been alive without recurrences of the fistula and tumor for about 6 years.

Case 3
A 68-year-old woman complained of bloody sputum after undergoing a right pneumonectomy for adenocarcinoma of the lung and received a diagnosis of BPF (Fig 4). The BPF was about 3 mm in diameter, and the intracavitary lumen was inspected using a bronchoscope (model 3C10; Olympus). The patient was bronchoscopically treated four times over 1.5 months. Absolute ethanol was injected into 12 to 41 points surrounding the fistula. A large amount of ethanol actually overflowed the injection points and was aspirated through the suction nozzle of a bronchoscope. The fistula had healed with a constrictive scar at the bronchial surface 84 days after the diagnosis (Fig 4). The patient died of interstitial pneumonia 9 months later.

Case 4
A 68-year-old woman complained of bloody sputum after undergoing a right pneumonectomy for adenocarcinoma of the lung and received a diagnosis of BPF (Fig 4). The BPF was about 3 mm in diameter, and the intracavitary lumen was inspected using a bronchoscope (model 3C10; Olympus). The patient was bronchoscopically treated four times over 1.5 months. Absolute ethanol was injected into 12 to 41 points surrounding the fistula. A large amount of ethanol actually overflowed the injection points and was aspirated through the suction nozzle of a bronchoscope. The fistula had healed with a constrictive scar at the bronchial surface 84 days after the diagnosis (Fig 4). The patient died of interstitial pneumonia 9 months later.

Case 5
A 66-year-old man complained of air leakage from the drain on several days after right upper lobectomy for small cell carcinoma of the lung and BPF was diagnosed. Although absolute ethanol was injected into 16 points outside and inside the orifice of the fistula, it remained patent by bronchoscopic observation (data not shown). As chest radiograph findings of BPF were not improved, another open lung surgical procedure was performed 6 days after the bronchoscopic treatment. No air leakage from the lesion was observed, and the fistula was closed. The patient is still alive and has had no clinical relapse of the fistula for 70 months.

Fistulas in five consecutive patients were successfully closed by injecting absolute ethanol using a bronchoscope, leading to the healing of pneumonia, empyema, or mediastinitis. The closure of each BPF was bronchoscopically confirmed without any complication. The mean survival time after cure was 43 months (range, 9 to 70 months). Four patients died of relapses of lung cancer, stomach cancer, interstitial pneumonia, or unknown cause. One patient treated 70 months ago is still alive.

**DISCUSSION**

Fibrin and its derivatives have been widely used to close BPFs. However, this report is the first to close fistulas by injecting absolute ethanol into the tissue.
surrounding the fistula. Local injection of absolute ethanol was initially used for bleeding in the gastrointestinal tract, which was followed by its use in extracting an intramural polypoid tumor protruding into the airway. These treatments were based on the findings of degeneration of cancer cells by the consolidation of tumor tissue. Absolute ethanol induces rapid dehydration and scar formation of the tissue. Ethanol injection quickly induced scar formation in a reproducible manner in our patients. This observation is coincident with those in other reports on the treatment of early gastric cancer, in which local edema, necrosis, and ulcer formation were observed soon after ethanol injection. Histopathologically, the proliferation of fibroblasts within 3 weeks and the complete reconstruction of the tissue by fibrous scarring have been reported. Ideally, ethanol should be injected into the area between the subcutaneous layer and the subjacent muscle layer, but this may be very difficult to accomplish. However, as it has been reported that the injection of 0.1 mL absolute ethanol did not cause a deep ulceration, we injected 0.1 mL absolute ethanol into the bronchial tissue to obtain similar results. Again, a rapid injection of absolute ethanol into tissue may cause tissue toxicity, leading to necrosis. Therefore, we injected ethanol slowly in small amounts. To prevent tissue necrosis, ethanol should not be concentrated in a small area.

The mechanical occlusion of swollen mucosa epithelium due to regional edema may initially close the orifice of the fistula. Tissue granulation generally covers the spongiosa in 2 to 3 weeks. The processes of healing in animal models after a similar procedure are as follows: increased redness, indicating an increase of tissue blood supply, occurs 3 days after ethanol injection, and, in addition, a disintegration of the fibrin and an increase in tissue granulation are present; and 2 months after ethanol injection, connective tissue and fibrin were completely covered over with epithelial tissue.

In our patients with BPFs having orifices of \( \leq 1 \) mm in diameter, the inner lumen of the fistula was initially narrowed by edema immediately after ethanol injection, and subsequently the fistula was covered with fibrous scarring. A fistula that is \( > 3 \) mm in diameter was often difficult to close because the patients would expectorate the fibrin plug. Absolute ethanol alone was not effective on occlusion of fistulas \( > 3 \) mm in diameter.

The American Society of Thoracic Surgeons has reported on 96 patients with BPFs after pneumonectomy. The successful closure of the fistulas was achieved by surgical intervention in 21 patients and bronchoscopically in 11 patients. However, the overall postoperative mortality rate was 31%, and those patients died of complications of BPFs, such as aspiration pneumonia and empyema with sepsis. Compared to the results of that report, our finding that all patients treated with absolute ethanol injection were cured without recurrence is meaningful.

Because bronchoscopic treatment requires only local and light anesthesia for the patient, it can avert risks associated with general anesthesia. In patients treated under local and light anesthesia, small amounts of overflowed ethanol induce coughing. No patients experienced either ethanol-induced pneumonia or a significant decrease in Pa\( \text{O}_2 \). Thus, bronchoscopic ethanol injection to close fistulas is safe and can be applied clinically in similar manner to other methods under local anesthesia. Absolute ethanol injection applied directly to the fistula through a flexible bronchoscope under direct observation is thought to be a safe and cost-effective method, even if the patient has a high risk of pulmonary or cardiovascular complications. Systemic effects of ethanol, such as acute intoxication and infection, may not be a consideration. From the viewpoint of cost-effectiveness, our nonsurgical treatment may be very useful in reducing the cost of and length of hospitalization, because this procedure does not use expensive medical materials, equipment, and personnel compared with surgical treatment. Although further studies, including case-controlled studies, may be necessary to substantiate the observations in these cases, we would recommend this treatment as a first-line therapy for postoperative central BPFs with small orifices \( < 3 \) mm in diameter.

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Severe Erythroderma as a Complication of Continuous Epoprostenol Therapy*

Gregory S. Ahearn, MD; M. Angelica Selim, MD; and Victor F. Tapson, MD, FCCP

Epoprostenol is a vasodilator that is produced by vascular endothelial cells and is currently the “gold standard” therapy for patients with severe primary pulmonary hypertension or pulmonary hypertension secondary to collagen vascular disease. Hypersensitivitvity to the drug has not been reported. We report a case of a patient with pulmonary hypertension and undifferentiated connective tissue disease who, after 2 months of treatment with epoprostenol, presented with rapidly progressive erythema, scaling, nausea and vomiting, and fever. Test results from a skin biopsy specimen were consistent with a drug reaction. The patient’s condition improved after rapid tapering of her epoprostenol and administration of corticosteroids. Epoprostenol may be associated rarely with severe erythroderma.

(CHEST 2002; 122:378–380)

Key words: allergic reaction; connective tissue disease; drug reaction; epoprostenol; erythroderma; pulmonary hypertension; skin biopsy

A llergic drug reactions occur most commonly with the administration of sulfonamides, anticonvulsants, allopurinol, and nonsteroidal anti-inflammatory drugs, but may occur following the administration of almost any drug. Dermatologic manifestations are a continuum ranging from diffuse erythema to fulminant toxic epidermal necrolysis. Such reactions occur in all human populations and all age ranges. Continuous IV epoprostenol is the drug of choice for severe primary pulmonary hypertension or pulmonary arterial hypertension due to the scleroderma spectrum of diseases.1,2 Patients receiving epoprostenol therapy often develop mild-to-moderate erythema. We present the first reported case of severe erythroderma associated with the initiation of therapy with this drug, a previously unreported complication.

CASE REPORT

A 56-year-old white woman presented to her local medical doctor with increasing dyspnea over several months, which was associated with occasional substernal chest pain and a nonproductive cough. Her medical history was significant for undifferentiated connective tissue disease, gastroesophageal reflux disease, and morbid obesity. Her evaluation was consistent with pulmonary arterial hypertension secondary to undifferentiated connective tissue disease. She underwent cardiac catheterization, which revealed a right atrial pressure of 13 mm Hg, a right ventricular pressure of 80/8 mm Hg, a pulmonary artery pressure of 90/40 mm Hg, and a pulmonary capillary wedge pressure of 14 mm Hg. The cardiac output was 5.1 L/min with a cardiac index of 2.5 L/min/m². The pulmonary vascular resistance was 6.32 Wood units.

She was referred to Duke University Medical Center for further evaluation and treatment of primary pulmonary hypertension. Because of the severity of her symptoms, she was admitted to the hospital and was started on a regimen of IV epoprostenol therapy. Her dyspnea and chest pain improved, and she was asymptomatic. However, after 2 months of treatment, she developed severe erythroderma associated with a drug reaction. The patient’s condition improved after rapid tapering of her epoprostenol and administration of corticosteroids. Epoprostenol may be associated rarely with severe erythroderma.

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