No recurrence of mediastinal abscess or new infiltrate was noted, and the patient’s symptoms responded rapidly to antibiotic therapy. She returned to work and was counseled that she would most likely continue to expectorate broncholiths, but that, once she was treated adequately with antibiotics, episodes of recurrent infection would be unlikely.

**Discussion**

Broncholithiasis, manifested as the “spitting of stones,” is a rare disorder that has been recognized for centuries based on the writings of Aretaeus, Galen, and Aristotle. The natural history of this disease remains poorly defined, however, and the clinical presentation is variable and often nonspecific. The incidence of either fever or purulent sputum suggestive of respiratory infection is estimated to be between 11% and 61%, based on previously reported case series.1,2,7,9,10 The most common infectious complication resulting from broncholithiasis appears to be bacterial pneumonitis due to airway obstruction by a broncholith and the associated airway inflammation and edema. Lung abscesses and bronchoesophageal fistulas are potentially more serious complications of symptomatic broncholithiasis and are responsible for cases of prolonged or recurrent infection. In our case, the patient appears to have developed an abscess due to retrograde movement of the *H influenzae* organisms from the bronchi into the mediastinum, presumably during the passage of a broncholith. There was no evidence based on history, radiographic studies, or bronchoscopy to suggest fistula formation. Our review of the medical literature did not reveal any previously reported cases of mediastinal abscess formation associated with the passage of a broncholith.

Bacterial mediastinal abscesses most frequently occur secondary to surgical procedures, including median sternotomy for cardiac surgery, mediastinoscopy, and mediastinoscopy. Esophageal perforation and leakage secondary to these procedures, surgery, and spontaneous causes, as well as the extension of oral and cervical infections are other important causes of bacterial mediastinitis. A smaller proportion of mediastinal infections is caused by the extension of subdiaphragmatic infections, pneumonia, lung abscesses, and pleural empyema.11

Two possible reasons that mediastinal abscess has not been previously reported as a complication of broncholithiasis may include a low incidence and a lack of clinical recognition of this complication. First, while the extrusion of broncholiths may not be uncommon in the setting of mediastinal calcifications, the generally sterile environment of the tracheobronchial tree is not predisposed to bacterial seeding of the mediastinum before the airway mucosal injury has healed. Second, broncholithiasis may go unrecognized in cases of mediastinal abscess because the most common symptoms, which include cough, hemoptysis, and chest pain, are nonspecific and a history of lithoptysis is uncommon. A history of lithoptysis was noted in 3 to 16% of cases in which broncholithiasis was documented at bronchoscopy or surgery in previous series.1,2,7,9,10

Our patient’s history of spontaneously resolving and then recurring asthma provided another potential clue, in retrospect, to the diagnosis of broncholithiasis. Her symptoms of cough, wheezing, and purulent sputum, in the absence of lithoptysis, initially suggested the more common clinical problem of asthma. Her lack of response to standard asthma medications and the intermittent nature of her asthma symptoms, however, as well the complete absence of symptoms for a period of years, is not typical for asthma and is quite consistent with symptomatic broncholithiasis. Groves and Effler1 specifically mentioned the occurrence of symptoms of an “asthmatic nature” in their series of 27 patients with broncholithiasis as a justification for the selected bronchoscopic evaluation of some patients with chronic, nonsurgical pulmonary disease.

From a therapeutic standpoint for our patient, who continues to intermittently experience lithoptysis, there are no data to support further surgery. Should she develop complications such as recurrent mediastinal abscess, localized bronchiectasis, or fistulas, this recommendation may change, but there is no evidence to suggest a benefit from the removal of calcified lymph nodes at the present time.

**References**

8 Davis EW, Katz S. Broncholithiasis: a neglected cause of bronchoesophageal fistula. JAMA 1956; 150:555–557
9 Schmidt HW, Clagett OT, McDonald JR. Broncholithiasis. Thorac Cardiovasc Surg 1950; 19:226–245
11 Heitmiller RF, Yang SC. Thoracic Emergencies In: Eisele DW, McQuone SJ, ed. Emergencies of the head and neck. St. Louis, MO: Mosby, 2000; 301–316

**Hereditary Pulmonary Emphysema**

László Bense, MD, PhD; Gunnar Ekblin, PhD; Odont D, He; and Rolf Lewander, MD, PhD

To further elucidate the etiology of spontaneous pneumothorax (SP), a study was made of three non-smoking patients who had experienced several episodes of chest radiograph-verified familial SP (FSP) and 11 unaffected relatives, 5 of whom were smokers.
and 6 of whom were never-smokers. Fourteen healthy subjects without SP served as a control group. All three groups underwent the same clinical, laboratory, and radiologic examinations, including CT scans of the lungs, with the aim of detecting any changes in the pulmonary parenchyma. Emphysema-like changes (ELCs) were detected on CT scans in each of the three patients with FSP. The unaffected relatives of the FSP patients showed no sign of FSP, but four of the six never-smokers and three of the five relatives who were smokers displayed pulmonary emphysema and ELCs on CT scans. No abnormalities were seen on pulmonary CT scans of the 14 control subjects. The present results indicate that ELCs and pulmonary emphysema may be genetically determined.

Key words: familial spontaneous pneumothorax; hereditary pulmonary emphysema

Abbreviations: AAT = α1-antitrypsin; ELC = emphysema-like change; FSP = familial spontaneous pneumothorax; SP = spontaneous pneumothorax

The condition in which air is present in the intrapleural cavity without a known cause is called spontaneous pneumothorax (SP). The occurrence of familial SP (FSP) was first reported by Faber1 in 1921. Family studies2–13 have been published since that time on a number of cases of FSP. Information on smoking habits in these reports is sparse. The FSP cases reported in the literature and those included in the present study provide evidence that at least some of the SP cases are genetically determined. An autosomal-dominant trait has been suggested as an explanation for FSP.2,7,9

Attention has been paid to the human leukocyte antigen region on chromosome 6.10 From their study, Sharpe et al10 concluded that SP may be linked to the human leukocyte antigen genes, a possibility supported by Sugiyama et al.12

A number of extrinsic factors (ie, smoking) and intrinsic factors are involved in the pathogenetic mechanism of this disease. Among the intrinsic factors that were previously observed, bilateral bronchial anomalies of a type causing obstruction seem to be a prerequisite for the occurrence of SP in never-smokers.13 This view is compatible with and supports the role of heredity in patients with FSP.

In smokers, the rupture of the alveolar wall into cavities of the pulmonary tissue is referred to as pulmonary emphysema, and in those who have never smoked, it is referred to as emphysema-like changes (ELCs).15,16 ELCs have been observed in nonsmoking SP patients.15,16

The overall purpose of the present article is to determine whether ELCs are considerably more common in FSP-free relatives in a family (with as many as three verified FSP cases) than among SP-free control subjects with similar smoking habits and sex and age distributions.

The study was approved by the Ethics Boards of University Hospitals, Akademiska in Uppsala, Sweden, and the Karolinska Institute in Stockholm, Sweden. Each subject gave his or her written consent prior to participation.

Materials and Methods

Family Cases

The study initially consisted of three members of a family, two women and one man, who had experienced FSP even though they had never smoked (Fig 1). One of the female patients had had at least 20 episodes of FSP on the left side and 8 on the right side. The other female FSP patient had had four episodes of FSP on the left side. The female FSP patients had been operated on because of frequent recurrences of FSP. None of the female FSP patients had catamenial SP. The male FSP patient had had one episode of FSP on the right side that had been treated with Bülau drainage (ie, a seal under water).

Eleven unaffected family members, five smokers and six who had never smoked, also were included in the study. The FSP patients and the majority of their relatives complained of an occasional cough but were free of malignant, inflammatory, and cardiopulmonary disease. Echocardiography was carried out 10 weeks after this study in one of the unaffected female relatives who had never smoked. Regurgitation was observed at the valva tricuspidalis, with a systolic flow (measured by Doppler echocardiography) of 2.5 m/s. That implied an approximate systolic pressure of 30 mm Hg in the pulmonary artery.

Dropouts

Four members of the family who were unaffected by FSP were unable to participate in the study. One man had cerebral paresis, and three women lived too far away to attend the examinations.

Control Subjects

The control group consisted of 10 healthy subjects, who had been described previously,15,16 and four smokers (three women and one man) who had respiratory symptoms of COPD. The latter four subjects were included in order to match the smokers among the unaffected relatives.

Methods

All patients, relatives, and control subjects underwent chest radiographs and CT scans of the lungs. In the three FSP patients,
CT scans were performed at least 3 years after the latest FSP episode. Chest radiographs were requirements for subsequent CT scans.

CT scans of the lungs were performed with a helical apparatus (GE High Speed Helical CT; General Electric; Paris, France) with the subject in the supine position. The subject was instructed to hold his or her breath after an ordinary expiration during an exposure time of 5 s. Body mode with 5-mm-thick CT sections, pitch 2, and 5-mm intervals were used for the whole lung. Two window settings, with optimal representation of the lung parenchyma and emphysema, were used in all examinations. The images were examined by an experienced radiologist, who was not aware of whether the image belonged to a patient or a control subject.

The CT scan examination was focused on the detection of the main variable, that is, the existence of any cavities in the pulmonary parenchyma, which were expressed as an estimated percentage of the volume of the right or left lung. They were defined on CT scans as lesions with a diameter of at least 3 mm and with an attenuation value of gas, surrounded by pulmonary parenchyma and with no contact with the airway wall.

Cavities detected in the pulmonary tissue in smokers were referred to as pulmonary emphysema. Corresponding cavities in those patients and subjects who had never smoked were referred to as ELCs, because they were not induced by known emphysema-promoting factors such as smoking or α₁-antitrypsin (AAT) deficiency. The percentage of distributions of any observed ELC or pulmonary emphysema within the apical, middle, and basal regions of the lung was recorded separately.

Laboratory Study

The concentrations of AAT, haptoglobin, and orosomucoid in the serum were measured by standard methods in all subjects.

Statistical Analysis

In the analysis of significance, Fisher’s Exact Test was used.

Results

Laboratory Findings

The serum haptoglobin, orosomucoid, and AAT concentrations were checked in the patients 3 years after the last episode of FSP. The serum haptoglobin and orosomucoid levels were normal in each individual of the studied groups. The serum AAT concentration was within the reference range (reference range, 1.0 to 1.7 g/L) in each person, except a smoker relative whose AAT concentration was 2.0 g/L.

Chest Radiograph

The posteroanterior and lateral chest radiographs revealed nothing pathologic in the pulmonary tissue or in the pleura in the patients, the relatives, or the control subjects. The pulmonary emphysema or ELCs observed on CT scans could not be discerned on chest radiographs.

CT Scans

ELCs were detected on CT scans in each of the three FSP-affected patients (100%), which is in accordance with our previous findings in other patients.15,16 The 11 relatives of the three FSP patients showed no clinical or radiologic signs of FSP. Four of the six relatives who never smoked (66%) and three of the five relatives who smoked (60%) showed ELCs and pulmonary emphysema, respectively (see Fig 1).

Thus, 7 of the 11 relatives who had no subjective, clinical, or radiologic signs of FSP had pulmonary emphysema and ELCs, whereas no ELC or pulmonary emphysema was found in the control subjects (p < 0.001 [one-sided Fisher’s Exact Test]; see Table 1).

Discussion

Relationship of smoking and age to pulmonary emphysema is known.17 The recent detection18 of pulmonary emphysema by CT scanning in 44% of healthy smokers who are approximately 60 years old suggests that emphysema may not be caused only by smoking. Our CT scan study15 of SP patients who had never smoked showed ELCs. To our knowledge, there has been no previous investigation of the pulmonary tissue to determine the occurrence of ELCs and emphysema in unaffected relatives of patients who had never smoked but who had FSP.

The present study was designed with the principal aim of detecting ELCs and pulmonary emphysema in FSP patients who had never smoked and, in particular, in their relatives whether or not they had ever smoked. The relatives were compared with matching nonrelated healthy control subjects, both smokers and never-smokers, with respect to the presence and intrapulmonary location of the ELCs and pulmonary emphysema.

ELCs were found in the three FSP patients, which is in conformity with our previous findings in SP patients.15 We did not expect to find ELCs in the four relatives of the six who had never smoked and who also were free even from symptoms of FSP, a finding that suggests a hereditary factor. The third and the seventh families in the third generation, and their children, strongly support the hypothesis of hereditary emphysema, because emphysema occurred in the third generation and, subsequently, in the fourth generation despite the fact that none of those relatives smoked or were affected by AAT deficiency.

Pulmonary emphysema was found in three of the five smokers among the relatives. The nonrelated control subjects who smoked displayed no pulmonary emphysema despite their smoke exposure, which exceeded that of the

<table>
<thead>
<tr>
<th>Emphysema/ELC</th>
<th>Relatives to FSP Cases</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Present</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

*The three FSP patients were excluded from the analysis. p < 0.001 (one-sided Fisher’s Exact Test).
smoker relatives by 72% (measured Brinkman index, 252 vs 146, respectively).

The present study indicates that ELCs and pulmonary emphysema may be genetically determined. Further studies are required to confirm the results of our investigation in the studied family.

ACKNOWLEDGMENT: We thank each member of the family anonymously, according to their wish.

REFERENCES
1 Faber EE. Spontaneous pneumothorax hos 2 soskende in 2 siblings. Hospital Stidende 1921; 64:573–574