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Fluid-containing emphysematous bullae: a spectrum of illness

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ABSTRACT: Fluid-containing emphysematous bullae are an under-reported complication of chronic obstructive pulmonary disease. The roles of bronchoscopy in the work-up and of antibiotics in the treatment are undefined.

This study reports the combined results from the analysis of 16 cases treated at the present authors' institution and 36 previously reported cases.

The median age at presentation was 58 yrs and the median duration of follow-up was 60 weeks. A third of the patients were asymptomatic, while two-thirds presented with symptoms, including 10% who had evidence of a severe lung infection. Methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacteroides melaninogenicus* were cultured from the bullae fluid in three symptomatic patients. Sputum and blood cultures were uninformative. Bronchoscopy, performed in two-thirds of the cases, added no diagnostic information. Antibiotic treatment did not result in a more rapid resolution of the air fluid level. Percutaneous drainage was safe and effective in four patients.

In conclusion, patients with fluid-containing bullae present with a spectrum of illness. Antibiotic treatment does not hasten radiographic resolution and bronchoscopy has no diagnostic or therapeutic role.

KEYWORDS: Chronic obstructive pulmonary disease, emphysema, fluid-containing emphysematous bulla, infected emphysematous bulla, lung bulla

Fluid-containing emphysematous bullae are an unusual complication of chronic obstructive pulmonary disease (COPD). As patients with COPD can develop a variety of cavitary lung lesions, identifying the correct diagnosis can be challenging [1–3]. The diagnosis of fluid-containing emphysematous bulla can only be made with certainty if there is interval development of a fluid level in a pre-existing emphysematous bulla [4, 5]. Only a few of the small number of studies available have utilised this unequivocal criterion to establish the diagnosis in their patients [5–9]. The role of bronchoscopy in the work-up and of antibiotics and percutaneous drainage in treatment remains undefined. The present study reports the combined results from 16 cases of fluid-containing emphysematous bullae treated at the authors' institution and 36 previously reported cases.

MATERIALS AND METHODS

Identification of new cases

Due to the low incidence of fluid-containing emphysematous bullae a retrospective study design was chosen. As there is no International Classification of Diseases code for this diagnosis [10], a computerised search strategy was used to locate cases. Using the computerised medical records of the Michael E. DeBakey VA Medical Center (Houston, TX, USA), a search was carried out for radiology reports and discharge summaries containing the words ''fluid level'', ''infected'', ''bulla'' and ''cyst'' in varying combinations. In total, 353 documents were located dating from May 1991 to January 2007. These were then screened manually to select cases where there was unequivocal evidence of interval development of an air-fluid level in a pre-existing emphysematous bulla. Thus, 18 cases were selected; two cases could not be included because essential parts of the medical record were not available. All patients had an extensive smoking history with clinical and spirometric evidence of obstructive airway disease.

Identification of prior studies

Using MEDLINE, all studies from 1966 to February 2007 were searched. Due to the lack of a medical subject heading for emphysematous bullae, a text search for ''bulla'', ''emphysema'', ''cyst'', ''fluid'' and ''infection'' in varying combinations was carried out. The reference lists of all identified manuscripts were also searched. In total, seven case series were found [3, 5–9, 11]; case reports containing individual cases were not

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included. The case series were reviewed by one of the authors (D. Chandra) to identify those where the fluid was noted to have developed in pre-existing emphysematous bullae. Four studies were selected adding a further 36 cases, which led to a final sample size of 52 cases [5–8].

Data on 34 variables was extracted from each of the 16 medical records and the four published articles. All statistical tests used were conventional. The study protocol, which included waiver of patient consent, was approved by the Institutional Review Board at Baylor College of Medicine (Houston).

RESULTS

Table 1 describes the demographics, clinical features at presentation and findings on initial work-up. Table 2 provides information on treatment and follow-up. Pulmonary examination did not reveal findings beyond those expected in patients with advanced COPD. Sputum cultures grew a variety of organisms generally implicated in respiratory infections in COPD patients; however, none could be confirmed as causative because bulla fluid culture results were not available in those patients, and blood cultures were uniformly negative.

Microbiology of infected bullae

Culture results from bullae fluid were available in four patients. The first patient was a 58-yr-old male with severe COPD (forced expiratory volume in one second 18% predicted), who was receiving oral clarithromycin and ethambutol for treatment of pulmonary *Mycobacterium avium-intracellulare* infection detected 6 months previously. The patient presented to the Michael E. DeBakey VA Medical Center (Houston) in 1996 with a 3-week history of fever and cough productive of green sputum. On admission the patient was breathing comfortably on room air, had a temperature of 36.9 °C, a white blood cell (WBC) count of 17,000 cells·mm^{-3} and a chest radiograph which showed interval development of an air-fluid level in a right upper lobe bulla. Percutaneous needle aspiration was performed 5 days after admission without placement of an indwelling catheter. Fluid cultures yielded *Pseudomonas aeruginosa*. The resolution of symptoms and disappearance of the air-fluid level was associated with 14 days of treatment with ceftazidime and gentamicin.

The second patient, a 57-yr-old male who presented in 2005, underwent drainage with an indwelling catheter with therapeutic intent on admission as he was extremely ill (temperature of 38.9 °C and WBC count of 34,700 cells·mm^{-3}). On entering the cavity, 500 mL of pus was aspirated and cultures grew Methicillin-resistant *Staphylococcus aureus*. There was dramatic improvement in symptoms after drainage. Further details of the patient's clinical course have been published previously [4].

The third and fourth patients have been reported previously by PETERS *et al.* [7]. One patient recovered uneventfully after drainage of the fluid containing bulla. Cultures grew *Bacteroides melaninogenicus*. However, culture results where negative for the fourth patient who had received empiric antibiotic treatment for 6 days prior to aspiration. Further details of the clinical presentation of these two patients have been published previously [7].

Work-up, treatment and follow-up

Bronchoscopy was performed in two-thirds of the patients but the results were noncontributory. As in the sputum cultures, bronchial washing yielded organisms that could not be confirmed as causative by bullae fluid cultures or blood cultures. Cytology for malignant cells was uniformly negative. Agents from almost every antibiotic class available were used

TABLE 1 Study characteristics of patients with fluid-containing emphysematous bullae

Subjects	52
Age yrs	58 (51–67.5)
Male	98.1
Aspiration risk present[#]	37.1
Subjective fever	32.1
Cough	56.6
Purulent sputum	41.5
Chest pain	
Pleuritic	26.5
Nonpleuritic	10.2
Respiratory rate breaths·min^{-1}[¶]	20 (18–24)
Temperature °C[+]	37.0 (36.9–38.0)
WBC count cells·mm^{-3}[§]	9.65 (7.2–14.67)
Positive blood cultures[f]	0
Positive sputum AFB cultures[f]	0
Positive sputum cultures	26.4
Lobe involved	
Right upper	41.5
Left upper	22.7
Upper lobe	11.3
Right lower	11.3
Left lower	9.5
Right middle	3.8
Adjoining infiltrate present	43.4

Data are presented as n, median (interquartile range) or per cent. WBC: white blood cell; AFB: acid fact bacilli. [#]: available for 42 patients; [¶]: available for 15 patients; [+]: available for 39 patients; [§]: available for 28 patients; [f]: performed in 17 patients.

TABLE 2 Bronchoscopy, treatment and follow-up for 52 patients with fluid-containing emphysematous bullae

Antibiotic prescribed	80.4
Percutaneous aspiration performed[#]	7.5
Bronchoscopy performed	66.0
Time to radiographic resolution of fluid level days	74 (20.7–142.5)
Reduction or complete scarring of affected bulla by end of follow-up[¶]	21.3
Duration of follow-up days	412 (47–720)

Data are presented as per cent or median (interquartile range). [#]: an indwelling catheter was left in place in half of the patients who underwent aspiration; [¶]: available for 47 patients.

for treatment. Antibiotic use was not associated with time to resolution of the air-fluid level in patients with ($p=0.81$) or without symptoms ($p=0.52$).

DISCUSSION

The pathogenesis of fluid accumulation in emphysematous bullae is controversial. The benign nature of this illness in most patients led MAHLER and co-workers [6, 12] to propose that the fluid was sterile and developed as a reaction to inflammation in the surrounding lung. This was clearly not the case in at least three out of the four patients who underwent bullae aspiration in the present study. However, all these patients had symptoms of a lung infection. The current authors believe that the hypothesis of MAHLER and co-workers [6, 12] may only hold true for patients who are asymptomatic, although it will remain unproven until bulla fluid from such patients is aspirated and analysed. In the absence of published data on the portal of entry of bacteria into the bulla, it can be speculated that the infection arises from the surrounding lung parenchyma or *via* haematogenous spread.

Patients with fluid-containing emphysematous bullae present with a spectrum of illness varying from an absence of symptoms to the presence of symptoms and a severe lung infection (*i.e.* temperature $\geqslant 38.3$ °C or WBC count $\geqslant 15{,}000$ cells·mm^{-3}). A majority of patients, however, are symptomatic without a severe infection. The presence of this spectrum of illness has not been described previously. Contrary to prior reports [5], no correlation was found between the presence of symptoms of an infection and the presence of an infiltrate in the parenchyma surrounding the bulla ($p=0.528$).

Some authors have recommended bronchoscopy to rule out an occult malignancy or mycobacterial infection masquerading as fluid-containing bullae [6, 7]. The results from the present study strongly argue against this recommendation.

Radiological evidence of the existence of a bulla prior to the accumulation of fluid is a *sine qua non* for the diagnosis of fluid-containing bulla [4, 6]. Its presence greatly simplifies the management of the COPD patient who presents with a new air-fluid level on a chest radiograph. When prior radiology studies are not available, the presence of other bullae in a patient with established obstructive airway disease, a thin-walled cavity and disproportionately less symptoms than the chest radiograph would all raise suspicion for this diagnosis [6, 7].

Medical management of fluid-containing bullae has been controversial because it is unclear if an antibiotic should be given, and, if so, which agent should be chosen [5–7]. The absence of an association between antibiotic treatment and time to resolution of the fluid level leaves little justification for routine antibiotic use in asymptomatic patients. The efficacy of antibiotics is harder to judge in symptomatic patients in the current study because no data was available on time to resolution of symptoms or fever, which are more meaningful markers of recovery than resolution of the air-fluid level. Confusion regarding the antibiotic of choice stems from uncertainty about the microbiological aetiology of these infections [5–7]. The only conclusion that can be drawn from the present microbiological results is that causative organisms can vary widely and if a rapid clinical response with empiric antibiotics does not occur then obtaining bulla fluid cultures may be prudent.

Percutaneous drainage of fluid-containing lung bullae has previously been strongly discouraged [5–7]. The four patients who underwent this procedure all experienced rapid improvement in symptoms without procedural complications.

The current study is limited by its retrospective design. Wide variation in management probably existed between treating physicians. However, given the very low incidence of the condition, this was the only type of study design feasible. Although the strict inclusion criteria resulted in a smaller sample size, it was felt that the inclusion criteria were necessary to ensure the quality of the data.

In conclusion, patients with fluid-containing bullae can present with a severe lung infection. Data on causative organisms is limited, and includes a wide spectrum of bacteria. Based on this limited evidence, the present authors suggest that management decisions be tailored to the acuity of presentation. For asymptomatic patients antibiotic treatment does not appear beneficial. Symptomatic patients may benefit from antibiotic treatment, while those with severe symptoms, high-grade temperature ($\geqslant 38.3$ °C) and leukocytosis may benefit from additional percutaneous drainage. Bronchoscopy should not be performed unless there is clear indication of an underlying malignancy, such as a mass adjoining the affected bulla.

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