Clinical problems in cardiopulmonary disease

Clinical Conference on Management Dilemmas
An Expanding Right Upper Lobe Cavity*

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Pulmonary clinicians often are faced with management problems for which there are no answers at hand, either because there is no literature which definitely gives answers or because the circumstances surrounding the clinical cases are unusual enough to prevent the application of existing scientific knowledge. When faced with these problems, clinicians are forced to make decisions based on a logical extension of their scientific knowledge into uncharted clinical waters. They are forced to make judgments based on the conviction of their speculations and the prior experiences of others and of themselves.

This case conference addresses difficult management problems without singularly correct decisions; its object is not necessarily to seek consensus. Defining the exact issues, formulating rationales for decision-making, and committing to the decisions themselves are all equally important in this presentation. This is a real case in which the decisions were made by the "Treating Pulmonologist" without input from the other participants. The "Responses of Pulmonary Experts" are given only with the knowledge of the case presentation up to the moment at which each expert gives his or her decision and without the knowledge of any of the other opinions rendered. The last "Commentary" is given only with the knowledge of the full case presentation and the "Follow-up by the Treating Pulmonologist" but without the knowledge of any of the other opinions rendered. The "Commentary" is the last opinion in the sequence of this presentation, but it is not necessarily offered as the definitive solution to the problems posed in the case. The reader is the ultimate arbiter in this presentation of decision-making alternatives.

Case Presentation

A 67-year-old white woman, who never smoked presented with tuberculosis in the late 1940s and was treated with bed rest. Several years later, the tuberculosis reactivated, and she was treated with therapeutic pneumothorax and pneumoperitoneum. She was treated for "recurrence" of tuberculosis in 1960 with isoniazid, streptomycin, and p-aminosalicylic acid and again for "recurrence" in 1981 with rifampin, ethambutol hydrochloride, and other drugs. Her medical history disclosed that she had chronic rhinitis, sinusitis, a left nephrectomy for recurrent nephrolithiasis, asthma, and allergies to penicillin and sulfa drugs.

The patient was followed up in a clinic for asthma and sinusitis, and although she was intermittently compliant, several courses of oral tetracycline, beclomethasone nasal spray, nasal decongestants, and analgesics were prescribed without benefit. She lost 16 pounds over a 3-year period. In July 1993, she expectorated one half cup

Figure 1. Chest x-ray film in July 1993, revealing bilateral apical pleural thickening, much greater on the right; thickening and calcification of the entire pleura on the left; bilateral interstitial scarring; cavitization atelectasis and marked scarring of the upper lobe of right lung; and a healed left rib fracture.
of "fresh" blood followed by blood mixed with green sputum. She also complained of right-sided ear and facial pain, nasal congestion, postnasal drip, and right-sided rib discomfort. She weighed 90 pounds. A chest x-ray film showed bilateral apical pleural thickening, much greater on the right, thickening and calcification of the entire pleura on the left, bilateral interstitial scarring, cicatriziation atelectasis and marked scarring of the right upper lobe, and a healed left rib fracture (Fig 1). She was admitted to the hospital and treated with oral clindamycin and azithromycin. Her sputum gradually decreased in volume and color, and hemoptysis resolved although she continued to produce small amounts of clear sputum. Bronchoscopic examination and biopsy revealed bronchiectasis and chronic inflammation but no evidence of tuberculosis or cancer. Bronchoscopic washings were negative for routine bacteria, acid-fast bacilli, and malignant cells but were positive for *Aspergillus fumigatus*.

The patient was maintained on a regimen of rotating oral antibiotics but experienced abdominal discomfort and diarrhea which made her less willing to take medication. A sputum culture grew *Pseudomonas aeruginosa*, and she was given oral ciprofloxacin, but the response was poor and prompted two more admissions to the hospital for intravenous antibiotics. The patient insisted she had sinusitis, since right ear and facial pain persisted along with a sensation that her green sputum was really postnasal drip. Physical examination of the ear, nose, and throat was within normal limits, and a CT scan of the sinuses was normal.

In April 1994, she developed mild digital clubbing. A chest x-ray film showed a nodular density with surrounding air in the right upper lobe, while a CT scan of the chest revealed a 6-cm, thick-walled cavity in the right upper lobe and a patch of right lower lobe pneumonia (Fig 2). Sputum cultures grew Aspergillus, and serum tests were positive for Aspergillus precipitins. Sputum was negative for malignant cells. Pulmonary function test results are shown in Table 1.

The patient was treated with oral itraconazole, 400 mg bid, which did not result in clinical improvement and which she discontinued because of abdominal discomfort, bloating, and diarrhea. She continued to do poorly with persistent weight loss, increasing sputum production, intermittent dyspnea, disturbed sleep, and worsening ear and facial pain despite trials of several different antibiotics including cefuroxime, clarithromycin, and ciprofloxacin. In September 1994, she also developed a low-grade fever. She then weighed 38 kg (85 lbs). Staining of the sputum with Gram's stain showed Gram-negative rods, and culture again grew Aspergillus. Sputum smears and cultures were negative for acid-fast bacilli. Cytologic study of the sputum was negative for malignant cells. A chest x-ray film and CT scan revealed that the right upper lobe cavity was now 8 cm with a polypoid lesion adherent to the cavity's inner surface via a stalk (Fig 3). She was given a 1-week course of intravenous ciprofloxacin, and her fever disappeared but the other symptoms

**Table 1—Patient’s Flow-Volume Loop in April 1994**

<table>
<thead>
<tr>
<th>Pulmonary Function Test</th>
<th>Measured</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>1.30 L</td>
<td>45</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.10 L</td>
<td>48</td>
</tr>
<tr>
<td>FEF₂⁵−₇⁵%*</td>
<td>1.04 L</td>
<td>43</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>84.71%</td>
<td>113</td>
</tr>
</tbody>
</table>

* Forced expiratory flow, mid-expiratory phase.
persisted. The drug regimen was changed to oral ciprofloxacin, but her symptoms began to worsen after 2 months of therapy. Finally in November 1994, her cough and sputum production were continuous so that she could not sleep. She was producing several cups of green sputum daily and could not get out of bed because of extreme lassitude, weakness, and dyspnea. She agreed to be admitted again to the hospital.

She was a thin, mildly dyspneic, and elderly white woman with uninterrupted coughing and green sputum production. She weighed 37 kg (83 lbs) and stood 5 feet 4 inches tall. The blood pressure was 130/60 mm Hg; heart rate, 92 beats per minute; respiratory rate, 20 breaths per minute; temperature, 37°C; and O₂ saturation while breathing room air, 98%. Her nasal mucosa was inflamed with mild right maxillary sinus tenderness. A lung examination showed she had diffuse bilateral rhonchi and wheezes. Heart and abdominal examinations were within normal limits. Her digits were mildly clubbed. A chest x-ray film (Fig 4) showed that the right upper lobe cavity had increased another 1 cm in diameter.

**Figure 3.** In September 1994: Left: chest x-ray film demonstrating that the upper lobe cavity of the right lung was then 8 cm. Right: chest CT scan revealing a polypoid lesion adherent to the cavity’s inner surface via a stalk.

**Figure 4.** Chest x-ray film in November 1994, demonstrating a 1-cm increase in the size of the upper lobe cavity of the right lung.

**Responses of Pulmonary Experts:**
Robert M. Smith, MD, San Diego, Calif

We are in the difficult position of recommending therapeutic options, none very palatable, for this woman. It is likely she has an aspergilloma in a prior tuberculous cavity, possibly subsequent to colonization of an intracavitary thrombus during the previous bout of hemothysis. It is prudent, however, to entertain other diagnoses before proceeding. The persistent sinus and nasal symptoms might suggest concurrent Wegener’s granulomatosis. This seems unlikely, but another CT scan of the sinuses and measurement of antineutrophil cytoplasmic antibodies with a cytoplasmic pattern (cANCA) level are warranted. Similarly, another bronchoscopy for other infectious agents is prudent. A mycetoma may be fixed to the wall but is typically mobile in the cavity. Malignancy is a distant possibility given the polypoid nature of the intracavitary lesion. In the final analysis, however, I think that other diagnoses are unlikely.

Systemic antifungal therapy for intracavitary mycetoma may suppress symptoms but barely provides a durable remission.¹ Intracavitary instillation of amphotericin B has been advocated, particularly with the associated symptom of hemothysis.² However, this technique has never been directly compared with other approaches, and overall experience is extremely limited. At least two instances of life-threatening hemothysis have been associated with catheter placement.²,³ a complication which is not surprising in view of the hypervascularity of the cavity wall. The possibility of nephrotoxicity associated with topical amphotericin B is difficult to estimate but is an additional concern in this patient with one kidney.

Despite her marginal pulmonary function test results, I believe surgical resection of the involved region of the lung may be the best option for this woman.
Although it is a procedure associated with high operative mortality and a difficult postoperative course, resection of this nonfunctioning lung is unlikely to worsen lung function. In a series of 44 patients who had surgical operations for parenchymal aspergilloma (including some with function comparable to our patient), Massard et al reported a 9% operative mortality. Mortality may be greater for those with more severely compromised function, and, therefore, the patient and the consulting surgeon must play an active role in any decision-making process. Measurement of arterial blood gas levels, regional pulmonary function, and pulmonary arterial pressures will help provide a more accurate assessment of operative risk and condition the decision-making process. Preoperative angiography with embolization of the vessels feeding the cavity may reduce intraoperative hemorrhage.

Stephen K. Field, MD, Calgary, Alberta, Canada

I think the diagnosis is aspergilloma forming in an area of tuberculous scarring and bronchiectasis. Finger clubbing, asthma, and sinusitis could be explained by allergic aspergillitis complicating aspergilloma.

An aspergilloma can develop in a cavitating bronchogenic carcinoma or area of active tuberculosis. The absence of mycobacteria and malignant cells in both sputum samples and bronchial washings over a period of 14 months in a patient with an enlarging cavity make tuberculosis and cancer unlikely.

I doubt further invasive investigations such as subsequent bronchoscopy or percutaneous needle aspiration will be helpful, and they pose some risk. Aspergillus was cultured repeatedly and tests for precipitins were positive. However, mucus plugs were not noted, and spirometry demonstrated restriction rather than obstruction. A trial of steroids might help her asthma and sinusitis if allergic aspergillitis were responsible.

Despite numerous antibiotic trials, the patient continued to deteriorate and the cavity continued to enlarge. Therefore, I would favor treating her aspergilloma. Traditionally, pulmonary resection is the favored treatment, but I would favor trials of conservative therapy since her clinical condition and lung function are poor.

An earlier trial of itraconazole caused gastrointestinal upset, but I would favor trying it again since it is the easiest treatment option. Intravenous amphotericin B often is not effective for aspergillomas, and nephrotoxicity would be a concern in a patient with one kidney but would be helpful if invasive aspergillitis were present.

Although data are scant, intracavitary amphotericin B has been reported to be effective in aspergilloma and would be my next option if itraconazole and intravenous amphotericin B were not tolerated or were unsuccessful. I would include acetylcysteine to expedite lysis of the aspergilloma and aminocaproic acid to reduce bleeding with intracavitary amphotericin B.

Surgery would be my last option. Limited thoracoplasty without lung resection might be an option. If surgery were contemplated, a vigorous trial of steroids and hyperalimentation should be undertaken preoperatively to insure that her nutritional status and lung function are optimal.

Follow-up by the Treating Pulmonary Consultant:
Jeff Schnader, MD, Manhasset, NY

My clinical impression of the patient was that she was dying of progressive cachexia from a relentless lung infection with copious suppuration. She was exhausted yet could not sleep because of unremitting cough and continuous expectoration of sputum. I was alarmed by the progressive increase in the size of her cavity which I feared represented irreversible destruction of what was left of her lung parenchyma. I resolved that something definitive had to be done or the patient would die.

I made several conclusions at this point in the case. First, I was satisfied that the patient’s central problem was semi-invasive aspergilliosis causing necrosis of right upper lobe lung tissue with resultant cavity formation and expansion. A mycetoma was also seen within the cavity as part of this process. Preexisting damage of the lung parenchyma, usually from prior sarcoidosis, radiation cicatization, or tuberculosis (as in this case), and usually in the upper lobes, seems to be the required substrate for aspergilliosis in the semi-invasive and mycetoma forms. One might speculate that an abnormality in the underlying tissue cripples the ability of the immune system to eliminate the fungus. Numerous sputum samples confirmed the presence of Aspergillus in this case, and a lack of response to antibacterial therapy supported aspergilliosis as the patient’s central disease process. There was no evidence of active tuberculosis or cancer. Interestingly, carcinoma would have been a good explanation for the cavity expansion and intractable inflammation had Aspergillus not been present. Finally, it appeared likely that there was a superimposed bacterial infection, probably from Pseudomonas which grew from her sputum, exacerbating the Aspergillus-induced suppuration.

There were several treatment options which I considered. Oral therapy with itraconazole is an alternative to intravenous therapy with amphotericin B although it is still somewhat controversial. However, because itraconazole had been tried and had failed in the current patient, I decided this drug would not yield the definitive result that I was seeking. Another option was intravenous amphotericin B in either the conventional or liposomal form. But results with this drug have been unrewarding, and its nephrotoxic side effects...
were of concern in the current patient who had only one kidney.

Although surgery (lobectomy) might have resulted in a definitive therapeutic result, I rejected this option for three reasons. First, although lung resection would not necessarily prevent recurrence of aspergillosis, it presented a significant risk of making the patient a respiratory cripple in view of her poor lung function (FEV$_1$=1.10 L). Second, the patient was cachectic and appeared too sick to withstand surgery. Finally, because the anatomy of her lung was deformed and because the lung was plastered up against the inner surface of the chest cavity by a pleural peel, the surgery would be prolonged and carry high risks for excessive bleeding, bronchopleural fistula, Aspergillus empyema, pneumonia, and lung laceration. In a recent series, 44 patients who underwent surgery suffered 72 major complications with a mortality of 9.5%.4

One last option was direct instillation of amphotericin B into the right upper lobe cavity. Munk et al reported resolution of aspergillomas in three patients after single intracavitary injections of 15 mg of amphotericin B reconstituted in gelatin. Giron et al injected 50 mg of amphotericin B reconstituted in glycerin into the cavities of 15 patients every 1 to 3 weeks in conjunction with bronchial artery embolization and noted disappearance of aspergillomas in 8 patients. Others have given daily injections of amphotericin B via an indwelling percutaneous catheter inserted directly into the cavity, generally up to 50 mg daily,2,13,14 with good results. Catheter placement should be low risk when the lung is tacked up to the pleura with a thick pleural peel which would prevent collapse, as in this case. Injection of material via a bronchoscope did not appeal to me because I was uncertain that the drug would actually get into the cavity and because of the risks and cumbersome nature of the procedure. Using percutaneous catheter placement into the cavity, I speculated there would be direct delivery of the drug to the fungus with high intracavitary, but low extracavitary amphotericin B levels. But although one might speculate about good fungicidal activity and less systemic toxicity, there is a potential for both major and minor side effects.2,3,11,12,14

I admitted the patient to the hospital in November 1994 and prescribed a continuation of a regimen which included inhaled steroids for bronchospasm and oral ciprofloxacin for possible superimposed bacterial infection. Under fluoroscopy, a 10F pigtail catheter was placed into the cavity percutaneously. Lavage of the cavity with saline solution was cytologically negative for malignant cells, and bacterial cultures were positive for Aspergillus but there was no bacterial growth.

On the day after catheter placement, a 5-mg test dose of amphotericin B in 20 mL of sterile water was instilled through the catheter. The patient was repositioned every 15 minutes, assuming the right lateral decubitus, supine, left lateral decubitus, prone, and upright positions. In the left lateral decubitus and supine positions, she coughed violently and expectorated the drug, so these positions were eliminated. Thereafter, she was given 50 mg of amphotericin B in water daily and tolerated it well.

Over a period of 20 days, she received 1 g of intracavitary amphotericin B, and the dyspnea and sleeplessness disappeared. Her cough had almost disappeared with only clear, scant sputum, and her ear and facial pain had diminished. Her lungs were clear on examination. However, appearance of the cavity on a CT scan and chest x-ray film did not change (although the right lower lobe pneumonia had disappeared), and culture of material from the cavity remained positive, but with less heavy growth of Aspergillus. A decision to remove the catheter was made by a covering physician, and the patient was discharged in December 1994, on a regimen of oral ciprofloxacin, 250 mg bid; itraconazole, 100 mg qd; and a steroid inhaler.

Two weeks after discharge, she felt well, was active, had gained 1.8 kg (4 lbs), and had only a mild cough with scant clear sputum. By 6 weeks after discharge, she had gained 4 kg (9 lbs), and weighed 42 kg (92 lbs), and felt well. But after 2 months, in February 1995, she again had increasing sputum production, hemoptysis, malaise, dyspnea, and weight loss. I readmitted the patient, had a catheter placed in the right upper lobe cavity, lavaged and suctioned the cavity, and began another course of intracavitary amphotericin B at 50 mg qd. The patient did well with eventual resolution of all symptoms. After the first 4 weeks of therapy, she was discharged home and came to my office daily, Monday through Friday, for her intracavitary infusions. She received an additional 2.1 g of amphotericin B during this second course for a total of 3.1 g. A chest x-ray film revealed that the cavity had decreased in size by 1 cm. Sequential cultures of sputum and cavity lavage fluid yielded progressively diminishing amounts of Aspergillus growth until smears showed no organisms, and there was no growth on the cultures. I felt that the lack of growth was an appropriate therapeutic endpoint, and therefore, in April, I pulled out the catheter.

At one point, during treatment as an outpatient, and after her cavity was lavaged with a turbid return, the patient began having myalgia and chills for an hour’s duration about 4 h after each drug infusion. I reduced the dose to 30 mg daily after this, with significant reduction but not elimination of symptoms. Serum potassium and creatinine values remained normal and unchanged throughout therapy. Blood levels of amphotericin B were undetectable (<0.1 mg/mL). As of mid May 1995, she is asymptomatic except for postnasal drip. She weighs 44 kg (97 lbs), which represents
a total gain of 6.4 kg (14 lbs).

Commentary:
Steven M. Albeda, MD, Philadelphia

The treatment of patients with symptomatic pulmonary aspergillomas remains a vexing problem for pulmonary physicians and thoracic surgeons. To date, no clear guidelines for treatment exist. Because the disease is relatively uncommon, no one physician or center has seen enough cases to conduct careful scientific studies, and, to my knowledge, no multicenter trials are underway. Decision-making must thus be based on information derived from small patient series, case reports, and "armchair pathophysiology."

The "epidemiology" of patients with aspergillomas has changed in the United States over the past 25 years. Unlike many of the earlier series in which most patients developed fungus balls within previously "empty" upper lobe cavities (often the result of old tuberculosis), most cases seen now are in patients with other types of underlying lung disease. The other important factor to consider is that many of the cases that we label as "aspergillomas" are, in fact, not due to colonization of previous lung cavities but the result of years of slowly progressive "semi-invasive" or "chronic-necrotizing" Aspergillus infection. The case described herein likely falls into this category because of the clearcut radiographic progression of the lesion over time.

Patients with aspergillomas tend to present with two types of clinical problems. One major concern is hemoptysis. Although chronic, blood-tinged sputum is common in these patients, they occasionally have bouts of massive and, at times, life-threatening hemoptysis. The second symptom complex is due to chronic pulmonary infection and is characterized by low-grade fever, weight loss, cough, and sputum production. Often, patients have both hemoptysis and systemic symptoms, as did this patient.

Treatment options are limited. In the rare patient who can tolerate surgery and who has localized disease, surgery is the treatment of choice. Unfortunately, the patient described in this report is typical in that her severe underlying lung disease and cachexia precluded surgery. In my opinion, the decision to avoid surgery was a good one. Removal of aspergillomas in such patients carries an extremely high mortality and morbidity rate and is commonly accompanied by air leak, empyema, and ventilatory failure. Realistic therapeutic options were thus limited to medical treatment with antifungal agents. Although amphotericin B is the standard treatment for fungal disease, it has been demonstrated that systemic therapy for "traditional" aspergillomas is not effective. The utility of intravenous amphotericin B in semi-invasive Aspergillus infection is still uncertain although it has been reported to have efficacy. I agree with Dr. Schnader that, in this case, a course of high-dose amphotericin B would probably be associated with high morbidity. The use of itraconazole is an intriguing new option to consider although there are very few data to show its efficacy. I agree with a therapeutic trial as was attempted in this patient.

The use of intracavitary antifungal agents for aspergillomas has a long history, although no large groups of patients have been systematically studied. Our group has used intracavitary amphotericin B primarily to treat those patients with aspergillomas who have active hemoptysis. In our original series of six treatments, and in our subsequent experience with approximately 15 patients (unpublished data: 1988-1995; Steven M. Albeda, MD), treatment has almost uniformly been associated with the cessation of bleeding. One patient suffered a major complication—an episode of massive hemoptysis during catheter placement. Of note is that, with rare exception, we have not seen evidence of radiographic regression of the aspergilloma. Based on these results and the successful experience of investigators like Hargis et al, other groups have begun to use intracavitary amphotericin B to treat the systemic symptoms of aspergilloma. Two recent articles highlight the success of this approach. Consistent with these reports, the use of intracavitary amphotericin B proved remarkably successful in terms of both symptomatic improvement and in inducing frank radiographic improvement in the patient described herein.

What can we learn from Dr. Schnader's approach? I think that this case suggests that intracavitary amphotericin B can be an effective therapy in selected patients with semi-invasive Aspergillus infection and systemic symptoms. This case along with others in the literature also indicates that, when performed by skilled physicians, this treatment modality appears to be quite safe and is associated with minimal side effects. Since other treatments carry such high risk-benefit ratios, it is my opinion that more widespread use of this technique should be used, with surgery and prescription of IV amphotericin B held as last-resort treatments.

Follow-up Addendum:
Jeff Schnader, MD, Manhasset, NY

The patient reached a maximum weight of 44.5 kg (98 lbs) and was stable for 4 more months. Sputum cultures were and continue to be repeatedly negative for any fungal growth. However, in September, 1995, the patient began to lose weight and have a moderate increase in sputum which grew Pseudomonas aeruginosa, resistant to ciprofloxacin. In October, 1995, she was admitted to the hospital for antibiotic therapy weighing 38.6 kg (85 lbs). A right upper lobe catheter was once again placed, and tobramycin was administered into the cavity. As of December, 1995, the patient
continued on intracavitary tobramycin and felt much better with less sputum production. She was refusing surgery.

REFERENCES