Case Conference on Management Dilemmas*

Progressive Pneumonia in a Patient Receiving Long-term Steroid Therapy

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Abbreviations: INH = isoniazid; PZA = pyrazinamide; VATS = video-assisted thoracoscopic surgery

Pulmonary clinicians are often faced with management problems for which there are no answers at hand, either because there is no literature that 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 74-year-old white man was admitted to the hospital in January with a 2-day history of pleuritic chest pain and a 2-week history of a painful, swollen, erythematous right lower extremity. He had smoked 150 pack-years. 16 months prior to hospital admission, he was begun on a regimen of steroids for “COPD,” which was then tapered to 5 mg/d and which he took until his current admission. Although there was a remote history of tuberculosis, he denied recent exposure. He denied weight loss but complained of sweats, day and night. On examination, his temperature was 38.2°C; heart rate was 60 beats/min; BP was 90/60 mm Hg; weight was 67.5 kg. He was wheezing mildly. The right leg was red, tender, and heavily edematous; the thigh girths were 61 cm on the right and 56 cm on the left. There was no lymphadenopathy or hepatosplenomegaly. WBC count was 7,400/mm³. The chest radiograph revealed multilobar infiltrates, especially in the right upper lobe (Fig 1). Impedance plethysmography of the lower extremities revealed a thrombus in the right thigh, and the patient was begun on a regimen of steroids for “COPD,” which was then tapered to 5 mg/d and which he took until his current admission. Although there was a remote history of tuberculosis, he denied recent exposure. He denied weight loss but complained of sweats, day and night. On examination, his temperature was 38.2°C; heart rate was 60 beats/min; BP was 90/60 mm Hg; weight was 67.5 kg. He was wheezing mildly. The right leg was red, tender, and heavily edematous; the thigh girths were 61 cm on the right and 56 cm on the left. There was no lymphadenopathy or hepatosplenomegaly. WBC count was 7,400/mm³. The chest radiograph revealed multilobar infiltrates, especially in the right upper lobe (Fig 1). Impedance plethysmography of the lower extremities revealed a thrombus in the right thigh, and the patient was begun on a regimen of heparin IV and then warfarin (Coumadin) shortly thereafter. A ventilation/perfusion scan was “normal.” The patient was placed on a regimen of cefazolin and changed to cefuroxime and erythromycin for suspected cellulitis and pneumonia. Treatment with...
prednisone, 5 mg/d, was continued, and bronchodilator therapy was begun. On day 4 of hospitalization, he had cough, white sputum, and temperature of 38.8°C. WBC count was 7,000/mm³. Chest radiograph appeared unchanged. Sputum cultures grew *Serratia marcescens* sensitive to cotrimoxazole, and the antibiotics were changed to cotrimoxazole.

On the seventh hospital day, the patient was seen by the treating pulmonologists. Further history revealed that he had tuberculosis 34 years prior to hospital admission when, he recalled, he was treated with “a shot and a pill.” After further reflection, he believed that he received IM streptomycin and that he took a pill for 7 months for the tuberculosis. There was no history of exposure to pets, bats, caves, chickens, ongoing construction, or soil in occupations of digging, excavating, or farming. He was empirically begun on a regimen of isoniazid (INH), rifampin, ethambutol, and pyrazinamide (PZA). Baseline liver functions revealed the following: aspartate transaminase, 35 U/L (normal, 14 to 50); alanine transaminase, 29 U/L (21 to 72); alkaline phosphatase, 104 U/L (43 to 122); total bilirubin, 0.6 mg/dL; and γ-glutamyl transferase, 92 U/L (8 to 78). Chest radiograph was repeated and showed mild progression of the right upper lobe infiltrate. A purified protein derivative and anergy panel were nonreactive. Three initial sputa were smear negative for acid-fast bacilli and fungi. Because the patient was receiving both warfarin and heparin with slow recovery of his prothrombin time and partial thromboplastin time after their temporary discontinuation, and because he had unexpected episodes of dizziness with chills, bronchoscopy was delayed, but finally performed on hospital day 20. In the microbiology laboratory, the BAL was negative upon staining for acid-fast bacilli and fungi. Transbronchial biopsy specimen was cultured for acid-fast bacilli and fungi, but biopsy specimens sent to the pathology laboratory did not survive processing and were reported as insufficient for evaluation. As a result, no histopathologic findings were reported.

Over the next 10 days, the patient continued taking anticoagulants and INH, rifampin, ethambutol, and PZA. Although he appeared cachectic, he was improving clinically with a voracious appetite, diminished cough, and disappearance of sputum. Chest examination still revealed bibasilar rales, but his leg swelling and tenderness were gone. There was a bout of bloody diarrhea with hypotension for which the cause was not clearly identified, but he recovered rapidly back to his prebleed baseline and was restarted on a regimen of anticoagulants.

On day 34 of hospitalization, the BAL, bronchial washings, and transbronchial biopsy specimens (obtained on day 20) were reported growing *Histoplasma capsulatum* (Fig 2); mycobacteria were not yet growing on culture. Histoplasma complement fixation titers and immunodiffusion for H and M bands were ordered. Further discussion with the patient revealed that he had recently been living at his daughter’s farmhouse where blackbirds and pigeons roosted in the surrounding trees, and that he had cleaned out the leaves from the farmhouse gutters in the autumn just 3 months before. He was begun on a regimen of amphotericin B IV, 0.7 mg/kg/d.

Over the next week, there was a subtle general worsening of...
the patient’s clinical state. His weight was now 56.7 kg, a 10.8-kg loss since hospital admission. He was again mildly dyspneic, his cough was worse with recurrence of yellow sputum, and he began complaining of pleuritic chest pain again. There was no wheezing, and the rales were unchanged. He was still receiving anticoagulant medication. Chest radiograph revealed a new, large right pleural effusion with progression of the right lung infiltrates and some progression of the densities in the left lung (Fig 3). Liver function tests revealed the following: aspartate transaminase, 103 U/L (normal, 14 to 50); alanine transaminase, 96 U/L (21 to 72); alkaline phosphatase, 186 U/L (43 to 122); total bilirubin, 1.6 mg/dL; and γ-glutamyl transferase, 348 U/L (8 to 78). Sputum examination was smear negative for pathogens.

RESPONSES OF THE PULMONARY EXPERTS

Dr. Robert P. Baughman, Cincinnati, OH

This patient has developed two pulmonary problems that may be related. The first is the progressive right upper lobe infiltrate with associated left upper lobe disease. The second is a new right pleural effusion that occurred during his hospitalization. In addition to these pulmonary problems, he has an acute deep venous thrombosis. At the time of presentation, his lung scan was interpreted as normal and we do not have any further information. He could have the additional problem of a pulmonary embolism.

The one thing we know for sure about this patient is that he has histoplasmosis. The identification of histoplasmosis in his bronchoscopy sample is one of the ways to confirm infection. The fact that his sputum was negative for fungus is not surprising, since histoplasmosis is far less likely to be cultured in the sputum, even in patients with cavitary disease. The chest radiographic pattern is consistent with chronic cavitary histoplasmosis. The progression of infiltrate over a 4-month period would suggest increased disease activity, perhaps due to recurrent exposure. The patient recently moved to his daughter’s farmhouse, where he is described as performing clean-up chores. Cleaning up from blackbirds, pigeons, and other fowl has been associated with acute disease or worsening underlying disease. Another contributing agent could be the corticosteroids that would have suppressed his cellular immune response. Since cellular immunity is how histoplasmosis is contained, corticosteroids could have worsened his disease.

Why did the patient’s condition get worse within a week of starting amphotericin B therapy, including the development of a pleural effusion? The patient may not have received sufficient drug to affect the fungus. Amphotericin B has a dose-dependent effect for the treatment of chronic cavitary histoplasmosis. In addition, not all patients respond. In one series, 8 of 11 patients treated with amphotericin were cured, which is still better than the 6 of 9 untreated patients who died. Although the azoles, such as ketoconazole, itraconazole, or fluconazole have all been shown to be useful in some patients with histoplasmosis, they are less effective. Thus, the effusion could be due to histoplasmosis, although it has rarely been reported.

Obviously, the patient could have an additional problem. One consideration is a pulmonary embolism, due to his deep venous thrombosis. Anticoagulation should have controlled the problem but it is not always successful. Another possibility is malignancy, although the effusion seems to have come on fairly quickly. The next step would be to perform a diagnostic thoracentesis. Further treatment would depend on the results of that test. If fungus or empyema was identified, then drainage would probably be necessary. If the thoracentesis findings were nondiagnostic, then further testing to look for pulmonary embolism would be warranted. A repeat ventilation perfusion scan may demonstrate a new defect. If this is equivocal, a pulmonary angiogram or a dedicated, spiral CT study would be helpful.

COMMENTS BY THE TREATING PULMONOLOGISTS

Dr. Jeff Schnader and Dr. Elsira Pina, Dayton, OH

We were satisfied that the patient had histoplasmosis. His exposure to blackbirds and their feces...
mixed in gutter detritus seemed too remote to lead to an acute histoplasma pneumonia that should have had an incubation of only 1 to 3 weeks. However, blackbird roosts in particular are known to be associated with histoplasma exposure in humans, so this exposure is attractive as the point source of chronic histoplasmosis in our patient to which chronic steroid use probably contributed. Steroids are known to depress the cell-mediated immune response and lymphocyte function, and it is the lymphocyte that appears central to host defenses against histoplasma infection. This patient was anergic, deficient in this response. Four months prior to hospitalization, his chest radiograph (Fig 1) showed changes consistent with histoplasma exposure or infection, possibly supporting progressive disease during steroid treatment as the cause in his case. Although possible, there was no evidence of other organ involvement to indicate disseminated histoplasmosis.

We were concerned that whatever immunosuppression had resulted from steroids to predispose this patient to histoplasmosis could also predispose him to reactivate old tuberculosis at the same time. His history of prior antitubercular therapy was unclear, and prior antitubercular therapy may not have been adequate. At the time that the diagnosis of histoplasmosis had been made, the patient had progressed to the point of being at risk of death should proper treatment have been mistakenly withheld. He looked terrible clinically, and we were uncomfortable waiting while he might pass the point of being well enough to undergo an intervention. Therefore, for antitubercular therapy to be discontinued, we wanted better evidence that there was no concomitant tubercular infection. Along these lines, the transbronchial biopsy specimen was never evaluated histopathologically, and we believed that a tissue diagnosis was needed. One could argue that this should have been done earlier, but the patient’s condition seemed to improve initially with antitubercular therapy, and his anticoagulation, which was associated with the rockier moments in his hospital course, posed a logistical barrier to procedures. We concluded that only one procedure, without need for a repeat procedure or repeated discontinuations of anticoagulation, should be performed and that it should accomplish several goals: it should provide adequate pleural and lung tissue for pathologic examination, it should drain all of the patient’s pleural fluid that was likely responsible for some of the patient’s new symptoms, and it should be of low morbidity. A limited thoracic procedure, eg, thoracoscopy, seemed a logical choice and was recommended. Although the biopsy tissue turned out to be nondiagnostic, it unquestionably revealed disease of the lung and pleura, apparently in an early phase of healing. Thus, the lack of tubercular organisms in the tissue seemed enough evidence against tuberculosis to stop antitubercular treatment.

Hospital Course

The patient was continued on a regimen of INH, rifampin, ethambutol, and PZA, and the cardiothoracic surgery department was consulted. Because the patient had intermittent episodes of chest pain, a dipyridamole thallium stress test was performed and was normal. After he had received 14 days of amphotericin IV (590 mg total dose), his creatinine concentration rose from 1.1 to 2.3 mg/dL. Amphotericin therapy was held for 4 days with improvement in the serum creatinine value from 2.3 to 1.6 mg/dL. CT scan of the chest is shown in Figure 4. Video-assisted thoracoscopy with pleural biopsy, lung biopsy, and total pleural fluid drainage was finally performed. Special stains of the pleural and lung biopsy specimens revealed no acid-fast bacilli, no evidence of granulomas, no evidence of fungal forms, and no malignancy. Extensive, active fibrosis with chronic inflammation of the lung and pleura was evident. All specimens from the initial bronchoscopy were (and continued to remain) culture negative for mycobacteria. Treatment with all antituberculous medications was thus discontinued. Histoplasma complement fixation titers were positive at 1:64; immunodiffusion for both H and M bands was positive. Amphotericin therapy was discontinued in view of the renal dysfunction and lack of significant tissue load of histoplasmosis. The patient was begun on a regimen of oral itraconazole, alternate therapy for non-life-threatening chronic and disseminated histoplasmosis. Its advantages include less toxicity than amphotericin, eg, lack of renal toxicity and less hepatic toxicity. A corticotropin stimulation test revealed no adrenal insufficiency, and the patient’s prednisone dosage was tapered. The corticotropin test is of interest because of the patient’s prior steroid use and because in a series of proven disseminated histoplasmosis, 82% of patients had adrenal involvement and 7% had overt adrenal insufficiency. Postoperatively, the patient continued to have an air leak from the right chest tube so that pleurodesis with doxycycline was performed, and the air leak resolved. The patient’s condition continued to improve with normalization of liver functions. On postoperative day 14, the patient was discharged home on a regimen of warfarin and itraconazole. Chest radiographs at time of hospital discharge and 10 weeks later showed progressive healing of the lungs (Fig 5), and after 6 months he was still doing well.
Commentary

Dr. Jeffrey Glassroth, Philadelphia, PA

This patient presented his physicians with a number of difficult clinical questions. First, and perhaps most important, what was the nature (ie, diagnosis) of the pulmonary process? A related question, given the protracted course, was whether there was only a single process to explain all the clinical findings? What was the relation, if any, to the patient’s long-term steroid treatment? Finally, one might ask in retrospect, could a diagnosis have been made sooner or more simply than it was?

There appears little doubt that the patient had histoplasmosis, probably of the progressive pulmonary variety. The isolation of the fungus from multiple pulmonary specimens and the report of relatively high titer complement fixing antibodies and a positive (and highly specific) immunodiffusion test with both H and M bands present provide conclusive evidence for that diagnosis. Although these serologic tests were obtained about 3 weeks into his illness and hospitalization, positive serologic tests often do not become positive before 1 or 2 months after infection.17 Indeed, even then, 30 to 50% of patients will not seroconvert. This patient’s multiple positive serologic tests would be compatible with acquisition of infection several months earlier, perhaps at the time of his residence at his daughter’s farmhouse. Indeed, the baseline chest radiograph (Fig 1A, left) shows right apical infiltration of the type occasionally seen in persons with underlying emphysema who develop progressive primary histoplasmosis.

Does histoplasmosis explain all of the clinical manifestations of this patient’s illness? This question is more problematic. Although the patient had a history of prior inadequately treated tuberculosis, was anergic, and initially had chest radiographic changes compatible with tuberculosis, the negative acid-fast bacilli tests of sputum and bronchoscopy specimens would be unlikely in progressive, cavitary pulmonary tuberculosis. Likewise, his lack of response to a four-drug antituberculosis regimen is further evidence against that diagnosis. Although he had documented deep venous thrombosis, the initial apical localization of his pulmonary infiltrates and later the large and progressive right pleural effusion argue against pulmonary embolic disease as an explanation for the illness. The presence of bibasilar crackles and later an isolated right pleural effusion should have raised the possibility of congestive heart failure. However, his loss of weight and pleuritic chest pain, lack of an S3 gallop, and other radiographic findings are against this diagnosis. While a number of other causes of multifocal pulmonary infiltrates (eg, recurrent aspiration pneumonia, vasculitis, bronchiolitis obliterans with organized pneumonia, etc) might be raised, none really fit the available clinical information well.

Did this patient require all the invasive studies that were performed? Certainly the bronchoscopy was needed. Although patients with progressive pulmonary histoplasmosis may produce sputum positive for the fungus, shedding of the fungus is a very intermittent phenomenon; numerous (ie, five, six, or more) sputum specimens may be needed to obtain a positive culture. The small size of this fungus and its frequent intracellular localization make positive smear results even less frequent.18 In retrospect,
However, the thoracoscopic biopsy added little to the patient’s management, and I do not believe it should have been pursued. The patient had received only about 1 week of treatment for histoplasmosis at the time of the procedure and probably needed additional time to respond. Having reasonably excluded other conditions, and with firm support for a diagnosis of histoplasmosis, one might have argued for a longer period of observation.

Finally, what role, if any, did long-term, low-dose steroid therapy play in this patient’s illness? Certainly, the pattern of disease is consistent with histoplasmosis as it occurs in immunocompetent hosts. There was no evidence of extrapulmonary disease, other than perhaps pleural reaction, that could clearly be attributed to the fungus. Although the patient was anergic, this might be explained by the fact that he was chronically ill. The limited information available correlating tuberculosis skin test reactivity with steroid use suggests that doses of prednisone <15 mg/d (or equivalent other preparations) are not generally associated with anergy. However, skin test reactivity and protective immunity are not necessarily correlated. Ultimately, the relation of prednisone to this patient’s illness is unknowable given the current state of knowledge on this subject.

**Comment by Thoracic Surgeon (Not Involved in This Patient’s Care)**

*Dr. Samuel Adebonojo, Dayton, OH*

This patient presented with a diagnostic dilemma that required prompt clinical diagnosis for appropriate therapy. The chest radiograph (Fig 1) obtained 4 months prior to hospital admission showed right apical infiltrate and fibrosis probably from old pulmonary tuberculosis. Although the culture from the transbronchial biopsy specimen showed microconidia and mycelial forms of histoplasmosis, initially the patient did not respond to antifungal therapy, thus raising the possibility of reactivation of pulmonary tuberculosis. The development of significant pleural effusion further heightened the need to obtain adequate specimens from the lung and pleura as well as drainage of the pleural effusion for definitive diagnosis.

The diagnosis of most pulmonary parenchymal diseases in immunocompromised patients can be made on findings from BAL, transbronchial biopsy, and transthoracic needle aspiration, or on clinical response to empiric therapy. But when all these fail to provide a conclusive diagnosis and clinical improvement, then other invasive methods of obtaining a diagnosis are indicated. Video-assisted thoracoscopic surgery (VATS) is therefore a logical choice under these circumstances.

However, one may argue that VATS, in this particular patient, is relatively contraindicated because of apical scarring and pleural synphysis from old pulmonary tuberculosis and the ongoing pleuritis from histoplasmosis. Besides, there are no specific pulmonary nodules that could be targets for wedge biopsy. As many thoracic surgeons have discovered, dissection around the apex of the lung in patients with pulmonary tuberculosis is fraught with the danger of exsanguinating hemorrhage from the subclavian vein, often with fatal outcome. Since biopsy

**Figure 5.** Left: Chest radiograph taken 25 days after hospital discharge. Right: Chest radiograph taken 3 months after hospital discharge.
from this apical portion of the lung would require extensive dissection, there are possibilities of significant bleeding, especially in a patient receiving oral anticoagulants for thrombophlebitis.

The presence of active histoplasmosis also raises the question of whether VATS is the best approach in this patient because of possible fibrosing mediastinitis, a known complication of histoplasma infection, and apical fibrosis from old tuberculosis. I am therefore not surprised that VATS was not diagnostic in this patient as the surgeon was probably unwilling to risk the potential complication of hemorrhage by attempting to free the lung from the right apex. I would have preferred a limited axillary incisional approach to accomplish the same goals with biopsy specimens of the lung in three places: right upper, middle, and lower lobes. This approach gives better control over necessary lysis of pleural adhesions with less morbidity of air leak. It also allows the use of a single-lumen endotracheal tube instead of the double-lumen tube needed during anesthesia for VATS. However, VATS was helpful in achieving two goals, ie, drainage of the pleural effusion and biopsy specimens of pleura and lung, albeit without adding much to the information already known. It must be emphasized that an appreciation for the indications, limitations, and potential complications of VATS in the diagnosis and management of pulmonary disease will help in the proper selection of patients and satisfactory outcome.

Prolonged air leak is not an uncommon complication after VATS lung biopsy. It occurs in 5 to 15% of cases, especially in immunocompromised patients and patients receiving steroid therapy. Usually, most air leaks will stop within 3 to 7 days, but when air leak persists >7 days, chemical pleurodesis or talc slurry rectifies this problem in >95% of cases. ACKNOWLEDGMENT: We would like to thank Dr. Robert M. Smith for reviewing this manuscript.

REFERENCES