aggregation manifesting as smoke-like echoes in the left atrium and thrombus formation. In support of this hypothesis is the fact that smoke-like echoes in the left ventricle have also been reported to be associated with thrombi in patients with severely depressed left ventricular contraction secondary to myocardial infarction. Mikell and co-workers reported that in an experimental study of left ventricular thrombi, a soft amorphous mass called the "tail of thrombus" was demonstrated adjacent to the hard core of thrombus. Histologic examination showed that this "tail of thrombus" was a fresh clot consisting of red blood cells and may represent the intermediate stage between red blood cell aggregation and thrombus formation, however, not all reports of smoke-like echoes in the left atrium have been noted to be associated with thrombi. Garcia-Fernandez et al reported four cases of long-standing rheumatic mitral valve disease with left atrial smoke-like echoes, one of which underwent mitral valve surgery. In none of their patients was thrombus detected during two-dimensional echocardiographic examination or at operation.

Recently, Daniel and co-workers compared the conventional transthoracic and transesophageal techniques in the echocardiographic detection of smoke-like echoes in the left atrium in 38 patients with mitral stenosis and 31 patients after mitral valve replacement. Smoke-like echoes were not seen in any patient using transthoracic echocardiography but could be clearly identified by transesophageal echocardiography in 42 patients. Fourteen of these 42 patients had a history of arterial embolism, and six had left atrial thrombi proven by surgery or echocardiography (or both); however, of the 27 patients without smoke-like echoes only one had arterial embolism, and none had thrombus in the left atrium. It is clear from this study that transesophageal echocardiography is much more sensitive than transthoracic echocardiography for detecting smoke-like echoes.

The reports of Behn upon and co-workers, together with our experience, seem to suggest that there is indeed a close association between left atrial smoke-like echoes and thrombus formation. The study of Daniel and co-workers also indicates that arterial embolism is more frequent in such patients. They have suggested that anticoagulants should be given to prevent these complications; however, it is interesting to note that none of our five patients had a history of thromboembolism, although only one patient was receiving anticoagulant therapy.

REFERENCES

Chronic Cavitary Histoplasmosis

Failure of Oral Treatment with Ketoconazole

Carlos A. Quinones, M.D.; Allen G. Reuben, M.D.;
Richard J. Haniff, M.D.; Daniel M. Mushir, M.D.;
Arnold B. Corin, M.D.; and George A. Sarosi, M.D., F.C.C.P.

Ketoconazole appears to be a safe drug in the treatment of chronic cavitary histoplasmosis. Primary failure and relapse have been described, requiring amphotericin B, even after long therapy with ketoconazole. Four typical cases are presented. We caution about such potential failures and stress the importance of close observation of patients begun on therapy with ketoconazole for chronic cavitary histoplasmosis. (Chest 1989; 95:914-16)

Oral treatment with ketoconazole has become a desirable alternative therapy to amphotericin B in the management of patients with chronic cavitary histoplasmosis because of its reported clinical efficacy, lower toxicity, and ease of administration; primary treatment failures or relapses with ketoconazole have been infrequently reported. We have recently been involved in the care of four patients who were receiving ketoconazole for treatment of chronic cavitary histoplasmosis and who had an unfavorable clinical response; two were considered primary drug failures, and two had relapses after prolonged therapy.

CASE REPORT

Case 3

This 56-year-old man with a 50-pack-year smoking history suffered the acute onset of fever, pleuritic chest pain, dyspnea, myalgias, and productive cough. His fever abated spontaneously, although cough and sputum production gradually worsened. After six months, he sought medical attention. Physical examination revealed rhonchi and rales in the right upper pulmonary fields. The chest roentgenogram demonstrated bilateral upper lobe interstitial infiltrates with cavitation (Fig 1). The PPD test was nonreactive, with a positive Candida control. A specimen from transbronchial biopsy revealed caseating granulomas and grew Histoplasma capsulatum.

Initially, the patient was treated with amphotericin B, with an attempt to achieve 0.6 mg/kg/day, but after he had received a total dose of 742 mg, moderate renal insufficiency ensued. Amphotericin B was discontinued, and therapy with ketoconazole at a dosage of 400 mg/day was initiated. In the next ten weeks, the patient reestablished his sense of well-being and gained 6 kg (14 lb). His chest roentgenogram during this time remained unchanged. Culture of sputum continued to yield H capsulatum. After a total of 30 weeks of therapy with ketoconazole, the patient had gained an additional 4 kg (9 lb). His chest roentgenogram demonstrated moderate improvement, and cultures of sputum failed to grow H capsulatum. Therapy with ketoconazole was eventually discontinued after a total of 65 weeks of therapy.

The patient was seen again two months later, with a two-week history of increased sputum production and one week of recurrent chest pain. Culture of sputum now revealed florid growth of H capsulatum.

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Chronic Cavitary Histoplasmosis (Quinones et al)
RESULTS

Table 1 describes the clinical characteristics of four patients with chronic cavitary histoplasmosis whose condition either failed to respond to ketoconazole or who had a relapse after an apparently successful course of therapy.

A patient was diagnosed as having chronic cavitary histoplasmosis if the chest roentgenogram demonstrated parenchymal cavitation with concurrent isolation of *H* *capsulatum* from either sputum (three patients) or lung biopsy (one patient). Laboratory identification of *H* *capsulatum* was made by characteristic appearance after growth on Sabouraud agar, conversion from mycelial to yeast form, and exoantigen production. We defined primary treatment failure as the progression of disease or failure to improve, as judged either clinically or by roentgenographic changes, during the administration of therapy. Relapse was defined as the recurrence of disease after a therapeutic course had been completed.

### Table 1—Clinical Data on Four Patients with Chronic Cavitary Histoplasmosis

<table>
<thead>
<tr>
<th>Case, Sex, Age, yr</th>
<th>Associated Illnesses*</th>
<th>Source of Positive Cultures</th>
<th>Dosage and Duration of Ketoconazole</th>
<th>(Initial) Response to Ketoconazole</th>
<th>Total Dose of Amphotericin B</th>
<th>Response to Amphotericin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, M, 45</td>
<td>Bronchiectasis</td>
<td>Sputum</td>
<td>800 mg/day × 56 wk</td>
<td>Failure</td>
<td>1,500 mg†</td>
<td>Improved</td>
</tr>
<tr>
<td>2, F, 46</td>
<td>COPD</td>
<td>Bronchial washings</td>
<td>800 mg/day × 45 wk</td>
<td>Relapse</td>
<td>2,400 mg</td>
<td>Improved</td>
</tr>
<tr>
<td>3, M, 56</td>
<td>COPD</td>
<td>Transbronchial biopsy</td>
<td>400 mg/day × 65 wk</td>
<td>Relapse</td>
<td>742 mg†</td>
<td>Improved</td>
</tr>
<tr>
<td>4, M, 64</td>
<td>COPD</td>
<td>Sputum</td>
<td>400 mg/day</td>
<td>Failure</td>
<td>1,000 mg†</td>
<td>Improved</td>
</tr>
</tbody>
</table>

*COPD. Chronic obstructive pulmonary disease.
†Patients currently on retreatment with ketoconazole after given dose of amphotericin B.

DISCUSSION

Chronic cavitary histoplasmosis is a progressive pulmonary infection caused by the dimorphic fungus, *H* *capsulatum*. This organism is capable of producing apical cavitary disease, progressive fibrosis, and, ultimately, irreversible injury to the lungs. Spontaneous healing with conservative management has been recorded, especially in those individuals whose lesions do not result in a persistent cavity; however, treatment with antifungal agents is warranted for those patients who have persistent cavitation, a cavity wall of greater than 2 mm in thickness, or progressive symptoms. Several changes in treatments for chronic cavitary histoplasmosis have occurred since the description of the disease. Studies from the 1960s attested to the efficacy of amphotericin B in arresting the infection and reducing the four-year mortality by 50 percent; reported cure rates ranged between 60 percent and 100 percent. Such encouraging data were tempered by the various drawbacks of systemic therapy with amphotericin B, namely, the need to administer intravenous doses and the complications of therapy, including anemia and azotemia.

The approval of ketoconazole as an antifungal agent for systemic mycotic infections was enthusiastically received by those physicians who desired a more convenient and less toxic choice of therapy for their patients with chronic cavitary histoplasmosis. In 1983, Slama reported the findings from a series of seven nonimmunocompromised patients with progressive cavitary histoplasmosis who were treated with a single dose of 200 mg of ketoconazole per day for six months; six of the seven showed clinical cure with absence of serious side effects. While information regarding duration of follow up was not disclosed, Slama concluded that therapy for progressive cavitary histoplasmosis with ketoconazole appeared to be safe and effective and should be considered in the choice of initial therapy in nonimmunocompromised patients. A prospective randomized clinical trial was published in 1985 by the Mycoses Study Group of the National Institute of Allergy and Infectious Disease, comparing low-dose (400-mg) and high-dose (800-mg) daily oral therapy with ketoconazole in the treatment of nonlife-threatening forms of histoplasmosis, including chronic cavitary disease. The overall success rate was 84 percent, with both regimens demonstrating similar efficacy. Such effectiveness compared favorably with the use of systemic therapy with amphotericin B.

Despite these rather impressive reported results with
ketoconazole, our experience, added to the conclusion of Wheat et al., does not fully support this initial optimism. Our four patients either had a relapse after more than one year of treatment (two cases) or were judged to be primary treatment failures (two cases). All of our patients were thought to have been compliant with their schedules for medication. None was receiving antacids or cimetidine or had undergone a gastrectomy, all of which are known to impair absorption of ketoconazole from the gastrointestinal tract.\textsuperscript{7,8} In addition, none of the patients was receiving glucocorticoids or had other congenital or acquired immunodeficiencies. While in vitro data have previously demonstrated that \textit{H capsulatum} is not only inhibited but killed by relatively small concentrations of ketoconazole, in vitro susceptibility or resistance to ketoconazole does not necessarily predict clinical response.\textsuperscript{9} Testing, therefore, remains problematic and was not pursued by our laboratories.

In view of this experience, we concur that once the diagnosis of chronic cavitary histoplasmosis has been established, oral treatment should be instituted with ketoconazole at 400 mg/day; however, careful follow-up evaluations, including chest roentgenograms and cultures of sputum when indicated, should be obtained at appropriate intervals during the course of therapy and especially at the end of treatment. In the case of primary treatment failure, systemic therapy with amphotericin B is likely to be required, although suppression of recurrent disease might be obtained by extended treatment with ketoconazole. Preliminary prospective data using itraconazole have shown clinical effectiveness against histoplasmosis;\textsuperscript{10} additional data may show that this drug could supplant ketoconazole in treating chronic cavitary histoplasmosis, therefore obviating our concerns.

REFERENCES

Nd-YAG Laser-Induced Endobronchial Burn* Management and Long-Term Follow-Up

Steve Krautz, M.D.; Atul C. Mehta, M.D., F.C.C.P.; Herbert P Wiedemann, M.D., F.C.C.P.; Glenn DeBoer, M.D.; Kenneth D. Schoepf, C.R.N.A.; and Marian Z. Tomasewski, M.D.

Endobronchial fires are a rare complication of Nd-YAG laser photoresection. Short-term morbidity is secondary to sloughing mucosa and mucous plugging. Aggressive pulmonary hygiene, including frequent bronchoscopies and possibly a tracheostomy, may be required. The major long-term complication is obstruction of the Airways from granulation tissue. Long-term follow-up is required to evaluate and treat clinically significant granulation tissue in the Airways.

\textit{F}ires can produce pulmonary injury through different mechanisms, the most common being smoke inhalation;\textsuperscript{1} however, direct thermal injury to the endobronchial tree rarely occurs because of the ability of the upper Airways to dissipate heat.\textsuperscript{4} The advent of laser therapy for Airways lesions introduces a situation in which a direct thermal injury can more readily occur. A small number of case reports have described endobronchial ignition of combustible materials, such as the ET tube and the FOB, by both the Nd-YAG and carbon dioxide lasers.\textsuperscript{2,4} Even though much has been written about the prevention of such a complication and its immediate management, the current literature does not provide information on long-term management. We experienced an endobronchial fire during an Nd-YAG laser photoresection. This case not only illustrates our experience with the immediate and short-term management, but also describes our observations of the long-term sequelae.

CASE REPORT

A 65-year-old white man with a permanent tracheal stoma from a prior thyroidectomy and neck dissection for Hurthle cell carcinoma developed hemoptysis and dysphonia. An exophytic lesion from metastatic carcinoma produced a 90 percent subglottic tracheal obstruction, and laser photoresection was considered. Under general anesthesia, ventilation was delivered through a PVC ET tube wrapped with metal tape to the level of the cuff and inserted through the tracheostomy site. The lesion was approached transnasally with the FOB. The procedure was performed using contact as well as noncontact laser tips and biopsy forceps. A total of 6,600 joules was delivered with 417 pulses of 10 to 40 W and 0.4-second duration over two hours. Oxygenation was maintained with an FIO\textsubscript{2} of 40 percent. Suddenly, black smoke began to arise from the ET tube while using a contact tip at 30 W and 0.4-second pulse. An endobronchial fire was suspected, and the FOB and ET tube were removed immediately. The tip of the ET tube was charred, and a perforation was noted immediately proximal to the balloon and distal to the metal tape wrapping. Ventilation was reestablished by

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