Aspergillomas Complicating Sarcoidosis*
A Prospective Study in 100 Patients
Christine Wollschlager, M.D.; and Faroq Khan, M.B., F.C.C.P.

During a ten-year study period, we evaluated 100 histologically-proven sarcoid patients for the development of aspergillomas. Serum precipitins against Aspergillus antigens were used to screen all patients regardless of sarcoid stage. Twelve patients had serum precipitins and were further investigated with tomography and serial serum precipitins testing. Ten of these 12 patients had aspergillomas and two patients died of massive hemoptysis. No aspergillomas occurred in stages I, II, or non-cystic stage III patients. All ten aspergillomas developed in the 19 stage III patients with cystic parenchymal damage. We believe that aspergillomas in sarcoidosis are not as rare as previously reported, but occur commonly in chronic cystic sarcoidosis. Additionally, we found serial testing for serum precipitins to be valuable both for the screening of cystic sarcoid patients for aspergillomas and for the management of this complication.

An aspergilloma is caused by the saprophytic colonization with Aspergillus species of a chronic cavity in destroyed lung tissue. Diseases classically associated with the development of an aspergilloma include tuberculosis, lung abscess, pulmonary infarcts, bronchiectasis, cystic fibrosis, and pulmonary neoplasms. In recent retrospective reviews, sarcoidosis has only occasionally been considered an important predisposing disease for an aspergilloma, and as recently as 1979, aspergillomas were said to be rare in sarcoidosis. At the Queens Hospital Center Sarcoid Clinic, we follow more than 260 histologically-confirmed cases of sarcoid. In 1970, we observed that aspergillomas were the cause of life-threatening hemoptysis in two patients with chronic sarcoidosis. Therefore, in 1971, we began a prospective evaluation of our sarcoid patients to determine the frequency and course of aspergilloma development and to assess the value, if any, of serial testing for serum precipitins to Aspergillus antigens in this patient population.

METHODS
We evaluated a total of 100 consecutive sarcoid patients for the presence of an aspergilloma during the ten-year period from 1971 to 1981. All patients had histologically-confirmed sarcoidosis and regularly attended our Sarcoid Clinic. As each patient was entered into the study, we obtained both a PA chest roentgenogram and serologic testing for precipitating antibodies to Aspergillus antigens (serum precipitins). All serum precipitins were performed by the New York State Department of Health. A standard gel precipitation technique was used, and all sera were tested against one antigen each from A niger and A terreus and 12 antigens from A fumigatus.

*From the Division of Pulmonary Medicine, Department of Medicine, Queens Hospital Center Affiliation of the Long Island Jewish-Hillside Medical Center and School of Medicine, Health Sciences Center, State University of New York at Stony Brook, NY. Presented in part at the IVth European Congress on Diseases of the Chest in Thessaloniki, Greece, June 1981.

Manuscript received September 26; revised accepted March 2.
Reprint requests: Dr. Wollschlager, Division of Pulmonary Medicine B-520, Queens Hospital Center, Jamaica, New York 11432

Test results were reported either nonreactive or positive according to the number of precipitation bands that developed. In addition, the specific Aspergillus species that reacted with the patient's sera was also reported.

All patients who were reported to have serum precipitins were further evaluated for the presence of an aspergilloma by another chest roentgenogram, chest tomography, and repeat serum precipitins. We diagnosed an aspergilloma by (1) thoracotomy or by (2) the presence of serum precipitins in a patient with tomography showing a crescent sign, or unilateral pleural thickening over a cystic area on PA chest film. The diagnosis of an aspergilloma was not considered firmly established if only serum precipitins were present without the roentgenographic or surgical findings of an aspergilloma.

RESULTS
The 83 women and 17 men in this study ranged in age from 16 to 72 years; eight were white and 92 were black. All ten patients who developed an aspergilloma were black. Table I shows the distribution of the study population and the development of aspergillomas according to sex and roentgenographic stage of sarcoidosis. The 32 stage III patients were further classified roentgenographically as noncystic in 13 and cystic in the 19 patients whose roentgenograms showed abnormal cystic air spaces. The ten aspergillomas occurred only in the 19 stage III cystic patients, an incidence of 53 percent in this subset of stage III. Additionally, we found a difference in aspergilloma frequency according to sex. Although the 17 men comprised only 17 percent of the study population, seven of these men developed aspergillomas, a frequency of 41 percent versus only 4 percent in women.

During the ten year course of this study, we identified two groups of patients according to their results in testing for serum precipitins against Aspergillus antigens. The first group comprised 88 patients without serum precipitins; no aspergillomas developed in any of these patients during the study period. In contrast to these patients, we found a group of 12 patients with

CHEST / 86 / 4 / OCTOBER, 1984 585
serum precipitins (Table 2). Ten of these patients developed an aspergilloma, which was confirmed by tomography in eight and PA chest film in two patients (No. 5 and 10) by new filling defects in known cavities. One of these patients (No. 5) died of massive hemoptysis before tomography was done. The other patient (No. 10) had complete clearing of the lesion in the cavity and his serum precipitins disappeared on two repeated testings suggesting spontaneous lysis of his aspergilloma. In the two other patients with serum

Table 2—Clinical and Historic Data in 12 Sarcoiud Patients with Serum Precipitins to Aspergillus Antigens

<table>
<thead>
<tr>
<th>Patient No./Age/Sex</th>
<th>Sarcoiud Stage</th>
<th>Steroids</th>
<th>Serum Precipitins*</th>
<th>Roentgenography‡</th>
<th>FFB Cultures§</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven aspergillomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/44/M</td>
<td>III</td>
<td>None</td>
<td>+3</td>
<td>LUL ASP (T)</td>
<td>A fumigatus</td>
<td>Has mild hemoptysis; no therapy; well two years.</td>
</tr>
<tr>
<td>2/55/F</td>
<td>III</td>
<td>None</td>
<td>+3</td>
<td>RUL ASP (T)</td>
<td>Not Done</td>
<td>Intermittent hemoptysis No therapy; well five years</td>
</tr>
<tr>
<td>3/26/M</td>
<td>III</td>
<td>None</td>
<td>+2</td>
<td>LUL ASP (T)</td>
<td>Negative</td>
<td>No therapy; well four years; precipitins now negative</td>
</tr>
<tr>
<td>4/45/M</td>
<td>III</td>
<td>None</td>
<td>+4</td>
<td>RUL ASP (T)</td>
<td>Not Done</td>
<td>S/P Resection of RUL ASP; well four years; precipitins now negative</td>
</tr>
<tr>
<td>5/48/F</td>
<td>III</td>
<td>10mg qD</td>
<td>+4</td>
<td>RUL cavity (C)</td>
<td>Not Done</td>
<td>Died of massive hemoptysis before tomography was done.</td>
</tr>
<tr>
<td>6/27/M</td>
<td>III</td>
<td>20mg qD</td>
<td>+3</td>
<td>RUL ASP (T): 1972</td>
<td>A fumigatus</td>
<td>S/P Resection of RUL ASP (1972), ten year course of recurrent ASP; died of massive hemoptysis 1980</td>
</tr>
<tr>
<td>7/34/M</td>
<td>III</td>
<td>10mg qD</td>
<td>+†</td>
<td>RUL ASP (T)</td>
<td>Negative</td>
<td>S/P RUL extracorporeal cavernostomy; well eight years No hemoptysis; Died 1 year later of rectal carcinoma. Autopsy: LUL ASP Mild hemoptysis; severe restrictive lung disease</td>
</tr>
<tr>
<td>8/67/M</td>
<td>III</td>
<td>None</td>
<td>+3</td>
<td>LUL ASP (T)</td>
<td>Not Done</td>
<td>No hemoptysis; Died 1 year later of rectal carcinoma. Autopsy: LUL ASP Mild hemoptysis; severe restrictive lung disease</td>
</tr>
<tr>
<td>9/38/F</td>
<td>III</td>
<td>None</td>
<td>+1*</td>
<td>RUL ASP (T)</td>
<td>A niger</td>
<td>Mild hemoptysis; severe restrictive lung disease Probable spontaneous lysis of ASP; precipitins now negative ×2; cavity clear</td>
</tr>
<tr>
<td>10/31/M</td>
<td>III</td>
<td>None</td>
<td>+1</td>
<td>RUL cavity (C)</td>
<td>Not Done</td>
<td>Probable spontaneous lysis of ASP; precipitins now negative ×2; cavity clear</td>
</tr>
<tr>
<td>No aspergillomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/67/F</td>
<td>I</td>
<td>None</td>
<td>+1</td>
<td>Hilar adenopathy no cavities, no ASP (T)</td>
<td>Not Done</td>
<td>Asymptomatic, repeat precipitins negative ×2.</td>
</tr>
<tr>
<td>12/52/F</td>
<td>III</td>
<td>None</td>
<td>+1</td>
<td>Interstitial infiltrates, no cavities</td>
<td>Not Done</td>
<td>Died three years later in hepatic failure; no evidence for ASP.</td>
</tr>
</tbody>
</table>

* The number listed refers to the number of precipitin bands formed to A fumigatus except for patient 9 who was repeatedly positive only to the single A niger antigen used.
† Only a "positive reaction to A fumigatus" was reported. The number of bands was omitted from the official report.
‡ C is conventional chest x-ray film; T, chest tomography; ASP, aspergilloma; RUL, right upper lobe; and LUL, left upper lobe.
§ FFB is flexible fiberoptic bronchoscopy wash specimen.
precipitins (No. 11 and 12), an aspergilloma was unlikely, since both patients had only a single precipitin band and no roentgenographic findings suggesting an aspergilloma.

**Discussion**

In a prospective study, we documented the occurrence of ten aspergillomas in a study group of 100 sarcoid patients in a ten-year period. The stage III cystic patients were at particular risk for this complication, since all ten aspergillomas developed in this group. Since Aspergillus species form aspergillomas by the saprophytic colonization of cystic spaces, it is not surprising that all aspergillomas developed in this subset of patients, but the high rate of occurrence of aspergillomas in these patients is striking. We believe that the incidence of aspergillomas in sarcoidosis is markedly underestimated in the literature. In 1979, Kapan and Johns found only 12 aspergillomas in a retrospective review of more than 600 cases of sarcoidosis. In 1970, Freundlich et al. found only ten aspergillomas in the roentgenograms of 300 sarcoid patients and all ten were in patients with "cavitary sarcoid." In contrast, aspergillomas were found in 20 percent of patients with healed tuberculous cavities of >2.5 cm in a three-year period. It is possible that a higher incidence of aspergillomas would have been found if their period of observation had been closer to our ten year duration.

Since there are many etiologies for hemoptysis in a lung damaged by sarcoidosis, we believe it is essential to know if an aspergilloma is causing this symptom should therapy become necessary. Massive hemoptysis can occur with an aspergilloma and has been reported to be the "second most common cause of death in sarcoidosis." 

Chronic hemoptysis can also be a persistent, disabling symptom in patients with an aspergilloma. Pulmonary resection may be contraindicated in sarcoid patients with massive hemoptysis on the basis of inadequate pulmonary reserve. Recent reports describe successful nonsurgical management of severe hemoptysis and medical therapy may include intracavitary amphotericin-B or bronchial artery embolization. We believe that our study accurately reflects the frequency of aspergilloma development in sarcoidosis, and we have shown that testing for serum precipitins to Aspergillus antigens is a valuable adjunct to the care of sarcoid patients. No patient with a negative test had an aspergilloma (Table 3), although aspergillomas have been reported to occur in up to 7 percent of patients with nonreactive sera. In addition, serial measurement of serum precipitins was particularly helpful in alerting us to those patients who are at increased risk for developing an aspergilloma, since patients with serum precipitins are reported to be twice as likely to develop an aspergilloma than patients with nonreactive sera. We documented seroconversion from nonreactive to positive serum precipitins in six patients (No. 1,2,5,6,8,9). Conversely, the finding of seroconversion to nonreactive was useful in three ways. First, a favorable clinical response was seen to therapy associated with seroconversion in three patients, as had been reported by others. Secondly, seroconversion to nonreactive in patient 10 corresponded to spontaneous lysis of his aspergilloma which may occur in about 10 percent of cases. Thirdly, two repeat tests in patient 11 confirmed the improbability of an aspergilloma in this stage I patient.

We found a significant difference in the frequency of aspergillomas in male patients (41 percent) compared to female (4 percent). This percentage is skewed by the number of male patients both in the study group and in our Sarcoid Clinic. It has been noted that men do not use clinic facilities as often as women and men tend to have more symptomatic diseases when they do attend clinic. Although this may partially explain our findings, we are presently unable to fully explain this phenomenon. Finally, it has been conjectured that immunosuppression may play a role in the development of aspergillomas. Since corticosteroids are often used to treat sarcoidosis, we evaluated the possible effects of this drug in contributing to aspergilloma formation. Only three of our patients were taking prednisone when the aspergillomas were found, and two were using doses of only 10 mg per day. In addition, aspergillomas form in patients who do not use corticosteroids but who have other cavitary diseases such as healed cavitary tuberculosis. Therefore, corticosteroids probably are of little importance in the development of aspergillomas in sarcoidosis.

In conclusion, we have prospectively documented that aspergillomas are quite common (53 percent) in stage III cystic sarcoidosis. No aspergillomas were found in stage I, II or noncystic stage III. Men with cystic stage III sarcoidosis have a higher frequency of aspergillomas than women. Corticosteroid usage ap-

---

**Table 3—Distribution of the 100 Sarcoid Patients According to the Number of Precipitin Bands**

<table>
<thead>
<tr>
<th>No. Precipitin Bands</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>1</td>
<td>88</td>
</tr>
<tr>
<td>≥2</td>
<td>0</td>
</tr>
</tbody>
</table>

*One patient's results were reported only as 'positive' but the number of bands was not given (patient 7). One patient had one band to the single A niger antigen used on two separate tests but no response to the multiple A fumigatus antigens.*
pears to have no role in aspergilloma formation. It is important to identify patients who have or are developing an aspergilloma so that appropriate medical or surgical therapy can be promptly instituted if hemoptysis ensues. We recommend that chest roentgenograms of patients with cystic sarcoid be regularly reviewed for the subtle changes of an early aspergilloma and that serial screening for serum precipitins to various Aspergillus antigens be obtained in this patient population.

ACKNOWLEDGMENT: The writers thank Dr. Joseph Guarneri and Dr. Phyllis Della Latta for their generous assistance with the microbiological data, Dr. Fred Rosner for his helpful review, and Ms. Terry Ishman for preparation of this manuscript.

REFERENCES


8 Coleman RM, Kaufman L. Use of the immunodiffusion test in the serodiagnosis of aspergillosis. Appl Microbiol 1972; 23:301-08


11 Libshitz HI, Atkinson GW, Israel HL. Pleural thickening as a manifestation of aspergillosis superinfection. Am J Radiol 1974; 120:683-86


20 Johns CJ. Management of hemoptysis with pulmonary fungus ball in sarcoidosis. Chest 1982; 82:400-01


