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Association of Presence of *Aspergillus* Antibodies with Hemoptysis in Patients with Old Tuberculosis or Bronchiectasis but No Radiologically Visible Mycetoma

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Old tuberculosis and bronchiectasis are the two most important causes of chronic structural changes of lungs in our locality. In the absence of radiologically visible mycetoma, the cause of hemoptysis in these two groups of patients is largely unknown. A 17-month prospective study was carried out to compare the prevalence of *Aspergillus fumigatus* and *Aspergillus flavus* antibodies in hemoptysis patients with old tuberculosis or bronchiectasis but no radiologically visible mycetoma (cases, $n = 38$), hemoptysis patients with other diagnosis (control group 1, $n = 29$), and patients with old tuberculosis or bronchiectasis but no hemoptysis (control group 2, $n = 47$) by a recently developed sensitive and specific *A. fumigatus* and *A. flavus* antibody assay. There were a significantly larger number of patients with antibody against *A. fumigatus* or *A. flavus* among the cases than among the patients in control groups 1 and 2 ($P < 0.05$ in both comparisons). Molds were not recovered from any of the patients. Among the 10 cases with *Aspergillus* antibody, eight and two had antibody against *A. flavus* and *A. fumigatus*, respectively. We conclude that there was an association between the presence of *Aspergillus* antibodies and hemoptysis in patients with old tuberculosis or bronchiectasis, suggesting that these patients probably had occult infections caused by the corresponding fungi. Development of serological tests against other *Aspergillus* species as well as other causes of mycetoma will probably increase the detection of occult mold infections in patients with existing parenchymal lung diseases, and treatment of fungal microinvasion may help to alleviate hemoptysis in these patients with bronchiectasis or old tuberculosis who have *Aspergillus* antibodies.

Hemoptysis is one of the frequent complications in patients with old tuberculosis or bronchiectasis. It is well known that molds will colonize and proliferate in the lung parenchymal cavities of patients with old tuberculosis, leading to mycetoma formation. Fungal species that have been implicated as causative agents of mycetoma include *Aspergillus* species, *Pseudallescheria boydii*, *Coccidioides* species, *Penicillium* species, *Cladosporium cladosporioides*, and *Schizophyllum commune*, of which the most common are *Aspergillus* species (4, 9, 11, 13–15, 20). The true incidence of aspergillous mycetoma, or aspergilloma, is unknown, but it has been estimated that it occurs in 11 to 17% of patients with tuberculous cavities (1). The most frequent symptom associated with mycetoma is hemoptysis, which occurs in about 74% of these patients, and the hemoptysis may occasionally be massive and life-threatening. However, the causes of hemoptysis in most cases of hemoptysis complicating old tuberculosis without mycetoma formation are still unknown. As for bronchiectasis, although bronchial artery proliferation has been shown to be associated with hemoptysis, the role of molds in causing hemoptysis in these patients is largely unknown (12).

Recently, we cloned the *AFMP1* and *AFLMP1* genes, which encode the first antigenic cell wall secretory galactomannoproteins Afmp1p and Aflmp1p, respectively, in *Aspergillus fumigatus* and *Aspergillus flavus*, respectively (18, 21). Furthermore, we have shown that serological assays with recombinant Afmp1p are sensitive and specific for the diagnosis of aspergilloma (3, 17). Clinical evaluation revealed that the assay was 100% sensitive for patients with aspergilloma caused by *A. fumigatus*, and no false-positive results were found for serum samples from 80 healthy blood donors, six patients with typhoid fever, four patients with melioidosis, 20 patients with penicilliosis marneffei, five patients with candidiasis, and four patients with cryptococcosis, indicating a high specificity of the test.

In this study, with the help of these antibody assays and mold cultures of bronchoalveolar lavage specimens, we compared the prevalence of *A. fumigatus* and *A. flavus* antibodies in patients with hemoptysis complicating old tuberculosis or bronchiectasis but no radiologically apparent mycetoma formation on high-resolution computed tomography (HRCT) scan, those with hemoptysis due to other causes, and those with old tuberculosis or bronchiectasis but without hemoptysis. The role of molds in causing occult microinvasion and hemoptysis in patients with existing structural abnormalities of the lung parenchyma is also discussed.

MATERIALS AND METHODS

Patients, study design, and inclusion criteria. The study protocol was reviewed and approved by the Hospital Ethics Committee. Patients presenting to the Department of Medicine & Geriatrics of the United Christian Hospital in Hong Kong with hemoptysis as the predominant symptom in a 17-month period (June 2001 to October 2002) were recruited to the study. Clinical details were recorded on a standard form. Complete blood counts, liver and renal function tests, and coagulation studies were performed. Serum antineutrophil cytoplasmic antibod-

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ies were checked for diagnosis of pulmonary hemorrhage associated with vasculitis. Sputum specimens were collected for bacterial, fungal, and mycobacterial cultures and cytological examination for malignant cells. Chest radiographs were taken and examined by a thoracic radiologist. Patients who had an obvious diagnosis at this stage (e.g., active tuberculosis) without further need for bronchoscopy and HRCT of the thorax were excluded from the study.

All patients finally included in the study were subject to fiber optic bronchoscopic examination and HRCT of the thorax. Bronchial washes were obtained from the segment corresponding to the abnormal areas on radiographs and were sent for bacterial, fungal, and mycobacterial cultures. Bronchial and transbronchial biopsy specimens were obtained as appropriate. HRCT of the thorax was examined by a thoracic radiologist, and the presence of bronchiectasis and lesions suggestive of mycetoma were noted. Blood was collected for *A. fumigatus* and *A. flavus* antibody detection.

The final diagnosis was reached after analysis of the clinical, laboratory, and radiological findings. Patients with a final diagnosis of allergic bronchopulmonary aspergillosis and mycetoma were excluded from the final statistical analysis. Allergic bronchopulmonary aspergillosis is defined by a history of asthma, circulating blood eosinophilia of more than 1,000 eosinophils/ml, immediate cutaneous reactivity to *Aspergillus* skin test antigen, precipitating antibodies against *Aspergillus* antigen, elevated total serum immunoglobulin E concentration, history of recurrent pulmonary infiltrates, and central bronchiectasis. Mycetoma is defined by the presence of a mobile mass within an existing cavity (air crescent sign) on HRCT, with or without culture of mold from respiratory tract specimens.

The patients with a final diagnosis of hemoptysis complicating bronchiectasis or old tuberculosis were considered cases, and those with any other diagnosis for their hemoptysis were considered controls (control group 1). A case of old tuberculosis was defined by a history of tuberculosis with a documented completed course of antituberculous treatment and a documented bacteriological cure and/or a chest radiograph or HRCT of the thorax showing fibrocalcified or cavitary lesions that had been stable over time. A case of bronchiectasis was defined by compatible clinical features with HRCT showing bronchial dilation, bronchial wall thickening, lack of normal bronchial tapering, or air-fluid levels in distended bronchi.

During the same study period, another group of patients followed up in the same department for old tuberculosis or bronchiectasis but without a history of hemoptysis were also recruited (control group 2). Blood was collected for *A. fumigatus* and *A. flavus* antibody detection, but bronchoscopic examinations were not performed with these patients as they did not have hemoptysis.

Detection of antibody against *A. fumigatus* and *A. flavus*. Detection of antibody against Afmp1p of *A. fumigatus* and Aflmp1p of *A. flavus* was performed by enzyme-linked immunosorbent assays (ELISAs), with positive results confirmed by Western blot assay (3, 17, 18). For the ELISA, each well of an immunoplate (Nunc, Roskilde, Denmark) was coated with 0.5 ng of purified glutathione *S*-transferase (GST)-Afmp1p or GST-Aflmp1p protein for 12 h and then blocked in phosphate-buffered saline with 2% bovine serum albumin. One hundred microliters of patient serum at 1:3,000 dilution was added to the wells of the recombinant protein-coated plates in a total volume of 100 μl and incubated at 37°C for 2 h. After washing with washing buffer (phosphate-buffered saline with 2% bovine serum albumin) three times, 100 μl of 1:10,000-diluted horseradish peroxidase-conjugated goat anti-human antibody (Zymed, S. San Francisco, Calif.) was added to the wells and incubated at 37°C for 30 min. After washing with washing buffer three times, 100 μl of 3,3′,5,5′-tetramethylbenzidine single solution (Zymed) was added to each well and incubated at room temperature for 15 min. One hundred microliters of 0.3 M H_2SO_4 was added, and the absorbance at 405 nm of each well was measured. Each sample was tested in duplicate, and the mean absorbance for each serum was calculated.

For the Western blot assays, recombinant Afmp1p and Aflmp1p samples were run on sodium dodecyl sulfate–10% polyacrylamide gels and electroblotted onto nitrocellulose membranes (Bio-Rad, Hercules, Calif.). The blots were cut into strips and the strips were incubated with patient sera diluted 1:500. Antigen-antibody interaction was detected with the ECL fluorescence kit (Amersham Life Science, Buckinghamshire, United Kingdom).

Statistical analysis. Comparison was made between the characteristics of cases and those of control groups 1 and 2. Comparisons of continuous variables were performed with a one-way analysis of variance test, and post hoc analyses were performed with Bonferroni's correction. A Mann-Whitney test and chi-square test were used for nonparametric and categorical variables, respectively. Comparison was also made between the characteristics of cases positive for antibody and those negative for antibody against *A. fumigatus* or *A. flavus*. A P of <0.05 was considered statistically significant.

TABLE 1. Diagnosis of patients in the case and control groups

Group (no. of patients)	Diagnosis	No. (%) of patients
Cases (38)	Bronchiectasis	29 (25.4)
	Old tuberculous cavities	9 (7.9)
Control group 1 (29)	Bronchogenic carcinoma	8 (7.0)
	Active tuberculosis[a]	6 (5.3)
	Acute pneumonia	5 (4.4)
	Acute bronchitis	4 (3.5)
	Lung abscess	3 (2.6)
	Carcinoma of the larynx	1 (0.9)
	Cryptogenic bronchiectasis	2 (1.8)
Control group 2 (47)	Bronchiectasis	17 (14.9)
	Old tuberculous cavities	30 (26.3)

[a] One case of active tuberculosis was culture documented, and the other five were diagnosed by compatible histological and radiological findings and a clear response to specific antituberculous treatment.

RESULTS

A total of 125 patients were recruited into the study. One patient had allergic bronchopulmonary aspergillosis and 10 had mycetoma and were therefore excluded, leaving 114 patients in the final analysis (mean age = 63.5 years, male/female ratio = 82:32). Thirty-eight patients (33.3%) were cases, with 9 (7.9%) and 29 (25.4%) having final diagnoses of old tuberculosis and bronchiectasis, respectively. Twenty-nine patients (25.4%) were in control group 1, with the breakdown of their diagnoses depicted in Table 1. Forty-seven patients (41.2%) were in control group 2, with 17 (14.9%) bronchiectasis and 30 (26.3%) old tuberculosis diagnoses.

A comparison of the characteristics of patients with hemoptysis who had bronchiectasis or old tuberculous cavities (cases) and the two control groups is shown in Table 2. Cases had significantly larger number of patients with histories of hemoptysis, significantly larger hemoptysis blood volume, significantly larger number of patients with positive bacterial growth in their bronchial washing specimens, and significantly larger number of patients with antibody against *A. fumigatus* or *A. flavus* than patients in control group 1 ($P < 0.05$ in all four comparisons). Furthermore, cases also had a significantly larger number of patients with antibody against *A. fumigatus* or *A. flavus* than patients in control group 2 ($P < 0.05$). Molds were recovered from none of the patients.

Since positive bacterial growth could be a confounding factor in the statistical analysis, further analysis was performed after removal of data for cases and controls with positive bacterial growth in their bronchial washing specimens (14 from cases and 4 from control group 1). In this subset analysis, 8 out of the 24 patients in the cases but only 1 out of the 25 patients in control group 1 had antibody against *A. fumigatus* or *A. flavus* ($P < 0.01$), indicating that the presence of *Aspergillus* antibodies is independently associated with bronchiectasis or old tuberculosis in patients with hemoptysis.

The characteristics of patients with hemoptysis who had bronchiectasis or old tuberculous cavities (cases) positive for antibodies against *A. fumigatus* or *A. flavus* are shown in Table 3. The median age was 64.5 years (range, 46 to 78 years). The male/female ratio was 6:4. The median number of hemoptysis episodes in the past was one (range, 0 to 6). The median

TABLE 2. Comparison of characteristics of patients with hemoptysis who had bronchiectasis or old tuberculous cavities (cases) and those with other diagnoses (control group 1) and bronchiectasis or old tuberculous cavities without hemoptysis (control group 2)

Characteristic	Value for group[g]			*P*
	Cases (n = 38)	Control group 1 (n = 29)	Control group 2 (n = 47)	
Age (yr, mean ± SEM)	63.5 ± 1.9	60.6 ± 3.0	65.3 ± 1.9	NS[h]
Sex (M:F)[i]	25:13	20:9	37:10	NS
Clubbing				
Present	5	0	6	NS
Absent	33	29	29	
History of hemoptysis				
Present	19	6		<0.05
Absent	19	23		
Hemoptysis blood vol (ml, median)	125	20		<0.05
Hemoglobin (g/dl, mean ± SEM)	12.8 ± 0.3	12.9 ± 0.4	13.1 ± 0.4	NS
White cell count (10^9/liter, mean ± SEM)	8.1 ± 0.4	9.1 ± 0.7	8.9 ± 0.8	NS
Neutrophil count (10^9/liter, mean ± SEM)	5.9 ± 0.5	6.5 ± 0.6	7.4 ± 0.7	NS
Lymphocyte count (10^9/liter, mean ± SEM)	1.6 ± 0.2	1.4 ± 0.1	1.5 ± 0.4	NS
Eosinophil count (10^9/liter, mean ± SEM)	0.08 ± 0.02	0.24 ± 0.05	0.17 ± 0.05	NS
Erythrocyte sedimentation rate (mm/h, mean ± SEM)	39 ± 5	38 ± 8	35 ± 8	NS
Albumin/globulin ratio (mean ± SEM)	1.10 ± 0.04	1.17 ± 0.04	1.17 ± 0.04	NS
Bronchial washing culture results				
No growth or commensals	24	25		<0.05
Positive bacterial growth	14	4		<0.05
Pyogenic bacteria	12[a]	3[b]		<0.05
Mycobacteria	2[c]	1[d]		NS
Antibody against *A. fumigatus* or *A. flavus*				
Present	10	1[e]	3[f]	<0.05
Absent	28	28	44	

[a] Includes six cases of *Pseudomonas aeruginosa* infection, two cases of *Annii bauma* infection, and one case each of *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Staphyloccus aureus*, and *Klebsiella pneumoniae* infection.
[b] Includes one case each of *P. aeruginosa*, *K. pneumoniae*, and *Streptococcus pneumoniae* infection.
[c] Includes one case each of *Mycobacterium avium-intracellulare* complex and *Mycobacterium chelonae* infection.
[d] Includes one case of *Mycobacterium tuberculosis* infection.
[e] The patient with positive *A. flavus* antibody in control group 1 had bronchogenic carcinoma.
[f] Two and one patients with positive *A. flavus* antibody in control group 2 had bronchiectasis and old tuberculosis, respectively.
[g] Except where indicated, values are numbers of patients.
[h] NS, not significant.
[i] M, male; F, female.

volume of hemoptysis blood was 200 (range, 10 to 1,000) ml. Seven (70%) and three (30%) cases had bronchiectasis and old tuberculosis, respectively. Eight (80%) and two (20%) cases had antibody against *A. flavus* and *A. fumigatus*, respectively (Fig. 1).

A comparison of the characteristics of cases that were positive and negative for antibodies against *A. fumigatus* or *A. flavus* is shown in Table 4. Cases that were positive for antibodies against *A. fumigatus* or *A. flavus* had significantly lower hemoglobin levels and significantly higher erythrocyte sedimentation rates.

TABLE 3. Characteristics of cases positive for antibodies against *Aspergillus fumigatus* or *Aspergillus flavus*

Patient no.	Sex	Age (yr)	No. of hemoptysis episodes in the past	Vol[b] of hemoptysis blood (ml)	Hemoglobin (g/dl)	Diagnosis	*Aspergillus* antibody present[a] (OD)	
							A. fumigatus	*A. flavus*
1	F	75	1	250	10.8	Old tuberculosis	−	+ (0.389)
2	F	61	0	1,000	10.7	Bronchiectasis	−	+ (0.694)
3	M	46	2	150	14.7	Bronchiectasis	−	+ (1.370)
4	F	72	1	880	9.1	Bronchiectasis	−	+ (0.791)
5	M	75	0	250	12.2	Bronchiectasis	+ (0.464)	−
6	F	67	6	100	11.0	Bronchiectasis	−	+ (0.312)
7	M	78	4	600	11.0	Bronchiectasis	−	+ (0.572)
8	M	67	3	20	13.1	Bronchiectasis	−	+ (0.417)
9	M	62	0	10	12.9	Old tuberculosis	−	+ (0.482)
10	M	69	0	50	10.0	Old tuberculosis	+ (0.694)	−

[a] The optical density (OD) cutoff values for the Afmplp-based and Aflmplp-based ELISAs were 0.219 and 0.263, respectively.

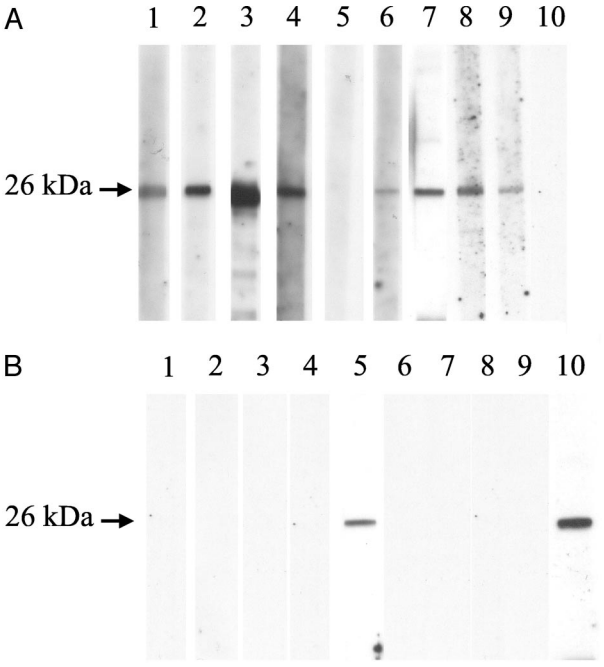

FIG. 1. Western blot analysis of purified Aflmp1p of *A. flavus* (A) and Afmp1p of *A. fumigatus* (B). The lane numbers correspond to the patient numbers in Table 3. Strong antigen-antibody interaction was detected with the sera of eight patients against Aflmp1p (lanes 1, 2, 3, 4, 6, 7, 8, and 9) (A) and those of two patients against Afmp1p (lanes 5 and 10) (B).

DISCUSSION

Old tuberculosis and bronchiectasis are the two most important causes of chronic structural changes in lungs in our locality. Since one of the most important causes of bronchiectasis in our locality is old tuberculosis, it is often difficult to distinguish between the two categories, and there is significant overlap between the two groups of patients. In this study, we demonstrated that the prevalence of *A. fumigatus* and *A. flavus* antibodies in patients presenting with hemoptysis who had old tuberculosis or bronchiectasis without radiologically visible mycetoma formation was significantly higher than those with hemoptysis due to other causes. Because of the possibility that the difference was due just to the association of *Aspergillus* infections with old tuberculosis and bronchiectasis but was not related to hemoptysis, another group of controls, patients with old tuberculosis or bronchiectasis without hemoptysis (control group 2), was selected. It was also demonstrated that the presence of *Aspergillus* antibodies in patients with old tuberculosis or bronchiectasis with hemoptysis was significantly higher than in those without hemoptysis, indicating that the presence of *Aspergillus* antibodies was associated with hemoptysis in patients with old tuberculosis or bronchiectasis.

As for fungal culture, despite the presence of antibodies, *Aspergillus* species were not recovered from any of the respiratory tract specimens collected from the patients. In fact, among the 10 patients with mycetoma that we excluded from the study, only three had positive mold cultures, one with *A. fumigatus* and two with *A. flavus*. This is in line with the low rate of positive culture of only about 40% in patients with mycetoma reported in another study (10). Due to the very small lesions of less than 5 mm that were not detected by computed tomography scans, a very small amount of fungal shedding, and the possibility of the presence of cells in a viable but nonculturable state, it is not surprising that none of the cases yielded positive mold culture results.

We speculate that *Aspergillus* species causes hemoptysis in patients with old tuberculosis or bronchiectasis without mycetoma formation through microinvasion of the damaged respiratory epithelium. It has been demonstrated that *A. fumigatus* secretes fumagillin, a chemical that inhibits angiogenesis (7). Similarly, *Aspergillus clavatus* secretes cytochalasin E, which is a potent and selective inhibitor of capillary endothelial cell proliferation in an experimental model (16). On the other hand, it has been shown that in patients with aspergillomas, the levels of vascular endothelial growth factor (VEGF) in serum were raised, and the level was related to the area of lung involvement, PaO_2 level, and the presence of hemoptysis (8). Furthermore, the expression of VEGF was high in alveolar macrophages in the lesion of aspergillomas, and VEGF expression in macrophages was induced by hypoxia and lactate and its expression promoted angiogenesis and increased vascular permeability (5, 19).

We speculate that the immediate surrounding of an aspergilloma is rendered ischemic by substances like fumagillin and cytochalasin E, enhancing necrosis and inflammation. Subsequent recruitment of alveolar macrophages into this hypoxic environment induces the macrophage to express VEGF, which enhances angiogenesis around the aspergilloma. Thus, it is con-

TABLE 4. Comparison of cases positive and negative for antibodies against *Aspergillus fumigatus* or *Aspergillus flavus*

Characteristic	Value for cases that were antibody:		P^e
	Positive (n = 10)	Negative (n = 28)	
Age (yr, median)	64.5	68.0	NS
Sex (M:F)[d]	6:4	19:9	NS
Vol of hemoptysis blood (ml, median)	200	100	NS
Hemoglobin (g/dl, median)	11.0	13.1	<0.05
White cell count (10^9/liter, median)	6.7	7.7	NS
Neutrophil count (10^9/liter, median)	4.6	5.4	NS
Lymphocyte count (10^9/liter, median)	1.1	1.5	NS
Eosinophil count (10^9/liter, median)	0.1	0.1	NS
Albumin/globulin ratio (median)	1.0	1.2	NS
Erythrocyte sedimentation rate (mm/h, median)	63	22	<0.05
Bronchial wash culture results			
No growth or commensals	8	16	NS
Pyogenic bacteria	2[a]	10[b]	NS
Mycobacteria	0	2[c]	NS

[a] Includes two cases of *P. aeruginosa.*
[b] Includes four cases of *P. aeruginosa*, two cases of *A. baumannii*, and one case each of *H. parainfluenzae*, *M. catarrhalis*, *S. aureus*, and *K. pneumoniae*.
[c] Includes one case each of *M. avium-intracellulare* complex and *M. chelonae*.
[d] M, male; F, female.
[e] NS, not significant.

ceivable that *Aspergillus* species might set foot on damaged respiratory epithelium in bronchiectasis and old tuberculous cavities and that the interplay between antiangiogenic factors secreted by the *Aspergillus* species and VEGF secreted by alveolar macrophages promote necrosis and hypervascularity around the infected areas. In the present study, the patients with confirmed diagnoses of bronchiectasis or old tuberculosis with *Aspergillus* antibody tended to bleed significantly. The definition of massive hemoptysis has ranged from 100 to 1,000 ml in 24 h (6). If one takes 100 ml as the cutoff, 7 out of the 10 patients with bronchiectasis or old tuberculosis and *Aspergillus* antibody had massive hemoptysis. This is also supported by the fact that the seropositive cases had significantly lower hemoglobin levels, and they showed a trend to bleed more than the seronegative patients.

In Western countries, *A. fumigatus* is the most important *Aspergillus* species that causes invasive aspergillosis and aspergilloma. On the other hand, *A. flavus* is the most common one associated with human disease in our locality and in other Asian countries (2, 22). In our previous study, we demonstrated that *A. flavus* is responsible for causing 38% whereas *A. fumigatus* is responsible for causing only 19% of invasive mold diseases in bone marrow transplant recipients. This is in line with the observation in the present study, in that 80% of the seropositive patients had antibody against *A. flavus*, whereas only 20% of them had antibody against *A. fumigatus*. In fact, in the 10 patients with mycetoma diagnosed in the period of the study, four of them were positive for *A. flavus* antibody, but only two were positive for *A. fumigatus* antibody.

Development of serological tests against other *Aspergillus* species as well as other causes of mycetoma will probably increase the detection of occult mold infections in patients with preexisting parenchymal lung diseases. We have demonstrated that *Aspergillus* antibody assays are highly sensitive and specific for the diagnosis of aspergilloma. However, only 6 of the 10 patients with mycetoma diagnosed in the period of the study had antibody against *A. fumigatus* or *A. flavus*. Furthermore, we have also demonstrated that 28% of the invasive mold diseases in our bone marrow transplant recipients were caused by *Aspergillus* species other than *A. fumigatus* and *A. flavus* (22). It is therefore logical to assume that the remaining four patients with mycetoma were infected by *Aspergillus* species other than *A. fumigatus* or *A. flavus* or other molds such as *P. boydii* and *Penicillium* species (4, 9, 11, 13-15, 20). We speculate that about six to seven out of the 37 patients with bronchiectasis or old tuberculosis should be positive for antibody against other *Aspergillus* species or other molds.

Treatment of fungal microinvasion may help to alleviate the hemoptysis in these patients with bronchiectasis or old tuberculosis who had *Aspergillus* antibody. Massive hemoptysis in patients with bronchiectasis or old tuberculosis can be life-threatening and is a condition dreaded by patients and clinicians alike. Due to their marginal respiratory functions, these patients are often poor surgical candidates for resection of the diseased lung segments affected by bronchiectasis and inactive tuberculosis. Bronchial arterial embolization may afford palliation in some patients, but new collateral formation and rebleeding may occur in the long run (6). As mold microinvasion may be the cause of hemoptysis in these patients, further studies with antifungal therapy may open up a new avenue of treatment for some of these patients with hemoptysis complicating bronchiectasis or old tuberculosis.

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