

# Colonizing Fungi in Cavitory Lesions of Lung – A Clinicopathological Study

## Akciğerin Kaviter Lezyonlarında Kolonize Olan Funguslar - Klinikopatolojik Bir Çalışma

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### ABSTRACT

**Objective:** Patients with preexisting lung cavities are prone to develop fungal masses inside the cavity. Though *Aspergillus* sp. is the most common fungus colonizing these cavities other fungi may rarely show colonization.

**Material and Method:** Retrospective study carried out in a tertiary care hospital from 1993 to 2008. All patients diagnosed with a fungal ball on chest radiographs/CT chest with subsequent histological confirmation were analysed. Demographic data, clinical, radiological and surgical findings were retrieved from the medical records. Histopathology slides were reviewed along with special stains for fungi. Fungi were identified on morphology and/or culture.

**Results:** There were 25 patients in the study period with 20 males and 5 females. A past history of tuberculosis was present in 17 patients. The colonizing fungi were identified as *Aspergillus* sp. in 20, dematiaceous fungi in 3 and mixed infection (*Aspergillus* sp. and *Candida* sp.) in 2. Culture confirmation was available in five specimens, which showed *Aspergillus fumigatus* in 2, *Aspergillus flavus* 1, *Pseudallescheria boydii* 1 and *Candida albicans* (in mixed infection) in 1.

**Conclusion:** Fungi other than *Aspergillus* sp. can colonize pulmonary cavities. Hence an attempt at identification of the colonizing fungus either with morphological or cultural evidence should be done. (*Tur Toraks Der* 2011; 12: 19-26)

**Key words:** Lung, *Aspergillus*, fungi, *pseudallescheria*, *candida*

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### ÖZET

**Amaç:** Akciğer kavitesi mevcut olan hastalar kavite içinde fungal kitle oluşmasına yatkındır. *Aspergillus* sp. bu kaviteyi kolonize eden en yaygın fungus olmakla birlikte, ender olarak diğer funguslar kolonizasyon gösterebilir.

**Gereç ve Yöntem:** Üçüncü basamak bir hastanede 1993'ten 2008'e retrospektif bir çalışma gerçekleştirildi. Göğüs radyografisi/ CT' sinde mantar topu gözlenen ve daha sonra histolojik olarak doğrulanan bütün hastalar analiz edildi. Demografik veriler, klinik, radyolojik ve cerrahi bulgular tıbbi kayıtlardan elde edildi. Histopatoloji slaytları funguslar için özel boyalarla değerlendirildi. Funguslar morfoloji ve/ veya kültüre dayalı olarak tanımlandı.

**Bulgular:** Çalışma döneminde 20 erkek ve 5 kadın olmak üzere 25 hasta mevcuttu, 17 hastada geçmişte tüberküloz öyküsü vardı. Kolonize eden mantar 20 hastada *Aspergillus* sp. olarak, 3 hastada dematiyasöz fungus olarak ve 2 hastada karışık enfeksiyon (*Aspergillus* sp. ve *Candida* sp.) olarak tanımlandı. Kültür doğrulaması beş örnekte sağlanabildi; bunlar 2 hastada *Aspergillus fumigatus*, 1 hastada *Aspergillus flavus*, 1 hastada *Pseudallescheria boydii* ve 1 hastada *Candida albicans* (karışık enfeksiyonda).

**Sonuç:** *Aspergillus* sp. dışındaki funguslar pulmoner kaviteyi kolonize edebilir. Bu nedenle kolonize eden mantarın morfoloji veya kültürle tanımlanması için çaba gösterilmelidir. (*Tur Toraks Der* 2011; 12: 19-26)

**Anahtar sözcükler:** Akciğer, *Aspergillus*, mantar, *Pseudallescheria*, *Candida*

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### INTRODUCTION

Patients with preexisting lung cavities are prone to develop fungal masses inside the cavity. The lung cavities may be formed due to healed tuberculous lesions, histoplasma or sarcoid lesions, lung abscess, benign cysts, cystic bronchiectasis or cystic degeneration in malignancies [1,2]. The fungus that colonizes the cavitory lesions of the lung most commonly belong to *Aspergillus* sp.

and hence, the fungal masses are usually called aspergillomas. After formation of a fungal ball with *Aspergillus* sp., antifungal agents are usually ineffective. Rarely, fungi other than *Aspergillus* sp. may colonize the cavities in the lung [1,3-9]. Identification of the colonizing fungus may have implications in the management and prognosis. In this study we aim to identify the colonizing fungus based on morphology and/or culture.

## MATERIAL and METHOD

This was a retrospective study from January 1993 to December 2008. All patients who were diagnosed as having a fungal ball on chest radiograph or CT chest and underwent surgery or biopsy were included in the study. In view of the retrospective observational nature of the study ethical approval was not obtained. The demographic data, clinical features, predisposing conditions, radiological features, surgery performed, post operative complications were noted in all patients from their medical records. Immunological tests were not carried out in any patient. The histopathology slides were reviewed with Hematoxylin and eosin, (H&E), Gomori's methenamine silver (GMS) stain and periodic acid Schiff (PAS) stain, for fungal morphology, Masson Fontana (MF) stain for melanin and Perls stain for hemosiderin. Culture reports of sputum, bronchoalveolar lavage (BAL) or tissue from surgical specimens were collected wherever available. When culture was not available, fungi were identified based on morphology alone as follows:

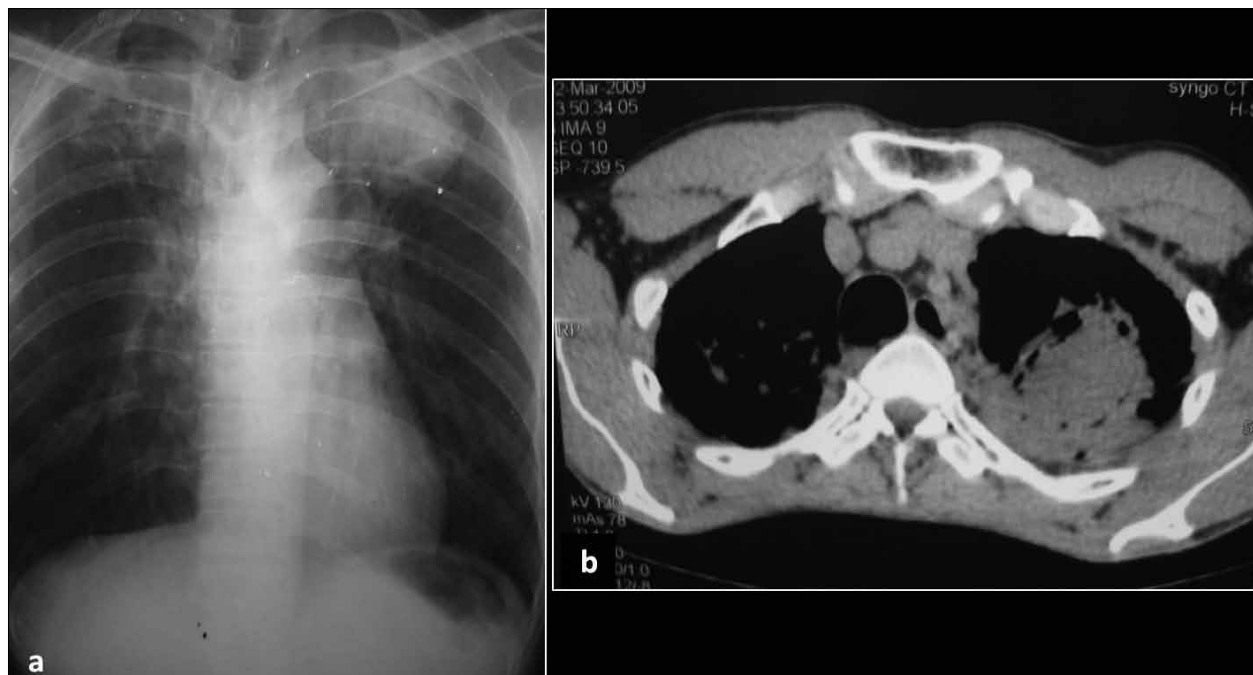
Slender septate hyphae with parallel walls and acute angle branching were identified as septate molds probably *Aspergillus* sp; septate hyphae with brown colour and acute angle branching were identified as *dematiaceous* fungi; Pseudohyphae and budding yeast forms were identified as *Candida* sp. The underlying lung pathology was noted in all specimens.

## RESULTS

There were 25 patients in the study period with 20 males and 5 females and ages ranging from 12 to 55 years (mean 38 years). The demographic data, clinical

features, associated conditions, surgery performed, post operative complications, pathology, culture and treatment were given in Table 1. The commonest presenting feature was hemoptysis in 20 (84%) patients. A past history of tuberculosis was present in 17 (68%) patients. The fungal ball was suspected in all patients on chest radiograph and confirmed on CT of the chest (Figure 1a-b). Chest radiography showed fibrocavitary lesions in 15 and meniscus sign in 10 patients. Collapse consolidation was seen in 2 patients. CT chest showed an intracavitary mass with a crescent in all patients with associated bronchiectatic changes in 9 patients. Bronchoscopy was done in all patients and BAL was sent for cytology and culture as a routine but it was sterile and non contributory. Sputum grew *Candida albicans* in one patient. Lobectomy was the most common surgery performed in 19 (76%) followed by segmentectomy in 4 and lobectomy with segmentectomy in 5 patients. In one patient, only biopsy of the fungal ball was available for histology. There were no post operative deaths. Post operative complications occurred in 2 patients. The resected specimens (n=24) showed bronchiectatic changes in 9; and multiple tubercles in lung parenchyma grossly in 4. The cavity was single in 18 and multiple in 5. The wall of the cavity was thick walled in 12 (Figure 1). Pleural thickening was noted in 8. The fungal ball was soft, brownish to grey brown and friable, partly filling the cavity in almost all the specimens (Figure 2).

Histology of the fungal ball showed masses of fungal hyphae with dead eosinophilic hyphae in the centre and basophilic viable hyphae at the periphery near the wall of the cavity (Figure 3a). There were few red cells, fibrin



**Figure 1.** (a) Chest radiograph showing soft tissue density lesion in the left upper lobe with thin crescent of air demonstrable on superior aspect. (b) CT scan of the chest showing a large cavitary lesion involving left upper lobe of the lung with soft tissue density mass lesion within. Crescent of air is demonstrable surrounding the mass lesion

**Table 1.** Clinical features, surgery performed, complications, pathology, fungal morphology/culture and treatment particulars of pulmonary cavitory lesion

Case No.	Age (yrs)/ Gender	Clinical Presentation	Surgery Performed	Complications	Gross Findings	Fungus on Morphology/ Culture	Treatment
1	42/M	Hemoptysis H/o TB	Rt. Upper lobectomy	Nil	Pleural thickening, thick walled cavity (3x2 cms) filled with brownish friable material, bronchiectatic changes. Multiple caseating nodules	<i>Aspergillus</i> sp. No culture TB granulomas	Antibiotics ATT
2	36/M	Hemoptysis, cough with expectoration, SOB; H/o TB	Lt. Upper lobectomy	Nil	Thick walled cavity (5x4 cms) filled with greenish yellow granular material	<i>Aspergillus</i> sp. No culture TB granulomas	Antibiotics ATT
3	39/M	Hemoptysis, cough with expectoration, fever	Rt. Middle lobectomy	Nil	Irregular thick walled cavity filled with brown friable material; Bronchiectatic changes	<i>Aspergillus</i> sp. No culture No e/o TB granulomas FB giant cell reaction	Antibiotics
4	40/M	Fever cough	Biopsy from cavity in Rt. UL	Nil	NA	<i>Aspergillus</i> sp. No culture No lung parenchyma seen	Antibiotics
5	40/M	Hemoptysis, cough H/o TB	Segmentectomy from Lt. UL	Nil	Thick walled cavity (2x1 cm) filled with brown friable material	<i>Aspergillus flavus</i> No e/o TB granulomas	Antibiotics
6	26/M	Hemoptysis H/o TB, DM	Lt. Upper lobectomy	Wound infection	Irregular pleural thickening Two cavities filled with brownish material; Bronchiectatic changes	Dematiaceous fungi No culture TB granulomas	Antibiotics ATT
7	32/M	Hemoptysis H/o TB	Lt. Upper lobectomy	Nil	Two thick walled ( 2x2 cms each) cavities filled with brownish material	<i>Aspergillus</i> sp. No culture No e/o TB granulomas	Antibiotics
8	26/M	Recurrent hemoptysis H/o TB	Segmentectomy from Lt. UL	Minor air leak empyema	Irregular thick walled cavity (2x2 cms) filled with brown friable material. Bronchiectatic changes	<i>Aspergillus</i> sp. No culture TB granulomas	Antibiotics ATT
9	50/M	Massive hemoptysis H/o TB	Lt. upper lobectomy	Nil	Thick walled cavity (4x4 cms) filled with greyish-brown material	<i>Aspergillus</i> sp. No culture No e/o TB granulomas	Antibiotics
10	28/M	Hemoptysis Lt. sided chest pain	Segmentectomy from Lt. UL	Nil	Thick walled cavity (3x3 cms) filled with brown material; Bronchiectatic changes	<i>Aspergillus</i> sp. No culture No e/o TB granulomas	Antibiotics
11	34/M	Hemoptysis	Lt. upper lobectomy	Nil	Two smooth walled cavities (2x1.5 cms each) filled with grey brown material Bronchiectatic changes	<i>Aspergillus</i> sp. + yeast forms of candida sp. Sputum culture – <i>Candida albicans</i> No e/o TB granuloma	Antibiotics
12	25/M	Fever, cough with expectoration H/o TB	Segmentectomy from Rt. UL	Nil	Thick walled cavity (5x4 cms) filled with brownish-black material	<i>Aspergillus</i> sp. No culture. No e/o TB granuloma No e/o TB granulomas	Antibiotics

13	32/F	Hemoptysis	Rt. Middle lobectomy	Nil	Cavity (1.5x 1 cms) filled with grey-brown material	<i>Aspergillus</i> sp. No culture No e/o TB granulomas	Antibiotics
14	38/M	Recurrent hemoptysis Dry cough TB	Lt. upper lobectomy	Nil	Thick walled cavity (2x2 cms) filled with grey-brown friable material	<i>Dematiaceous fungi</i> No culture No e/o TB granulomas	Antibiotics
15	40/F	Rt. Sided chest pain, cough with expectoration H/o TB	Rt. Upper lobectomy	Nil	Thick walled cavity (2x2 cms) filled with brownish friable material	<i>Aspergillus</i> sp. No culture No e/o TB granulomas FB giant cell reaction, Calcification	Antibiotics
16	12/F	Hemoptysis fever	Rt. lower lobectomy	Nil	Multiple cavities filled with grey-brown material; Bronchiectatic changes	<i>Aspergillus</i> sp. No culture; No e/o TB granulomas	Antibiotics
17	46/M	Hemoptysis H/o TB	Rt. Upper & middle lobectomy	Nil	Multiple cavities filled with grey-brown material Bronchiectatic changes	<i>Aspergillus</i> sp. No culture; TB granulomas	Antibiotics ATT
18	37/M	Hemoptysis H/o TB, chronic smoker	Lt. upper lobectomy	Nil	Cavity (2x1 cms) filled with friable material	<i>Aspergillus</i> sp. No culture; No e/o TB granulomas	Antibiotics
19	52/M	Hemoptysis Recurrent respiratory tract infection H/o TB, DM	Lt. upper lobectomy	Nil	Pleural thickening Thick walled cavity (2x2 cms) filled with friable material	<i>Aspergillus</i> sp. No culture; No e/o TB granulomas	Antibiotics
20	45/M	Hemoptysis	Rt. Upper lobectomy	Nil	Thick walled cavity (3x3 cms) filled with dark brown material	Dematiaceous fungi Culture - <i>Pseudoallescheria boydii</i> No e/o TB	Antibiotics Itraconazole
21	50/M	Lt. sided chest pain H/o TB, DM	Lt. upper lobectomy	Nil	Thick walled cavity (2x2 cms) filled with friable material	<i>Aspergillus fumigatus</i> No e/o TB granulomas	Antibiotics
22	41/F	Hemoptysis, cough H/o TB	Lt. upper lobectomy	Nil	Thick walled cavity (3x2 cms) filled with grey brown material	<i>Aspergillus</i> sp. No culture; No e/o TB granulomas	Antibiotics
23	50/M	Hemoptysis, cough H/o TB	Rt. Upper lobectomy	Nil	Thick walled cavity (3x4 cms) filled with friable material	<i>Aspergillus</i> sp. No culture; No e/o TB granulomas	Antibiotics
24	35/F	Hemoptysis, H/o TB	Lt. upper lobectomy	Nil	Two thick walled ( 2x2 cms each) cavities filled with brownish material Bronchiectatic changes	<i>Aspergillus fumigatus</i> No e/o TB granulomas	Antibiotics
25	55/M	Hemoptysis, H/o TB	Lt. upper lobectomy	Nil	Cavity (2x3 cms) filled with grey brown friable material	<i>Aspergillus</i> sp. No culture; No e/o TB granulomas	Antibiotics

Abbreviations: H/o - history of; TB - tuberculosis; SOB - shortness of breath; Lt. - left side; Rt. - right side; DM - diabetes mellitus; Ul - upper lobe; NA - not available; e/o - evidence of; FB - foreign body; ATT - antituberculous therapy

**Table 2.** Comparison of present study with major reported series of pulmonary cavitary lesions

	<b>Akbari et al<sup>7</sup>, 2005 n=60</b>	<b>Pratap et al<sup>10</sup>, 2007 n=72</b>	<b>Shah et al<sup>11</sup>, 2008 n=41</b>	<b>Regnard et al<sup>12</sup>, 2000 n=89</b>	<b>Caidi et al<sup>13</sup>, 2006 n=278</b>	<b>Brik et al<sup>14</sup>, 2008 n=42</b>	<b>Okubo et al<sup>15</sup>, 2007 n=24</b>	<b>Present study n=25</b>
Period of study	1985-2003	1990-2002	1992-2006	1977-1997	1982-2004	2001-2008	1992-2006	1993-2008
M:F	36:24	47:25	25:16	61:26	161:117	28:14	21:3	20:5
Age range (mean)	42.7±11.8	26-58 (32)	16-65	13-73 (49)	16-70 (32)	(44.5)	(58.4)	12-55
Underlying disease	TB (40.4%) Bronchiectasis (28.3%)	TB (84.7%) Bronchiectasis (12.5%) Lung abscess (2.8%)	TB - 26 (63.4%) Bronchiectasis - 6 Lung abscess - 3	TB (70%)	TB (73%)	TB (40.4%) Bronchiectasis (33.3%) Lung abscess (11.9%)	75 %	TB - 17 (68%)
Most common symptoms	Hemoptysis (93.3%)	Hemoptysis (65.28%)	Hemoptysis (85.4%)	Hemoptysis (72%)	Hemoptysis (83%)	Hemoptysis (83.3%)	Medically unmanageable localized infection	Hemoptysis 21 (84%)
Surgical treatment	55	41	22	32	130	85.7%	13	19 (76%)
Lobectomies	02			21	51	8.3%	02	04 (16%)
Segmentectomies	02	21	11	10	45	6.7%	05	
Pneumonectomies				05	33			
Lobectomies with segmentectomies								
Bilobectomies	01	10		02	17	6.7%		01(4%)
Thoracoplasties		06			03			
Cavernostomy	02			17		47%		
Others			06 (autopsy)				04	
Post operative complications (deaths)	26.1% (4.3%)	28.6% (2.8%)	NA (14.6%)	(5.7%)	40.2% (5.7%)	28.5% (3.3%)	41.6% (4.2%)	8%
Type of fungus	<i>Aspergillus</i> sp.	<i>Aspergillus</i> sp.	<i>Aspergillus</i> sp.	<i>Aspergillus</i> sp.	<i>Aspergillus</i> sp.	<i>Aspergillus</i> sp.	<i>Aspergillus</i> sp.	<i>Aspergillus</i> sp. - 20 Dematiaceous fungi - 3 Mixed infection - 2
Culture confirmation	Nil	Nil	Nil	Nil	Nil	Nil	Nil	<i>Aspergillus fumigatus</i> - 2 <i>Aspergillus flavus</i> - 1 <i>Pseudoallescheria boydii</i> - 1 <i>Candida albicans</i> - 1

Abbreviations: TB - tuberculosis

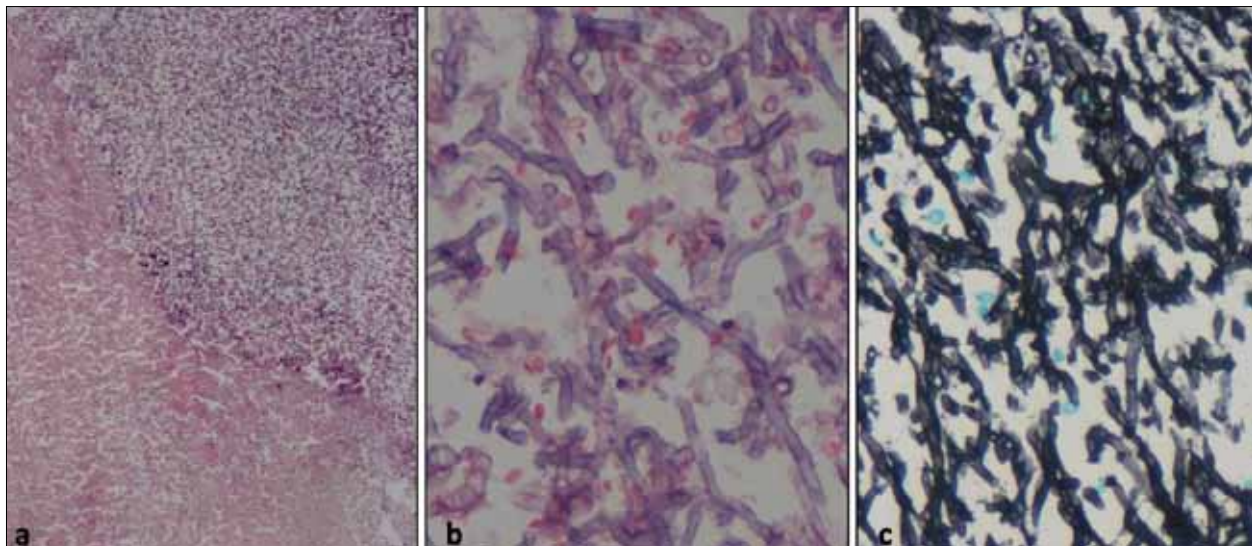


and neutrophils on the surface of the fungal ball. In four samples, there was a foreign body giant cell reaction, but no invasion into the lung parenchyma.

The fungal hyphae were slender, septate and with parallel walls and acute angle branching in 22 samples. No conidiophores were identified on H&E stain. The morphology was better delineated on GMS and PAS. In two samples, there were pseudohyphae and budding yeast forms of *Candida* sp. in addition to the septate hyphae. Masson



**Figure 2.** Cut surface of left apical segmentectomy specimen showing a large cavity with thick fibrotic wall and luminal brownish friable material (black arrow)

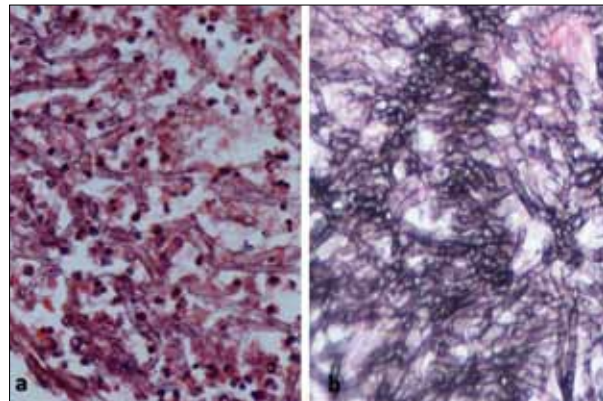


**Figure 3.** Histologic sections of aspergilloma. (a) Eosinophilic dead fungal hyphae (lower left) and basophilic viable hyphae (upper right) (H&E stain; X40). (b) Narrow septate, acute angled branching hyphae of *Aspergillus* sp. admixed with few red cells and neutrophils (H&E stain; X400). (c) Silver methenamine stain highlighting the fungal hyphae (GMS stain; X400)

Fontana stain showed variable positivity for melanin in the fungal hyphae. The fungal hyphae were negative with Perls stain. The walls of the cavity and alveolar macrophages showed positivity with Perls stain on morphology. These were identified as septate molds, most probably *Aspergillus* sp. (Figure 3b-c) Culture confirmation was available in only three and two of them grew *Aspergillus fumigatus* and one *Aspergillus flavus*. The culture grew *Candida albicans* in one sample of sputum.

In three specimens, the fungal hyphae were slender, septate and brown coloured on H&E stain and showed acute angle branching (Figure 4a-b). The hyphae were intensely positive with Masson Fontana stain and negative with Perls stain. On morphology, the fungi were identified as dematiaceous fungi. Culture was available in one sample which grew *Pseudallescheria boydii*.

The adjacent lung showed bronchiectasis with lymphoid follicles and nonspecific inflammation in 9 speci-



**Figure 4.** (a) Section from fungal ball showing slender and brown coloured hyphae of *Pseudallescheria boydii* (H&E stain; X400). (b) Masson Fontana stain confirming the presence of melanin within cell wall of *Pseudallescheria boydii* (Masson Fontana stain; X400)

mens. There were necrotizing granulomas with caseation in 5 samples.

## DISCUSSION

There are very few reported series of pulmonary cavitory lesions with fungal balls from India [2,10,11]. Most of the published series from the West and from India were clinical - highlighting the associated conditions, clinical presentation, surgical procedures, complications and long term outcome [2,10-15]. Table 2 compares the present study with the recent published series. None of the series highlight the fungal pathology or culture studies. Pulmonary tuberculosis was the commonest cause for cavitory lesion for a fungal ball in developing countries like India as well as in developed countries [2,10-14]. In our series, clinical evidence of tuberculosis was present in 68% cases as the cause for cavitory lesions. The diagnosis of tuberculosis was essentially clinical and radiological as histological evidence of tuberculosis in the resected specimen was seen in only 5/24 (20.8%) specimens. Hemoptysis was the commonest presenting feature and indication for surgery in our series. This was in agreement with other series [2, 10-12]. Diabetes mellitus as an associated or predisposing condition was seen in 2 of our patients and the majority of our patients were immunocompetent. A fungal ball or mycetoma consists of spherical mass of mycelia and hyphae with fibrin and neutrophils that partly fill the cavity without invading the tissue [8]. In two of our specimens, focal foreign body giant cell reaction was seen. Fungal balls are usually caused by fungi belonging to *Aspergillus* sp but rarely by dematiaceous fungi including *Pseudallescheria boydii*, *Fusarium* and *Sporothrix scheinkii*, *Mucor* (zygomycetes) and yeast fungi like *Candida species*, *Coccidioides* sp. [1,8]. Most of the colonizing fungi were referred to as *Aspergillus* sp. based on morphology alone, but it is difficult to differentiate *Aspergillus* sp. from dematiaceous fungi like *Pseudallescheria boydii* and *Fusarium* based on morphology alone without culture confirmation [16]. *Aspergillus fumigatus* was the commonest species colonizing the cavitory lesions of the lung, but other species of *Aspergillus* like *niger* and *flavus* were also reported to colonize [17]. There was culture confirmation in only three samples of *Aspergillus* sp., of which two grew *Aspergillus fumigatus* and one grew *Aspergillus flavus* in the present series. The low yield on culture may be due to the dead or necrotic hyphae that make up most of the fungal ball, with very few viable hyphae at the periphery. The lack of culture confirmation may also be partly due to failure on the part of the surgeons to submit the fungal balls for culture as routine, although sputum and BAL were routinely subjected to culture. There was no growth except for one sample of sputum which grew *Candida albicans*.

There were three dematiaceous fungi in the present series identified as brown coloured hyphae on morphol-

ogy and confirmed with Masson Fontana stain. *Pseudallescheria boydii* is an opportunistic pathogen that rarely involves the lung. The clinical and morphological appearances are similar to aspergillosis, but it is usually resistant to treatment with Amphoterecin B [7]. Voriconazole is reported to be effective in pulmonary pseudallescheriasis [18]. Our patient received itraconazole post-operatively.

Surgery was the treatment of choice for fungal balls to prevent hemoptysis and growth of mycetoma and eradicate the pyogenic component and prolong life [2]. The long term outcome for aspergillomas was good in a major series reported and the post operative complication rate varied from 5.7 to 41.6% [2,10-15].

Fungal serologic tests with aspergillin, histoplasmin, blastomycin and coccidioidin are useful in the preoperative diagnosis in assessing the correct organism [3]. However these tests are not widely available in developing countries like India. Surgery remains the mainstay of treatment if hemoptysis is massive and recurrent as in all our patients. Long term outcome with surgery was good in aspergillomas in various reported series [2,10-15]. Apart from minor post-operative complications, all patients in our series had a good outcome after surgery. Systemic and local administration of antifungal agents is of uncertain efficacy in aspergillomas [2,8]. Dematiaceous fungi like *Pseudallescheria boydii* require antifungal therapy after surgery [18]. Hence attempts at identification of colonizing fungus either on morphology or culture and immunological tests if available should be carried out.

## Conflict of Interest

No conflict of interest is declared by the authors.

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