

# To Determine the Prevalence of Fungal Infection Among Patient with Sputum Negative Old Treated Pulmonary Tuberculosis

Jai Kishan, Ajit Yadav, Sameer Singhal

## Abstract

A descriptive study was conducted in the Department of Respiratory Medicine in a tertiary care center of Ambala. Aim of the study was to determine the prevalence of fungal infection among patient presents with sputum negative old treated pulmonary tuberculosis. The study was carried out among 39 post treated cases of Pulmonary Tuberculosis, whose sputum or bronchial wash showed isolation of *Aspergillus*. Demographic details and clinical findings were noted. Data collected were entered into Excel spreadsheet and quantitative data were expressed as number and percentage. The presentation of pulmonary aspergillosis in treated cases of pulmonary TB varies from aspergilloma (51.3%) to chronic necrotizing pulmonary aspergillosis (38.4%) to allergic bronchopulmonary aspergillosis (10.3%). Hemoptysis (79.5%) of varying severity was the most common symptom. Most of the patients were farmers by occupation. The most common species were *Aspergillus fumigatus*; others were *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* in 23.2%, 20.5%, and 12.8 %, respectively. Here we conclude that *Aspergillus fumigatus* was the most frequently isolated species in our region and aspergilloma was the commonest pulmonary manifestation as post-TB sequel.

## Key Words

ABPA, CPA, Aspergilloma, Pulmonary Tuberculosis

## Introduction

Pulmonary mycosis is a parasitic disease of the lungs. It very well may be brought about by either endemic or opportunistic organisms or a blend of both. Case mortality in pulmonary mycosis can be as high as 90% in immune deficient patients, however insusceptible patients generally react well to antifungal treatment (1,2).

*Aspergillus* species are universal molds found in the organic matter. More than 100 species have been recognized, most of the human disease is brought about by *Aspergillus fumigatus* and *Aspergillus niger* and, less oftentimes, by *Aspergillus flavus* and *Aspergillus clavatus*. The transmission of parasitic spores to the human host is by means of inhalation (3). *Aspergillus* causes a range of sickness, from colonization to immune sensitive responses to chronic necrotizing diseases to quickly dynamic angioinvasion, frequently bringing about death (4).

ABPA is a hypersensitive immune response to *Aspergillus fumigatus* colonization of the tracheobronchial area and happens in relation with asthma and cystic fibrosis (CF). Unfavorably susceptible contagious sinusitis may likewise happen alone or with ABPA. Bronchocentric granulomatosis and malt specialist's lung are two extreme immune sensitive lung sicknesses that are brought about by *Aspergillus* species, yet they are uncommon (5). An aspergilloma is a parasite ball (mycetoma) that creates in a previous pit in the lung parenchyma. Hidden reasons for the cavitary malady may incorporate treated tuberculosis or other necrotizing disease, sarcoidosis, CF, and emphysematous bullae. The chunk of parasite may move inside the cavity, it might cause hemoptysis (6).

CNPA is a sub-intense procedure normally found in patients with some level of immunosuppression, most

From the Department of Respiratory Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana- India

Correspondence to: Dr. Ajit Yadav, Junior Resident, Department of Respiratory Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala (Haryana)

regularly that related with fundamental lung infection, liquor addiction, or long-haul corticosteroid treatment. Since it is unprecedented, CNPA frequently stays unrecognized for a considerable length of time or months and can cause a dynamic cavitory infiltration (5).

Obtrusive aspergillosis is a quickly dynamic, regularly lethal contamination, related with noteworthy mortality, with a rate of 30-95%, that happens in patients who are seriously immunosuppressed, including the individuals who are significantly neutropenic, the individuals who have gotten bone marrow or strong organ transplants, and patients with cutting edge AIDS or interminable granulomatous malady (7).

Fungal infections in lung often pose a difficult diagnostic challenge due to lack of any pathognomic clinical syndrome and characteristic radiological features. In India and other developing countries, the problem is further confounded by preponderance of pulmonary tuberculosis and paucity of diagnostic mycology laboratories (8). Clinical and radiological characteristics of pulmonary mycosis are very similar to that of pulmonary tuberculosis thereby making the disease easily misdiagnosed and mistreated as tuberculosis. Thus, the present study was undertaken with the aim to determine the prevalence of fungal infection among patients present with sputum negative old treated pulmonary tuberculosis.

### Material and Methods

The present study was conducted in the Department of Respiratory Medicine, MMU, Mullana, Ambala. This observational study was carried out among 110 old treated TB patients admitted in the hospital.

#### Inclusion criteria:

1. Not immunocompromised patients aged 18 years and above.
2. Patients with clinical signs and symptoms such as productive cough, weight loss, bronchiectasis or hemoptysis sustained for at least three months
3. Positive sputum and/or positive smear and/or culture for Aspergillus and/or positive lung histopathology suggestive of aspergillosis.
4. Chest X-ray/CT scan of the chest infiltrates suggestive of aspergillosis

#### Exclusion criteria:

1. Patients with previous antifungal treatment in the last two months before the clinical review
2. Patients with asthma or other disease with a

similar presentation (active PTB, endemic mycoses, Wegener's granulomatosis).

3. Hemodynamically unstable patients.

The study protocol was reviewed by the Ethical Committee of Hospital and was granted ethical clearance. After explaining the purpose and details of the study, a written informed consent was obtained from the patients who participated in the study. It was emphasized that strict confidentiality would be maintained at all times and the patients could withdraw at any time without being penalized.

Patients were enrolled and subjected to further clinical assessment and laboratory investigations; X-ray chest PA view, Sputum for AFB, Fungal culture, MGIT, Culture sensitivity, CBC and eosinophilic count and IGG specific to aspergillosis. Daniel criteria were used to diagnose Aspergilloma. CNPA (Chronic necrotizing pulmonary aspergillosis) on the basis of clinical, radiological, and microbiological criteria and ABPA (Allergic bronchopulmonary aspergillosis) is diagnosed by Rosenberg-Patterson criteria (9) which included a history of asthma and immediate cutaneous hyperreactivity to Aspergillus antigens or elevated specific serum IgE and elevated total IgE (>1000 IU/ml)

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages and mean.

### Results

A total of 39 patients were finally diagnosed with Aspergillosis out of all 110 old treated pulmonary tuberculosis. The mean age of the study patients was  $42.8 \pm 17.2$  years. Males outnumbered females by a ratio of 3:2. By occupation, 21 patients were farmer, 6 were laborer, 4 drivers and 8 patients belong to other occupations

**Table 1: Prevalence of Aspergillosis and Demographic Details of Study Population**

|                     |                       |
|---------------------|-----------------------|
| Aspergillosis       | 39 (35.45%)           |
| Age (mean $\pm$ SD) | 42.8 $\pm$ 17.2 years |
| Male: Female ratio  | 3:2                   |
| <b>Occupation</b>   |                       |
| Farmers             | 21 (53.8%)            |
| Laborer             | 6 (15.4%)             |
| Driver              | 4 (10.3%)             |
| Others              | 8 (20.5%)             |

(Table 1). Hemoptysis (79.5%) of varying severity was the most common symptom, followed by wet cough (38.5%), chest pain (33.3%), weight loss (41.0%), dyspnea (30.7%), fever (20.5%), dry cough (10.3%) and no symptoms found in (15.4%) (Table 2).

*Aspergillus fumigatus* was the most common species isolated in 28 patients followed by *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* in 23.2%, 20.5%, and 12.8 % cases, respectively (Table 3). Table 4 showed different forms of aspergillus as: 51.3% patients with simple aspergilloma, 38.4% patients of CPA and 10.3% patients with ABPA.

**Table 2: Clinical Symptoms Among Subjects Diagnosed with Aspergillosis**

| Symptoms    | N (%)      |
|-------------|------------|
| Hemoptysis  | 31(79.5%)  |
| Wet cough   | 15 (38.5)  |
| Chest pain  | 13 (33.3%) |
| Weight loss | 16 (41.0%) |
| Dyspnea     | 12 (30.7%) |
| Fever       | 8 (20.5%)  |
| Dry cough   | 4 (10.3%)  |
| No symptom  | 6 (15.4%)  |

**Table 3: Distribution of Species of Aspergillus Among Subjects Diagnosed with Aspergillosis**

| Species of Aspergillus       | N (%)      |
|------------------------------|------------|
| <i>Aspergillus fumigatus</i> | 17 (43.5%) |
| <i>Aspergillus flavus</i>    | 9 (23.2%)  |
| <i>Aspergillus niger</i>     | 8 (20.5%)  |
| <i>Aspergillus terreus</i>   | 4 (12.8%)  |

**Table 4: Distribution of Different Forms of Aspergillus Among Subjects Diagnosed with Aspergillosis**

| Form of Aspergillus | N (%)      |
|---------------------|------------|
| Aspergilloma        | 20 (51.3%) |
| CPA                 | 15 (38.4%) |
| ABPA                | 4 (10.3%)  |

## Discussion

Pulmonary tuberculosis is essentially a chronic destructive disease of the lungs. Caseation, necrosis and fibrosis lead to the formation of cavities with bronchiectatic dilations. These destroyed areas of the lung will no doubt continue to remain in the body even after the tubercle bacilli has been totally eliminated. These cavities form an ideal culture plate for the tubercle bacilli

and many other organisms including the fungi by providing plenty of oxygen along with necrotic tissue material. The fungal organisms tend to settle in the cavities and destroyed dilated bronchi, as a rule, after the tubercle bacilli has disappeared from these areas. Moreover, the prolonged anti-tubercular therapy in tuberculosis, which may last for well over 2 years with or without corticosteroids by itself, becomes a potent predisposing factor for the onset of superinfection by the fungal organisms. Therefore, it is not surprising to come across frequent references in the literature regarding the association of mycological super-infection with active pulmonary tuberculosis (10).

*Aspergillus* species are commonly found in every region of the world. *Aspergillus* species are commonly found in soil and decaying vegetation. They can be found in household dust, building materials, ornamental plants, flower arrangements, tobacco, food, and water. Conditions enhancing dispersal of molds are activities such as construction, demolition, excavation, disturbance of dust accumulations during routine cleaning, water leaks, and moisture accumulation (10). Among them, twenty are pathogenic in humans. *Aspergillus* species release conidia at high concentrations (1–100 conidia/m<sup>3</sup>) that are small enough (2–3 µm) to reach the pulmonary alveoli and cause a variety of pulmonary diseases (11). In the present study the presentation of aspergillosis varies from aspergilloma, CPA to ABPA in treated pulmonary TB patients.

In the present study, the prevalence of pulmonary aspergillosis was 35.45%. 49% prevalence was obtained by Yadu *et al.* (12). In a recent study conducted by Najeeb and Nagmoti (13), the prevalence observed was 52%. This might be due to the more exposure of the patients to the predisposing factors and environmental conditions favoring the growth of the fungus.

In our study, most of the patients were middle-age persons and there was a minor difference in the presentation in gender, with predominance in men. These results are similar to other investigations (14-17) and according to experts the disease is more frequent in middle-aged men (18). Aging affects the anatomy of the lungs, degenerating lung parenchyma and the elastic fibers around the alveolar duct. This process starts after the age of 40 years and results in expansion of airspaces and reduction in supporting tissue, so, over time, the risk of acquiring a chronic infectious/non-infectious disease increase (19).

*Aspergillus fumigatus* was the predominant species

isolated in 43.5% cases which is in line with the findings of Shahid *et al.* (20) The other species isolated were *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* in 23.2%, 20.5%, and 12.8 % cases respectively.

### Limitations

1. It is a single centre study and study results cannot be generalized.
2. An impediment of our investigation was that anti *Aspergillus* antibody agent was not used in every single speculated patient. On the off chance that could have been incorporated, likely the number of aspergillosis patients in treated aspiratory TB would have been higher.

### Conclusion

Our study concluded that *Aspergillus fumigatus* was the most frequently isolated species in our region and aspergilloma was the commonest pulmonary manifestation as post-TB sequel. The schemes for the diagnosis of respiratory diseases often underestimate fungal infections, especially pulmonary aspergillosis, because the appropriate tests are not performed. Clinicians must be aware of radiological and clinical signs of this disease and should look for support in microbiological tests, particularly for IgG antibodies detection. The correct identification would modify health statistics on tuberculosis and other diseases and could improve life expectancy for these patients and save resources from a mistaken diagnosis.

### References

1. Meersseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. *Clin Infect Dis* 2007;45(2):205-16.
2. Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2007;30(4):782-800.
3. Bennett JE. *Aspergillus* species. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 4th ed. New York: Churchill Livingstone, 1995. p. 2306-10.
4. Virnig C, Bush RK. Allergic bronchopulmonary aspergillosis: a US perspective. *Curr Opin Pulm Med* 2007;13(1):67-71.
5. Ader F, Bienvenu AL, Rammaert B, Nseir S. Management of invasive aspergillosis in patients with COPD: rational use of voriconazole. *Int J Chron Obstruct Pulmon Dis* 2009;4(2):279-87.
6. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. *Eur Respir J* 2011;37(4):865-72.
7. Naidich DP, Rom WN. Pulmonary aspergilloma and AIDS. A comparison of HIV infected and HIV-negative individuals. *Chest* 1997;111(3):612-18.
8. Randhawa HS. Respiratory and systemic mycosis: an overview. *Indian J Chest Dis Allied Sci* 2000;42:207-19.
9. Rosenberg M, Patterson R, Muintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunological contains for diagnosis of ABPA. *Am Thor Med* 1977;86:405 10.
10. Beck Sagué C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980 1990. National nosocomial infections surveillance system. *J Infect Dis* 1993;167:1247 51.
11. Latgé JP. *Aspergillus fumigatus* and aspergillosis. *Clin Microbiol Rev* 1999;12:310 50.
12. Yadu R, Nawange SR, Singh SM, Gutch RS, Gumasta R, Nawange M, *et al.* Prevalence of opportunistic fungal infection in patients with pulmonary tuberculosis in Madhya Pradesh, Central India. *J Microbiol Biomed Res* 2015;1:1-12.
13. Najeeb MAB, Nagmoti MB. Prevalence of fungi as opportunistic pathogens in active and post treated pulmonary tuberculosis cases - a comparative study. *EC Microbiology* 2019;15(2):153-57.
14. Muldoon EG, Sharman A, Page L, Bishop P, Denning DW. *Aspergillus* nodules, another presentation of chronic pulmonary aspergillosis. *BMC Pulm Med* 2016;16(1):123.
15. Hedayati MT, Azimi Y, Droudinia A, Mousavi B, Khalilian A, Hedayati N, *et al.* Prevalence of chronic pulmonary aspergillosis in patients with tuberculosis from Iran. *Eur J Clin Microbiol Infect Dis* 2015; 34:1759-65.
16. Chawla K, Kosaraju K, Rayasam S, Mukhopadhyay C. Clinico-microbiological profile of chronic pulmonary aspergillosis from a tertiary care centre in southern India. *J Clin Diagn Res* 2013;7:2712-15.
17. Amiri MRJ, Siami R, Khaledi A. Tuberculosis status and coinfection of pulmonary fungal infections in patients referred to reference laboratory of health centers Ghaemshahr City during 2007-2017. *Ethiop J Health Sci* 2018;28(6):683-90.
18. Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: Case series, proposed nomenclature change, and review. *Clin Infect Dis* 2003;37:265-80.
19. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging* 2006;1:253-60.
20. Shahid M, Malik A, Bhargava R. Prevalence of aspergillosis in chronic lung diseases. *IJMM* 2001;19(4):201-05.