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ORIGINAL ARTICLE

Spectrum of Aspergillus infections in post TB patients

G N Srivastava[1], Srayani Kanchi[2], Ragini Tilak[3]

ABSTRACT

Background: Fungal colonisation of airways in Post TB patients, can lead to a spectrum of diseases based on the immune response of the host. This study was aimed at studying the different entities of this spectrum. **Methods:** A cross sectional observational study was conducted over 100 patients of post TB patients to make an observation of the diseases of the spectrum of Aspergillus infections. **Results:** Of the 100 patients who were studied, IPA was found in 24 (48%), ABPA in 13(26%), CPA in 5(10%) patients out of the 50 diabetics. ABPA in 23 (46%) patients, Simple colonization, CPA in 11(22%) and 4 (8%) patients showed IPA out of the 50 non-diabetics. **Conclusion:** Chronic pulmonary Aspergillosis was the most common disease from Aspergillus among Post TB patients. Diabetes was associated to invasive forms of Aspergillosis, Invasive Pulmonary aspergillosis (IPA) and subacute invasive pulmonary aspergillosis (SAIA).

Keywords: Aspergillus, Post TB, Chronic pulmonary aspergillosis, Allergic bronchopulmonary aspergillosis, Invasive pulmonary aspergillosis.

Introduction

Aspergillus is a mould, whose spores are found almost everywhere. An immuno-competent host, with a normal pulmonary structure, on exposure to the spores, might not develop any infection, and by the innate immune response and defence mechanisms, will not allow colonisation of the hyphae in the respiratory tract. The high prevalence of Aspergillus infections in immuno-compromised host is well known and extensively studied in post transplant patients, GVHD patients, PLHIV etc. In patients with abnormal permanent modification of pulmonary structure, post TB; which is highly prevalent in TB endemic countries like India; Aspergillus has been identified frequently colonizing the airways, and causing disease, with varied presentations. The spectrum of diseases falling under the umbrella of Aspergillus infections include, The Allergic type (Severe Asthma with Fungal Sensitization, Allergic Bronchopulmonary Aspergillosis); Chronic Pulmonary Aspergillosis (Aspergillus Nodule, Asergilloma, Chronic Cavitary Pulmonary Aspergillosis, Chronic Fibrotic Pulmonary Aspergillosis, Subacute Invasive Aspergillosis) and Invasive Pulmonary Aspergillosis.

.The presentation or the disease that develops depends on the host factors. The immune status, pulmonary structure abnormalities present in the patient, lead to a particular immune response, which leads to disease. In patients with hyper immune status, with atopy, allergic hypersensitivity to inhaled Aspergillus spores is seen. This response is seen in patients suffering from Bronchial Asthma, and can be of two types, Severe asthma with fungal sensitization (SAFS) and Allergic bronchopulmonary Aspergillosis (ABPA) based on the serological markers and radiographic changes. Recently, ABPA has been reported in patients without atopic history, cystic fibrosis and asthma; but with structural lung diseases caused by permanent deformities of the airway by tuberculous infections.

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1. Professor & Head of Department of TB & Respiratory Diseases, Institute of Medical Sciences, BHU, Varanasi
2. Junior Resident, Department of TB & Respiratory Diseases, Institute of Medical Sciences, BHU, Varanasi
3. Professor, Department of Microbiology, Institute of Medical Sciences, BHU, Varanasi

Corresponding Author: Dr. Sravani Kanchi, Junior Resident, Room # 53, Kasturba Hostel, BHU, Varanasi 221 005;
Email: sravani11.kanchi@gmail.com ; Mobile – 7505482930

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Colonization of cavities and dilated bronchi by hyphae of Aspergillus has been observed in patients with structural lung diseases. Destruction of cilia and bronchiectasis lead to inability of expectoration of the fungal elements, and increased mucus production and anatomical deformity form a favourable environment for hyphal growth. In some patients, colonisation of airways by hyphae without development of disease has also been observed. Post tubercular cavities are frequently colonized by hyphae, without tissue invasion. This type of Aspergillus infection is called Chronic pulmonary Aspergillosis. Based on the radiographic extent of involvement and underlying lung anatomy, it can be of many types like Aspergillus nodule, Aspergilloma, Chronic Cavitary Pulmonary Aspergillosis (CCPA), Chronic Fibrotic Pulmonary Aspergillosis (CFPA) and Subacute Invasive Aspergillosis (SAIA).

In immuno-compromised patients, the hyphae are not confined to the airways and cavity and invade into the lung parenchyma and vascular structures, leading to Invasive Pulmonary Aspergillosis. Previously, largely described in critically ill ICU patients, severely immuno-compromised conditions. Recently, IPA has been reported in patients without severe immuno-compromise in Post TB patients with co-morbidities like diabetes mellitus, chronic steroid use.

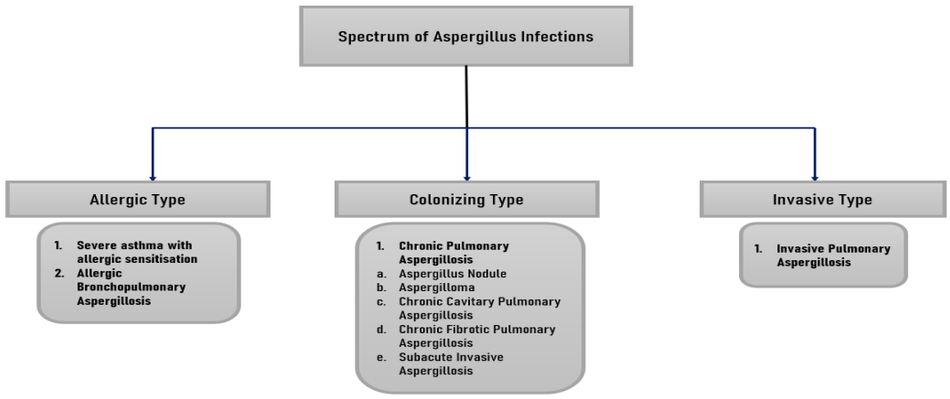

Figure 1: *Types of diseases in the spectrum of Aspergillus Infections of the lower respiratory tract.*

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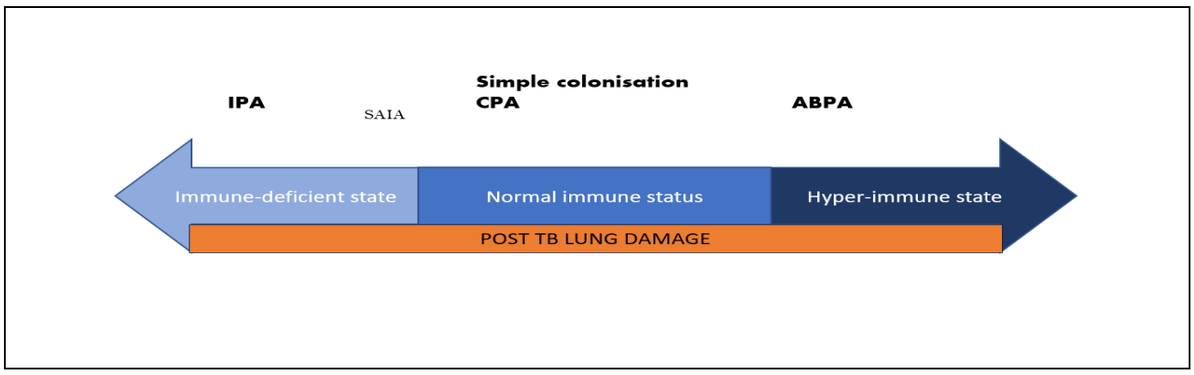
Figure -2: *Host factors interaction with Aspergillus, for disease presentation.*



Materials and Methods

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Aims and objectives of the study –

1. To evaluate clinical, immunological, microbiological and radiological features of aspergillus infection in Post Tuberculosis patients with and without diabetes mellitus.
2. To study the relationship between aspergillus infection causing disease spectrum with diabetes mellitus.

Inclusion and exclusion criteria:

Inclusion criteria:

1. Age above 18years
2. Patient willing to provide signed informed consent
3. Post TB patients with fungal infections.

Exclusion criteria:

1. Age group less than 18 yrs.
2. Patient not willing to provide signed informed consent.
3. Patient on chemotherapy/immunotherapy.

   Chronic kidney disease/chronic liver disease

Statistical analysis: All data were analyzed by using a statistical software package called statistical program for social sciences version 16 (SPSS, CHICAGO, IL). All calculations were also done by this program. Differences with p value less than 0.05 were considered as statistically significant.

Results

With the help of clinical examination and a battery of investigations, a spectrum of fungal diseases were diagnosed, that include

1. Colonisation of airways by fungi
2. ABPA
3. Aspergilloma type of Chronic Pulmonary Aspergillosis
4. Invasive Pulmonary Aspergillosis
5. Mucormycosis

A few patients also had a combination of ABPA and IPA.

Table 1:

DM	ABPA		ABPA plus IPA		Aspergilloma		Colonisation		IPA		Mucormycosis	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
No	23	63.9	0	0	11	68.8	8	100.0	4	14.3	4	50.0
Yes	13	36.1	4	100.0	5	31.3	0	0	24	85.7	4	50.0
Total	**36**	**100.0**	**4**	**100.0**	**16**	**100.0**	**8**	**100.0**	**28**	**100.0**	**8**	**100.0**

In Table 1, show the 63.9% of ABPA patients were non-diabetic, and 36.1 % were diabetic. The group of patients with Aspergilloma had 68.8% non-diabetic patients. Diabetics formed the major chunk of 85.7% in IPA patients. Simple colonisation was seen in 0% diabetics.

Invasive Pulmonary Aspergillosis was found in 24 patients out of the 50 diabetics, followed by ABPA in 13 patients. 4 patients in this group had IPA along with a hypersensitivity reaction causing ABPA. Chronic Pulmonary Aspergillosis in the Aspergilloma form was seen in 5 patients and 4 patients had Mucormycosis. There were no diabetic patients with simple colonization fungi and no disease. ABPA was the disease in 23 patients out of the 50 non-diabetics. Simple colonization with no disease was seen in 8 patients.

Table -2: Diagnosis of patients

Diagnosis	Diabetes Mellitus			
	Yes		No	
	No.	**%**	**No.**	**%**
ABPA	13	26.0	23	46.0
ABPA plus IPA	4	8.0	0	0.0
Aspergilloma (CPA)	5	10.0	11	22.0
Colonisation	0	0.0	8	16.0
IPA	24	48.0	4	8.0
Mucormycosis	4	8.0	4	8.0
Total	**50**	**100.0**	**50**	**100.0**

P<0.001

CPA was the second most common form of fungal infection among non-diabetics, was seen in 11 patients of this group. There were 4 patients of Invasive Pulmonary Aspergillosis and 4 of Mucormycosis.

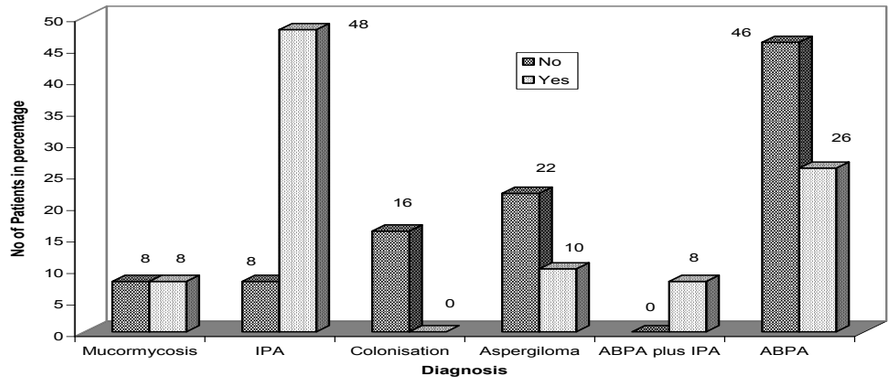
As described above and represented graphically below, IPA was the most common fungal infection among Post Tubercular Diabetic patients and ABPA was the most common disease in Post Tubercular Non diabetic patients **(Fig.-1).**

Discussion

Fungal infections of the lower respiratory tract have been seen more commonly in immuno-compromised individuals, and in people with underlying chronic lung disease. Post tubercular patients are a major cohort of population that has underlying airway distortion, bronchiectasis, fibro-cavitary disease and destroyed lung. They are most commonly infected by Aspergillus species and the infections causes a spectrum of diseases based on the immune status of the host.

- Colonization of the airways by fungi, without any symptomatic and serological presentation.
- Allergic sensitization with ABPA
- Chronic pulmonary aspergillosis with Aspergilloma and no serological marker of invasion.
- Invasive Pulmonary Aspergillosis.

Figure-1: Diagnosis of Diabetic patients



Present study was carried out in 100 post tuberculosis patients, 50 Diabetics and 50 Non-diabetics, in which fungal infection was suspected. Patients selected from TB and Respiratory diseases department in Sir Sundarlal Hospital, Institute of Medical Sciences, BHU. The objective of the study was to study and evaluate the spectrum of fungal diseases and their clinico-serological presentation in post tubercular patients and relation with diabetes mellitus. The study period was from May 2019 to July 2021.

Colonization of respiratory tract by fungi without any clinical presentation and serological markers, was seen in only 16% of the non-diabetic patients of the group. It is common in patients with airway diseases like asthma, bronchiectasis and post tuberculosis lung disease to have airway colonisation by fungi. The immune response and disease progression depends on a number of host factors like, immune status, airway distortion etc. Patients with a hyperimmune state and genetic predisposition can be seen to develop allergic hypersensitivity to the colonized fungi and can present as severe asthma with fungal sensitivity (SAFS) and allergic bronchopulmonary aspergillosis (ABPA). SAFS is a presentation seen in asthma patients and has not been studied in post tuberculosis patients. Presence of ABPA in post tuberculosis airway disease has been seen in recent times. Owing to the pulmonary impairment after tuberculosis infection, a favourable environment for fungal colonisation is seen. Possibly due to waning of Th1 response post tubercular treatment and underlying atopy in some patients, makes them prone to development of ABPA against the colonized fungi. In our study, 26% of the diabetic group and 46% of the non-diabetic group were suffering from ABPA, among the post tubercular fungal infection patients. This suggests that diabetics were less prone to developing ABPA due to their impaired immune status unlike the non-diabetic patients. 33.3% of patients with ABPA in our study group were in the age group of 41-50 years. Major symptom profile of ABPA patients included, hemoptysis (66.7%), Dyspnea (77.8%), Cough with expectoration (77.8%) and blackish sputum production (11.1%). 66.7% of patients showed septate hyphal growth on KOH mount examination of sputum and 33.3% had growth on fungal culture examination. ABPA is a hypersensitivity reaction to the presence of colonised fungi in the airways, leading to bronchiectasis. Presence of fungal hyphae in expectorated sputum hence does not signify presence of an invasive disease. A total serum IgE, marker of

hyper allergic reaction, of greater than 1000IU/ml was seen in 88.9% of the patients, with positive IgE specific for Aspergillus in 100% of them. IgG and IgM antibodies signify presence of exposure to Aspergillus in the past and recent past, respectively. IgG specific for Aspergillus was found to be positive in 100% of ABPA patients, and IgM specific for Aspergillus was found in 55.6% of patients. In comparison to our outcomes, results from other published literature from India about clinical profile in ABPA include, Behera et al (1994) that showed history of anti TB drugs intake in 34% of patients[1] and Shah et al (2003)[2] and another study of 2007 [3] showed previously treated pulmonary TB in 84% and 91% of the patients suffering from ABPA. An elevated serum IgE of greater than 100 IU/ml was seen in 100% of the patients with specific aspergillus IgG, IgE positivity in 81% of the patients.

Chronic pulmonary aspergilloma, which is a non-invasive fungal colonisation of the airways and cavities, in the form of Aspergilloma and aspergillus nodule, was seen in 10% of the diabetic group and 22% of the non-diabetic group. Among these, 88.8% had a fibro-cavitary lung disease, causing chronic cavitary pulmonary aspergillosis and Chronic fibrotic pulmonary aspergillosis. 12.2% had normal lung parenchyma with aspergillus nodule. Presence of post tubercular fibro-cavitary disease can be a predisposing factor for fungal colonisation and fungal ball formation. Absence of an invasive disease with a radiological evidence of fungal ball is suggestive of CPA. Symptoms of presentation in CPA include, hemoptysis (100%), dyspnea (25%), and cough with expectoration (25%). Sputum KOH mount with fungal hyphae was seen in 50% of the patients, with only 25% having a positive fungal growth on culture. Positivity of IgG (25%) and IgM (25%) specific for Aspergillus was seen in serum. Serum IgE more than 1000IU/ml was never seen, but a moderate rise of 500-1000IU/ml was present in 25%. Radiological imaging showed, fibrocavitary disease in 75% of the patients, and 25% had a normal lung parenchyma with aspergillus nodule. An observational study by Nyugen et al in Vietnam, about chronic pulmonary aspergillosis among post TB patients in Vietnam[4], showed that 12.5% of patients were diabetic, comparable to our result showing 31.3% of CPA patients were diabetic. This could be due to higher diabetes prevalence in Indian population. Major symptom profile included productive cough (81.6%), hemoptysis (47.4%), dyspnea (55.3%) and cavitary disease was seen in 21.1% of the patients. Some Indian case series of CPA include Sehgal et al (2018) that had 269 patients with 85.5% having pulmonary TB. Median age was 44.3 years and male female ratio was 1.15:1[5], comparable to our study.

Invasive pulmonary aspergillosis was seen in 56% of diabetic patients suffering from fungal disease and only 8% of the non-diabetic group. This suggests a major role of presence of diabetes mellitus in developing IPA in a post tuberculosis patient. Impairing the phagocytosis by macrophages, impairing cytokine production, and most importantly neutrophil dysfunction; helps the fungi to evade host defence mechanisms and invasion of fungal hyphae into the lung parenchyma. It is detected through presence of fungal hyphal antigens in the blood stream and histopathological presence of fungal hyphae in the lung parenchyma. Among IPA patients, 85.7% were suffering from diabetes mellitus. Major symptoms of presentation in IPA patients were hemoptysis (71.4%), dyspnea (57.1%), cough with expectoration (57.1%) and blackish sputum (42.9%). Sputum KOH mount examination showed septate hyphae in 25% patients and a growth on fungal culture was seen in 71.4% patients. Serum specific IgG and IgM for aspergillus were found to be positive in 14.3% and 42.9%, respectively. Serum galactomannan assay was measured and found to be raised in 100% of the patients. In our present study IPA was seen in 28% of the study group, which is comparable to a study done by Svasankari S et al in Kanchipuram India, which had 30.8% of PTB patients suffered from IPA.[6] Another study by Sunita et al in 2008, showed 46% prevalence of fungal invasive disease in TB patients.[7] An international study conducted by D Rotjanapan et al, an epidemiologic and clinical study of invasive mould infections, in five Asian countries in 2018, showed 30.9% suffering from invasive disease were diabetics, without other immunosuppressing factors like neutropenia, prolonged steroid use ($p<0.006$)[8].Clinical presentation profile included breathlessness (49.7%), hemoptysis (12.9%). The difference in symptom

profile can be attributed to subjective error of perception and higher prevalence of destroyed lungs among Indian population due to infection from TB at young age.

Conclusion

Fungal infections of the lung are common in patients with underlying lung disease due to permanent destruction of lung parenchyma caused by pulmonary tuberculosis. Aspergillus species cause a wide spectrum of disease in the post TB patients, with a similar clinical profile of presentation. Host immune factors and genetic factors play a major role in the progress of disease and its course after initial fungal colonisation. Allergic sensitisation, ABPA, which is widely known to be cause of bronchiectasis in severe asthma patients, is also seen in post tuberculosis patients with destroyed lung, fibro-cavitary disease and post tuberculosis obstructive airway disease. Diagnosis of specific disease can be done through an array of investigation parameters, serological and sputum based. Diabetes mellitus is a major factor in compromising immune system and leading to cause invasive pulmonary aspergillosis.

Inspite of ubiquity of fungal agents, spores in the air, only immune-compromised patients have the predilection to have colonisation of fungal hyphae in airways. The immune status of the patient further denotes the appropriate immune reaction to the colonised fungi. Immune reaction dominated by allergic response, causes allergic sensitisation and ABPA. A less responsive immune status and presence of cavitary lesions form a favourable environment for formation of fungal ball, aspergilloma and causing CPA. Immune debilitated patients develop IPA, due to invasion of fungal hyphae into the lung parenchyma and vascular spillage of hyphal antigens. Fungal lung diseases of Aspergillus species can be of grave consequences with major symptom being hemoptysis, hence need extensive study and further research over early diagnosis and treatment, to reduce misdiagnosis of post tuberculosis patients.

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