J. Biol. Chem. Research. Vol. 26, No. 2: 28-34 (2009)
(An International Journal of Life Sciences and Chemistry)

ISSN 0970-4973 (Print)
Published by Society for Advancement of Science®

jbiolchemres@gmail.com
info@jbcr.in

REVIEW ARTICLE

Aspergillus Induced Respiratory Diseases

Surya Kant and D.M. Rizvi
Department of Tuberculosis and Chest Disease, King George's Medical College, Lucknow – 226 003 U.P., INDIA

ABSTRACT

Fungi are a group of Thallophyta devoid of chlorophyll obtained their nourishment either as saprophyte or parasite. It produces spores which are prevalent in air and water etc. may act as fungal allergens as are small enough to be respirable thus affect skins, lungs and other organs are in direct contact with other. Several species of fungi are pathogenic, also causes allergic disorders viz. asthma, alveolitis and urticaria etc.

Recent studies identified 19 out of 700 species as Aspergillus distributed worldwide because a board spectrum Aspergillus induced respiratory diseases inducing chronic obstructive pulmonary disease (COPD), Bronchial asthma, Aspergillus and alveolitis etc. The details of disease have been described in tables.

Keywords: Aspergillus species, Respiratory diseases, Asthma, Alveolitis and Urticaria.

INTRODUCTION

The fungi are a group of spore bearing, often filamentous organism which lack chlorophyll and therefore obtain their food by either a saprophytic or a parasitic existence. Many fungi exist in a unicellular form (known as yeast) which reproduces by asexual budding. In the filamentous form, each filament is known as 'hypha' and a mass of hyphae is known as 'Mycelium'. The filamentous forms can produce spores which are adapted to survival in adverse conditions and to dispersal by air, water or animals. The air is full of fungal spores, and most of these spores are small enough to be respirable , and generally therefore fungal disease affect the skin and lungs, organs in direct contact with air. The fungi can exert pathogenic effects in the lung, by allergic sensitization, by colonization, or by invasion and tissue damage. All air bone fungal spores have at least the potential to cause asthma, and many if inhaled in high dosage, may cause alveolitis.

Classification of pathogenic fungi and the respiratory disease caused by them are given in Table 1.

ASPERGILLUS INDUCED RESPIRATORY DISEASES

Only 19 of the nearly 700 species of *Aspergillus* cause human infections. *A. fumigatus* is the most frequently pathogenic species; other species include *A. niger, A. flavus, A. terreus, A. clavatus, A. glaucus* and *A. nidulans. (*Metzger et al. 1984, Loham, and Carpenter, 1982 and Ridell et al, 1968*).* The distribution of Aspergillus is worldwide and it is commonly found on stored hay or gain, decaying vegetation, soil, dung and various organic debris. It's spore size (2.5 to 3μm) and optimum temperature and oxygen requirements make it ideally suited to survival within the airways. In addition it seems to have developed sophisticated defense against *Aspergillus,* these mechanisms have probably evolved for protection against amoebae in the soil, the natural predators of fungal spores (Old and Darbyshire 1968).

The spectrum of *Aspergillus* induced respiratory disease is given in Table 2.

The various manifestations have been briefly described below.

1. Simple colonization: It is the existence of *Aspergillus* on body surfaces and bronchi without eliciting any pathological responses. Chronic obstructive Pulmonary Disease (COPD) patients are at an increased risk due to frequent use of corticosteroids and antibiotics.

2. Allergic bronchial ashtma: It occurs when an atopic individual is sensitized to *Aspergillus* spores (Conidia). These patients show positive immediate skin reaction to *Aspergillus* antigens. Management is like any bronchial asthma.

3. Allergic Broncho Pulmonary *Aspergilosis* (ABPA): ABPA occurs in atopic individuals with Asthma or cystic fibrosis. (Bardana et al, 1975 and Mearns et al. 1965). In ABPA inhaled *aspergillus* conidia induce bronchial allergic reactions in the form of Bronchospasm (Type I, IgE mediated immediate hypersensitivity reaction) and bronchial and peribronchial inflammation (Type III or immune complex mediated reactions in which IgC precipitating antibodies are involved), which give rise to mucus plugs and can progress to mucoid impaction resulting in atelectasis and transient pulmonary infiltrates. Chronic inflammation of bronchi results in bronchiectasis and pulmonary fibrosis. (Wardlaw and Geddes, 1992)

Clinical Presentation: ABPA presents with recurrent wheezing, Malaise with low grade fever, cough, expectoration (blood streaked), chest pain and pulmonary infiltrates.

Radiographic Findings: may be transient or permanent transient findings may be the result of parenchymal infiltrates, mucoid impactions or secretions in damaged bronchi[10]. Permanent findings include proximal bronchiectasis, cavitation, local emphysema, contracted upper lobes and honey comb fibrosis.

Diagnosis of ABPA: The diagnostic criteria are given in Table 3 and 4. Patterson and Co workers have defined 8 criteria. Individuals meeting 7 of these make the diagnosis of ABPA highly likely, and the presence o all 8 criteria confirms the diagnosis.

Management: The staging of ABPA and the stage wise management is given in Table 5.

Corticosteroid therapy for ABPA is in the form of Prednisolone 1 mg/kg/day till resolution of chest radiographic changes, followed by 0.5 mg/kg/day for 2 weeks and then 0.5mg/kg on alternate days for the next 3-6 months, to be followed by gradual tapering no faster than 5 mg. per month.

4. Bronchocentric granulomatosis: Is most likely represents a severe but localized manifestation of ABPA (Wardlaw and Geddes, 1992). It is characterized histologically by necrotizing granulomatous replacement of bronchial mucosa with eosinophilic infiltration of bronchioles.

Clinical presentation is with chronic symptoms of malaise, fever, cough, dyspnoea, chest pain and haemoptysis associated with a focal lesion on chest X-ray, often in the upper lobe[14]. Diagnosis is made by biopsy and histopathology.

Treatment (a) Excision of lesion is curative.

(b) Corticosteroids may be needed, as in ABPA, if lesions are multiple.

5. Extrinsic allergic alveolitis: In non atopic individuals, heavy or repeated exposure to Aspergillus conidia and mycelia may result in Type III and Type IV hypersensitivity reactions affecting the alveoli.

It manifests as cough, dyspnoea, fever, chillis, myalgias and malaise, 4-8 hours after exposure to antigen[15]. Seen in malt workers, distillers, brewers and others exposed to moldy straw or grain. Repeated exposure may lead to the 'malt worker's Lung' or 'Farmer's Lung' and to the development of granulomatous disease and interstitial fibrosis. It is managed by avoidance of exposure and corticosteroids.

6. Aspergilloma (mycetoma/fungus ball): It is the saprophytic colonization of a parenchymal cavity by Aspergillus (the usual species is A. fumigatus). It may be secondary or primary. Secondary aspergilloma is the usual form, in which the fungus colonizes and proliferates in a preexisting pulmonary parenchymal cavity, most commonly it is a tuberculosis cavity[17], but primary aspergilloma is the condition where the cavity forms due to proliferation of Aspergillus, it can form in condition like invasive pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis and ABPA.

Haemoptysis is the most frequent symptoms of asperilloma (occurring in 74% cases)[16]. Diagnosis is suggested by chest radiography[18]. Management can be decided according to severity of symptoms.

No symptoms – leave well alone.

Minor haemoptysis – Symptomatic treatment

Larger haemoptysis – Elective treatment – (Bronchial artteriography and resection)

or cavernoscopic evacuation of g fungus.

Massive haemoptysis – Embolization, followed by elective treatment.

Direct intra cavitary installation of antifungal agents like Amphotericin B, Sodium iodide, Natamycin, Miconozole, Ketoconazole and 5 FC have shown promise.[19]

7. Bronchial Stump Aspergillosis (BSA): If silk suture is used to suture the blind end of a bronchus after lung resection, the portion of the suture which is exposed to the bronchial lumen lead to establishment of *Aspergillus* infection at that site (favoured by local)inflammation, compromised tissue viability and high capillarity of silk thread). Presentation is with cough, sputum production (which may be putrid) and haemoptysis, usually 6-12 months after surgery.

Treatment – Bronchoscopic removal of suture is curative.
– Prevention can be done by using Nylon Monofilament suture, instead of silk[20].

8. Chronic Necrotizing Pulmonary Aspergillosis (CNPA): It is a slowly progressive form of Aspergillosis seen in patients with systemic immuno compromise, as a result of corticosteroids diabetes mellitus, alcoholism, poor nutritional status, or in those with underlying pulmonary disease such on COPD, sarcoidosis, inactive tuberculosis pneumoconiosis and radiation fibrosis. The body reacts to this tissue invasion by fibrosis and granulomatous reaction and it presents with chronic symptoms of fever, weight loss, productive cough and haemoptysis. Treatment is by antifungals agents (Amphoterium B with or without 5 FC or itraconazole).

9. Invasive Pulmonary Aspergillosis (IPA): It is seen in severely immuno compromised hosts, such as, patients of acute lymphocytic leukaemia or acute myteloblastic leukaemia with granulocytopenia during treatment, patients receiving high dose corticosteroids + immunosuppressive therapy as in transplant recipients and chronic granulomatous disease.

The hyphae proliferate and invade the lung parenchyma and pulmonary arterioles into which the hyphae may embolize and produce dissemirated disease and embolic phenomena in other organs.

Clinical presentation is with fever followed by mild cough with pleuritic chest pain and progression to pneumonia in 1-2 days. Radiographically the typical lesion is, one or more well defined nodules or a patchy density which later progresses to diffuse consolidation or cavitation. Definitive diagnosis is made by histopathology, but empiric therapy is strongly indicated in the appropriate clinical setting if the lesions are not responding to broad spectrum antibiotics. Treatment – Intra venous Amphotericin B in high doses (1 to 1.5 mg/kg/day.

Table 1. Classification of pathogenic fungi and the respiratory diseases caused by them

Class	Genus	Mian Disease
Zygomycetes	*Absidia* *Mucor* *Rhizopus*	Mucormycosis
Ascomycetes	*Allomyces* *Emmonsiella*	Blastomycosis Histoplasmosis
Basidiomycetes	*Filobasidiella*	Cryptococcosis
Hypomycetes	*Aspergillus* *Coccidioides* *Paracoccidiodes* *Pseudoallerscheria* *Sporothrix*	Aspergillus Coccidioidomycosis Parococcidiodomycosis Mycetoma Sporotrichosis
Blastomycetes	*Candida*	Candidiasis

Table 2. The spectrum of *Aspergillus* induced respiratory diseases.

Clinical Manifestation	Immune Status	Lung Architecture (Underlying)	Degree of Tissue Invasion
I. Simple colonization	Normal	COPD	None
II. Hypersensitivity Reactions a. Allergic Bronchial Asthma b. ABPA c. Bronchocentric granulomatosis d. Extrinsic allergic alveolitis	Hyperactive normal response	 Normal Excess airway mucus Excess airway mucus Normal	 None None None None
III. Colonization a. Aspergillosis	Normal	Preexisting cavity	None
IV. Invasive Disease a. Bronchial Stump Aspergillosis b. Chronic Necrrotizing pulmonary Aspergillosis c. Invasive Pulmonary Aspergillosis	Normal Suppressed Immune Response Severely depressed immune response Neutropenia	Pneumonectomy Normal Normal	* * ***

Table 3. Criteria for the diagnosis of ABPA.

PRIMARY

- **I.** Episode bronchial obstruction (Asthma).
- **II.** Peripheral blood eosinophilia (> 1000/ml^3).
- **III.** Immediate type skin reactivity to as per *Aspergillus* antigen.
- **IV.** Precipitating serum antibodies against *Aspergillus* antigen.
- **V.** Elevated total serum IgE (>1000 ng/ml).
- **VI.** Elevated serum IgE specific to *A. fumigatus*.
- **VII.** History of pulmonary infiltrates (transient or fixed).
- **VIII**. Central bronchiectasis.

SECONDARY

- *A. fumigatus* in sputum.
- History of expectoration of brown plugs or flecks.
- Arthus reactivity (late skin reactivity) to *Aspergillus* antigen.

Table 4. Serologic studies of value in diagnosis of ABPA.

Serologic Test	Positive
1. Total serum IgE	> 1000 ng/ml.
2. Precipitation test	Precipitation band present.
3. IgE antibody index	> 2 compared with asthma pool.
4. IgG antibody index	> 2 compared with asthma pool.
All four results positive	– Diagnostic of ABPA
Three results positive	– Consistent with ABPA
Two results positive	– Repeat serology in 3 – 6 months
One positive or all negative	– ABPA excluded.

(Required if immediate type skin hypersensitivity to A. fumigatus is positive, using a Prick test)

Table 5. Staging system for ABPA.

Stage	Symptoms	Radiographic features	Laboratory features	Management
Acute	Fever, productive cough, wheezing	Pulmonary infiltrates mucoid impaction	Blood eosinophilia increased serum IgE +ve skin test	Corticosteroids to achieve remission
Remission	Asymptomatic	Normal	Decrease in IgE and blood eosinophilia	Follow up (monthly IgE levels)
Exacerbation	All or some of acute stage symptoms	All or some of acute stage findings	Atleast a doubling of IgE in a symptomatic patients and an increase in IgE in symptomatic patients.	Retreat with corticosteroids to induce remission
Corticosteroid Dependent	Symptomatic, Steroid requiring asthma	Variable	Usually continued elevation of IgE	Long term corticosteroids
Fibrotic	Severe dyspnoea, Fibrotic lung disease + Broncho – spasm.	Pulmonary fibrosi/ bronchiectasis (central)	Restrictive + irreversible and reversible obstructive features	Long term corticostteroids

REFERENCES

Metzger, J.B, Gragusi, V.F and Kerwin, D.M. 1984. Pulmonary oxalosis caused by *Aspergillus niger. AM. Rev. Respir. Dis.* (129), 501.

Loham, M.N and Carpenter, J.L. 1982. *Aspergillus terreus*, a pathogen capable of causing infective endocarditis, pulmonary mycetoma and allergic bronchopulmonary aspergillosis. *AM Rev Respir Dis* (129), 769.

Ridell, H.F.V, Channell, S. and Blyth, W. 1968. Allergic alveolitis in a malt worker. *Thorax* (23), 271.

Lehrer, R.I. and Jan, R.G. 1970. Interaction of *Aspergillus fumigatus* spores with human leucocytes and serum. *Infect*. *Immun* (1), 345.

Robertson, M.D, Seaton, A., Milne, L. J. R. and Raeburn, J.A. 1987. Resistance of spores of *Aspergillus fumigatus* to ingestion by phagocytic cells. Thorax (42), 466.

Old, K.M. and Darbyshire, J.F. 1978. Soil fungi as food for giant amoebae. *Soil. Biol. Biochem* (10), 93.

Bardana, E.J, Sobti, K.L, Cianciulli, F.D. and Noonan, M.J. 1975. *Aspergillus* antibody in patients with cystic fibrosis. *Am. J. Dis. Chold.* (129), 1164.

Mearns, M.B, Young, W. and Batten, J.C. 1965. Pulmonary infiltrations in cystic fibrosis due to allergic *Aspergillus*, *Thorax* (20), 1164.

Wardlaw, A. and Geddes, D.M. 1992. Allergic bronchopulmonary aspergillosis. A review *J. Royal Soc. Med.* (85), 747.

Address for Correspondence: Dr. Surya Kant, Department of Tuberculosis and Chest Diseases, King George's Medical College, Lucknow, 226 003, (U.P.) INDIA.