



Invasive Aspergillosis: Etiology, Clinical Presentation, Laboratory Diagnosis and Treatment

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Review Article

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Abstract

Aspergillosis is an opportunistic infection, usually seen in the patients having underlying diseases especially acquired immunodeficiency syndrome (AIDS). The present review article highlights the mechanism of infection, virulence factors, latest diagnostic methods and treatment strategies of aspergillosis in a precise manner.

Keywords: Aspergillosis, Broncho-alveolar lavage, Neutropenia, Airborne spores, Potato dextrose agar, Lacto-phenol cotton blue stain, Impaired immune system, *Aspergillus fumigatus*

Introduction

Fungal pathogens cause opportunistic infections [1-5]. The patients who are having underlying diseases usually present with these infections [6,7]. The major cause is due to their impaired immune system. *Aspergillus* is an ubiquitous fungus that forms conidia (airborne spores). When these conidia are inhaled by an immunosuppressed individual, it leads to invasive aspergillosis [8-10]. In normal individuals with healthy immune system, these airborne spores are promptly cleared by the cells of the pulmonary immune system. However, the outcome is completely different in patients with suppressed immune system. Invasive aspergillosis is a cause of major morbidity and mortality in

patients with immunocompromised states like patients with organ transplantation and AIDS (Figure 1) [11-15].

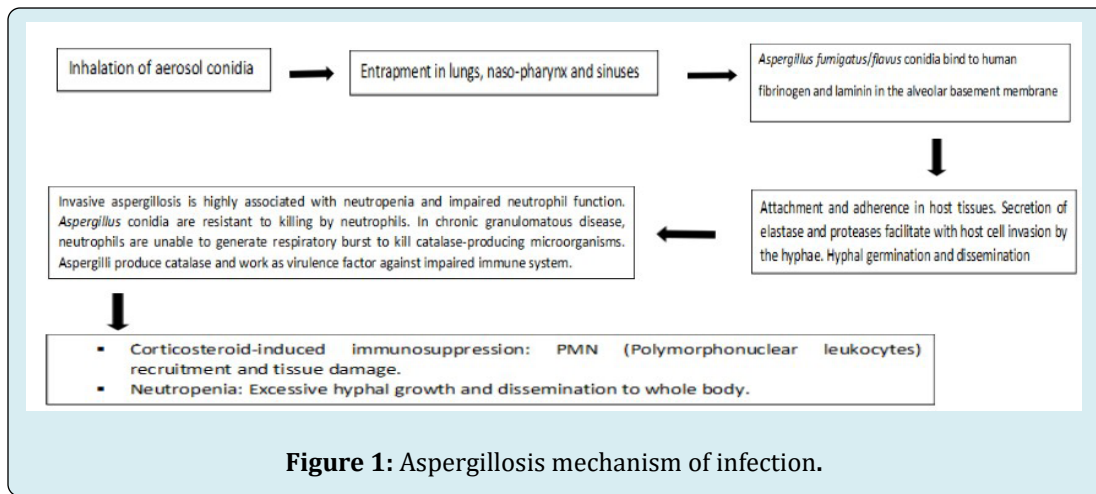
Invasive aspergillosis primarily involves lungs with necrotizing pneumonia being the key manifestation. As already mentioned, pathogenesis involves underlying conditions that weakens the immune system of the body. Few classic conditions associated with invasive aspergillosis are prolonged neutropenia, allogeneic hematopoietic cell transplant, receipt of high doses of corticosteroids and conditions associated with impaired cellular immune responses. Histologically, invasive aspergillosis is characterized by vascular invasion, consequent infarction and necrosis [16].

Virulence Factors

Aspergillus fumigatus/flavus virulence factors:

- Polysaccharides (alpha-glucan, beta-glucan, chitin and galactomannan)
- α -amylase
- Elastase
- Protease
- Catalase
- Lipase/Phospholipase
- Pectinase
- Biofilm production
- Haemolysin

Mechanism of Infection (Figure 1)



Systemic Involvement and Clinical Presentation

Invasive aspergillosis typically involves the lungs. The clinical presentation involves fever, shortness of breath, hemoptysis and chest pain. On chest imaging studies, it could present in myriads of way: bronchopneumonia (patchy areas of consolidation), tracheo-bronchitis, single or multiple nodules and peri-bronchial infiltrates [17,18].

When angio-invasive pattern is seen, the spread of infection goes much beyond lung; it spreads to multiple organs, including liver, skin, eyes, and kidneys. Dissemination to multiple organs carry poor prognosis. Disseminated aspergillosis can also involve the central nervous system; presenting with seizures and focal neurologic signs. Mycotic aneurysm formation can also be seen in the central nervous system [19,20].

It can also involve heart, particularly endocardium. It would lead to development of endocarditis. Other than candida species, *Aspergillus* species are the well-known cause of mycotic endocarditis. Endocarditis caused by *Aspergillus* species is common in patients with prosthetic cardiac valves. Such patients typically present clinically with fever and embolic phenomenon; shedding of emboli is common due to friable nature of the vegetations [16,21].

Ocular presentation with endophthalmitis is a distinctive disorder associated with disseminated, invasive aspergillosis. It could result in severe ocular pain and rapid visual loss. Gastrointestinal involvement, though rare, could present with appendicitis, entero-colitis and colonic ulcers. Cutaneous aspergillosis is common in patients with surgical trauma, burn injury and traumatic inoculation [16].

Histopathological Features

Histologically, invasive aspergillosis is characterized by vascular invasion and consequent areas of ischaemic necrosis, resulting infarction [1-21].

Laboratory Diagnosis

The diagnosis of invasive aspergillosis can be made by following methods:

Imaging

Chest X-ray and CT (Computerized tomographic) scan provide proper detailed examination and help in the diagnosis. The fungal ball, aspergilloma can be visualized and is the specific presentation of the disease [1-21].

Sputum Staining and Culture

The morning time sputum (Usually three samples) collected from the patient and transferred into appropriate culture medium (Potato dextrose agar) for culturing of the pathogen, Fig. 2a. This is performed to check and confirm that *Aspergillus* filaments are present in the sample. For identification of fungal pathogen the sputum staining can also be performed, especially the lactophenol cotton blue staining helps in the identification of Aspergilli conidia and hyphae *In-vitro*. This staining has its own limitations due to various factors (Figure 2b) [16,17].

Blood test

Blood test is useful for examination of the viable fungal spores in the blood. The blood sample collected in BacTec

bottles and incubated at 37°C for the growth of *Aspergillus* hyphae in the blood sample. Fungaemia, denotes the possible invasive aspergillosis in immunocompromised patients.

Biopsy/BAL (Broncho-alveolar lavage)

The fungus identified in histo-pathologic sections with septate hyphae dichotomous acute angle branching. Special stains, like PAS (Periodic acid Schiff) or gomori methanamine

silver are used to identify the hyphae and spores of the fungi. The cell wall made up of galactomannan and chitin and act as major antigen [16,17].

Antigen Detection

Galactomannan antigen detection in BAL (Broncho-alveolar lavage) fluid has been proven useful; particularly, in lung transplant recipients (Figure 3a & 3b, Figure 2) [16,19].

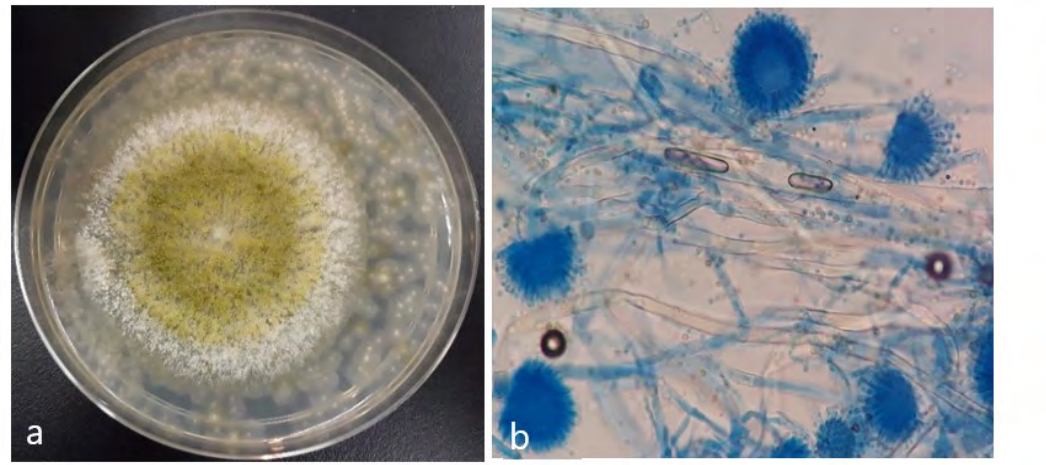


Figure 2: a) Pure culture of *Aspergillus flavus* on PDA (Potato dextrose agar). b) *Aspergillus flavus* bulby vesicle bearing metulae and phialides, which forms the conidia (dark blue colour) attached on conidiophore. (Lacto-phenol cotton blue stain).

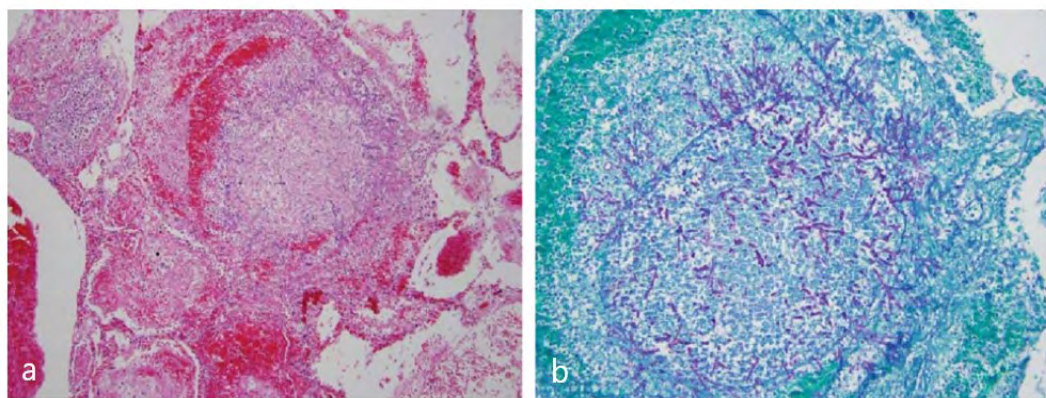


Figure 3: Invasive pulmonary aspergillosis. a) Pulmonary parenchyma with necrosis and pulmonary haemorrhage and *Aspergillus* hyphae (Haematoxylin and Eosin). b) Branching *Aspergillus* hyphae involving lung parenchyma (Grocott Methenamine Silver fungus stain) [16].

Treatment and Control

A large number of drugs are recommended by the WHO and found effective for the treatment of invasive aspergillosis such as voriconazole, itraconazole, caspofungin, amphotericin B and posaconazole. Most of the drugs inhibit

ergosterol synthesis, which is a major component of cell membrane in fungal pathogens [1-21].

Conclusion

Fungi usually cause opportunistic infection in humans.

The immunocompromised patients especially AIDS (Acquired immuno deficiency syndrome) patients reported with invasive aspergillosis.

Proper personel hygiene and healthier practices can minimize these kind of infections.

Authors' Contributions

Both of the authors have contributed to the preparation of this review and editing of manuscript.

Conflicts of Interest

There are no conflicts of interest exists.

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