

# Chapter 7

## Collateral Development of Invasive Pulmonary Aspergillosis (IPA) in Chronic Obstructive Pulmonary Disease (COPD) Patients



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### 7.1 Introduction

*Aspergillus* fungi of class Eurotiomycetes is the most frequently occurring fungi among this class. They are the inhabitants of humid soil. Amongst 250 species reported till date, *Aspergillus fumigatus* causes 90% of human infections. Although *A. fumigatus* is the chief infectious pathogen of human, other examples include *A. lentulus*, *A. fumigatiaffinis*, *A. fumisynnematus* and *A. felis* (Balajee and Marr 2006; Barrs et al. 2013). Its pathogenicity lies in the high sporulating capacity, and due to this very reason, the spore concentration ranging in the air increases from 1 to 100 (Streifel et al. 1983; Latgé 2001). These spores later release conidia in the air which are capable enough to reach the alveoli due to its minute diameter of 2–3  $\mu$ m. The air laden with these spores when inhaled majorly affects lung. With these disease-causing properties of *Aspergillus*, it was found that it may result in severe pathological conditions like chronic obstructive pulmonary disease (COPD), allergic bronchopulmonary aspergillosis and aspergilloma (McNeil et al. 2001). The current chapter deals with the COPD and its association with *Aspergillus* infection.

According to the WHO and the National Heart, Lung, and Blood Institute, COPD is defined as a “disease state characterised by airflow limitation that is not fully reversible”. Similarly, a disease called IPA is indicated by the lung parenchyma invasion and necrosis due to *Aspergillus* spp. It is further divided into two classes on the basis of invasion: subacute IPA representing the direct invasion of lung parenchyma by hyphal elements but with a slowly progressively COPD cavitary lung disease and chronic pulmonary aspergillosis which shows radiological signs of tissue destruction, but without evidence of hyphal invasion, with microbiological markers of *Aspergillus* infection. The term tracheobronchitis is used when *Aspergillus*

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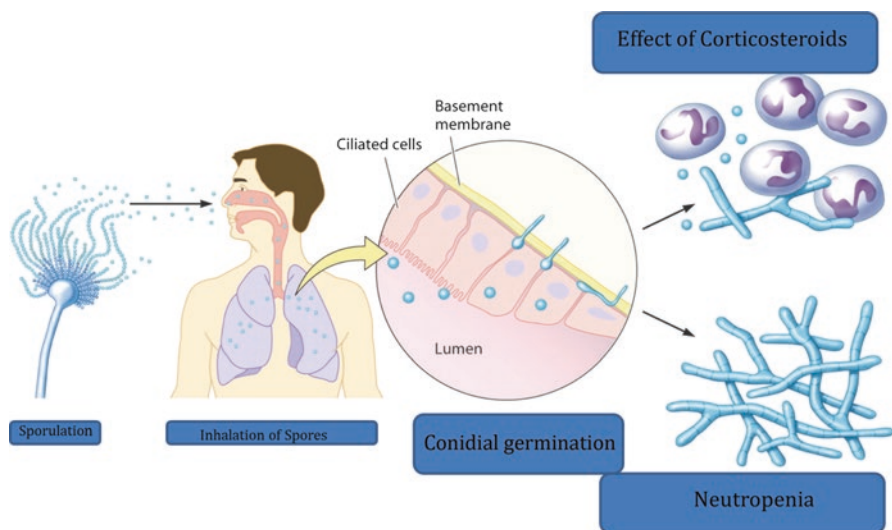
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organisms invade the tracheobronchial tree. Recent data are obtained through studies performed by autopsy, and an exponential increase has been found over the last 20 years (Groll et al. 1996; Yamazaki et al. 1999; Kontoyiannis and Bodey 2002). To keep this in check, the medications include immunosuppressive and corticosteroid therapies. Due to the adverse effect of these drugs, mortality rate has been increased further (Warnock et al. 2001; Pegues et al. 2001). Later a few clinical studies have shown the association of IPA with that of COPD. Due to the IPA association, doctors prefer steroids above other treatments available. This treatment even worsens the condition of the patient (Rello et al. 1998; Bulpa et al. 2001; Dimopoulos et al. 2003; Meersseman et al. 2004; Ader et al. 2005; Garnacho-Montero et al. 2005). With the colonization of *Aspergillus* spp. in lung airways, possibility of IPA in COPD increases, and thus (Pepys et al. 1959; Yu et al. 1986) it becomes critical to detect it at an early stage. It is specific in severe (Global Initiative for Chronic Obstructive Lung Disease (GOLD)) steroid-dependent stage IV COPD patients. To come up with the better therapeutic targets for any of the disease, we need to focus firstly on the epidemiology of the disease along with the pathophysiology and symptoms commonly occurring in that disease. The underneath topics will deal with the epidemiology, pathophysiology and symptoms associated with the disease in detail.

## 7.2 Epidemiology

Although the occurrence of COPD in IPA patients is very less and poorly documented, it has been shown through various demographic data that patients with COPD are at greater risk of developing IPA. Assessment of the incidence of IPA in



**Fig. 7.1** The respective figure shows the pathophysiology and steps of spore invasion in human respiratory tract (Dagenais and Keller 2009)

the population is difficult due to the lack of a consistent case, lack of a particular definition and lack of infection surveillance measures. Above all, the next problem lies in distinguishing the colonization of *Aspergillus* spp. with that of IPA, particularly at an early stage. However, there is growing evidence of data suggesting that COPD patients are at a greater risk of IPA. A review by Lin et al. (2001) of 50 patients shows that COPD was the underlying condition in 26 out of 1,941 (1.3%) patients with aspergillosis. In one large study conducted by Patterson et al. (2000a), 9% of 595 patients with invasive aspergillosis (IA) suffered from pulmonary disease, without a distinct pulmonary disorder. A study performed by Rodrigues et al. (1992) reported that COPD patients contribute to 1% of all cases of IPA in their institution. Steroidal drugs are shown to play a pivotal role in the emergence of IPA. Some authors have also investigated the correlation between the daily dose of corticosteroids and the probability of developing IA. It was suggested that the average dose of 1.25 mg/kg-1/day-1 of prednisone in renal transplant patients is the best method to develop a model for IPA (Gustafson et al. 1983). But the case was a bit different in the haematological patients treated with peripheral blood or bone marrow transplantation. In them, a dosage of 1 mg/kg-1/day-1 of prednisone for 21 days was enough to develop IPA (Grow et al. 2002). On summarising the data it was found that a dosage of 0.2 mg of prednisone per day or a cumulative dosage of 0.7 mg was associated with an increased risk of infections (Stuck et al. 1989). Various data provided by different authors support the patients undergoing corticotherapy for a longer duration of time are at a higher risk of developing COPD with IPA (Rello et al. 1998; Bulpa et al. 2001; Ader et al. 2005; Muquim et al. 2005). Despite the close association between steroids and IPA in COPD patients, it has been reported that some COPD patients may develop IPA without steroid exposure (Ali et al. 2003). Moreover, it has been reported that some infections, in particular viral infection, such as influenza (Urban et al. 1985; Bulpa et al. 1995) or cytomegalovirus (Warnock et al. 2001), may precede IPA, suggesting a role in causation (Ordroneau et al. 1987). Later, we will discuss the pathophysiology of the disease.

### 7.3 Pathophysiology

*Aspergillus* spp. is an airborne pathogen with a spore size of 2–3 µm in diameter. It is widely spread in the air, and when a person inhales spore-containing air, these penetrate through the airways to the lungs. Although the majority of conidia are excluded from the lungs by the ciliary action of the bronchial epithelium, some make their way through the respiratory tract to the lungs, hence leading to pathological conditions. In COPD patients, ciliary activity is impaired by tobacco smoke and multiple episodes of infection, as well as repeated epithelial damage. Thus, the impairment in defence mechanisms of the airways facilitates the binding of conidia to the epithelial layer (Latgé 2001). Stages of *Aspergillus* infection are depicted in the diagram below:

The phagocytic system is the next one in line to be affected (Shoham and Levitz 2005). It comprises the alveolar macrophages (AM) that play a prominent role in

destroying the *A. fumigatus* conidia and the neutrophils that kill hyphae and germinating spores (Schaffner et al. 1982; Levitz 1992; Roilides et al. 1993; Balloy et al. 2005). Other immune cells such as natural killer lymphocytes (Morrison et al. 2003) and the innate pulmonary host defences also play a role in protecting individuals against IPA (Walsh et al. 2005; Feldmesser 2005) and thus the COPD.

## 7.4 Prevention of Infection

Due to difficulty in diagnosis associated with IPA, mortality rate is still high (up to 90%, depending on the underlying disease), thus making prevention of infection very important (Warnock et al. 2001). The avoidance of infections may be taken in the following ways:

- To eliminate obvious environmental sources of *Aspergillus* spp.
- Cleaning the surfaces to avoid dust accumulation. Moreover to prevent outbreaks, environmental protection by enriching solid barriers must be applied during construction (Patterson et al. 2000a, b).
- Environmental protection by impenetrable barriers must be implemented during construction (Oren et al. 2001).

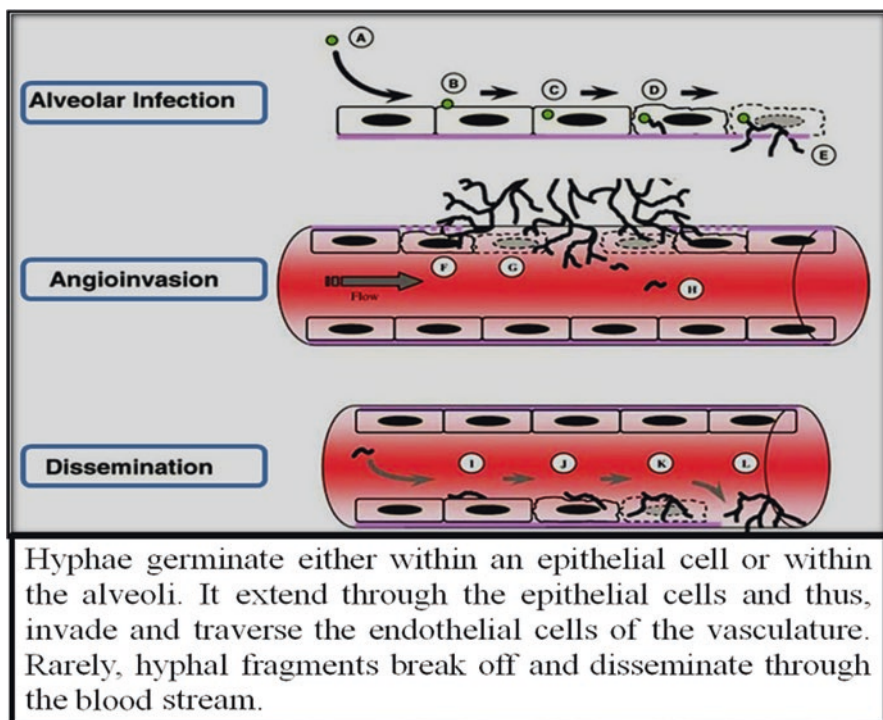


Fig. 7.2 Steps of germination and dissemination of fungal hyphae (Ben-Ami et al 2010)

- COPD patients should wear a high-efficiency mask or avoid exposure.
- Prevention must be focused on the avoidance of high load sources, e.g., constructions, cellars or lofts, composts, etc.
- IPA could also be a water-borne infection (Warris and Verweij 2005), and pillows may contain high loads of *Aspergillus* (Woodcock et al. 2006). Finally, if the patient is receiving corticosteroids, the dose should be decreased as much as possible or even stopped altogether.
- The dose of corticosteroids should be kept in check or should be decreased or stopped if possible.

## 7.5 Prognosis

Therapy of COPD with a fungal infection includes voriconazole. It was considered to be the first-line treatment of the disease (Caillot et al. 2001). The study was conducted on the guinea pigs with a dosage of 10 mg/kg/day. To turn our target to a better treatment option, the focus was made on amphotericin B at 1 and 1.25 mg/kg/day, respectively (Maertens et al. 2002; Montoya et al. 2003). Another study concluded that the efficacy of high-dose liposomal amphotericin B (at 5 and 10 mg/kg) was superior to that of voriconazole (10 mg/kg) in a mouse model of pulmonary aspergillosis (Comstock et al. 1974). Apart from these two drugs with distinct doses, it became necessary to design a clinical trial with a better formulation.

Due to economic constraints, voriconazole is still the prescribed treatment than amphotericin. Properties of the drug are as follows:

- Synthetic triazole.
- Exerts an inhibitory effect on two kinds of *Aspergillus* by cytochrome P450-dependent enzymes and the fungal respiration chain.
- Triazoles are generally considered as fungistatic.
- The drugs given in association with voriconazole concentrations are erythromycin, indinavir, ranitidine, cimetidine and omeprazole. Drugs that potentially decrease voriconazole concentrations are principally rifampicin and phenytoin.

## 7.6 Symptoms

Symptoms of the disease are not clearly distinguishable as pulmonary disease shows some common features, but some of the key features include:

- Fever and chills
- A cough that brings up blood (hemoptysis)
- Shortness of breath
- Chest or joint pain
- Headaches or eye symptoms
- Skin lesions

## 7.7 Conclusion

The pulmonary diseases are attributed to airborne foreign particles. Spores of *Aspergillus* are found to be a newer target to cause a fatal disease like COPD. This chronic disease when not treated at an earlier stage may lead to the development of another asymptomatic condition called invasive pulmonary aspergillosis. The symptoms and diagnosis of these pathogenic conditions are less distinct, and hence it becomes a challenge to cure them at an earlier stage. Due to the continuous advancement of technology, we have achieved success at certain levels. Drugs like voriconazole have been developed which aid in the treatment of the disease. Thus from the above chapter we may conclude that the chronic pulmonary disease may arise due to fungal penetration in lungs.

**Acknowledgement** Dr. Suchit Swaroop acknowledges the Experimental and Public Health Laboratory, Department of Zoology, University of Lucknow, for providing the facilities and space to conduct the study.

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