

Asthma and *Aspergillus*

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“One woe doth tread upon another’s heel
So fast they follow”

Hamlet

William Shakespeare

Inhalant allergens, in patients with allergic asthma, play a key role in bringing about the inflammation present in the airways. Fungi are increasingly being recognized as important inhalant allergens¹. Among the fungi, *Aspergillus*, a genus of spore-forming fungi found worldwide, is linked to asthma in more ways than one. This fungus derives its name from its resemblance to the brush, called an “aspergillum”, used for sprinkling holy water. Its spores are inhaled by one and all but in the healthy normal individual, they seldom have any effect. However, in the asthmatic subjects, the fungal spores are trapped in the thick and viscid secretions that are usually present in the airways. This generally develops in atopic subjects and is sustained by continuous inhalation of *Aspergillus* antigens, triggering asthma. The clinical spectrum of *Aspergillus*-associated hypersensitivity respiratory disorders includes *Aspergillus* induced asthma, allergic bronchopulmonary aspergillosis (ABPA) and allergic *Aspergillus* sinusitis (AAS)². Hypersensitivity pneumonitis too can be caused by *Aspergillus*, but this is generally seen in non-atopic individuals.

Aspergillus induced asthma is yet to receive the recognition that it deserves. The association between the mould *Aspergillus* and asthma makes it imperative to know the frequency of sensitization to *Aspergillus* in asthmatic subjects in each geographical region. The reported frequency of *Aspergillus* sensitization in patients with asthma has varied from 16-38% in different parts of the world³⁻⁶. In Delhi, we found that 30

(28.5%) of our 105 patients with asthma had a positive skin test to *Aspergillus* antigens⁶. A comparative study of the prevalence of sensitization to *Aspergillus* antigens among asthmatics in Cleveland and London found that 28% of patients from Cleveland and 23% from London had immediate skin reactivity to *Aspergillus* antigens⁵. The investigators also recorded that a positive *Aspergillus* skin test was related to severity of airway obstruction and stated that this was an unexpected finding. We too observed that asthma was more severe in patients sensitized to *Aspergillus* antigens as compared to those with skin test positive to antigens other than *Aspergillus*⁶. This was evidenced by a significantly longer duration of illness, earlier age of onset of disease, higher mean total leucocyte count, absolute eosinophil count and total serum IgE. More number of these patients had severe obstruction and greater number of prescriptions for oral steroids. Our findings were supported by recent publications that have highlighted the importance of fungal sensitization as a risk factor for the increasing severity of asthma^{7,8}. A European Committee respiratory health survey in 30 centres demonstrated that frequency of sensitization to *Alternaria alternata* and/or *Cladosporium herbarum* increased significantly with increasing asthma severity⁷. Previous studies have shown that sensitization or exposure to fungi increases the risk of death from asthma⁹ and also acute attacks of asthma requiring intensive care unit admission¹⁰.

The most frequently recognized manifestation of asthma caused by *Aspergillus* is, however, ABPA. Since the seminal description by Hinson *et al*¹¹ in 1952, ABPA has now been documented as a disease with a worldwide distribution¹². Although ABPA is predominantly a disease of the asthmatics, only a few asthmatics actually suffer from it. Furthermore, in spite of familial preponderance of asthma, familial occurrence of ABPA is a rarity¹³. The explanations for this still remain a subject of speculation. The prevalence of ABPA varies from 25-28% in *Aspergillus* skin test positive asthmatic subjects^{5,6,14}. This indolent disease is known to complicate 1-11% of patients with asthma^{6,14-17}. Our study of 105 subjects with asthma detected eight (7.6%) patients who fulfilled all the eight major criteria for the diagnosis of ABPA⁶. This was 26.6% of the 30 patients with positive skin reactivity to *Aspergillus* antigens, and 7.6% of the 105 patients with asthma. Earlier, Greenberger and Patterson¹⁶ evaluated 531 asthmatics and detected ABPA in 32 (6%) patients, 19 (3.6%) with central bronchiectasis and 13 (2.4%) with positive serology only. These variable prevalence rates probably reflect the lack of a single diagnostic criterion with a standardized test¹⁸. A set of criteria is required, as there is no single test that establishes the diagnosis apart from demonstration of central bronchiectasis (CB) with normal tapering bronchi¹². This feature, first described by Scadding¹⁹, is considered to be pathognomonic of ABPA. Although we have earlier shown that CB extended to the periphery in 30% of the lobes and 21% of the segments²⁰, the demonstration of CB with normal peripheral bronchi should continue to be regarded as a *sine qua non* for the diagnosis of ABPA in the absence of cystic fibrosis²¹. However, studies have shown that mild CB can also be seen in asthma²², and does not necessarily indicate the presence of ABPA. In essence, ABPA should be excluded in all asthmatic subjects with positive skin reactivity to *Aspergillus*.

Mucoid impaction akin to that in ABPA can also occur in the paranasal sinuses and is termed as AAS^{23,24}. This clinicopathological

entity, described more recently, is known to present with asthma in more than half the patients²⁵. Although it appears that the patient with ABPA provides a favourable *milieu* for the occurrence of AAS, it is perhaps surprising that in spite of similar histopathological features the coexistence of both these diseases has not often been reported^{26,27}. In our analysis of 95 cases of ABPA, 22 had radiological evidence of sinusitis²⁸. Nine of these patients consented to surgery, seven of whom were diagnosed to have concomitant AAS. In the remaining 13 patients the possibility of AAS could not be ruled out as they refused to undergo the invasive procedures required to establish the diagnosis. This suggests that the co-occurrence of ABPA and AAS may not be as rare as it appears and it is essential that the occurrence of AAS in ABPA and ABPA in AAS should be looked for²⁹. We have earlier shown that one-fourth of patients with perennial rhinitis had a positive skin reactivity to *Aspergillus* antigens³⁰. Since rhinitis is an important predisposing factor for sinusitis and also frequently coexists with asthma, these patients may be at a greater risk of developing AAS/ABPA.

Aspergilloma, a fungal ball that appears in a preexisting cavity due to saprobic colonization of *Aspergillus* species, can often present with asthma³¹. These patients frequently experience wheezing dyspnoea with signs of airway obstruction. In a study of 28 patients with pulmonary aspergilloma, asthma was present in 12 (43%)³². Cavities are not infrequent in ABPA³³ and, in such a background, formation of an aspergilloma^{27,31,34} might be accelerated by therapy with corticosteroids³⁵. Aspergillomas are also known to cause ABPA as they may function as a nidus for antigenic stimulation in a genetically predisposed individual³⁶.

The mould *Aspergillus* plays many a part in the occurrence of asthma. *Aspergillus* sensitization in patients with asthma not only increases the severity of the disease but may also be responsible for clinical entities like ABPA/AAS, which present with asthma. It is thus crucial to screen all asthmatic subjects for

sensitization to *Aspergillus* antigens so as to identify those at risk.

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