

# Allergic Bronchopulmonary Aspergillosis and *Candida albicans* Colonization of the Respiratory Tract in Corticosteroid-Dependent Asthma

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"Corticosteroids are fundamental to the treatment of asthma",<sup>1</sup> but prolonged use can alter pulmonary host defence mechanisms which results in the airway providing a hospitable environment for the growth of opportunistic fungi.<sup>2,3</sup> This can also lead to systemic mycosis.<sup>4,5</sup> Recent studies<sup>6,7</sup> have reported the occurrence of allergic bronchopulmonary aspergillosis (ABPA) among patients with corticosteroid - dependent asthma (CSDA) and have also highlighted the difficulty in diagnosis of ABPA in this group of asthmatics, as therapy with corticosteroids masks many of the characteristic features of the disease. This study on 35 patients of CSDA was prompted by the paucity of such information from the subcontinent.

## MATERIALS AND METHODS

The study comprised 35 patients with CSDA attending the Clinical Research Centre of the Vallabhai Patel Chest Institute. Corticosteroid-dependent asthma was defined as patients requiring prednisolone for the control of their symptoms for a minimum period of 3 months or more prior to presentation at mini-

**SUMMARY** Fungal studies were conducted on 35 patients with corticosteroid-dependent asthma (CSDA) and 20 asthmatics who had never received prednisolone. *Candida albicans* was repeatedly cultured from the sputa of 12 patients with CSDA. Isolation was more frequent in those patients who were receiving more than 10 mg prednisolone for more than six months. Nearly half of these patients demonstrated a positive immediate cutaneous reaction and precipitating antibodies against *C. albicans*. Although no pathological significance, beside colonization, could be attributed to this finding, it was felt that it would be prudent to restrict the daily dose of prednisolone to less than 10 mg, when administered for more than six months. Two patients with allergic bronchopulmonary aspergillosis (ABPA), were identified, one from each group. The possibility of ABPA, however, remained open in two other patients with CSDA. It is probable that some patients with CSDA may be suffering from ABPA but characteristic features of the disease are masked by corticosteroid therapy, making it difficult to diagnose.

mum doses of 7.5 mg daily or 15 mg on alternate days. Clinical assessment of all patients was done along with routine investigations of blood and urine, chest radiograph and spirometry. All studies were conducted with patients maintained on doses of prednisolone required for control of their symptoms. Twenty asthmatics who had never received corticosteroids functioned as controls and underwent an identical work up as the study population.

Mycological investigations included examination of sputum samples of patients from both, the study and control groups. A loopfull of each specimen was digested in 10 percent

KOH directly on a slide and observed microscopically for fungal elements. All specimens were also streaked on Sabouraud's dextrose agar (Emmon's modification) containing chloramphenicol (0.5 mg/ml) as well as chloramphenicol and cycloheximide (0.5 mg/ml).

One set of these inoculated tubes was incubated at 25° C and the other was incubated at 37° C for 4 weeks. The identity of *Candida albi-*

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*cans* was confirmed by Germ tube test and chlamyospore production. Identification of *Aspergillus fumigatus*, *A. flavus* and *A. niger* was based on their microscopic and macroscopic characteristics as seen on Sabouraud's agar at 25° C and 37° C.

Skin tests were performed intracutaneously on the forearm with antigens of *Aspergillus fumigatus*, *A. niger*, *A. flavus* and *Candida albicans* in dilutions of 1:500, obtained from Council of Scientific and Industrial Research-Centre of Biochemicals, Delhi. All sites were examined after 20 minutes for immediate reaction and periodically over 4-8 hours for type-III reaction and graded.<sup>8</sup> Preci-

pitating antibodies to *A. fumigatus*, *A. flavus*, *A. niger* and *C. albicans* were detected, by the gel double immunodiffusion technique of Ouchterlony.<sup>9</sup>

## RESULTS

There were 16 males and 19 females in the study group with an age range of 11-16 years. The control group consisted of 12 females and 8 males. No significant occupational history could be elicited in either group. Peripheral eosinophilia ( $> 500/\text{mm}^3$ ) was observed in 17 patients in the study group as compared to 13 in the control group. Chest radiographs showed transient pulmonary infiltrates in 3 patients with CSDA

and in 1 patient amongst the controls. Bronchography demonstrated central bronchiectasis in one patient in the study group.

A total of 164 sputum samples, 104 from the study group and 60 from the control group were studied for pathogenic fungi. *C. albicans* was isolated from 30 sputum samples from 12 patients of the study group as compared to a single patient from the control group. As many as 11 of these 12 patients receiving prednisolone had repeated heavy growth (arbitrarily taken as more than 10 colonies per culture) of the fungus, which was directly linked to the dose and duration of corticosteroid therapy

**Table 1.** Frequency of isolation of growth of *Candida albicans* in sputum of patients with corticosteroid-dependent asthma.

Dose of prednisolone (mg per day)	Duration of therapy			
	Less than 6 months		More than 6 months	
	Positive Sputum specimens	Patient number	Positive Sputum specimens	Patient number
Less than 10	0/0	0/0	5/28	2/8
11-20	8/11	2/5	15/50	6/17
21-30	0/3	0/1	3/6	1/2
More than 30	0/3	0/1	3/3	1/1
<b>Total</b>	<b>8/17</b>	<b>2/7</b>	<b>26/87</b>	<b>10/28</b>

**Table 2.** Salient characteristics of patients with allergic bronchopulmonary aspergillosis (ABPA) and probable ABPA.

Group	Age/Sex	Sputum culture for <i>A. fumigatus</i>	Cutaneous hypersensitivity against <i>A. fumigatus</i>		Serum precipitins	Peripheral eosinophilia	Chest X-ray	Bronchogram
			Type-I	Type-III				
1. Study	45, F	+	+	+	-	+	TPI	CB
	25, F*	+	+	-	-	+	TPI	ND
	37, M*	+	+	-	-	+	TPI	ND
2. Control	26, M	+	+	+	+	+	TPI	ND

\* Probable ABPA

TPI = Transient pulmonary infiltrates

CB = Central bronchiectasis

ND = Not done

(Table 1). *Aspergillus* species were isolated from sputum of 11 patients in the study group and 4 in the control group.

Of the 35 patients with CSDA, 6 had cutaneous reactivity to candidin and 11 to aspergillin. One patient exhibited both type I and III reaction against *A. fumigatus*. Only 1 patient had an immediate cutaneous reaction against *C. albicans* in the control group while 5 patients reacted positively to aspergillin, one of whom also demonstrated a type III reaction to *A. fumigatus*.

Serum precipitins against *C. albicans* were demonstrated in 8 patients with CSDA and in none of the control group. Of the 12 patients in whom *C. albicans* was cultured in the sputum, 7 had serum precipitins against *C. albicans*. Serum precipitins against *A. fumigatus* were detected in 1 patient each from both groups.

On the basis of clinical and radiological profile and supported by positive mycological, immunological and serological data, a diagnosis of ABPA was established in 2 patients, 1 from each group (Table II). Two other patients in the study group had transient pulmonary infiltrates, with peripheral eosinophilia, *A. fumigatus* in sputum and a type I cutaneous hypersensitivity against *A. fumigatus*. However precipitating antibodies were not detected in their sera and they refused to undergo bronchography.

## DISCUSSION

Oropharyngeal candidiasis has been documented in asthmatics on corticosteroids, both on aerosols<sup>10,11</sup> as well as on oral drugs.<sup>3</sup> Fungal colonization of the respiratory tract, as in this study, was related to the dose and duration of therapy which reflects the increased susceptibility of individuals receiving higher doses of corticosteroids for a longer duration. More than half the patients in our study with repeated heavy growth of *C. albicans* in the sputum demonstrated immediate cutaneous reactivity.

However, apart from colonization, no significance could be established, especially in view of the fact that many normal individuals have cutaneous reactivity to *C. albicans*.<sup>12</sup> Increased *C. albicans* colonization of the respiratory tract must, nevertheless, be viewed with concern, especially in light of the fact that corticosteroids alone or in combination with antibiotics, suppress neutrophilic responses to *Candida* which is crucial to the defence against this organism.<sup>13,14</sup> Furthermore, the possible role of *C. albicans* as an allergen in chronic asthma must also be considered.<sup>15</sup> Increased colonization assumes importance in context of the fact that *C. albicans* is not an airborne allergen, the only source of exposure being saprophytic growth in the body.<sup>16</sup> In view of our finding, it may therefore be prudent to restrict the dose of prednisolone to less than 10 mg daily, when given for more than six months.

Two of our patients, one from each group, had ABPA. Two other patients from the study group had transient pulmonary infiltrates, peripheral eosinophilia and an immediate cutaneous reaction to aspergillin. Serum precipitins to *Aspergillus* were not detected in these two patients nor did they consent to bronchography. A strong suspicion of ABPA, however, remained. Corticosteroid-dependent asthma stage IV of ABPA may be clinically very similar to that of CSDA not associated with ABPA.<sup>17</sup> In fact, in a study of 42 patients of CSDA, Basich *et al*<sup>7</sup> isolated 12 patients suspected of having ABPA. Our findings appear to indicate the opinion expressed by Basich *et al*<sup>7</sup> that corticosteroid therapy may mask ABPA making it a difficult disease to diagnose in asthmatics dependent on corticosteroids. Since some patients with CSDA may actually be undiagnosed cases of ABPA, vigorous attempts must therefore be made to rule out ABPA in patients requiring relatively high doses of corticosteroids to control their asthma.

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