Review

Allergic Bronchopulmonary Aspergillosis: A Perplexing Clinical Entity

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In susceptible individuals, inhalation of *Aspergillus* spores can affect the respiratory tract in many ways. These spores get trapped in the viscid sputum of asthmatic subjects which triggers a cascade of inflammatory reactions that can result in *Aspergillus*-induced asthma, allergic bronchopulmonary aspergillosis (ABPA), and allergic *Aspergillus* sinusitis (AAS). An immunologically mediated disease, ABPA, occurs predominantly in patients with asthma and cystic fibrosis (CF). A set of criteria, which is still evolving, is required for diagnosis. Imaging plays a compelling role in the diagnosis and monitoring of the disease. Demonstration of central bronchiectasis with normal tapering bronchi is still considered pathognomonic in patients without CF. Elevated serum IgE levels and *Aspergillus*-specific IgE and/or IgG are also vital for the diagnosis. Mucoid impaction occurring in the paranasal sinuses results in AAS, which also requires a set of diagnostic criteria. Demonstration of fungal elements in sinus material is the hallmark of AAS. In spite of similar histopathologic features, co-existence of ABPA and AAS is still uncommon. Oral corticosteroids continue to be the mainstay of management of allergic aspergillosis. Antifungal agents play an adjunctive role in ABPA as they help reduce the fungal load. Saprophytic colonization in cavitary ABPA may lead to aspergilloma formation, which could increase the severity of the disease. The presence of ABPA, AAS, and aspergilloma in the same patient has also been documented. All patients with *Aspergillus*-sensitized asthma must be screened for ABPA, and AAS should always be looked for.

Key Words: Allergic *Aspergillus* sinusitis; allergic bronchopulmonary aspergillosis; allergic fungal sinusitis; aspergilloma; *Aspergillus*; asthma

INTRODUCTION

Aspergillosis of the respiratory tract has diverse manifestations that range from hypersensitivity disorders to rapidly invasive disseminated disease.[1,2] These can be classified into 3 distinct clinical categories, *viz.* allergic aspergillosis, saprophytic colonization, and invasive aspergillosis (Table 1). Different presentations of the allergic form, usually seen in atopic individuals, include *Aspergillus*-induced asthma (AIA), allergic bronchopulmonary aspergillosis (ABPA), and allergic *Aspergillus* sinusitis (AAS). This review focuses on ABPA and highlights some of the other *Aspergillus*-related respiratory disorders.

ASPERGILLUS–INDUCED ASTHMA AND SEVERE ASTHMA WITH FUNGAL SENSITIZATION

Patients with asthma who have a positive immediate (type I) IgE-mediated hypersensitivity to *Aspergillus* are grouped as AIA. A wide variation to the tune of 16% to 38% has been observed in *Aspergillus* sensitization among asthmatics across the world.[3-5] One of the initial studies found a then considered "unexpected" finding of more severe airway obstruction in patients with AIA.[3] In our study of 105 patients with asthma, positive skin reactivity to *Aspergillus* antigens was noted in 30 subjects (28.5%).[5] The disease was more severe in these patients with AIA as evidenced by a statistically significant higher mean duration of illness ($P<0.001$), mean eosinophil count ($P<0.0001$), mean total IgE ($P<0.05$), and more usage of oral corticosteroids per year ($P<0.004$).

The term 'severe asthma with fungal sensitization' (SAFS) was coined for a subset of asthmatics that demonstrated sensitization to fungal antigens and had frequent exacerbations of asth-

Table 1. *Aspergillus*-associated respiratory disorders[1,2]

I. Upper respiratory tract
  1. Allergic aspergillosis
    - Allergic *Aspergillus* sinusitis (AAS)
  2. Saprophytic colonisation
    - Sinus fungal balls
  3. Invasive disease
    - Acute fulminant invasive sinusitis
    - Chronic invasive sinusitis
    - Granulomatous invasive sinusitis

II. Lower respiratory tract
  1. Allergic aspergillosis
    - (IgE mediated) *Aspergillus* induced asthma (AIA)
    - Allergic bronchopulmonary aspergillosis (ABPA)
    - Hypersensitvity pneumonitis
  2. Saprophytic colonisation
    - Aspergilloma
        simple
        complex (chronic cavitary pulmonary aspergillosis)
  3. Invasive disease
    - Invasive pulmonary aspergillosis
        acute
        subacute (chronic necrotising pulmonary aspergillosis)

ma that necessitated admission to the hospital.[6] Diagnostic criteria for SAFS include: (1) severe (poorly controlled) asthma, (2) either a positive skin prick test result for fungi (but not necessarily to *Aspergillus* species) or in vitro demonstration of antifungal IgE of at least 0.4 kU/L, (3) total serum IgE concentration <1,000 kU/L.[6] Unlike in ABPA, patients with SAFS do not have mucoid impaction or bronchiectasis. Another important difference between SAFS and ABPA is that while severe asthma is one of the diagnostic criteria for SAFS, ABPA also develops in those with mild or moderate asthma. Greenberger[7] has also highlighted the divergence between SAFS and ABPA.

Given the persistent fungal colonization of the bronchi in patients with allergic aspergillosis, a potential role for antifungal therapy has been suggested.[8] Significantly better asthma quality of life scores were found when itraconazole was administered to patients with SAFS.[9] However, a recent study using voriconazole for 3 months in moderate-to-severe asthmatics sensitized to *Aspergillus fumigatus (Af)* did not show any benefit.[10] The authors suggested that the beneficial effects of itraconazole in previous studies could possibly be due to its pharmacokinetic effects on corticosteroids.

ABPA

ABPA is the most significant manifestation of allergic aspergillosis that occurs worldwide but has not received the importance that it deserves.[11] Most commonly seen in patients with asthma and cystic fibrosis (CF), ABPA is caused by hypersensi-

tivity to *Aspergillus* antigens. In susceptible hosts, an allergic response is evoked by repeated inhalation of *Aspergillus* spores. The fungal antigens, chiefly of *Af*, elicit mainly a type I (IgE-mediated) reaction that is responsible for the disease presentation. Type-III (IgG-mediated immune complex) and Type-IV (cell mediated) responses have also been implicated, but tissue invasion does not occur.[12] When fungi other than *Aspergillus* are responsible for such a condition, it is termed as allergic bronchopulmonary mycoses (ABPM).[13,14] Based on specific pathophysiological mechanisms, it has been proposed that ABPA/ABPM be classified as a distinct endotype of asthma.[15]

Although 63 years have passed since this disease was first described in England,[16] we are still unable to fathom the reason why only a few patients with asthma are affected with ABPA. Individual host genetic susceptibility appears more significant than environmental factors in the causation of ABPA in these subjects. Moreover, although familial preponderance is very common in asthma, occurrence of ABPA among family members is rare.[17,18] We have detected familial occurrence in 4 pairs (4.9%) of first-degree relatives. One patient each in 3 of these 4 pairs also had concomitant AAS.[19]

Epidemiology of ABPA

The exact prevalence of this disease is still not known, and this is most likely due to the lack of a uniform diagnostic criterion and standardized tests.[20] This potentially destructive lung disease is yet to be included in the ninth revision of the International Classification of Diseases published in 1996.[21] Prior to 1968, when ABPA was unknown outside Europe, the prevalence of definite ABPA among asthmatics was around 8%-11%, while that of probable ABPA was approximately 22%.[22] After the first report from the United States in 1968,[23] awareness regarding ABPA grew across all continents. Between 1983 and 1986, Greenberger and Patterson[24] from the United States found ABPA in 32 (6%) out of 531 asthmatic patients having immediate cutaneous reactivity to *Aspergillus* antigens. In other studies, ABPA was detected in as many as 25% to 37% of asthmatics with a positive skin prick test to *Af*.[25] Among 105 patients with bronchial asthma, we noted a significantly longer duration of illness, earlier age of onset of asthma as well as rhinitis, higher mean total leucocyte counts, absolute eosinophil counts, and total serum IgE values in 8 patients diagnosed with ABPA when compared to those with *Aspergillus* sensitization only without ABPA.[5]

Western estimates suggest that ABPA complicates up to 6% of all chronic cases of asthma.[26] The prevalence of ABPA in patients with underlying CF ranges from 2% to 15%.[27] Denning *et al*.[28] in a scoping review based on the published studies on asthma and ABPA, attempted to ascertain the global burden of ABPA. The prevalence of ABPA in adult asthmatics, as analyzed from 5 prospective studies having at least 50 patients with asthma, was found to be 2.5% (range 0.72%-3.5%). Based on this,

the authors deduced that adult patients with ABPA across the globe could "potentially exceed 4.8 million."[28]

Since there were no consensus-based guidelines on ABPA so far, the International Society for Human and Animal Mycology (ISHAM), in September 2011, constituted a Working Group on ABPA complicating asthma.[29] Data on *Aspergillus* sensitization and ABPA published since circa 2000 was collected by the ISHAM Working Group.[29] The prevalence of *Aspergillus* sensitization among patients with asthma ranged from 5.5%-38.5%, and the prevalence of ABPA in asthma varied between 2.5% and 22.3% with a pooled prevalence of 8.4%.

Immunopathogenesis

Immune mediated mechanisms of lung destruction in ABPA are not fully understood. *Af* antigens elicits a polyclonal antibody response which is largely responsible for elevated levels of total IgE as well as *Af*-IgE and *Af*-IgG antibodies.[30,31] Increased interleukin (IL)-4, IL-5, IL-10, and IL-13 production due to the cellular Th-2 immunologic response suggests an immunocompetent host.[32,33] We have identified antibodies to a cytotoxic ribonuclease antigen (18 kD) and an elastinolytic protease antigen (45kD) in Indian patients with ABPA.[34,35] Genetic risk factors include expression of HLA-DR2 and HLA-DR5 genotypes, while HLA-DQ2 protected against ABPA.[36,37] In subjects with CF, increased chances of *Aspergillus* colonization of the airways and subsequent development of ABPA were found in those with CF transmembrane conductance regulator gene mutations.[38-40] Surfactant protein-A2 polymorphisms,[41] elevated levels of mannan-binding lectin due to the 1011A allele,[42] and toll-like receptor polymorphisms[43] also play an important role in the development of ABPA. An immunoproteomics approach would help identify synthetic peptide antigens of *Af* for skin testing, serodiagnosis, and potentially immunotherapy.[44,45]

Diagnosis

As our understanding of the disease is improving, diagnostic criteria continue to evolve. In 1952, Hinson *et al.*[16] reported 3 patients of "a kind not previously recognized". These patients presented with repeated episodes of fever, productive cough, wheezing dyspnoea, and occasional chest pain. Eosinophilia, pulmonary infiltrates in different areas on the chest roentgenogram, and *Aspergillus* mycelium on microscopic examination of the purulent sputum were found during acute attacks. Saccular bronchiectasis was noted in 2 cases. Due to certain peculiar features not usually observed in patients with pulmonary eosinophilia, the authors suggested to classify their 3 patients as a separate entity. Unlike the acute presentation of pulmonary eosinophilia, these patients had a protracted course of illness. It was also observed that production of sputum "plugs" correlated with clearing of radiologic infiltrates. Mucosal edema and bronchial spasm without any obstructing masses were found on bronchoscopy, while markedly dilated bronchi filled

with sticky, tenacious mucus were necropsy findings in 1 patient. The authors stated that, "...intense eosinophilic infiltration and excessive production of mucus represented an allergic response...." Since fungal masses were not observed, they did not group these patients under "mycetomata."

Diagnostic criteria

Once the disease was recognized in the United States in 1968 and thence globally, the key diagnostic features have been standardized.[46,47] Based on clinical, radiologic, and laboratory features, a set of 8 major and 3 minor criteria was proposed in 1977 by Rosenberg and Patterson,[46] which remains the most well-acknowledged criteria (Table 2). Although a set of criteria is required, there is no single test that establishes the diagnosis other than demonstration of central bronchiectasis (CB) with normal tapering bronchi, a feature still considered pathognomonic of ABPA.[48,49] However, CB has also been found to extend to the periphery in some segments.[50]

All the 8 major criteria may not be found at all times. Some of the features may be present only during the acute (stage 1) or the exacerbation (stage 3) states. Moreover, apart from CB and *Aspergillus* type-1 hypersensitivity, the other parameters are affected by therapy with prednisolone. This makes it difficult for all criteria to always be fulfilled in patients with ABPA. In 2002, Greenberger[51] advocated a set of minimally essential criteria, which includes (1) asthma, (2) immediate cutaneous reactivity to *Af*, (3) total serum IgE >1,000 ng/mL (417 kU/L), (4) elevated specific IgE-*Af*/IgG-*Af*, and (5) CB in the absence of distal bronchiectasis. Greenberger[7] in 2013 further proposed "truly minimal" diagnostic criteria that included items (1), (2), (3), and (5) of the aforementioned minimally essential criteria.

Central or proximal bronchiectasis with normal peripheral bronchi continues to be considered a *sine qua non* for the diagnosis of ABPA.[48] However, there exists a subset of patients with a milder form of the disease in whom CB may not be present. These serologically positive patients satisfy the remaining criteria for ABPA and are categorised as ABPA-S.[52] Specific treatment for ABPA should immediately be commenced so as to delay or prevent further lung damage. Later on when CB develops, the patient is classified as ABPA-CB.[53]

Even today, there is no agreement on the minimum number of criteria, either major or minor, required to diagnose ABPA.[54] The ISHAM Working Group[29] has proposed a set of revised criteria wherein the items are broadly divided into 'obligatory' and 'other' criteria (Table 2). Bronchial asthma and CF are identified as predisposing conditions for ABPA in this newly proposed set of criteria. The 2 features of the obligatory criteria are as follows: (1) positive immediate (type I) cutaneous hypersensitivity to *Aspergillus* antigen or elevated IgE levels against *Af* and (2) elevated total IgE levels >1,000 IU/mL. Both of these findings must be present to establish a diagnosis of ABPA. At least 2 out of 3 other criteria *viz.* (1) presence of precipitating or

Table 2. Evolving diagnostic criteria for ABPA

Rosenberg-Patterson criteria[46,47]	Minimal essential criteria[51]	'Truly minimal' criteria[7]	ISHAM Working Group[29]	ABPA in CF[55]
Major criteria 1. Asthma 2. Presence of transient pulmonary infiltrates (fleeting shadows) 3. Immediate cutaneous reactivity to *Af* 4. Elevated total serum IgE 5. Precipitating antibodies against *Af* 6. Peripheral blood eosinophilia 7. Elevated serum IgE and IgG to *Af* 8. Central/proximal bronchiectasis with normal tapering of distal bronchi *Minor criteria* 1. Expectoration of golden brownish sputum plugs 2. Positive sputum culture for *Aspergillus* species 3. Late (Arthus-type) skin reactivity to *Af*	1. Asthma 2. Immediate cutaneous reactivity to *Af* 3. Total serum IgE >1,000 ng/mL (417 kU/L) 4. Elevated specific IgE-*Af*/IgG-*Af* 5. CB in the absence of distal bronchiectasis	1. Asthma 2. Immediate cutaneous reactivity to *Af* 3. Total serum IgE >1,000 ng/mL (417 kU/L) 4. CB in the absence of distal bronchiectasis	*Predisposing conditions* 1. Bronchial asthma 2. Cystic fibrosis *Obligatory criteria (both should be present)* 1. Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Af* 2. Elevated total IgE levels (>1,000 IU/mL)* *Other criteria (at least two of three)* 1. Presence of precipitating or IgG antibodies against *Af* in serum 2. Radiographic pulmonary opacities consistent with ABPA 3. Total eosinophil count >500 cells/μL in steroid naïve patients (may be historical) (*If the patient meets all other criteria, an IgE value <1,000 IU/mL may be acceptable)	Presence of two of the following three: (i) Immediate skin reactivity to *Af* antigens, (ii) Precipitating antibodies to *Af* antigens, (iii) Total serum IgE >1,000 IU/mL; and at least two of the following six: (i) Bronchoconstriction, (ii) Peripheral blood eosinophilia >1,000/μL, (iii) History of pulmonary infiltrates, (iv) Elevated specific IgE-*Af*/IgG-*Af*, (v) *Af* in sputum by smear or culture, (vi) Response to steroids

ABPA, allergic bronchopulmonary asperillosis; *Af, Aspergillus fumigatus*; CB, central bronchiectasis; CF, cystic fibrosis; IgE, immunoglobulin E; IgG, immunoglobulin G; ISHAM, International Society for Human and Animal Mycology.

IgG antibodies against *Af* in serum, (2) radiographic pulmonary opacities consistent with ABPA, and (3) total eosinophil count >500 cells/μL in steroid naïve patients should be fulfilled. However, the Working Group[29] has suggested that this newly proposed criteria needs "validation and further refinement."

ABPA in CF

Based on the Epidemiologic Study of Cystic Fibrosis (ESCF) database,[55] a set of criteria for the diagnosis of acute ABPA in patients with CF has been laid down. The ESCF criteria adopted included the presence of 2 of the following 3: (1) immediate skin reactivity to Af antigens, (2) precipitating antibodies to Af antigens, and (3) total serum IgE >1,000 IU/mL; and at least 2 of the following 6: (1) bronchoconstriction, (2) peripheral blood eosinophilia >1,000/μL, (3) history of pulmonary infiltrates, (4) elevated specific IgE-*Af*/IgG-*Af*, (5) *Af* in sputum by smear or culture, and (6) response to steroids.

ABPA without asthma

Although ABPA is predominantly a disease of asthmatics, this entity has also been diagnosed in patients without asthma. After the first such description in 1981,[56] more than a score of patients have been documented. A noteworthy aspect of this subset of patients was that more than half were initially worked up for bronchogenic carcinoma. Furthermore, the remarkable radiologic similarity to pulmonary tuberculosis has important clinical implications in high tuberculous prevalent areas, as the patient reported by us was referred as 'multidrug-resistant tuberculosis' for evaluation.[57] The presence of broncholithiasis in ABPA without asthma has also been described.[58]

Clinical features

This immunologically mediated lung disease is usually indolent in nature and has a protracted course of illness. The presentation can range from mild asthma, with very few symp-

toms, to extensive lung disease that may manifest as respiratory failure. Patients encounter repeated episodes of acute exacerbations that, after treatment, are followed by periods of remissions. If left untreated, it more often than not results in a chronic fibrotic lung disease that mimics post tubercular fibrotic sequelae.[59] Apart from asthma, ABPA may also be associated with other clinical allergic diseases. Although these atopic conditions may manifest at an early age, ABPA is usually seen in the 20s or 30s, but has also been reported in children[60,61] and even in infants.[62] In a patient with poorly controlled asthma and peripheral eosinophilia, expectoration of golden-brown plugs in the sputum should raise the possibility of ABPA.[63] A third of the patients, in spite of extensive radiological lesions, may have few or no symptoms at all.[64] Hence, it appears that the severity or chronicity of the disease does not correlate with symptomatology.

We reviewed the clinical profile of 113 patients with ABPA, 70 of whom were males.[65] The mean age was 32 years, while the mean age of onset of asthma was 21 years. Respiratory symptoms included cough (99%), breathlessness (99%), expectoration (98%), wheezing (97%), and haemoptysis (41%). Nasal symptoms suggestive of upper airways allergy were present in 45%. Expectoration of sputum plugs was reported by 37% of the patients and nasal plugs by 6%. Approximately half of the patients had a personal/family history of atopy. A study from Korea highlighted that ABPA could possibly occur in patients with destructive lung disease due to tuberculosis.[66] Physical examination in ABPA may not be fruitful if the patient is asymptomatic. Rhonchi, crepitations, and bronchial breathing may be heard depending on the degree of the lung disease present. Persistent crackles, which do not clear after either a tussive effort or corticosteroid therapy, suggest extensive fibrosis. These patients may also exhibit cyanosis, digital clubbing, and features of cor pulmonale. Associated hypertrophic osteoarthropathy has also been reported.[67]

Roentgenologic manifestations

Ever since its first description, different radiologic modalities have played an integral part not only in diagnosing ABPA but also in monitoring the progress of the disease.[50,68] Various imaging techniques employed over a period of time include plain chest roentgenography, bronchography, and computed tomography (CT).

Plain chest roentgenography

The wide spectrum of plain chest radiographic appearances, transient or permanent in nature (Table 3), is responsible for the 'picturesque' nature of ABPA.[68-70] The transient opacities were first recognized by Hinson *et al.*[16] in their seminal description of ABPA in 1952 wherein they stated, "…serial radiographs are essential to show the sequence of incidents of lobar or segmental collapse and consolidation, first in one part, then in another and in either lung." Such 'fleeting shadows' were subsequently encountered in most patients with ABPA and were incorporated as 1 of the 8 major criteria enunciated by Rosenberg

Table 3. Radiological changes in ABPA[1,25,50]

Plain chest radiology	Computed tomography findings
Transient changes • Perihilar infiltrates simulating adenopathy • Air-fluid levels from dilated central bronchi filled with fluid and debris • Massive consolidation-unilateral or bilateral • Radiologic infiltrates • 'Toothpaste' shadows due to mucoid impaction in damaged bronchi • 'Gloved finger' shadows from distally occluded bronchi filled with secretions • 'Tramline' shadows representing oedema of the bronchial walls • Collapse-lobar or segmental *Permanent changes* • Central bronchiectasis with normal peripheral bronchi • Parallel-line shadows representing bronchial widening • Ring-shadows 1-2 cm in diameter representing dilated bronchi *en face* • Pulmonary fibrosis • Late changes-cavitation, contracted upper lobes and localised emphysema	*Bronchial abnormalities* • Bronchiectasis, usually central, as characterised by the 'signet ring' and 'string of pearls' appearances • Dilated bronchi with or without air-fluid levels • Totally occluded bronchi • Bronchial wall thickening • Parallel-line opacities extending to the periphery • High attenuation mucous plugs *Parenchymal changes* • Consolidation • Non-homogeneous patchy opacities • Parenchymal scarring of varying extent • Segmental or lobar collapse • Cavitation • Emphysematous bullae *Pleural involvement* • Pleural effusions • Spontaneous pneumothorax • Bronchopleural fistula • Pleural fibrosis • Pleural thickening

Fig. 1. Plain chest roentgenogram showing a left-sided perihilar opacity along with non-homogeneous infiltrates in all zones of both lung fields.

Fig. 2. Plain chest roentgenogram of the same patient taken 4 months later showing spontaneous resolution of the left-sided perihilar opacity. The bilateral non-homogeneous infiltrates have increased considerably (Figs 1 and 2 reveal 'transient pulmonary infiltrates' or 'fleeting shadows', which are characteristic of ABPA).

and Patterson.[46] While evaluating 1,340 chest roentgenograms in 113 patients with ABPA, fleeting shadows were documented in 89%.[65] These transient pulmonary infiltrates (Figs. 1 and 2) reflect disease activity and are usually observed in either the acute or the exacerbation stage. Mucoid impaction due to secretions in the damaged bronchi, which may clear with or without therapy, is responsible for the transient nature of these pulmonary infiltrates. No area of the lung remains unaffected, but the upper lobes are predominantly involved.[50] While these radiological opacities may be easily mistaken for pulmonary tuberculosis in countries with high tuberculosis prevalence, fleeting shadows can be observed on evaluation of serial radiographs of the patient.[71] 'Recurrent fixed shadows' may ensue when pulmonary infiltrates reappear at the same sites.[72]

The most commonly observed transient pattern is consolidation or non-homogeneous opacities, seen in up to 91% of patients with ABPA.[65,69,70] These are produced as a result of parenchymal infiltration by inflammatory cells, especially eosinophils. The consolidation often clears after therapy, or sometimes even spontaneously, and is not specific to ABPA. Perihilar or 'pseudohilar' infiltrates, found in 40%-77% of patients,[65,70] are seen surrounding the dilated, central bronchi that are filled with secretions. Such opacities may simulate hilar lymphadenopathy. However, true hilar adenopathy that resolved after therapy has also been reported in ABPA in adults[73] as well as in a child.[61]

Other transient radiologic features, *viz.* 'tramline' sign, 'toothpaste' shadows, 'gloved fingers' opacities, and 'V-Y' shaped or 'wine glass' shadows are also highly suggestive of ABPA. Bronchial wall edema, which is due to thickening but without any increase in diameter, gives rise to the 'tramline' sign. This fea-

ture, observed in 45%-92% of patients,[69,70] is not specific for ABPA as it is also visualized in patients with asthma, CF, and acute left heart failure. 'Toothpaste' or bandlike shadows, reported in 24%-65% of patients,[65,69,70] are formed due to mucoid impaction and retention of respiratory secretions in the distorted bronchi. 'Gloved fingers' opacities are cast by the expanded and rounded ends of the occluded distal bronchi. Such shadows, seen in 11%-23% of patients with ABPA,[65,69,70] may disappear after coughing or with treatment. Mucoid impaction in the bronchi of the upper lobes may lead to 'V-shaped'/'wine glass' shadows. This radiologic feature was observed in 27% of our patients.[65] Air-fluid levels due to secretions and debris in the dilated central bronchi, found in up to 20% of patients,[65,70] are also indicative of ABPA. Collapse, both lobar as well as segmental, are not uncommon in ABPA. Proximal occlusion of the bronchi has caused lobar collapse in 14%-39% of patients.[65,69,70] We have earlier documented a patient with concomitant ABPA and AAS presenting as a case of middle lobe syndrome.[74] Recently, we reported another patient who presented with middle lobe syndrome.[75] Although there was significant symptomatic improvement after 2 weeks, the radiological opacity persisted for 4 months. Subsequently, at 6 months while on therapy with prednisolone, the middle lobe reinflated spontaneously.

The irreversible, fibrotic changes in the bronchial walls and parenchyma lead to various permanent opacities, which tend to persist throughout life even when the patient is in remission. These can be depicted on the chest roentgenogram as parenchymal fibrosis in the form of reticulolinear markings or honey-

Fig. 3. Computed tomography of the thorax showing 'signet ring' (short, thick arrow) and 'string of pearls' (long, thin arrow) appearances, indicative of central bronchiectasis. Mucoid impaction and dilated bronchi are also visualized.

combing, contracted upper lobes, cavitation and localized emphysema. The most characteristic permanent change, however, is the occurrence of CB with normal peripheral bronchi.[76] This continues to be recognized as a hallmark of the disease.

Demonstration of CB

It is believed that bronchiectasis occurs in areas with previous consolidation. On plain chest roentgenograms, this is visualized either as parallel-line opacities, representing widening of the bronchi, or as ring opacities, 1-2 cm in diameter, representing dilated bronchi *en face*. Parallel-line shadows were observed in 65%-70% of patients with ABPA and ring shadows in 45%-68%.[65,69,70] Bronchography, once regarded as the gold standard for the demonstration of bronchiectasis but now considered obsolete, gave a one time complete picture of the whole tracheobronchial tree.[77]

Currently, CT of the thorax, high resolution in particular, is the modality of choice for the demonstration of bronchiectasis. When compared to bronchography, CT had a sensitivity of 83% and a specificity of 92% in detecting CB in patients with ABPA.[77] In children with severe asthma, CT scans helped rapidly and safely establish the diagnosis of ABPA.[78] Bronchiectasis on CT is characterised by the 'string of pearl' and 'signet ring' appearances (Fig. 3). Although demonstration of CB with normal peripheral bronchi should continue to be regarded as a *sine qua non* for the diagnosis of ABPA in patients without CF, extension of CB to the periphery was found in 30% of the lobes and 21% of the segments.[50]

Other CT appearances (Table 3)

Besides bronchiectasis, the other bronchial abnormalities observed on CT include dilated and totally occluded bronchi, air-
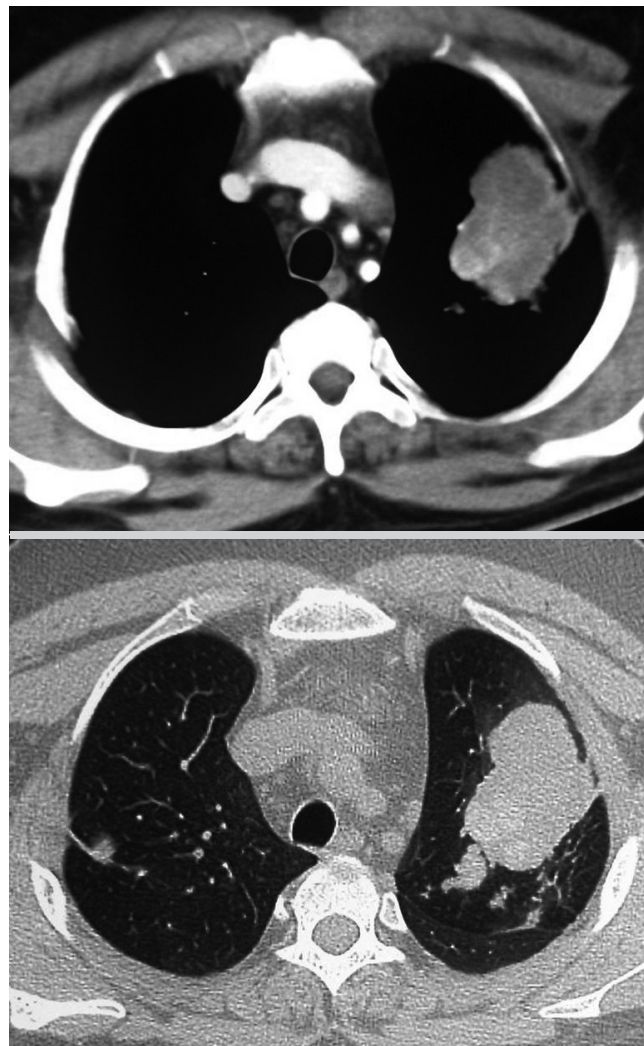
Fig. 4. High resolution computed tomography of the thorax (mediastinal window and corresponding section on the lung window) showing high attenuation mucous (HAM) impaction.

fluid levels within dilated bronchi, and bronchial wall thickening. Common parenchymal abnormalities are nonhomogeneous patchy consolidation and parenchymal scarring of varying extent, segmental or lobar collapse, cavities and emphysematous bullae.[68] Cavitary lung disease associated with fibrosis in ABPA can often be difficult to differentiate from fibrocavitary lung disease of tuberculous origin.[60,67,79]

On high-resolution CT, high-attenuation mucous (HAM) plugs (Fig. 4) were reported in 28% of patients with ABPA.[80] The ISHAM Working Group[29] has highlighted this finding and considers HAM a pathognomonic feature of ABPA. In an analysis of 155 patients with ABPA, the presence of HAM was associated with significantly higher levels of eosinophils, total IgE, and IgE-*Af* at the time of diagnosis.[81] Pleural abnormalities have also been observed in up to 43% of patients with ABPA.[50] Pleural effusion, most likely attributable to the mechanical effect of lung

collapse, was first documented in 1981 in 2 patients with ABPA.[82] We have also reported an ipsilateral pleural effusion secondary to lung collapse, which subsequently cleared on re-expansion of the lobe after steroid therapy, in a patient with ABPA, AAS and an operated aspergilloma.[83] Spontaneous pneumothorax, bronchopleural fistula, pleural thickening, and pleural fibrosis have also been described.[68,72]

Laboratory findings

Apart from radiologic investigations, the laboratory findings useful for diagnosing and monitoring ABPA include skin testing with *Aspergillus* antigens, peripheral eosinophil count, serum total IgE, *Af*-specific IgE and IgG, and precipitating antibodies against *Af*. Expectoration of golden brownish sputum plugs, one of the 3 minor criteria laid down by Rosenberg and Patterson,[46] often provides the first clue in patients with asthma and CF. A positive sputum culture for *Aspergillus* species, another of the minor criteria, was noted in about 58% cases.[63]

Eosinophil count

Peripheral blood eosinophilia, one of the major criteria, can often be demonstrated. During exacerbations, most patients have an absolute eosinophil count between 1,000 and 3,000 per cumm. However, eosinophilia is also found in many other lung diseases; while a normal eosinophil count may be seen in patients on treatment with corticosteroids. Since this test is not very specific, the ISHAM Working Group[29] has included this test under 'other' criteria. Sputum eosinophilia may be demonstrated in patients with productive cough.

Skin testing with Aspergillus antigens

Both type I (immediate) and type III (delayed) skin sensitivity with different *Aspergillus* antigens can be found in patients with ABPA. While the type III response is completely suppressed by steroid therapy, there is little or no effect on the type I reaction. Both intradermal and prick tests have been used by different researchers to diagnose ABPA. Depending on the geographical area and the manufacturing technique employed, the *Aspergillus* antigen extracts available are not uniform.[84] Currently, the prick test is used for the initial screening of ABPA. If the prick test is negative, then intradermal testing, which is more sensitive than the prick method, can be performed to elicit *Aspergillus* sensitization. However, higher false positive results are observed with intradermal tests.

Immediate skin hypersensitivity is not highly specific for ABPA. This is evidenced by the fact that approximately up to 40% of all asthmatics[29] and up to 56% of patients with CF[85] are sensitized to *Af*. To overcome this, recombinant *Af* allergens have now been cloned, purified and standardized for testing. In one of the initial studies in *Af* sensitized patients with CF, 3 out of 6 patients with ABPA did not demonstrate hypersensitivity with recombinant *Af* allergen I/a (rAsp f I/a).[86] When skin test-

ing with rAsp f 1, rAsp f 3, rAsp f 4 and rAsp f 6 was performed on 50 patients with CF (12 with ABPA, 17 with *Aspergillus* sensitization without ABPA, and 21 not sensitized to *Af*), no reactivity to 1:100 or higher dilutions of the cloned rAsp f 4 and rAsp f 6 was found in any of the 38 patients without ABPA.[87] The authors suggested that these 2 recombinant allergens are reliable markers for ABPA in CF.

Total serum IgE

Elevated total serum IgE is one of the minimal essential criteria[51] as well as a component of the "truly minimal" diagnostic criteria[7] both proposed by Greenberger. In spite of being recognized as a key criterion for diagnosing ABPA, there still remains a disagreement among different research groups in the cutoff level for IgE. In the Rosenberg-Patterson criteria,[46] the IgE level for diagnosing ABPA was greater than 1,000 IU/mL (-2,500 ng/mL). However, in the minimal essential criteria, Greenberger[51] has given a reduced serum IgE level (>417 IU/mL or 1,000 ng/mL) in order to establish the diagnosis. According to the 'ABPA in CF' consensus criteria, serum IgE >500 IU/mL is considered diagnostic.[27] The ISHAM Working Group[29] proposed a cutoff level of 1,000 IU/mL as was initially set forth by Rosenberg and Patterson.[46] This was so because the Working Group[29] "felt that a cutoff of 500 IU/mL may lead to overdiagnosis of ABPA." The cutoff IgE value needs to be validated across all populations as it could possibly be affected by both ethnicity and risk of exposure to *Aspergillus* antigens. In an electronic survey conducted by Greenberger *et al.*[54] among members of the American Academy of Allergy, Asthma, and Immunology (AAAAI), information was sought on the diagnostic criteria and management practices adopted for ABPA. The authors observed that 44.9% of allergists/immunologists used total IgE concentration ≥417 IU/mL when diagnosing ABPA while 42% respondents regarded IgE levels ≥1,000 IU/mL as the cutoff.

Specific IgE/IgG to A. fumigatus

Elevated IgE-*Af* and IgG-*Af* is also one of the minimal essential criteria[51] for the diagnosis of ABPA. Generally, double the serum values of IgE-*Af* and IgG-*Af* are found in patients with ABPA as compared to AIA.[47] If the controls' values are not available for comparison, then very high serum levels of IgE-*Af* or IgG-*Af*, in an appropriate clinical setting, may be diagnostic of ABPA. The ISHAM Working Group[29] has suggested IgE-*Af* level >0.35 kUA/L to be diagnostic.

The radioimmunoassay (RIA) method replaced the previously used enzyme-linked immunosorbent assay (ELISA) for estimating IgE-*Af* and IgG-*Af* as low levels of IgE-*Af* could not be detected by ELISA. However, the RIA technique was limited by the short shelf life of the radioisotope and exposure to radioactivity. Subsequently, the biotin-avidin-linked immunosorbent assay method was employed in 13 patients with ABPA, 9 with AIA, 12 with aspergilloma, and 9 controls without asthma,

which resulted in significantly higher IgE-*Af* levels in patients with ABPA, even at very high dilutions of 1:1,000.[88] The authors attributed this finding to a polyclonal antibody response to *Aspergillus* antigens in patients with ABPA but not in those with AIA. Similar to demonstration of skin hypersensitivity, ABPA can be distinguished from AIA with high specificity (100%) and sensitivity (90%) by using recombinant *Af* allergens.[89] High levels of specific IgE to recombinant *Af* allergens also helped detect ABPA in patients with underlying CF.[90]

Precipitating antibodies against A. fumigatus

By the double immunodiffusion technique of Outcherlony, precipitating antibodies against *Af* could be detected in the unconcentrated serum from 70% of patients.[63] Using concentrated serum, this detection rate improved to 92% of patients with a radiological infiltrate.[63] These precipitating antibodies have also been found in 10% of asthmatics without ABPA,[4] aspergilloma and in different forms of chronic pulmonary aspergillosis (CPA). Denning *et al.*[91] have correlated the presence of complicating features like fibrosis and cavitation with high titres of serum precipitins in patients with ABPA.

Pulmonary function testing

Pulmonary function testing does not help confirm the diagnosis of ABPA. In addition to airflow obstruction, a restrictive pattern with reduction in total lung capacity (TLC), vital capacity (VC), forced expiratory volume in the first second (FEV1) and reduced diffusion capacity for carbon monoxide (DLCO) may be observed when the patient presents in the acute or the exacerbation stage.[92,93] Normalization of some of these parameters may be noticed after treatment with corticosteroids and also during remission. A significant ($P<0.05$) reduction in FEV1, FEV1/VC ratio and FEF_{25-75} was observed in patients with ABPA having mean duration of illness greater than 10 years when compared to those with symptoms less than 10 years' duration.[93]

Staging

Five stages of ABPA[94,95] have been identified, *viz.* (i) acute, (ii) remission, (iii) exacerbation, (iv) corticosteroid dependent asthma, and (v) fibrotic lung disease (Table 4). Staging of the disease must be done when establishing the diagnosis and should be reassessed during follow-up visits whenever the patient improves or deteriorates. Improvement in symptoms, res-

Table 4. Staging in ABPA

Conventional staging[94,95]		
Stage I	Acute	The patient is first proved to have ABPA. All the usual features like elevated total as well as *Aspergillus*-specific IgE, radiological abnormalities, peripheral blood eosinophilia, and serum precipitins against *Aspergillus* are present.
Stage II	Remission	The patient is usually asymptomatic with well controlled underlying asthma. In addition, there should be no new radiological lesions without any rise in total IgE for a period of at least 6 months.
Stage III	Exacerbation	There is appearance of fresh pulmonary infiltrates that is often associated with doubling of remission total IgE levels and peripheral blood eosinophilia.
Stage IV	Corticosteroid dependent asthma	Patients generally become corticosteroid dependent and oral corticosteroids cannot be tapered off completely.
Stage V	Fibrotic lung disease	Radiographic abnormalities in the form of irreversible fibrosis and chronic cavitation persist. Serological parameters are usually negative.
ISHAM Working Group proposed clinical staging[29]		
Stage 0		Clinically stable and well controlled asthmatic subjects who do not have any signs and symptoms suggestive of ABPA but are diagnosed as ABPA when routinely investigated as per the criteria
Stage 1	Acute	Based on CT and/or bronchoscopic findings: 1a: with mucoid impaction 1b: without mucoid impaction
Stage 2	Response	Clinical as well as radiological improvement associated with at least 25% decline in serum IgE level at 8 weeks of therapy
Stage 3	Exacerbation	Any clinical and/or radiological worsening along with an increase in IgE level by >50% of baseline
Stage 4	Remission	Sustained clinicoradiological improvement accompanied by baseline IgE values (or less than 50% increase) for more than 6 months duration without systemic corticosteroids
Stage 5	5a: Treatment dependent ABPA	Either relapse occurs on two or more consecutive occasions within 6 months of stopping treatment or there is worsening of clinical, radiological or immunological parameters on tapering oral steroids/azoles
	5b: Glucocorticoid dependent asthma	When systemic steroids are required for control of asthma whilst activity of ABPA is under control
Stage 6	Advanced ABPA	Clinical signs of cor pulmonale and type-2 respiratory failure along with radiological features of fibrosis

olution of radiologic lesions, as well as a decline in total IgE and blood eosinophilia usually occurs with prednisolone therapy, or at times spontaneously. Exacerbations are entirely asymptomatic in approximately one-third of the cases, and may be detected either by the doubling of remission IgE values or demonstration of extensive radiologic opacities. Although remission for prolonged periods is not common, we reported an exacerbation after prolonged remission in a patient with ABPA and an associated aspergilloma.[96] Since therapy with prednisolone may mask the characteristic features of the disease, stage IV ABPA is clinically indistinguishable from corticosteroid dependent asthma without ABPA.[97]

In order to refine these stages, the ISHAM Working Group[29] has proposed a new clinical staging of ABPA in asthma (Table 4). Asymptomatic patients diagnosed with ABPA when routinely investigated as per the criteria were categorized as stage 0. This was done to recognize the disease as early as possible so that commencement of appropriate treatment even before the acute presentation (stage 1) could possibly prevent progression to end stage fibrosis. Stage 2 (response) sets in when there is clinical, radiological and serological improvement. However, this newly proposed staging would require prospective validation.

Radiological staging

A newly proposed radiological classification of ABPA that is based on thoracic CT findings has also been tabled by the ISHAM Working Group.[29] This new classification has 4 categories that correlate the immunological severity of ABPA with various CT features. As the disease progresses from mild to moderate to severe, the radiological classification is as follows: (1) serological ABPA (ABPA-S), (2) ABPA with bronchiectasis (ABPA-B), (3) ABPA with HAM (ABPA-HAM), and (4) ABPA with chronic pleuropulmonary fibrosis (ABPA-CPF). For inclusion in the ABPA-CPF group, there should be at least 2 other radiologic features, apart from bronchiectasis and HAM, *viz.* pulmonary fibrosis, parenchymal scarring, fibrocavitary lesions, aspergilloma, and pleural thickening.

Treatment

As described in the recent AAAAI Committee Report[54] on ABPA, the goals of treatment of ABPA are to: (i) control symptoms of asthma or CF, (ii) prevent or treat pulmonary exacerbations of ABPA, (iii) reduce or remit pulmonary inflammation, and (iv) mitigate progression to end-stage fibrotic or cavitary disease. Exclusion of ABPA in family members and identification of any potential environmental source of the incriminated fungus should also be stressed upon when managing a patient with ABPA. No definite prognostic indicators for progression or regression of the disease have been identified. In order to successfully achieve these goals, it is important to treat the disease aggressively during the early stages. Oral corticosteroids continue to remain the cornerstone for the management of ABPA. Ap-

propriately designed clinical trials for the treatment of ABPA are lacking. The role of antifungal drugs so far is at best adjunctive.

Corticosteroids

Oral corticosteroids, till date, remain the most effective drugs for treating ABPA.[98] The dosing schedule and duration of therapy for oral steroids remain poorly defined. For Stages I (acute) and III (exacerbation), the most widely accepted protocol is prednisolone 0.5 mg/kg/day given as a single morning dose for the initial 2 weeks and then switched to an alternate-day dose for the next 6-8 weeks.[51] Once the total serum IgE declines by at least 35% and resolution of radiologic infiltrates are noted, prednisolone is further tapered by 2.5 to 5 mg every 2 weeks.[99] After discontinuation of prednisolone, if achieved, the patient should be monitored every 6 to 8 weeks to ensure that remission is maintained. If there are any features suggestive of relapse, treatment should be recommenced as early as possible. Patients with stage IV ABPA (steroid-dependent asthma) usually require alternate day therapy with prednisolone 10-40 mg for many years to sustain symptom control. Daily prednisolone along with other interventions for the management of cor pulmonale and arterial hypoxemia are needed for patients with end stage lung disease (stage V).[26]

To minimize the well-known adverse effects of long term steroid therapy, we assessed the feasibility of a biweekly dosing schedule in 26 patients with ABPA with or without AAS.[100] Following an initial dosage of prednisolone 0.5 mg/kg/day for two weeks, patients were alternately prescribed either the conventional alternate-day regimen or a twice weekly dosing protocol was adopted. Patients receiving the biweekly regimen also showed a significant improvement in FEV1, total IgE levels, and eosinophil counts. Pulse therapy with intravenous methylprednisolone using 10 to 20 mg/kg/day for 3 consecutive days has been shown to be useful in managing severe and sometimes life-threatening exacerbations among children with ABPA and CF.[101] In conjunction with antifungal agents, this could be considered in patients not improving with oral steroid therapy. Inhaled corticosteroids alone help achieve asthma control, but neither do they prevent symptomatic exacerbations of ABPA nor delay progression of lung damage.

Antifungal agents

The exact role of antifungal agents in the treatment of ABPA is still debated. By reducing the fungal load, antifungal agents help control the antigenic stimulus and thus decrease the inflammatory response.[102] Earlier studies with older antifungal molecules, viz. natamycin, hamycin, amphotericin B, miconazole, clotrimazole and ketoconazole did not show much promise. Subsequently, studies with itraconazole demonstrated a reduction in daily corticosteroid doses without clinical deterioration. The Cochrane Database review[103] on azoles for ABPA concluded that itraconazole improved clinical outcomes.

The dosage of itraconazole recommended is 200 mg twice daily for 4 to 6 months, which is then tapered over the next 4 to 6 months. By inhibiting steroid metabolism and thereby exacerbating adrenal suppression, itraconazole might lead to cushingoid features when used for very long durations.

To avoid drug resistance and possible clinical failure due to suboptimal therapeutic levels, regular monitoring of itraconazole blood levels is advocated.[104] In ABPA, the newer azoles, voriconazole and posaconazole, have improved asthma severity in 70% and 78% of patients respectively.[105] However, skin cancer has been associated with long-term voriconazole therapy.[106] It is still not known whether itraconazole and other newer azoles would successfully replace oral steroids as first-line therapy for ABPA. The results of a randomized trial on monotherapy of itraconazole vs prednisolone in ABPA (MIPA study) are awaited (clinical trials.gov; NCT01321827).

Omalizumab

Omalizumab, a monoclonal antibody against IgE, has also been tried in the management of ABPA. Initial studies in patients with underlying CF have demonstrated a significant clinical improvement with reduction in hospitalisation and exacerbations.[107,108] Usage of oral corticosteroids in these patients also declined. Similar results have also been documented with omalizumab in patients with ABPA due to underlying asthma.[109,110] This potential of this drug in decreasing or avoiding oral steroids in patients with stage IV (steroid-dependent) disease should be investigated. Randomized trials with omalizumab and possibly other antibodies to IL-4Ra (dupilumab), IL 5 (mepolizumab), and IL 13 (lebrikizumab) are needed to assess their routine usage in ABPA.

ABPA and other pulmonary disorders

Rarely, ABPA has also recently been recognized in patients with chronic obstructive pulmonary disease.[111,112] The association of ABPA or an overlap condition that resembles ABPA was described in patients with hyper-IgE syndrome, chronic granulomatous disease, and Kartagener's syndrome.[25] In these congenital immunodeficiency neutrophilic conditions, it is essential to distinguish ABPA from invasive aspergillosis as mistreatment with systemic steroids may hasten the invasive process, resulting in increased morbidity.

ABPA AND OTHER *ASPERGILLUS*–RELATED DISORDERS

Although the clinical categories of *Aspergillus*-associated respiratory disorders usually remain mutually exclusive, similar immunopathologic responses may lead to the coexistence of different forms of respiratory aspergillosis. Concomitant occurrence of ABPA and AAS may not be all that uncommon.[18,74,83,113] Aspergilloma formation has also been documented in patients with ABPA.[67,79,114] We have twice so far reported concurrent

ABPA, AAS, and aspergilloma in a single patient.[83,115]

Allergic *Aspergillus* sinusitis

Just as in ABPA, *Aspergillus* antigens trigger immunologic reactions in the paranasal sinuses, thereby leading to AAS.[116,117] Those patients with rhinitis who were sensitized to *Aspergillus* are possibly at higher risk of developing AAS.[118,119] Here too, a set of criteria is required to establish the diagnosis of AAS. The key components of the diagnostic criteria for AAS are (1) radiological evidence of sinusitis of 1 or more paranasal sinuses; (2) necrosed amorphous tissue along with edematous polyps infiltrated by eosinophils on histopathological evaluation of material from the sinus; (3) demonstration of fungal elements in nasal discharge or in material obtained at the time of surgery by stain or culture; (4) absence of diabetes, previous or subsequent immunodeficiency disease, and treatment with immunosuppressive drugs; and (5) absence of invasive fungal disease at the time of diagnosis or subsequently. The other features considered include: (1) peripheral blood eosinophilia; (2) type I and type III cutaneous hypersensitivity to *Aspergillus*; (3) precipitating antibodies to *Aspergillus* antigens; (4) elevated total and *Aspergillus* specific IgE levels; and (5) characteristic CT appearances. Features, such as passage of nasal plugs, recurrent nasal polyps, and radiographic evidence of pansinusitis, in patients having an atopic background point toward an allergic fungal phenomenon in the upper airways.[113] 'Allergic mucin,' which is the characteristic nasal pathologic material comprising eosinophils, Charcot-Leyden crystals, cellular debris, and scattered fungal hyphae, is the hallmark of this disease.[116] The characteristic CT finding is the presence of heterogeneous densities with serpiginous areas of increased attenuation (Fig. 5) on noncontrast scans.[72] Histopathologic confirmation from the inspissated
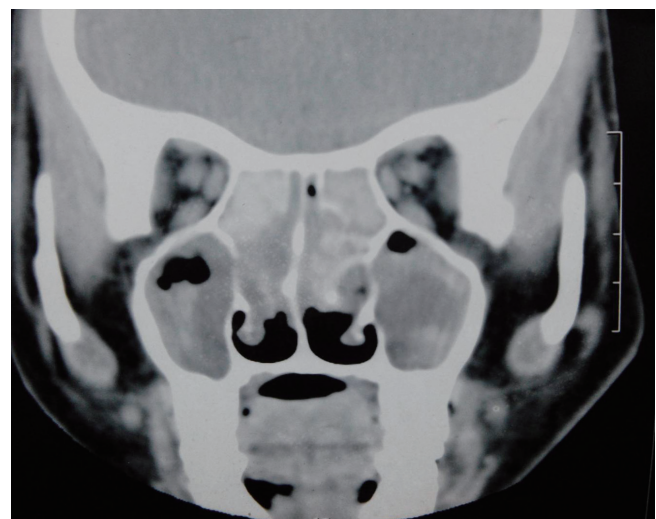
Fig. 5. Computed tomography of the paranasal sinuses showing hyperdense lesions in the ethmoid and maxillary sinuses bilaterally, suggestive of inspissated secretions.

mucus is a *sine qua non* for the diagnosis of AAS. The current approach to therapy includes an initial surgical debridement, followed by postoperative oral corticosteroids and supportive therapy.[113,120]

Aspergilloma

Chronic lung damage in ABPA, especially the presence of cavitating lesions, may provide a favourable milieu for aspergilloma formation.[67,79] Furthermore, steroid therapy could possibly accelerate the development of fungal balls in patients with cavitary lung disease.[114] *Vice versa*, it has also been seen that a pre-existing aspergilloma, by functioning as a nidus for antigen stimulation in susceptible individuals, may lead to ABPA subsequently.[121] We have postulated that the coexistence of an aspergilloma would likely lead to an increase in the severity of underlying ABPA.[122]

CPA

The entity CPA was first highlighted by Denning *et al*.[91] in 2003 when they identified a subset of patients with pre-existing structural lung disease who were chronically affected by *Aspergillus* but did not have any vascular or tissue invasion by the fungal hyphae. These patients were either immunocompetent or had only pulmonary (localised) immune suppression. On the basis of the radiological patterns, they were categorized as (1) chronic cavitary pulmonary aspergillosis (CCPA), (2) chronic fibrosing pulmonary aspergillosis (CFPA), and (3) chronic necrotizing pulmonary aspergillosis (CNPA). In CCPA, progressive cavitation or extension of a pre-existing cavity was noted; and if left untreated, development of chronic scarring and marked pulmonary fibrosis over time led to CFPA. In the presence of underlying confounding factors like alcoholism, smoking, AIDS, diabetes and corticosteroid treatment that caused mild to moderate immune dysfunction, a necrotizing condition developed, usually after enlargement of a thin-walled cavity. This condition occurred rapidly within weeks or gradually over months, and was labeled as CNPA. The classification of CPA has evolved over the last decade.[123,124] As these 3 forms are not easy to distinguish clinically, a new simplified classification for CPA has been proposed: (1) simple aspergilloma, (2) CCPA (complex aspergilloma) or slowly progressive CNPA (more than 3 months' duration) and (3) subacute invasive pulmonary aspergillosis or rapidly progressive CNPA of less than 3 months' duration.[123]

Diagnostic criteria

Patients with CPA usually have chronic respiratory and constitutional symptoms for at least 3 months, progressive enlargement and formation of new pulmonary cavities, positive serum precipitins against *Aspergillus* or isolation of *Aspergillus* spp. from the cavitary lesion, and elevated inflammatory markers (C-reactive protein, plasma viscosity or erythrocyte sedimenta-

tion rate). Diagnostic criteria for CPA also include exclusion of other pulmonary conditions like active tuberculosis and malignancy that mimic the symptoms as well as no obvious conditions suggesting an immunocompromised state.[91]

ABPA, SAFS, and CPA

When cavitation, fibrosis, pleural thickening and aspergilloma develop in patients with ABPA, CPA ensues. In a study of 126 patients with CPA, ABPA was the primary underlying condition in 15 subjects (11.9%) while SAFS was incriminated in 2 subjects (1.6%).[125] A scoping review[28] also attempted to estimate the global burden of CPA in patients with ABPA. Applying an annual 15% attrition rate while calculating the period prevalence of CPA over 5 years, the global case burden of CPA complicating ABPA was approximately 10% (range, 7%-20%).[28]

CONCLUSIONS

Sensitization to molds in patients with asthma is known to increase the severity of the disease.[126] Patients with asthma, eosinophilia, and history of repeated 'pneumonitis' should be evaluated aggressively for ABPA. This would help avoid diagnostic delay and prevent steady lung damage leading to end-stage fibrosis. In high tuberculosis-prevalent regions, the striking radiological resemblance often results in erroneous treatment with antituberculous drugs. Furthermore, poor access to costly and advanced diagnostic modalities like CT scans and mycoserological tests in low-income countries may hamper establishment of the diagnosis. The occurrence of other *Aspergillus*-related hypersensitivity respiratory disorders must be sought for in all patients with ABPA.[127,128]

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