

Allergic Bronchopulmonary Aspergillosis: All A Radiologist Needs To Know

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Abstract: Background: Allergic bronchopulmonary aspergillosis (ABPA) is an immunological lung disorder occurring due to hypersensitivity reactions mounted against the fungus *Aspergillus fumigatus*. Early diagnosis of ABPA is desirable as the disease can cause irreversible damage and end-stage lung disease. Diagnosis of ABPA is based upon a set of clinical, immunological and radiological criteria. Radiology not only plays an important role in the diagnosis of ABPA but is also essential during followup for detecting complications. A radiologist should be familiar with various clinical and serological criteria, so as to have a complete understanding of the disease process and to provide a confident diagnosis.

Objective: To describe the various clinical, laboratory and radiological findings in ABPA with a comprehensive review of various diagnostic criteria.

Methods: We searched the literature for various criteria that have been used for diagnosis of ABPA. We also extensively reviewed the radiology literature to look for various imaging findings described in ABPA. We searched the role of various imaging modalities used in evaluation of ABPA starting with conventional radiography to computed tomography and magnetic resonance imaging.

Results: In this article, we have reviewed the clinical, serological and radiological aspects of ABPA, with emphasis on the radiological findings. We have also described the various diagnostic criteria of ABPA.

Conclusion: In recent years, the role of radiology in ABPA has evolved. Radiology plays an important role not only in diagnosis but also for the classification and prognostication of the disease. A radiologist should also be familiar with the clinical spectrum and laboratory findings of the disease.

Keywords: Allergic bronchopulmonary aspergillosis, *Aspergillus fumigatus*, bronchiectasis, HRCT, high attenuation mucus, mucoid impaction.

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INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a manifestation of immune mediated response to ubiquitous fungus *Aspergillus fumigatus*, colonising the airways of pre-disposed individuals having asthma or cystic fibrosis [1]. Besides asthma and cystic fibrosis, rarely ABPA can complicate other lung diseases like chronic obstructive pulmonary disease (COPD), idiopathic bronchiectasis and chronic granulomatous disease [2-4]. Fungi other than *Aspergillus fumigatus* can also cause ABPA like syndrome known as allergic bronchopulmonary mycosis (ABPM). However it is very rare as compared to ABPA [5]. Early diagnosis of ABPA is necessary before irreversible pulmonary damage

occurs. Ever since its first description in 1952 by Hinson *et al* [6], diagnostic criteria of ABPA have been defined and redefined. A combination of clinical, serological and radiological criteria is used to diagnose ABPA. However at times, diagnosis of ABPA can be challenging despite presence of well established diagnostic criteria.

1. ETIOPATHOGENESIS

The name aspergillus has been derived from the Latin word asperge (literal meaning: to scatter) [7]. As suggested by its name, aspergillus is found ubiquitously throughout the globe and can survive under a wide range of temperature (15-53°C). *Aspergillus* enters the airways through inhalation in the form of spores, which are immunologically inert. A defective innate immune response (as in patients with asthma and cystic fibrosis) leads to germination of these spores [8]. Ineffective airway clearance in these patients is thought to be

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the predisposing factor for airway colonisation with aspergillus spores, which then germinate to form characteristic branching hyphae (branching at an angle of 45°).

Proteases and other toxins secreted by the fungal hyphae damage the bronchial epithelium thereby increasing the exposure of *A. fumigatus* antigens to dendritic cells. These cells prime helper T cells to secrete cytokines which lead to increased secretion of *A. Fumigatus* specific IgG, IgE and total IgE antibodies. Both type I and type III immunological reactions are involved in pathogenesis of ABPA. Necrotising granulomatous inflammation often occurs in ABPA, destroying the walls of bronchi and bronchioles [9].

It has been shown that genetic factors also play a role in pathogenesis of ABPA, and may protect or increase the susceptibility to ABPA [10]. ABPA predisposition has been shown to be increased by HLA antigens like DR2/DR5 and DR4/DR7, while HLA-DQ2 has shown a protective role against ABPA [10].

2. CLINICAL FEATURES

Prevalence of ABPA in asthma is 2-32% [11], and in cystic fibrosis 2-15% [12]. Most cases of ABPA are diagnosed between the third and fifth decades of life. It commonly affects young to middle-aged asthmatics and teenagers with CF. ABPA is extremely rare in paediatric asthma. Few cases of ABPA have been diagnosed in infants with CF [13]. Prevalence of ABPA increases with patient age [14]. Asthma of varying severity is almost always present in patients with ABPA. Allergic rhinitis, sinusitis, conjunctivitis and atopic dermatitis may be seen in some patients [7].

Like asthma, ABPA patients present with complaints of wheezing and cough. Occasionally only cough without wheezing may be the presenting symptom. Haemoptysis may be present in patients with bronchiectasis. Dyspnoea, malaise, fever and increased cough with flu like symptoms can be present in acute exacerbations and more severe cases. Expectoration of brownish sputum plugs is characteristic but uncommon feature of ABPA. Clubbing can be seen in approximately 16% of the patients [12]. Occasionally patients may be asymptomatic and diagnosed during routine screening [12]. Rarely patients with advanced ABPA can present with pulmonary fibrosis and cor pulmonale.

3. LABORATORY FINDINGS

Aspergillus skin test is cutaneous hypersensitivity response to subcutaneously injected *A. fumigatus* antigen. Immediate cutaneous response indicates type I reaction and is highly characteristic of ABPA. Delayed reaction after 6 hours indicates type III reaction. Serum total IgE levels are used for diagnosis and follow up of patients with ABPA. However they can be normal in active disease if patient is on steroids for any reason [12]. *A. fumigatus* specific IgG and IgE antibodies can be detected using fluorescent enzyme immunoassay and are hallmark of ABPA [15].

Serum precipitins against *A. fumigatus* measured by double gel diffusion provide only supportive evidence as they can be positive in other pulmonary disorders also [16-18]. Though peripheral eosinophilia (absolute eosinophil count >1000 cells/ μ l) is a diagnostic criterion for ABPA, its

absence does not rule out the disease [15]. Sputum culture is not of much help in diagnosis as a positive culture can be seen in variety of pulmonary diseases due to ubiquitous nature of the fungus. Pulmonary function tests in ABPA demonstrate an obstructive pattern [19-21]. However their role is limited to assessing the severity of the disease.

4. IMAGING FEATURES OF ABPA

4.1. Radiographic Findings in ABPA

Radiographic findings in ABPA are non-specific, thus posing a difficulty in making the diagnosis. Chest x-ray in ABPA may be normal in 50% cases [22]. Radiographic findings in ABPA can be divided into parenchymal and bronchial findings.

Parenchymal Findings

In active disease, ABPA manifests as rapidly clearing, transient or recurrent infiltrates on radiographs. Consolidation is also a common finding which has been shown to be due to parenchymal infiltration by eosinophils [23]. Consolidation can be lobar, segmental or subsegmental commonly involving the mid zones [24]. Occasionally a large mucus filled bronchus can mimic consolidation on radiograph [25]. Segmental or lobar atelectasis can also occur due to proximal mucoid impaction, which can be differentiated from consolidation by presence of volume loss in the former.

Bronchial Findings

Mucoid impactions in the proximal bronchi may appear as linear opacities with rounded distal margins due to distal occlusion giving characteristic “finger in glove” appearance (Fig. 1), or band-like opacities (toothpaste shadows). These shadows are transient and disappear following expectoration of sputum. Following expectoration toothpaste shadow may clear leaving behind a thin line outlining the bronchi appearing as “parallel line shadow”. “Tramline shadows” and “ring shadows” can also be seen in ABPA and represent permanent changes. “Tramline shadows” represent inflammatory response in peribronchial tissues and are seen as parallel hair-line shadows extending from the hila toward the periphery (Fig. 2) [26]. It should be noted that distance separating these parallel shadows is equal to width of the bronchus (as

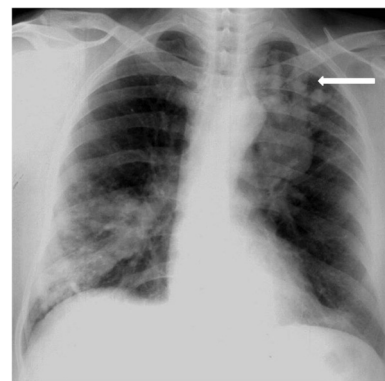


Fig. (1). Chest radiograph showing mucus impaction in bronchi as classic “finger in glove sign”. Also note mucoid impaction in proximal bronchus mimicking left parahilar mass.

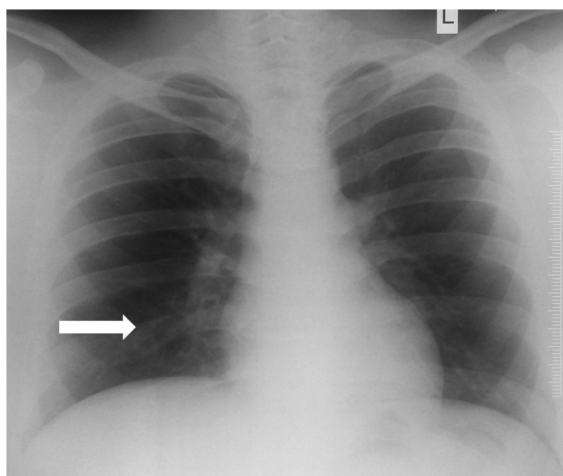


Fig. (2). Chest radiograph showing dilated bronchi in right lower zone with tram line sign (arrow).

there is no extrinsic damage to the bronchus), as opposed to “parallel line shadows” which are separated by a distance greater than the width of bronchi [22]. “Ring shadows” are circular hair line shadows (usually 1-2cm in diameter), representing the dilated bronchi. Transient air fluid levels can be seen in the dilated bronchi.

Mucus filled dilated central bronchi adjacent to hilum and mediastinum can mimic hilar or mediastinal lymphadenopathy, and are also known as pseudohilar opacities (Fig. 3). Hilar lymphadenopathy is a rare occurrence in ABPA and is usually secondary to lymphoid hyperplasia [27-33].

Table 1. Radiographic findings in ABPA.

Parenchymal findings
Migrating and rapidly clearing infiltrates
Consolidation
Atelectasis
Bronchial findings
Gloved finger shadow
Toothpaste shadows
Parallel line shadows*
Tramline shadows*
Ring shadows*
*: Indicates permanent findings. Rest of the findings described are transient

4.2. CT Findings in ABPA

Bronchiectasis

In ABPA, most common finding on HRCT chest is bronchiectasis [34]. HRCT is the investigation of choice for diagnosis of bronchiectasis in ABPA [35]. HRCT of the chest has a sensitivity and specificity of 96%–98% and 93%–99%, respectively, in the diagnosis of bronchiectasis [36,37].

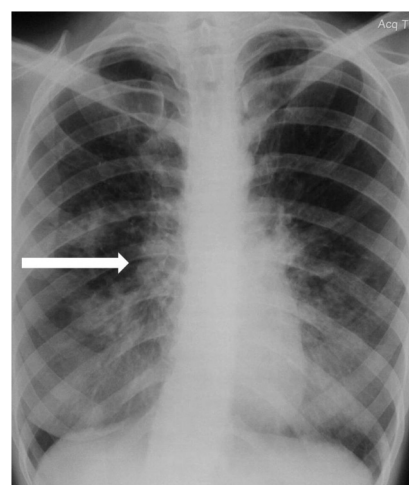


Fig. (3). Patient of ABPA presenting with acute exacerbation: Chest radiograph shows infiltrates in right mid zone. Mucoid impaction in central bronchi (arrow) mimicked hilar lymphadenopathy on radiograph.

Bronchiectasis is diagnosed on HRCT if the bronchoarterial ratio is greater than 1 (ratio of internal diameter of the bronchus to the external diameter of the adjacent artery) [38]. Bronchoarterial ratio may be elevated in asthmatics, in patients living at high altitudes and occasionally in normal patients [34]. Hypoxic pulmonary vasoconstriction is thought to be one of the factors responsible for elevation of bronchoarterial ratio in these patients [39]. Another limitation of bronchoarterial ratio is that it cannot be measured in patients with coexisting consolidation due to obscuration of adjacent arteries [40]. Other criteria for diagnosing bronchiectasis on HRCT are lack of peripheral tapering of bronchi and visible peripheral bronchi (in the peripheral 2cm of lung) [34].

Bronchiectasis is further classified into: cylindrical bronchiectasis (appearing as tram-track or signet-ring), varicose bronchiectasis (irregular, beaded appearance of bronchi) and cystic bronchiectasis (appearing as clustered bronchi) [41].

Central bronchiectasis is a characteristic finding in ABPA preferentially involving the upper lobes (Fig. 4). However there are no uniform criteria for its diagnosis. Authors have used different definitions including subjective criteria based upon proximity to hilum [42], dilated bronchi within medial two- third of the lung [43-45] or within medial half of the lung [15]. Although central bronchiectasis is considered to be a diagnostic feature of ABPA, peripheral bronchiectasis is not uncommon and has been reported in almost 40% of the involved lobes [15, 46, 47]. Thus significance of central bronchiectasis for diagnosis of ABPA is debatable.

Mucoid Impaction

Mucoid impaction is filling of the dilated bronchi by mucoid secretions. Mucus plugging in ABPA is generally hypodense. Sometimes impacted mucus in the bronchi can have higher CT attenuation values than adjacent paraspinous muscles (Fig. 5,6), and is known as high attenuation mucus (HAM). Presence of HAM in ABPA was first described by



Fig. (4). Axial HRCT section shows central bronchiectasis involving left upper lobe bronchi.



Fig. (5). Axial CT image of chest shows high attenuation mucus in bronchi, having attenuation more than adjacent paraspinal muscles.

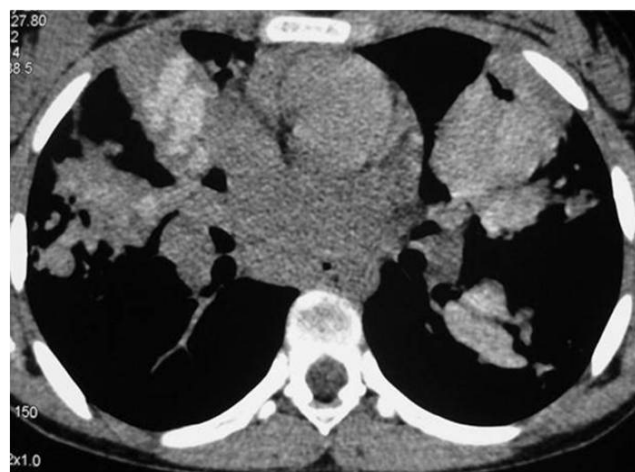


Fig. (6). Axial CT image of the chest showing high as well as low attenuation mucus impacted in bronchi of both upper lobes.

Goyal *et al.* in 1992 [48]. HAM is considered to be a pathognomonic finding in ABPA and can be seen in up to 30% of patients with ABPA [9,48-50]. Presence of calcium salts and certain metallic ions like iron and manganese [51] or desiccated mucus [52] are thought to be responsible for high attenuation of the mucus. HAM has also shown correlation with disease severity. In one study high density mucus in ABPA correlated with higher mean eosinophil counts, higher mean total serum IgE and *Aspergillus fumigatus* specific IgE and greater likelihood of disease relapse [50]. Mucoid impaction in distal small airways can manifest as centrilobular nodules with tree-in-bud appearance on HRCT (Fig. 7). Centrilobular nodules are more commonly seen in ABPA associated with cystic fibrosis than asthma [53].

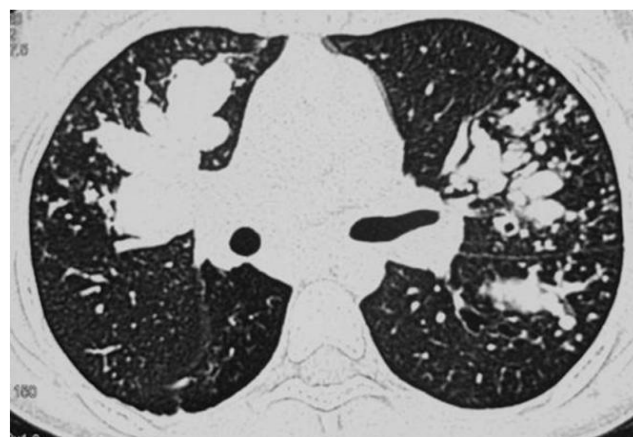


Fig. (7). Axial HRCT image of the chest showing centrilobular nodules in bilateral lungs depicting mucoid impaction in distal bronchioles.

Other Imaging Findings

Atelectasis can occur in ABPA due to mucoid impaction and can be segmental or subsegmental. Consolidation can also be seen in ABPA (Fig. 8). Small airway involvement can also occur in ABPA and can manifest as areas of mosaic attenuation with air trapping on HRCT secondary to bronchiolar obstruction [54].

ABPA can eventually progress to end stage lung disease with extensive bronchiectasis and fibrosis on CT [55]. Other imaging findings described in ABPA are parenchymal scarring, blebs, bullae, emphysematous change, cysts, fibrocavitary lesions and pleural thickening [15,56].

Uncommon Imaging Findings in ABPA

Pleural involvement in ABPA can be seen in form of pleural effusion [57-60] or secondary spontaneous pneumothorax [61,62]. Occasionally pulmonary hypertension can be the presenting manifestation in ABPA [63]. Aspergilloma formation in dilated bronchi has also been described [64-66]. Very rarely invasive aspergillosis has also been reported in ABPA, due to lowering of immunity secondary to steroid therapy or other coexisting immune suppressing illness [67]. Diffuse consolidation is seen on imaging.

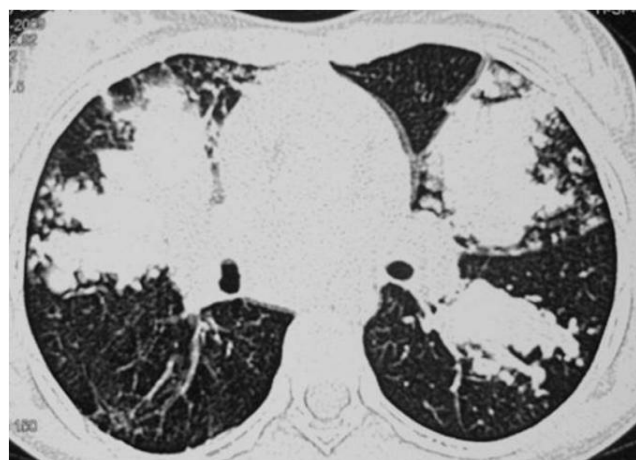


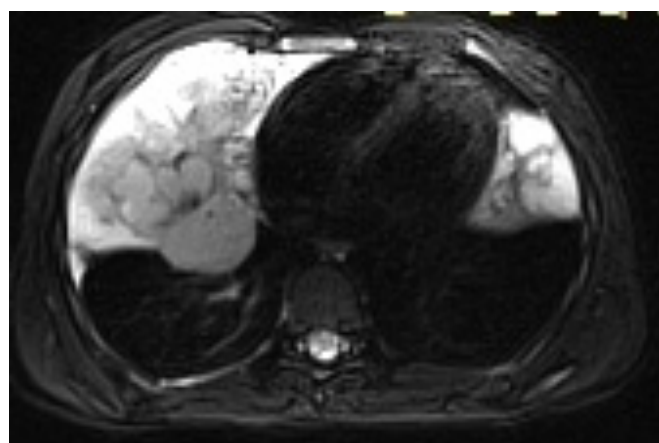
Fig. (8). Axial HRCT image showing consolidation and mucoid impaction in bilateral lungs.

Table 2. HRCT findings in ABPA.

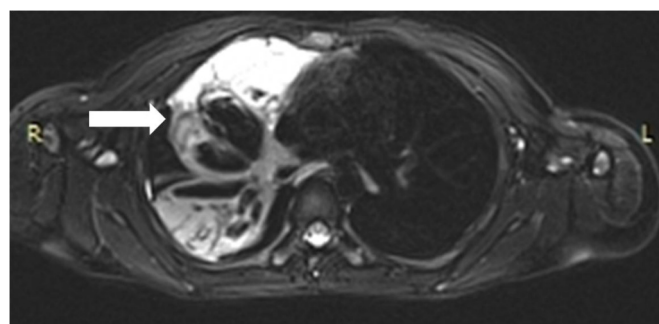
Common imaging findings	Other findings
Bronchiectasis:	Fibrocavitary changes
➤ Cystic	Parenchymal scarring
➤ Cylindrical	Emphysematous changes and cysts
➤ Varicose	Pleural thickening
Mucoid impaction:	Pleural thickening**
➤ Hypodense mucus plugs*	Aspergilloma**
➤ High attenuation mucus*	Invasive aspergillosis**
➤ Centrilobular nodules [#]	
Atelectasis	
Consolidation	
Mosaic attenuation with air trapping	
*: occurs due to mucoid impaction in larger bronchi	** uncommon findings
[#] : occurs secondary to mucoid impaction in distal bronchioles	

4.3. MRI in ABPA

Very few studies have been done to determine the role of MRI in ABPA. Franzen *et al* [68] reported that in comparison to CT, resolution of MRI is inadequate for diagnosing structural changes in ABPA. They concluded that MRI cannot be relied upon for diagnosing ABPA [68]. However, more recently it has been shown that mucoid impaction in dilated bronchi can be very well seen on MRI as T2 hyperintense lesions (Fig. 9A). T2 hypointense foci within these lesions correspond to HAM on CT (Fig. 9B), thereby suggesting a diagnosis of ABPA [69]. With technical developments in MRI sequences, it can have a role in imaging of ABPA in the near future.



9A



9B

Fig. (9). (A,B). (A) T2 HASTE axial image showing T2 hyperintense tubular lesions s/o bronchiectasis with mucoid impaction. Also note consolidation in adjacent lung parenchyma. (B) T2 HASTE axial image showing T2 hypointense mucus in dilated bronchi (arrow). Also note air fluid level in one of the dilated bronchi.

Differential Diagnosis of ABPA

Asthma: HRCT in asthmatic patients can show bronchiectasis with mucus plugging, bronchial wall thickening, mosaic perfusion and expiratory air trapping. At times it may be difficult to differentiate whether these findings are due to asthma per se or due to ABPA. However it has been shown that bronchiectasis, mucous impaction and centrilobular nodules are more commonly seen in patients with asthma and ABPA than in patients with asthma alone [53].

Cystic Fibrosis

Clinically, CF- lung disease without ABPA) shares many features with ABPA, thereby making the diagnosis of ABPA difficult in CF patients. On imaging both can manifest as pulmonary infiltrates, bronchiectasis and mucoid impaction [70]. However, high attenuation mucus on CT is a characteristic finding in ABPA which is not seen in CF lung disease without ABPA [71]. Thus presence of HAM can be used to differentiate between the two.

5. DIAGNOSIS OF ABPA

Diagnosis of ABPA is based upon a combination of clinical, immunological and imaging features. Various crite-

ria have been defined for diagnosis of ABPA which have been modified time and again. Rosenberg- Patterson criteria are used for the diagnosis for ABPA, which have been summarised in table:

Table 4. Rosenberg-Patterson criteria for the diagnosis of ABPA [72, 73].

Major criteria:
Bronchial asthma
Immediate cutaneous hypersensitivity to A fumigatus antigen
Serum total IgE levels (1000 IU/mL)
Serum A fumigatus specific IgG and/or IgE levels more than twice the mean plus two standard deviation values in patients with Aspergillus hypersensitive asthma
Central bronchiectasis on HRCT chest
Serum precipitins against A fumigatus
Fleeting or fixed pulmonary opacities on chest radiograph
Peripheral blood eosinophil count .1000 cells/ m L
Minor Criteria:
Sputum cultures demonstrating growth o f A fumigatus
Expectoration of brownish-black mucus plugs
Type III skin reactions to A fumigatus antigen
Presence of 6 out of 8 criteria makes the diagnosis almost certain.

Table 4. Minimal diagnostic criteria for ABPA [74].

ABPA- CB:
Asthma
Immediate cutaneous hyperreactivity to Aspergillus antigen
Central bronchiectasis
Elevated IgE
Raised A fumigatus-specific IgG and IgE
ABPA-S
Asthma
Immediate cutaneous hyperreactivity to Aspergillus antigen
Transient pulmonary infiltrates on chest radiograph
Elevated IgE
Raised A fumigatus-specific IgG and IgE

Role of Imaging in Diagnosis of ABPA

Presence of fixed or migratory pulmonary opacities on chest x-ray and central bronchiectasis on HRCT, are the two radiological criteria included in diagnostic criteria of ABPA. However there is no uniform definition of central bronchiectasis on CT. Also, peripheral bronchiectasis has been seen in up to 40% of patients as described earlier [15, 46, 47]. Presence of mucoid impaction and HAM are the characteristic imaging findings which help in differentiating ABPA from other diseases.

6. STAGING AND CLASSIFICATION OF ABPA

Based upon clinical and radiological features various classifications for ABPA have been suggested. Five stages of ABPA were identified by Patterson *et al*: acute, remission, exacerbation, steroid dependant asthma and fibrotic ABPA [75]. When patient presents for the first time with typical radiological and serological findings of ABPA, it is termed as acute stage. After giving steroids, patients usually enter remission stage with clearing of pulmonary infiltrates. Intermittent exacerbations of ABPA may be symptomatic or asymptomatic. Asymptomatic exacerbations are characterised by appearance of pulmonary infiltrates or increase in IgE. Most patients of ABPA gradually become steroid dependant. Despite treatment some patients may develop irreversible lung damage and fibrosis.

Based upon absence or presence of central bronchiectasis on radiographs, ABPA has been classified as ABPA-S or ABPA- CB [76]. ABPA-S is diagnosed on serological basis with no evidence of central bronchiectasis on radiography. It has been shown that ABPA- S has better prognosis with fewer exacerbations [76]. In another classification ABPA has been divided into ABPA-S, ABPA- CB and ABPA-CB with other radiological features (ABPA-CB-ORF), with ABPA-CB-ORF representing the most severe form of the disease. However HRCT findings in ORF represented immunologically inert, fibrotic stage of the disease [56]. In recent years yet another classification has been proposed based upon presence of high attenuation mucus. In this classification ABPA has been classified as ABPA-S, ABPA-CB and ABPA-CB with high attenuation mucus (ABPA-CB-HAM). The presence of high attenuation mucus (HAM) predicted immunological severity of the disease as well as risk for relapses [77]. Thus radiology not only has a role in diagnosis of ABPA, but also in predicting severity and relapses.

7. ABPA IN CHILDREN

Exact incidence of ABPA in children is unknown and only very few studies have been done on paediatric ABPA. As mentioned earlier in this article, it commonly affects teenagers with asthma and CF. Diagnosis of ABPA in children can be challenging as high levels of total IgE and aspergillus specific IgE are already present in children with asthma [78]. Though paediatric ABPA also presents with clinical features similar to adults, it should also be a consideration in children with uncontrolled pneumonia, who have been previously diagnosed with asthma or CF [79]. A recent study has reported 26% prevalence of ABPA in children with poorly controlled asthma [78]. Like adults, bronchiectasis was the most common imaging finding and was present in 64.2% of the children with ABPA [78]. MRI may have a role in future in the diagnosis of ABPA, as it avoids the radiation exposure in paediatric population [69]. However further studies are needed to establish its role.

CONCLUSION

In the recent years role of radiology in ABPA has evolved. Currently the imaging is not only limited to detection of central bronchiectasis. Imaging has been used for classification and prognostication of the disease. Certain

Table 5. Various classifications of ABPA.

Patterson <i>et al</i> [75]	Greenberger <i>et al</i> [76]	Kumar <i>et al</i> [56]	Agarwal <i>et al</i> [77]
Acute stage	ABPA-S	ABPA-S	ABPA-S
Remission stage	ABPA-CB	ABPA-CB	ABPA-CB
Exacerbation stage		ABPA-ORF	ABPA-HAM
Steroid dependant			
Fibrotic stage			

imaging features like HAM are helpful in determining the immunological severity and disease relapse. A radiologist should be aware of the diagnostic criteria of ABPA and should keep clinical and laboratory features in mind while evaluating a patient with suspected ABPA.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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