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REVIEW. IMMUNOLOGY. ALLERGOLOGY

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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Abstract. Aspergillus is a saprophytic mold and its natural habitat is the soil. It is found worldwide indoors and outdoors in potted soil, compost, freshly cut grasses, decaying vegetation and in sewers. Aspergillus produces a bountiful number of spores and releases 2—3 micron sized spores into the air daily. It grows best at 37—40 °C, which is similar to the temperature in the lungs. These spores will remain airborne for a long period of time. It is estimated that humans inhale hundreds of spores daily. Several fungi other than aspergillus have been known to be implicated. Hence, the term allergic bronchopulmonary mycoses would be more appropriate unless the specific fungus is identified — which could be candida, helminthosporium, curvularia, bipolaris, cladosporium, or others. The review article is focused on the prototype allergic bronchopulmonary aspergillosis, its epidemiology, pathogenesis, diagnosis and treatment. Bronchopulmonary aspergillosis should be considered in patients with poorly controlled asthma despite appropriate routine therapy and environmental control. The need for frequent courses of corticosteroids with temporary improvement should raise the index of suspicion and appropriate evaluation be done. Early recognition and prompt initiation of appropriate corticosteroid treatment regimen would reduce the risk of development or progression of bronchiectasis and lung tissue damage. Regular follow up and monitoring serum total IgE level can predict exacerbations and should prompt corticosteroid treatment. Long term follow-up is important as relapses can occur years of remission.

Key words: Allergic bronchopulmonary aspergillosis, allergic pulmonary mycosis, uncontrolled asthma, asthma, cystic fibrosis, bronchiectasis, aspergillus

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INTRODUCTION

Micheli first described the mold aspergillus in 1729 as it looks like aspergillum, the Latin term for a device used to sprinkle Holy water [1]. Bennett was the first physician to describe pulmonary aspergillosis as "numerous jointed transparent tubes, here matted together, there isolated... mingled with round or oval corpuscles, which, however, were larger and more developed" [2]. Later, Fresenius described *Aspergillus fumigatus* as having "green pigmentation

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with no fertile septate hyphae or conidiophores". The word fumigatus means smoky in Latin, referring to the fungus' smoky blue-gray color. An association with human disease was first described in 1847 of a woman dying with an unspecified lung infection [3]. Virchow described four cases of pulmonary aspergillosis in patients dying of other conditions in 1856. In 1887, Osler reported the case of a young woman who coughed up sputum for eleven years of mycelia and spores of aspergillus. In 1897, Renon was the first to associate aspergillus with asthma and that same year, Brown and Feinberg noted that between 1 and 20% of patients with asthma have positive skin tests to aspergillus extract [4]. The first report of allergic bronchopulmonary aspergillosis (ABPA) was proposed by Hinson et al in 3 patients in 1952, all of whom were asthmatics presenting with persistent wheeze, sputum production, fever, eosinophilia and pulmonary infiltrates. ABPA can be caused by a variety of aspergillus species, most commonly *A. fumigatus* but other species have been implicated including *A. niger, A. flavus, A. nidulans, A. oryzae, and A. terreus* [5].

Aspergillus is a saprophytic mold and its natural habitat is the soil [5]. It is found worldwide indoors and outdoors in potted soil, compost, freshly cut grasses, decaying vegetation and in sewers. Aspergillus produces a bountiful number of spores and releases 2—3 micron sized spores into the air daily [6]. It grows best at 37—40 °C, which is similar to the temperature in the lungs. These spores will remain airborne for a long period of time. It is estimated that humans inhale hundreds of spores daily.

Several fungi other than aspergillus have been known to be implicated. Hence, the term allergic bronchopulmonary mycoses (ABPM) would be more appropriate unless the specific fungus is identified — which could be candida, helminthosporium, curvularia, bipolaris, cladosporium, or others. In this review article, we will focus on the prototype allergic bronchopulmonary aspergillosis (ABPA).

EPIDEMIOLOGY

The exact prevalence of ABPA is unknown. It depends on a variety of factors including the severity of asthma, presence of immediate hypersensitivity to aspergillus, method of detection, and the diagnostic criteria used. It is estimated to affect about 2% of asthmatics and 1—15% of cystic fibrosis patients [7], without gender predilection. Typically, it affects asthma patients in their third or fourth decade [8].

PATHOGENESIS

Based mainly on in vitro studies, multiple theories have been proposed regarding the pathogenesis of ABPA.

The most common theory suggests that in patients with asthma and cystic fibrosis who are genetically predisposed and have increased pulmonary mucus viscosity, the inhalation of aspergillus spores causes colonization and deposition of the hyphae [9]. These hyphae release antigens which are disruptive to the epithelial barriers impeding mucociliary clearance. This results in the attraction of inflammatory cells that in turn release cytokines causing inflammation. The process is hypothesized to have a Th2 cell predominance over Th1 cell causing a release of IL-4, IL-5, and IL-13, resulting in eosinophilia and elevation of IgE [10]. The influx of these inflammatory cells is directly involved in tissue destruction. In the lungs, this can cause central bronchiectasis.

A second hypothesis is based on the findings of a study by Garcia et al who reported a different pattern of cellular responses in individuals with ABPA than those with only allergic asthma [11]. They observed a downregulation of chemokine receptors CCR4 and CXCR3 in vitro by allergen specific CD4+ T cells of ABPA patients, which is opposite to the effect in patients with only allergic asthma.

A third hypothesis is by Miller et al for cystic fibrosis patients suggesting that the cystic fibrosis transmembrane conductance regulator (CFTR) gene has a greater chance of mutating compared to healthy controls [12].

The pathogenesis of ABPA is attributed to mucoid impaction of the bronchi with fungal hyphae, eosinophilic pneumonia or bronchitis, and bronchocentric granulomatosis with tissue eosinophilia [13]. In the airways, septated hyphae with acute dichotomous branching is seen in the lumen without invasion of the mucosa. Aspergillus is found in sputum cultures in two thirds of patients although often is

not seen by microscopy. Key findings in sputum are Curschmann spirals (mucus plugs) and eosinophilic debris (Charcot-Leyden crystals) [14].

DIAGNOSIS AND EVALUATION

The diagnosis of ABPA should be based on clinical suspicion and supported by radiologic and laboratory findings. An important clinical feature of the presentation of ABPA is deterioration of pulmonary symptoms with increased wheezing and shortness of breath. These patients typically present with fever, malaise, productive cough with brownish mucus plugs, and occasionally hemoptysis [15].

The diagnosis is typically suspected in patients with recurrent asthma or cystic fibrosis exacerbations. It is important to rule out other causes before committing to the diagnosis of ABPA. Other causes of bronchiectasis could be post infection, immunodeficiency, or ciliary dysfunction. Several other causes of eosinophilia should also be considered such as eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis, hyper eosinophilic syndrome, hypersensitivity reactions, and parasitic infections.

In general, the evaluation should consist of obtaining a complete blood count, skin prick test to aspergillus, specific IgE to aspergillus, serum precipitins (or IgG antibody) to aspergillus, chest x-ray, and a high resolution computed tomography (HRCT) of the lungs [16]. If the skin prick test is negative, intradermal testing can be considered. In general, specific IgE to aspergillus alone suggests sensitization only which is not diagnostic of ABPA and is frequently present in patients with severe eosinophilic asthma. Total serum IgE should be obtained as this is useful during monitoring.

ABPA (or ABPM) should be considered among the cases of poorly controlled asthma or cystic fibrosis. Currently, the most widely accepted criteria are those proposed by Rosenberg and Patterson [17]. In patients with asthma, the severity of their condition does not determine diagnosis. If most of the criteria presented in table 1 are met, there is a high clinical suspicion of ABPA [18].

Таблица 1 / Table 1

Diagnostic criteria for ABPA in asthmatics /
Диагностические критерии аллергического бронхолегочного аспергиллеза (АБЛА) у пациентов с астмой

Major Criteria / Основные критерии	Minor Criteria / Второстепенные критерии
Chronic asthma / Хроническая астма	Golden brown mucus sputum production / Золотисто-коричневая слизь
Transient pulmonary infiltrates (fleeting) / Преходящие легочные инфильтраты (мимолетные)	Sputum positive for *Aspergillus* / Мокрота, положительная на *Aspergillus*
Immediate cutaneous hypersensitivity to aspergillus species / Немедленная кожная гиперчувствительность к видам аспергилл	Late skin reactivity to aspergillus species / Поздняя кожная реактивность на виды аспергилл
Elevated total serum IgE > 1000 ng/mL (417 IU/mL) / Повышенный общий сывороточный IgE > 1000 нг/мл (417 МЕ/мл)	
Precipitating antibodies to aspergillus species / Осаждение антител к видам аспергилл	
Blood eosinophilia / Эозинофилия	
Elevated serum specific IgG and IgE to *Aspergillus* / Повышенные сывороточные специфические IgG и IgE к *Aspergillus*	
Central/proximal bronchiectasis / Центральный/проксимальный бронхоэктаз	

Adapted from Rosenberg and Patterson [18].

Those criteria were later revised by Greenberger who reported that only asthma, immediate skin hypersensitivity to aspergillus, total serum IgE > 1000 ng/mL (> 417 IU/mL) and central bronchiectasis in the absence of distal bronchiectasis is required for the diagnosis [19]. Since central bronchiectasis is not required for diagnosis, some suggested that patients can be categorized into subgroups: ABPA-Seropositive and ABPA-Central bronchiectasis [20]. Agarwal and coworkers proposed that

all patients diagnosed with asthma must be screened for specific IgE levels to aspergillus [21]. If negative, total IgE levels and sensitization to other fungi should be obtained to rule out ABPM. In patients sensitized to aspergillus, total IgE levels below 1000 IU/mL and uncontrolled asthma suggest severe asthma with fungal sensitization as an alternative to ABPA. This subset of patients may benefit from anti-fungal therapy. In patients with fungal sensitization to aspergillus and a total IgE level greater than 1000 IU/mL, clinicians should obtain eosinophil levels, immediate skin hypersensitivity, and specific IgG to aspergillus. If any two of the criteria are positive, ABPA is confirmed and HRCT should be performed for staging of the disease. Although some authors suggest a significantly higher total serum IgE level of 1000 IU/mL (2400 ng/mL) for diagnosis [22], most authors follow the 1000 ng/mL (417 IU/mL) as a cutoff level. Table 2 shows the diagnostic criteria of ABPA in patients with cystic fibrosis [17].

Testing for IgG antibodies to aspergillus species (or other suspected molds) is performed by ELISA assay which replaced testing for precipitins by gel immunodiffusion [6]. Pulmonary function testing is valuable in monitoring the disease severity but not for the diagnosis of ABPA [17]. Spirometry typically shows an obstructive pattern but can also develop restriction in late stages of the disease. After treatment with corticosteroids or during remission, a normalization of these parameters often occur.

RADIOLOGIC FEATURES AND STAGING

Chest x-ray and often HRCT are recommended during evaluating patients for ABPA. Chest x-ray can show transient changes such as fleeting patchy areas of consolidation 17]. The infiltrates can appear as gloved finger shadows due to mucoid impaction in dilated bronchi. It can also present as a lobar or segmental atelectasis. When permanent changes occur, parallel-line shadows representing bronchial widening and ring shadows approximately 1—2 cm in diameter may be visualized. Additionally, it can be accompanied by pulmonary fibrosis.

High resolution chest tomography can reveal a variety of parenchymal findings including central bronchiectasis, consolidation, centrilobular nodules with tree-in-bud opacities, bronchial wall thickening, mosaic attenuation, and areas of atelectasis [23]. A characteristic finding of ABPA is bronchiectasis of greater than two lobes at lobar and segmental levels in a majority of the airways [14].

Based on radiologic features, criteria have been incorporated in classifying the stages of ABPA (Table 3). Five stages have been described: acute, remission, exacerbation, corticosteroid-dependent asthma, and fibrotic [24].

Table 2 / Таблица 2

Criteria for ABPA in cystic fibrosis patients /
Критерии аллергического бронхолегочного аспергиллеза у пациентов с муковисцидозом

Presence of 2/3 criteria / Наличие 2/3 критериев	**PLUS** **ПЛЮС**	Presence of 2/6 Наличие 2/6
Immediate skin hypersensitivity to aspergillus species / Немедленная гиперчувствительность кожи к видам аспергилл		Bronchoconstriction / Сужение бронхов
Precipitating antibodies to aspergillus species / Осаждение антител к видам аспергилл		Peripheral blood eosinophilia > 1000/μL / Эозинофилия > 1000/мкл
Total serum IgE > 1000 IU/mL / Общий сывороточный IgE > 1000 МЕ/мл		Chest x-ray abnormalities (infiltrates, bronchiectasis) / Нарушения рентгенографии грудной клетки (инфильтраты, бронхоэктазия)
		Elevated serum specific IgE and IgG to aspergillus species / Повышенные сывороточные специфические IgE и IgG к видам аспергилл
		Aspergillus in sputum / Aspergillus в мокроте
		Response to systemic corticosteroids / Ответ на системные кортикостероиды

Modified from Shah and Panjabi [17].

Table 3 / Таблица 3

**Staging of ABPA /
Стадии аллергического бронхолегочного аспергиллеза**

Stage I: Acute / Стадия I: острая	♦ Normal radiographic features or pulmonary infiltrate with mucoid impaction especially in the upper lobes / Нормальные рентгенологические признаки или легочный инфильтрат со слизистой оболочкой, особенно в верхних долях
Stage II: Remission / Стадия II: Ремиссия	♦ Radiologic infiltrate clear / Радиологический инфильтрат очищает ♦ Decreased in total serum IgE and eosinophilia / Снижение общего сывороточного IgE и эозинофилии ♦ Prednisone tapered and goal to discontinue / Преднизалон отменяется
Stage III: Exacerbation / Стадия III: обострение	♦ Reappearance of infiltrates and mucoid impaction in previously cleared areas or in new ones / Повторное появление инфильтратов и слизистой оболочки в ранее очищенных или новых участках ♦ Restart treatment with prednisone / Возобновить лечение преднизалоном
Stage IV: Corticosteroid-dependent asthma / Стадия IV: кортикостероид-зависимая астма	♦ Glucocorticoid-dependent with return of symptoms if tapering or discontinuation is attempted / Зависимость от глюкокортикоидов с возвращением симптомов при попытке снижения дозировки или отмены ♦ Normal chest radiography or fixed pulmonary opacities are visualized / Нормальная рентгенография грудной клетки или фиксированные легочные помутнения
Stage V: Fibrotic / Стадия V: фиброзная	♦ Permanent lung damage (i.e. bronchiectasis, pulmonary hypertension) / Постоянное повреждение легких (т.е. Бронхоэктазия, легочная гипертензия)

Modified from Greenberger and Patterson [24].

Patients can initially present at any stage. Although the common age for ABPA is young and middle-aged adults, children are not exempt, as illustrated in the following case.

CASE PRESENTATION

One of our patients was a 12-year-old female with a history of eczema and persistent asthma since early childhood. At 8 years of age, she had a severe asthma exacerbation that required admission to the intensive care unit for impending respiratory failure. Since 10 years of age, in spite of adequate routine asthma therapy, she had many exacerbations requiring frequent emergency treatment and five hospitalizations. There were no apparent triggers of the exacerbations. She was on combined fluticasone / salmeterol 230 mcg / 21 mcg 2 puffs twice daily, loratadine 10 mg in the morning and montelukast 10 mg at bedtime. However, she experienced a worsening of her asthma and a decline of her flow function on spirometry despite strict adherence to medications. She had persistent wheezing that required the intake of albuterol inhaler 3—4 times daily. She also received prednisone courses numerous times, including more than ten times during the past year, with improvement for short durations. During the recent hospitalization, the Allergy/Immunology service

was consulted. Her CBC was within normal limits, including absolute eosinophil count (100/μL) but the test was done while she was on systemic corticosteroid administration. Her serum total IgE level was 2040 IU/mL raising suspicion of ABPA. Serum specific antibodies to aspergillus were elevated for both IgE (28.5 IU/mL) and IgG (23.7 IU/mL). Chest X-ray showed bilateral hyperinflation, streaky atelectasis in the right middle lobe, and peribronchial cuffing. HRCT of the lungs did not show any infiltrates or bronchiectasis. She did meet the majority of ABPA criteria and was treated with 40 mg prednisone daily until follow up in the clinic. At follow up after two weeks, she reported marked improvement in her asthma symptoms, but continued to experience nocturnal chest tightness and coughing. Her spirometry revealed a FEV1 1.23 L (53%), FVC 2.10 L (81%), FEV1/FVC 59%, and FEF 25—75% 0.56 L/s (18%). Her IgE level dropped to 1350 IU/mL. Her eosinophil count was very low due to prednisone intake. The prednisone dose was reduced to 40 mg every other day (EOD) and beclomethasone dipropionate 1 puff twice a day was added to her regimen to improve small airway inflammation. After one month, she reported dramatic improvement in her symptoms and minimal nocturnal symptoms. Repeat spirometry showed a FEV1 1.95 L (81%),

FVC 2.45 L (92%), FEV1/FVC 80%, FEF 25—75% 1.80 L/s (51%). Her IgE level remained relatively stable at 1410 IU/mL. Due to subjective and objective improvement, her prednisone was decreased to 30 mg EOD until follow-up in two weeks. The drop of her initial IgE level from 2040 IU/mL to 1220 IU/mL after four months was associated with improvement in her FEV1 from 59% predicted to 81% predicted. She will continue regular follow up in the clinic and gradually reduce the prednisone dose according to her clinical course.

TREATMENT

The primary goals of treatment are to prevent the development or progression of bronchiectasis, preserve lung function, and improve pulmonary physiology. In general, inhaled corticosteroids are ineffective in preventing acute ABPA episodes [15]. Oral corticosteroids are the mainstay of therapy [25]. It is recommended to complete a minimal of three months of treatment starting with prednisone 0.5 mg/kg/day for two weeks, then alternate days for three months followed by staging of the disease. Some experts start at a higher dose at 0.75 mg/kg/day for 6 weeks, followed by 0.5 mg/kg/day for 6 weeks, and eventually taper over a period of 6—12 months to prevent disease recurrence [26]. There are no studies comparing regimens at this time, although most experts tend to favor longer therapy with higher dosages of prednisone [27]. Monitoring of total serum IgE level monthly is important in determining duration of treatment as well as in predicting pending relapse. In general, aiming for 35% reduction in IgE is suggestive of a good response and decreases the likelihood of relapse. It is important to consider the patient's clinical response, as occasionally the level of IgE does not drop by 35% when the initial total IgE is less than 2500 IU/mL [28].

In patients with corticosteroid-dependent ABPA, Stevens and coworkers reported clinical improvement with the use of 200 mg of itraconazole twice a day [29]. Liver function should be monitored regularly, and treatment is typically for three to six months although this varies depending on the re-

sponse [30]. The mechanism of action is thought to be due to a decrease in antigenic stimulus that causes inflammation in the bronchi [31]. Another proposed hypothesis is that it causes increased levels of serum corticosteroids by interfering with the metabolism. A major concern is that adrenal suppression has been observed with concomitant use of corticosteroids and itraconazole [32]. Voriconazole and posaconazole have also been used and has improved tolerance and bioavailability [33], but there are no studies that showed superiority over itraconazole.

Anti-IgE (omalizumab) therapy using doses recommended for asthma, showed promising results with improvement in respiratory symptoms in patients with ABPA [34]. In one study, sixteen adult asthmatic ABPA patients were treated with omalizumab for one year and had clinical improvement with fewer asthma exacerbations and requiring lower doses of corticosteroids. Currently, omalizumab is based on weight and total serum IgE and majority of patients exceed the recommended dose range due to grossly elevated IgE [14]. Based on available data, it remains a second line option for patients with ABPA.

Immunotherapy with aspergillus or other fungi have not been fully evaluated and is currently not recommended for treatment [35]. Patients who are on immunotherapy for allergic rhinitis can continue treatment safely.

CONCLUSION

ABPA should be considered in patients with poorly controlled asthma despite appropriate routine therapy and environmental control. The need for frequent courses of corticosteroids with temporary improvement should raise the index of suspicion and appropriate evaluation be done. Early recognition and prompt initiation of appropriate corticosteroid treatment regimen would reduce the risk of development or progression of bronchiectasis and lung tissue damage [36]. Regular follow up and monitoring serum total IgE level can predict exacerbations and should prompt corticosteroid treatment. Long term follow-up is important as relapses can occur years of remission.

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АЛЛЕРГИЧЕСКИЙ БРОНХОЛЕГОЧНЫЙ АСПЕРГИЛЛЕЗ

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Aspergillus является сапрофитной плесенью, его естественной средой обитания является почва. Он встречается по всему миру в помещениях и на открытом воздухе, в почве домашних растений, компосте, свежескошенных травах, гниющей растительности и в канализации. Aspergillus производит большое количество спор и выпускает споры размером 2—3 микрона в воздух ежедневно. Лучше всего растет при 37—40 °C, что соответствует температуре в легких. Эти споры остаются в воздухе в течение длительного периода времени. Подсчитано, что люди ежедневно вдыхают сотни спор. Известно, что заболевания вызывают не только Aspergillus, но и другие грибы. Следовательно, термин «аллергические бронхолегочные микозы» был бы более уместным, пока не идентифицирован конкретный гриб, который может быть кандидой, гельминтоспорием, куркулярией, биполирисом, кладоспорием или другими. Обзорная статья посвящена прототипу аллергического бронхолегочного аспергиллеза, его эпидемиологии, патогенезу, диагностике и лечению. Бронхолегочный аспергиллез возможен у пациентов с плохо контролируемой астмой, несмотря на соответствующую рутинную терапию и контроль окружающей среды. Раннее распознавание и своевременное начало соответствующей схемы лечения кортикостероидами уменьшит риск развития или прогрессирования бронхоэктазов и повреждения тканей легких. Регулярное наблюдение и мониторинг общего уровня IgE в сыворотке могут предсказать обострения и должны сопровождать терапию кортикостероидами. Важно долгосрочное наблюдение, поскольку рецидивы могут произойти через годы ремиссии.

Ключевые слова: аллергический бронхолегочный аспергиллез, аллергический легочный микоз, неконтролируемая астма, астма, муковисцидоз, бронхоэктаз, аспергиллез

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