Review Article

Recognition of allergic bronchopulmonary aspergillosis

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ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is a complicated inflammatory condition characterized by an allergic response to the fungus *Aspergillus* colonizing in the bronchus. It occurs most frequently in patients with asthma or cystic fibrosis. Oral corticosteroids are the standard therapy for ABPA. Antifungal drugs can clear the fungi in the airway, reduce the body's antigen load, decrease the body's allergic reaction, and reduce corticosteroid requirement. Total serum IgE should be used as an index for efficacy assessment during treatment and follow-up.

Key words: Allergic bronchopulmonary aspergillosis, diagnosis, treatment

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a complicated inflammatory condition characterized by an allergic response to the fungus *Aspergillus* colonizing in the bronchus. It occurs most frequently in patients with asthma or cystic fibrosis (CF). The occurrence of ABPA is associated with both genetic and environmental factors, and 2–32% of patients with asthma develop ABPA.[1,2] *Aspergillus fumigatus* is the most common causal agent of ABPA, followed by *Aspergillus flavus* and *Aspergillus niger*. Since ABPA lacks specific clinical manifestations, clinicians often have an insufficient awareness of this disease, thus resulting in misdiagnosis and missed diagnosis. If treated improperly, ABPA may recur and progress and thereby lead to bronchiectasis, mucus plug formation, and even pulmonary fibrosis, seriously affecting the patient's quality of life.

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CLINICAL FEATURES

Common symptoms of ABPA include cough, expectoration, wheezing, hemoptysis, and fever. ABPA patients may expectorate sputum plugs in tan color. Hemoptysis manifests mainly as blood-stained sputum. The development of fever is often associated with secondary bacterial infections. Long-term repeated recurrences of ABPA can lead to bronchiectasis, pulmonary fibrosis, difficulty in breathing, cyanosis, finger clubbing, and so on. High-resolution computed tomography (HRCT) of the chest can be normal or show transient or persistent infiltrates. Typical CT manifestations include central bronchiectasis, high-attenuation mucus plugs in expanded bronchi, finger-in-glove opacities, toothpaste shadows, and fibrosis or cavity formation in end-stage disease.[3] Based on imaging findings, ABPA can be divided into four types: serologic ABPA (ABPA-S), ABPA with bronchiectasis, ABPA with bronchiectasis and high-attenuation mucus plugs, and ABPA

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with bronchiectasis and chronic pleuropulmonary fibrosis. This classification can predict the severity and prognosis of the disease.[4]

DIAGNOSIS

The diagnosis of ABPA should be based on a combination of clinical, imaging, and immunological findings. The following diagnostic criteria[5] are often adopted: (1) Bronchial asthma; (2) elevated serum *Aspergillus*-specific IgE (>0.35 kUA/L); (3) elevated total serum IgE (>417 IU/mL); (4) an immediate intradermal reaction to *Aspergillus* antigen (type I allergic reaction); (5) precipitins to *Aspergillus* or demonstration of *Aspergillus*-specific IgG; (6) central bronchiectasis; (7) increased peripheral blood eosinophilic granulocytes (>1/mL); and (8) transient or persistent pulmonary infiltrates. When any five or more of the above items are met, a diagnosis of ABPA can be made.[5] However, research shows that only six or more of the above criteria can result in a satisfactory sensitivity and specificity for the diagnosis of ABPA. In addition, this diagnostic algorithm cannot reflect the weight of each criterion in the diagnosis of ABPA.[6] To overcome this limitation, Agarwal *et al*.[4] put forward a new diagnostic algorithm: (1) Predisposing factors: bronchial asthma or CF; (2) essential conditions: (i) Positive-type I reaction in intradermal *Aspergillus* antigen test or elevated serum *Aspergillus*-specific IgE; (ii) elevated serum total IgE (>1000 IU/mL). When serum total IgE is <1000 IU/mL, ABPA can still be diagnosed when all other criteria are met; (3) other criteria (at least two should be met): (i) Precipitins to *Aspergillus* or demonstration of *Aspergillus*-specific IgG; (ii) peripheral blood eosinophilic granulocytes >0.5/mL (before steroid therapy); (iii) imaging findings consistent with ABPA: transient lesions such as pulmonary consolidation, nodules, finger-in-glove opacities, toothpaste shadows, and wandering infiltrates, or persistent lesions such as tram-line shadowing, signet ring sign, bronchiectasis, and pleuropulmonary fibrosis.[4] This diagnostic algorithm is more comprehensive and reflects the weight of each criterion. Expectoration of sputum plugs in tan color, positive delayed-type *Aspergillus* antigen skin test, and positive *Aspergillus* cultures of sputum or bronchoscopy lavage can provide more support to the diagnosis of ABPA. *Aspergillus*-specific IgE and high-attenuation mucus plugs on chest CT are the most sensitive and specific indexes for the diagnosis of ABPA, respectively.[6]

DIAGNOSTIC SIGNIFICANCE OF VARIOUS CLINICAL INDEXES IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

The cutoff value of total serum IgE >417 IU/mL proposed by Patterson has a poor diagnostic specificity. In recent years, more and more studies adopted >1000 IU/mL as the cutoff value. Research suggests that 2347 IU/mL is the optimal cutoff value of total serum IgE for distinguishing asthma and ABPA.[7]

Serum *Aspergillus*-specific IgE (>0.35 kUA/L) has a higher sensitivity than intradermal *Aspergillus* antigen test in diagnosing ABPA, and it is therefore a better tool for screening ABPA in patients with asthma.[8] 1.91 kUA/L is the optimal cutoff value of serum *Aspergillus*-specific IgE for distinguishing asthma and ABPA.[7] Since the majority of ABPA patients have received steroid therapy or antiallergic drugs before a definite diagnosis is achieved, the absence of peripheral eosinophilia cannot exclude ABPA. Due to low sensitivity, galactomannan test has limited value in the diagnosis of ABPA.[9] The presence of high-attenuation mucus plugs on chest HRCT has a specificity of 100% in diagnosing ABPA.[6] Pulmonary function test lacks specificity in ABPA diagnosis, but can grade the severity of illness in ABPA patients and provide objective evidence for therapeutic efficacy.[10] The positive rates of sputum culture are low, ranging from 39% to 60%.[4]

TREATMENT

The goal of treatment in ABPA is not only to control asthma symptoms, improve airway inflammation, and promote the discharge of sputum plugs, but also to reduce the frequency of acute attacks and prevent the progression to bronchiectasis and pulmonary fibrosis.

Oral corticosteroids are the standard therapy for ABPA, and they can inhibit inflammatory reactions and the body's immune response to *Aspergillus* antigen. Oral or intravenous corticosteroids are necessary for acute-onset ABPA; however, the dose of corticosteroids should be timely adjusted based on IgE levels to prevent the occurrence of side effects associated with long-term corticosteroid use. At present, there are mainly two corticosteroid therapy regimens. The moderate-dose regimen proposed by Greenberger *et al*.[11] is 1–2 weeks of daily prednisone 0.5 mg/kg, followed by 6–8 weeks of alternate day therapy and then tapering by 5–10 mg for every 2 weeks until complete withdrawal. Total serum IgE is monitored for every 6–8 weeks and chest X-ray or CT is performed for every 4–8 weeks to assess therapeutic response. This regimen is used mainly in steroid-dependent or frequently-relapsing patients. The more aggressive regimen proposed by Agarwal *et al*.[10] is prednisolone 0.75 mg/kg/day for 6 weeks, then 0.5 mg/kg/day for 6 weeks, followed by a tapering dose of 5 mg for every 6 weeks to continue for a total duration of 6–12 months. Total serum IgE is monitored and chest CT is performed for every 6 weeks to assess therapeutic response and adjust the medication. This regimen is used mainly in steroid-sensitive or treatment-naive patients. A randomized controlled trial recently reported by Agarwal *et al*.[12] compared the efficacy and adverse drug reactions between the above two regimens and found that the efficacy of the moderate-dose regimen was not inferior to that of

the more aggressive regimen, but the adverse drug reactions associated with the former were significantly fewer. In North American and European countries, clinicians tend to choose the moderate-dose regimen for the treatment of ABPA.[13] It is important for clinicians to taper doses based on their experience, patient's symptoms, and examination results. Inhaled corticosteroids (ICS) should not be used as the first-line therapy for ABPA. When the dose of oral corticosteroids (methylprednisolone) is decreased to 8 mg/d, ICS can be added.[4]

Although corticosteroid therapy has a good efficacy in the treatment of ABPA, nearly 50% of patients may develop recurrence during dosage tapering, 20–40% may become corticosteroid dependent,[4] and many will develop side effects associated with the long-term use of corticosteroids. Antifungal drugs can clear the fungi in the airway, reduce the body's antigen load, decrease the body's allergic reaction, and reduce corticosteroid requirement. At present, there have been two clinical studies supporting the therapeutic efficacy of itraconazole in ABPA. Itraconazole is able to decrease oral steroid requirement by ≥50%, reduce total serum IgE by ≥25%, and improve pulmonary function, without increasing drug toxicity. Moreover, itraconazole can significantly decrease the frequency of acute attacks and reduce sputum eosinophils and serum levels of anti-A*spergillus fumigates* IgE and IgG.[14,15] The second-line antifungal drugs such as voriconazole and posaconazole have higher activity and bioavailability than itraconazole. A retrospective study including 20 twenty cases of severe asthma with ABPA and five cases of severe asthma with fungal sensitization found that in patients who failed itraconazole therapy, oral voriconazole or posaconazole can result in a clinical improvement in 70% of patients, a decrease in total serum IgE by 27%, in *Aspergillus*-specific IgE by 24%, and absorption of pulmonary infiltrates in >50% of patients, suggesting that patients who have a poor response to or are intolerant of itraconazole therapy may benefit from voriconazole or posaconazole therapy.[16] Moreira *et al*.[17] systematically analyzed 38 eligible studies on ABPA, including 4 randomized control trails (RCTs) and 34 observational studies involving 197 cases of asthma and 110 cases of CF, and found that antifungal therapy had a positive impact on the symptoms, frequency of exacerbation, steroid usage, and pulmonary function in patients with ABPA. Despite these studies, the relevant evidence is still insufficient, especially the lack of RCTs on ABPA with CF. Therefore, more clinical studies are required to confirm the efficacy of antifungal drugs. Currently, there has been no consensus on the dose and duration of antifungal drugs and indications for drug withdrawal. Clinical symptoms, total serum IgE, *Aspergillus*-specific IgE levels, and imaging changes can provide some reference for these issues. According to our experience, for patients with sputum plugs, antifungal therapy should be maintained until sputum plugs disappear on chest CT images so that the patient's symptoms and IgE level improve obviously. If the drug is withdrawn early, the disease is prone to relapse. It remains to be investigated whether antifungal azoles can replace oral corticosteroids as the first-line therapy for ABPA and how long antifungal treatment should last. Many relevant clinical studies (NCT01321827, NCT0244009, and NCT 01621321) are ongoing. Atomized amphotericin for inhalation has the advantages of high anti-A*spergillus* activity, good local effects, and no systemic side effects, and has been used for the treatment of ABPA. In recent years, a few nonrandomized controlled studies demonstrated that amphotericin has appreciated efficacy in the treatment of ABPA and suggested that amphotericin B should be considered when corticosteroid therapy combined with antifungal azole therapy has a poor efficacy or significant side effects.[18] A small-scale controlled clinical study indicated that compared with ICS alone, amphotericin B inhalation combined with ICS can reduce the frequency of acute attacks in ABPA in remission.[19] A registered controlled study (NCT02273661) assessed the efficacy of amphotericin B alone in the treatment of ABPA in remission, but its efficacy remains to be confirmed by multicenter studies.

It has been reported that omalizumab, a recombinant humanized monoclonal IgE antibody, can reduce steroid requirement and the frequency of acute attacks in asthma or CF patients with ABPA.[20,21] A small RCT confirmed that in asthma patients with ABPA, omalizumab 750 mg/month for a total duration of 4 months can reduce the frequency of acute attacks, decrease the level of fractional exhaled nitric oxide, and decrease the expression of FcεR1 on the surface of basophils and surface-bound IgE.[22] A multicenter RCT (NCT00787917) aiming to evaluate the application of omalizumab in CF patients with ABPA terminated prematurely because the patients were difficult to recruit. Although there are many case reports proving that omalizumab treatment can reduce steroid requirement and the frequency of acute attacks, omalizumab should not be recommended for CF patients with ABPA due to the current lack of evidence from controlled trials.[23] The curative effect of omalizumab remains to be confirmed by large-scale multicenter controlled clinical studies. Avoiding contact with high concentrations of mold in the environment, antiallergic treatment, expelling phlegm and arresting cough, and other supportive measures are effective adjuvant therapies.

CHOICE OF TREATMENTS

How do clinicians choose the treatment: corticosteroids alone, antifungal drugs alone, or the combination of both? It is currently recommended that for patients with ABPA-S, moderate-dose corticosteroid therapy alone can be used, and the dosage should be adjusted according to the patient's condition. ICS alone can be given in patients with mild disease or no symptoms. For patients with mucus plugs, severe deterioration of lung function, repeated acute

exacerbations, or hormone dependence, corticosteroid therapy combined with antifungal drugs should be administered to rapidly improve the patients' clinical symptoms, but drug interactions should be monitored. When the patient's condition becomes stable and the dose of oral prednisone is reduced to 10 mg, ICS can be given to withdraw oral corticosteroids. For critically ill patients or patients with a poor response to corticosteroid therapy plus antifungal drugs, high-dose pulse methylprednisolone therapy can be tried.[24]

FOLLOW-UP

Total serum IgE is a valuable index for ABPA diagnosis and patient follow-up.[25] A normal IgE level can exclude the presence of ABPA. Acute-onset ABPA patients are considered in remission when their IgE levels decrease by 25–50%. However, IgE levels cannot decline to the normal range in many patients. For these patients, a relatively stable baseline IgE level should be chosen after their condition becomes stable. Once IgE level is two times of the baseline level or greater, the possibility of ABPA recurrence should be suspected. It has been reported that compared with patients with asthma or CF alone, serum levels of thymus and activation-regulated chemokine (TARC) were significantly elevated in asthma or CF patients with ABPA. After systemic steroid therapy, serum levels of TARC decreased significantly, and the change was more sensitive than that of total serum IgE. However, the significance of serum level of TARC in disease diagnosis, treatment, and follow-up remains to be confirmed by larger clinical studies.[26] ABPA is a disease that requires long-term follow-up and monitoring.

CONCLUDING REMARKS

ABPA is a potentially fatal disease. If not treated, ABPA may lead to bronchiectasis and pulmonary fibrosis, seriously affecting patients' quality of life and threatening their life. In China, due to insufficient awareness of clinicians in primary hospitals about ABPA, misdiagnosis and delayed treatment often occur.[27,28] For patients with asthma or other allergic diseases who have a marked increase in total serum IgE level and eosinophil count and imaging findings suggestive of bronchiectasis, atelectasis, and other abnormalities, ABPA should be considered. Especially, when chest HRCT suggests central bronchiectasis with mucus plugs, further examinations should be performed to confirm the diagnosis of ABPA. Oral corticosteroids are the standard therapy for ABPA. Antifungal drugs can clear the fungi in the airway, reduce the body's antigen load, decrease the body's allergic reaction, and reduce corticosteroid requirement. During treatment, drug side effects and drug interactions should be monitored, and medications should be adjusted based on total serum IgE level and imaging findings.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Agarwal R. Burden and distinctive character of allergic bronchopulmonary aspergillosis in India. Mycopathologia 2014;178:447-56.
2. Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. Med Mycol 2013;51:361-70.
3. Phuyal S, Garg MK, Agarwal R, Gupta P, Chakrabarti A, Sandhu MS, *et al.* High-attenuation mucus impaction in patients with allergic bronchopulmonary aspergillosis: Objective criteria on high-resolution computed tomography and correlation with serologic parameters. Curr Probl Diagn Radiol 2016;45:168-73.
4. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, *et al.* Allergic bronchopulmonary aspergillosis: Review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy 2013;43:850-73.
5. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977;86:405-14.
6. Agarwal R, Maskey D, Aggarwal AN, Saikia B, Garg M, Gupta D, *et al.* Diagnostic performance of various tests and criteria employed in allergic bronchopulmonary aspergillosis: A latent class analysis. PLoS One 2013;8:e61105.
7. Agarwal R, Aggarwal AN, Garg M, Saikia B, Chakrabarti A. Cut-off values of serum IgE (total and A. fumigatus -specific) and eosinophil count in differentiating allergic bronchopulmonary aspergillosis from asthma. Mycoses 2014;57:659-63.
8. Sehgal IS, Agarwal R. Specific IgE is better than skin testing for detecting *Aspergillus* sensitization and allergic bronchopulmonary aspergillosis in asthma. Chest 2015;147:e194.
9. Agarwal R, Aggarwal AN, Sehgal IS, Dhooria S, Behera D, Chakrabarti A. Performance of serum galactomannan in patients with allergic bronchopulmonary aspergillosis. Mycoses 2015;58:408-12.
10. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: Lessons from 126 patients attending a chest clinic in north India. Chest 2006;130:442-8.
11. Greenberger PA, Bush RK, Demain JG, Luong A, Slavin RG, Knutsen AP. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol Pract 2014;2:703-8.
12. Agarwal R, Aggarwal AN, Dhooria S, Singh Sehgal I, Garg M, Saikia B, *et al.* A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. Eur Respir J 2016;47:490-8.
13. Moss RB. Treating allergic bronchopulmonary aspergillosis: The way forward. Eur Respir J 2016;47:385-7.
14. Wark PA, Hensley MJ, Saltos N, Boyle MJ, Toneguzzi RC, Epid GD, *et al.* Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: A randomized controlled trial. J Allergy Clin Immunol 2003;111:952-7.
15. Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, *et al.* A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 2000;342:756-62.
16. Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. J Asthma 2012;49:423-33.
17. Moreira AS, Silva D, Ferreira AR, Delgado L. Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic

fibrosis: A systematic review. Clin Exp Allergy 2014;44:1210-27.
18. Sehgal IS, Agarwal R. Role of inhaled amphotericin in allergic bronchopulmonary aspergillosis. J Postgrad Med 2014;60:41-5.
19. Ram B, Aggarwal AN, Dhooria S, Sehgal IS, Garg M, Behera D, *et al.* A pilot randomized trial of nebulized amphotericin in patients with allergic bronchopulmonary aspergillosis. J Asthma 2016;53:517-24.
20. Lehmann S, Pfannenstiel C, Friedrichs F, Kröger K, Wagner N, Tenbrock K. Omalizumab: A new treatment option for allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Ther Adv Respir Dis 2014;8:141-9.
21. Aydin Ö, Sözener ZÇ, Soyyigit S, Kendirlinan R, Gençtürk Z, Misirligil Z, *et al.* Omalizumab in the treatment of allergic bronchopulmonary aspergillosis: One center's experience with 14 cases. Allergy Asthma Proc 2015;36:493-500.
22. Voskamp AL, Gillman A, Symons K, Sandrini A, Rolland JM, O'Hehir RE, *et al.* Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol Pract 2015;3:192-9.
23. Jat KR, Walia DK, Khairwa A. Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. Cochrane Database Syst Rev 2015;(11):CD010288.
24. Singh Sehgal I, Agarwal R. Pulse methylprednisolone in allergic bronchopulmonary aspergillosis exacerbations. Eur Respir Rev 2014;23:149-52.
25. Agarwal R, Aggarwal AN, Sehgal IS, Dhooria S, Behera D, Chakrabarti A. Utility of IgE (total and *Aspergillus fumigatus* specific) in monitoring for response and exacerbations in allergic bronchopulmonary aspergillosis. Mycoses 2016;59:1-6.
26. Hartl D, Latzin P, Zissel G, Krane M, Krauss-Etschmann S, Griese M. Chemokines indicate allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Am J Respir Crit Care Med 2006;173:1370-6.
27. Xu XY, Shi Y. A case of allergic bronchopulmonary aspergillosis. Chin J Pract Intern Med 2009;29:764-5.
28. Zhang L, Liu CT. Allergic bronchopulmonary aspergillosis: A case report. Med J Chin Peoples Liberation Army 2007;32:339.