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Allergic bronchopulmonary aspergillosis: xxi century. A modern view of the problem

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Molds of the genus *Aspergillus* are widely ubiquitous in the environment. They are one of the most frequent pathogens of fungal respiratory infections [23]. Approximately 250 species of *Aspergillus* are known but only about 20 of them are pathogenic for humans. For example, *A. fumigatus, A. flavus, A. niger, A. terreus* etc. frequently cause pulmonary diseases. [23] Molds are able to exist in water, soil, on vegetative or other organic debris; they grow on walls and ceilings of buildings containing moisture, such as cellars. Hospitals, ventilation and water supply systems, dust associated with construction sites are habitats for most of Aspergillus organisms [6]. Their spores get into the air and then on food, houseware, human skin and mucous membranes [5].

First research articles devoted to aspergillus disease of lungs were published in the middle of XVIII century and over the next hundred years this pathology was described quite thoroughly [23]. However, aspergillosis was not very interesting to scientists as a clinical or scientific problem. Over the last thirty years the number of patients with depressed immunity had been increasing, mostly due to development of transplantology, successes in treatment of oncological diseases with immunosuppressive agents or cytostatics. Besides, the number of HIV-infected humans increased [1]. For now, *Aspergillus* species are opportunistic fungal pathogens that can be found in postmortem studies of immunocompromised patients most frequently [23]. However, aspergillosis lesion of lungs may occur not only in patients with immunodeficiency. Allergic bronchopulmonary aspergillosis (ABPA) is caused by hypersensitivity to aspergillus antigens and manifests with poorly controlled severe asthma [31]. In this review there is a short characteristic of main clinical forms of pulmonary aspergillosis and thorough description of diagnostic and treatment problems of ABPA.

Clinical forms of aspergillosis. Inhalation of Aspergillus spores is the most common way for contamination. Therefore, lungs are the most frequent organs to be affected. It should be noted that *Aspergillus* can be found in the lungs of healthy people. Pulmonary aspergillosis proceeds in one of such forms as invasive pulmonary aspergillosis (IPA), chronic necrotizing pulmonary aspergillosis (CNPA), ABPA and aspergilloma [6].

IPA usually occurs in patients with severe immunodeficiency. For example, in patients with prolonged neutropenia, hematologic malignancies, HIV-infection, patients receiving immunosuppressive therapy because of organ transplantation or receiving systemic corticosteroids for a long period of time [31]. However, this syndrome may occur in patients without typical risk factors. For example, in patients with chronic obstructive pulmonary disease (COPD), alcoholic hepatitis, patients undergoing treatment in intensive care unit etc. [6, 25]

CNPA is characterized by local invasion and can be found mainly in patients with moderate immunodeficiency, COPD, diabetes mellitus. Also it may occur in patients having other infectious diseases, for example, tuberculosis [6].

Aspergilloma, or ‘fungus ball’, is a growth of *Aspergillus* mycelium in cavities formed in lung parenchyma after such pathological processes as tuberculosis, destructive pneumonia, bronchiectasis etc. Besides, aspergilloma can arise in paranasal sinuses [7].

ABPA represents the pulmonary reaction of hypersensitivity to *Aspergillus* antigens and manifests as severe bronchial obstruction [25].

Aspergilloma and ABPA are noninvasive forms of lung diseases caused by *Aspergillus* [25].

The syndromes described above may coexist or transform from one to another. For example, patients with ABPA may in parallel have aspergilloma or may experience IPA in future.

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Researchers suggest that such overlap syndromes develop because of severe concomitant pulmonary pathology, treatment with corticosteroids, genetic predisposition, viral infections etc [35]. 'Fungus balls' occur in patients with ABPA rarely and there are not many cases described in literature. Bronchiectasis developing in patients with ABPA may progress and transform into cavities that are colonized by *Aspergillus*. Also aspergilloma may occur as a result of existing fibro-cavernous disease (for example, tuberculosis) that has escalated because of treatment with corticosteroids [25].

ABPA epidemiology. *K. Patterson* and *M. Strek* established that approximately 7–15% of patients taking corticosteroids due to severe asthma have ABPA. At the same time only 2% of patients with non severe asthma have ABPA [30]. These data indicate that on the one hand ABPA may determine severity of asthma and on the other hand more aggressive therapy for asthma contributes to fungal colonization. Hypersensitivity to *Aspergillus* antigens is an important factor for development of ABPA. *Agarwal* et al. conducted the meta-analysis of 21 trials and discovered that 28% of patients with asthma have hypersensitivity to *Aspergillus* antigens [13]. Thus, ABPA is not sufficiently diagnosed among the asthmatic patients.

Pathogenesis of ABPA. Despite the fact that first reports about ABPA were published in 1890, nowadays the pathogenesis of this disease is not understood completely. The mechanisms involved in ABPA development are quite complex. Researchers suggest that such factors as high concentrations of spores and hyphae in the environment, genetic factors, properties of bronchial secretions, preactivation of bronchial epithelium cells etc. influence the occurrence of ABPA [38]. The relationship between the quantity of inhaled spores and the probability of the disease development has not been convincingly established. Although *Radin* et al. suggest that the number of inhaled spores correlates with the risk of exacerbations [32], and *OJ Dzublik* and co-authors consider that concentration of spores in the environment correlates with number of asthma attacks [2].

I Tillie-Leblond and *AB Tonnel* noted that there is genetic predisposition to ABPA. It is associated with the presence or absence of special antigens on cell membrane. These antigens are encoded by the genes of Major histocompatibility complex (MHC). Type 2 helper T cells (Th2) of patients with ABPA contain only six serotypes of HLA-DR molecules (MHC class II antigens) on their surfaces. Genetic investigations have shown that HLA-DR molecules, particularly DR-2, DR-5, DR-4, DR-7, are associated with occurrence of ABPA. At the same time HLA-DQ2 molecules (MHC class II antigens) are associated with resistance to this disease. Thus, combinations of genetic elements may determine the probability of ABPA development [38]. *Marchand* et al. discovered that mutations of gene encoding Cystic fibrosis transmembrane conductance regulator (CFTR) occurred in patients with ABPA more frequently than in asthmatic patients without ABPA, despite the fact that level of sweat chlorides was the same in both groups of patients, meaning that mutations of CFTR gene may be involved in occurrence of ABPA [27]. Also *Saxena* et al. discovered the relationship between the polymorphism in one of Surfactant protein A2 domains and predisposition to ABPA and severity of the disease [34].

Aspergillus spores are inhaled and then penetrate into mucous membrane. The optimal temperature for growth of fungus varies from 24 to 37 degrees Celsius [5]. Therefore, spores grow well at body temperature and form mycelium in bronchial lumen. *Aspergillus* produce proteolytic enzymes damaging the bronchial epithelium and antigens get into the systemic circulation [24]. *A. fumigatus* activates epithelial cells, leading to increased secretion of interleukins IL-6 and IL-8, and also enhances epithelial detachment [38]. The production of IL-8 leads to the migration of neutrophils, lymphocytes and eosinophils into the site of tissue damage. A local inflammation process develops, contributing to an even greater penetration of the antigen in the bloodstream and, consequently, an even greater sensitization of the macroorganism. A vicious circle forms and causes the severity of clinical symptoms of ABPA. Functions of IL-6 in immune response are extremely diverse. For example, it stimulates the proliferation and differentiation of T- and B-lymphocytes. Besides, *Aspergillus* antigens activate T- and B-lymphocytes. Th2 are predominantly activated in patients with ABPA [38].

A. fumigatus-specific IgE level is higher in bronchoalveolar lavage (BAL) fluid than in blood. The same is true for specific IgA levels. However, there is no difference between the level of specific IgG in serum and in BAL. Probably, specific IgE and IgA to *A. fumigatus* are synthesized locally at the inflammation site [38].

The tissue damage (development of bronchiectases) in patients with ABPA is a result of neutrophils' and eosinophils' migration to inflammation site. Levels of these cells are higher in sputum of patients with ABPA and bronchiectasis than patients without bronchial destruction. The size of the bronchiectases detected in the computed tomography (CT) study correlates with the number of eosinophils and neutrophils in the sputum, however, they are not related to the level of total IgE in serum [39]. *Gibson* et al. demonstrated that IL-8 gene expression and protein levels in sputum of patients with ABLA were higher than in the control group and that the degree of these differences correlated with the degree of neutrophilia in the bronchi and severity of respiratory tract obstruction [22]. Thus, IL-8 may be a leading mediator in the tissue damage occurring in patients with ABPA.

Clinical presentation. ABPA is usually suspected based on clinical symptoms [25]. Bronchial obstruction often is the only symptom, especially at the beginning of the disease. Therefore, these patients are treated as patients with asthma. The diagnosis of ABPA is established later when asthma becomes more severe, steroid-dependent, with atypical symptoms such as malaise, fever, cough (or cough becomes worse), chest pain, hemoptysis, plugs or purulence in sputum. Production of brown-black mucous plugs is observed in 31–69% of patients [12]. The patients receiving adequate long-term controlling medications are usually asymptomatic.

In most cases no informative findings during physical examination are present. Nail clubbing is not typical and seen in patients that have bronchiectases for a long period of time. Patients with consolidation of lung tissue or pulmonary fibrosis may have Velcro-like crackles heard upon auscultation. Symptoms of ABPA complications (for example, pulmonary hypertension) also can be found during physical examination.

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Diagnosis. Diagnosis of ABPA can be confirmed by serological and radiological tests.

An immediate cutaneous hypersensitivity to antigens of *A. fumigatus* reflects the presence of *A. fumigatus*-specific Ig E. Antigens may be recombinant or crude [12]. The sensitivity of positive result is about 90%. However, more than 40% of patients with asthma but without ABPA may develop positive result of skin test to *Aspergillus* [12]. So the presence of hypersensitivity to *Aspergillus* is not sufficient for diagnosing ABPA.

Molecular (or component) allergology develops actively during the last years. It is based on estimating of sensitization to different molecules of *Aspergillus* antigens. It means that not extracts of antigens but components of antigens are used for diagnosis [19]. This diagnostic approach allows to differentiate between ABPA and usual asthma with sensitization to *Aspergillus* and, probably, to choose the optimal vaccine for antigen-specific immunotherapy (ASIT) in future. According to the nomenclature of allergens, approved by the WHO, 23 molecules of *Aspergillus* antigens are extracted [8]. Molecules Asp f1, Asp f2, Asp f3, Asp f4, Asp f6 are used for diagnostic tests in practice. Asp f2 molecule is a major component. *Kurup* et al. conducted the investigation to detect *Aspergillus* components specificity for diagnostic of ABPA. Their research demonstrated that every patient with ABPA had positive results of skin test with all components. Meanwhile patients with asthma but without ABPA had positive results with Asp f1 and Asp f2 molecules. Authors concluded that these components are specific for ABPA [26].

Serum IgE measurement may also be used for both diagnosis and follow-up of ABPA. If a patient is not receiving treatment with systemic corticosteroids and the serum IgE level is normal, the diagnosis of ABPA as a cause of patient's symptoms should be excluded [12]. Serum IgE level >1000 MU/ml before treatment is a diagnostic criterion for ABPA. After treatment IgE level declines but doesn't reach normal values in most cases [16]. As a marker of ABLA activity, serum IgE level should be investigated in 6–8 weeks after the start of treatment and every 8 weeks during the next year [25].

There is no consensus opinion about *A. fumigatus*-specific IgE level that may be used for ABPA diagnosis. Some authors suggest to use a value of more than twice the level of patients with Aspergillus-sensitized asthma. A value >0.35 kUA/L is accepted for ABPA diagnosis [12].

Serum precipitins (IgG) to *A. fumigatus* are found in 69–90% of patients with ABPA and in 10% of patients with asthma. High levels of *Aspergillus*-specific IgG can be found in patients with other forms of aspergillus disease, for example, CNPA. Therefore, this marker is not specific for ABPA. A patient with ABPA having both pulmonary fibrosis or cavities and high levels of IgG may, probably, have concomitant CNPA [12].

There are no specific radiologic features of ABPA. High-resolution computed tomography (HRCT) is an important investigation when aspergillosis is suspected. HRCT allows to find changes that cannot be seen on plain chest radiograph. It also can help to assess the size and location of bronchiectases. The usual findings on CT include bronchiectases, mucoid impaction, mosaic attenuation, aspergilloma, centrilobular nodules, tree-in-bud opacities and signs of fibrosis [14].

It is thought that the central bronchiectases (located in the medial part of the lungs [9]) and peripheral bronchial constriction are probable signs of ABPA [14]. However, peripheral bronchiectases are found in 26–39% of cases [29, 33]. The International Society for Human and Animal Mycology (ISHAM) suggested to consider the central bronchiectases as a complication of ABPA but not as a diagnostic criterion [12].

Mucoid impaction of airways is one of the most probable signs of ABPA. Mucus plugs in ABPA patients have hypodense structure. Although about 20% of patients have plugs with higher CT attenuation values. Mucus that is visually denser than paraspinal skeletal muscles is a pathognomonic sign that can help to differentiate bronchiectases in patients with ABPA and subjects with other pathology [12].

In some cases, fibrosis of upper lung lobes may occur. However, its pathogenesis is unknown and needs further investigation [12].

There are descriptions of other CT-signs of ABPA in the literature: 'tram-track' sign (double linear shadows that means thickened parallel walls of cylindrical bronchiectasis); 'finger in glove' sign (tubular shadows going from the root of the lung to periphery look like a gloved finger and represent dilated mucous-impacted bronchi); 'toothpaste-shaped' opacities; 'tree-in-bud' sign (small, centrilobular, 1–2 mm, branching Y- or V-shaped structures with thickening on the ends, represents thickening of bronchiolar walls, lumen dilation and impaction with mucus).

Eosinophilia in peripheral blood of more than 1000 cell/μL is one of the diagnostic criteria of ABPA. The last investigations demonstrated that such values are found only in 40% of patients with ABPA [15]. Eosinophilia in lungs may be much higher than in peripheral blood smear in patients with ABPA. Therefore, normal level of eosinophils in complete blood count does not exclude ABPA [39]. High blood eosinophilia may be found in patients with different diseases, that's why the specificity of this criterion is doubtful.

Sputum culture as additional test is used for diagnosis of ABPA. However, the results are not significant, due to the fact that fungi growth can be observed in sputum of patients with other aspergillosis. In patients with ABPA *Aspergillus* in sputum may be found in 39–60% of cases. It depends on the number of specimens examined [12]. It is interesting that in sputum of many patients with ABPA fungi growth is nor detected but *A. fumigatus* DNA may be established by polymerase chain reaction (PCR) [20]. Investigation of sputum culture may be useful to determine the resistance of *Aspergilus* to antifungal agents.

Pulmonary function tests are used for assessment of asthma severity. Typical signs of bronchial obstruction can be found (decrease of FEV1 and FEV1/FVC ratio).

Lung biopsy is not recommended for use to diagnose ABPA in routine clinical practice [25]. Morphological investigation is applied for scientific purposes. Ch. Gardner conducted a retrospective study of 18 specimens taken from patients with ABPA. Granulomatous inflammation with histiocytes, lymphocytes and eosinophils in bronchioles were found in 15 specimens. There was a mucoid impaction in bronchial lumen

in 11 specimens and fungi hyphae without tissue invasion were found [18].

Methods allowing to determine presence of Aspergillus antigens in biological fluids are used for diagnosis of other aspergillosis, particularly IPA. One of them is determination of galactomannan by enzyme-linked immunosorbent assay (ELISA). Galactomannan is a polysaccharide releasing during Aspergillus growth [11]. There is evidence that its appearance in serum may precede clinical or radiological manifestations of aspergillosis [28]. Therefore, it can be used for early diagnosis. Agarwal et al. conducted the study in order to determine galactomannan level in serum of patients with ABPA. 120 patients were included in the study (70 patients with ABPA, 20 – with asthma). Serum galactomannan was positive in 18 patients with ABPA (25.7%) and in 9 patients with asthma but without ABPA (18%). The sensitivity of method was 25.7%, and the specificity was 82%. Thus, the researcher made a conclusion that determination of serum galactomannan has a limited role in diagnosis of ABPA [17]. Fayemiwo et al. conducted a similar study to determine galactomannan and DNA of Aspergillus in sputum of patients with ABPA. They also did not succeed to prove the efficiency of these methods in diagnosis of allergic form of aspergillosis [21]. Probably, it is more expedient to use these tests in diagnosis of overlap syndromes, for example ABPA and IPA.

Rosenberg et al. in 1977 and Greenberger et el. in 1986 standardized criteria for diagnosis of ABPA [25]:

- manifestations of asthma or cystic fibrosis;
- positive results of skin-tests on Aspergillus antigens;
- serum precipitins to A. fumigatus;
- total serum IgE > 1000 MU/ml;
- lung infiltrates;
- central bronchiectases;
- eosinophilia in complete blood count.

The most authors agree with these criteria. However, the expert group of ISHAM proposed to group the diagnostic criteria by importance [12]. The group of predisposing conditions includes the presence of bronchial asthma or cystic fibrosis; the group of obligatory criteria includes positive results of skin-tests and elevated IgE levels; and other criteria are the presence of precipitins to A. fumigatus, radiographic pulmonary opacities, total eosinophilia > 500 cell/μL. If patients have all obligatory criteria and at least 2 other criteria, diagnosis of ABPA can be made [12].

Greenberg et al. suggested the radiological classification of ABPA [25]. According to this classification all patients may be divided into two groups depending on presence or absence of bronchiectasis. The first group is ABPA with central bronchiectasis (ABPA-CP), the other one is serological ABPA (ABPA-S) [25]. The expert group of ISHAM proposes a new radiological classification: serological ABPA (ABPA-S), ABPA with bronchiectases (ABPA-B), ABPA with high-attenuation mucus (ABPA-HAM) and ABPA with chronic pleuropulmonary fibrosis (ABPA-CPF). On their opinion this classification is more reasonable, because it takes more CT-signs of ABPA into account [12].

Patterson et al. identified 5 stages of ABLA, depending on severity of clinical manifestations [25].

Stage I (acute) manifests with severe uncontrolled asthma, elevated IgE levels, peripheral eosinophilia, pulmonary infiltrates, elevated levels of A. fumigatus-specific IgE and Ig G. In clinical practice the correct diagnosis is rarely established on this stage.

On stage II (remission) IgE level declines, but stays somewhat elevated; eosinophilia is absent; there are no radiological changes; specific IgG may be slightly elevated.

Stage III (exacerbation) is characterized by the same features as Stage I but it can be used only for patients with confirmed ABPA. IgE level increases in 50% from patient's baseline.

Stage IV (steroid-dependent) occurs in patients with asthma, treated with systemic corticosteroids for a long period of time. Exacerbations manifest with deterioration of asthma, radiological changes, increasing of IgE level. Central bronchiectases may be found on CT. Unfortunately, in most cases the diagnosis is established only on this stage.

On stage V (fibrosis) irreversible changes in lungs occur. Patients have clinical signs of respiratory failure (dyspnea, cyanosis, nail clubbing) and chronic cor pulmonale. IgE level can be either high or low. The most authors use Patterson's classification in their work and consider it quite complete and expedient for use in practice. It is convenient to choose the correct tactics of a patient's management.

Treatment. Purpose of treatment includes asthma control, prevention and treatment of exacerbations, prevention of bronchiectasis development and reduction of antigen load due to the Aspergillus colonization of bronchi [3].

The basic medications for ABPA treatment are oral corticosteroids [25]. Corticosteroids inhibit hypersensitivity and immune response, but does not contribute to the eradication of Aspergillus from the respiratory tract. There is no data on optimal dosage of medicines or duration of treatment available. Many regimens of treatment with corticosteroids are described in literature but all of them are based on individual experience of a patient's management. If patients receive low doses of corticosteroids without antifungal drugs, the exacerbations of ABPA occur more frequently or steroid dependency develops (in about 45% of cases). Use of high doses or long-term use of steroids demonstrated good results in prophylaxis of exacerbations. Besides, transition to the steroid-dependent stage was observed in only 13.5% of cases. But the number of side effects was greater [12]. Comparative studies between two treatment regimen were not conducted.

Use of inhaled corticosteroids allow to reach high concentration of substance in bronchi with minimal side effects. The medicines from this group demonstrated good results in the treatment of bronchial obstruction symptoms, asthma control and prevention of exacerbations. However, there no evidence that inhaled corticosteroids can prevent the lung damage [12].

Antifungal agents are used in order to reduce the need for oral corticosteroids. They reduce the strength of immune response by decreasing antigen stimulation [12]. It should be noted that only a few sporadic investigations were conducted in order to determine the efficiency of antifungal drugs in treatment of ABPA patients [3]. Double blind placebo-controlled trial were conducted in San-Jose (California, the USA) in 2000. The first group of patients

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got itraconazole for treatment of ABPA, patients from the second group got placebo. Patients with antifungal medicines had better results. Their total IgE level decreased by 25%, the need for corticosteroids reduced (dose decreased by 50%), exercise tolerance increased, infiltration disappeared, results of spirometry improved by 25% [36]. The meta-analysis of available data demonstrates that use of itraconazole improves clinical symptoms for about 16 weeks [3]. But there is not a single study reporting about remission for more than 6 months. It is also unknown if antifungal drugs or corticosteroids are able to prevent the development or cause regression of bronchiectases. There is evidence that long-term use of antifungal medicines may cause Aspergillus resistance. That's why it is rather difficult to choose the right management tactics for patients with ABPA. There are not official recommendations on treatment of ABPA for today.

One of the side effects of oral corticosteroids usage is the depression of the immune system. It may cause more active growth of Aspergillus and increase the antigen stimulation. Thus, another vicious circle forms. Therefore, new methods of treatment are needed. ASIT demonstrated impressive results in asthmatic patients with hypersensitivity to fungal antigens, particularly, A. fumigatus antigens. Significant improvements of patients' pulmonary function parameters were noted and skin sensitivity to fungal antigens decreased in 12 month of treatment [10]. But this clinical trial was conducted in asthmatic patients without ABPA.

The investigation of Fungalen (Bulgaria) efficiency in treatment of asthmatic patients with fungal hypersensitivity was conducted. This medication contains extracts of allergenic fungi, particularly, A. fumigatus. After treatment 73.9% of patients had improvements in disease course, long remission was observed in 13% of patients and asthma severity improved in 34% of cases [4].

Svirshchevskaya and Kurup stated that ASIT is unlikely to facilitate the course of ABPA. It is associated with the multifactorial pathogenesis of this disease. At the same time, they emphasize, that it is reasonable to conduct more clinical studies in this direction [37]. It does make sense, because new antigen components of A. fumigatus are produced, new vaccine for antigen-specific immunotherapy are developed and their efficiency has not been investigated yet.

Another perspective method of treatment of ABPA is the use of monoclonal antibodies to Ig E. Due to the use of Omalizumab clinical manifestations improved, exacerbations occurred less frequently, need for corticosteroids reduced [12]. However, most trials were conducted on small groups of patients. So that's impossible to give any recommendations about the usage of monoclonal antibodies to IgE in patients with ABPA.

Conclusion. ABPA is a disease with a complicated insufficiently explored pathogenesis, which is based on hypersensitivity to Aspergillus. It is characterized by symptoms of predominantly severe uncontrolled asthma, as well as eosinophilia, the presence of infiltrates on the chest X-ray examination, elevated levels of total and specific Ig E. The basic principles of treatment are immunosuppression and eradication of the pathogen from the macroorganism. Due to the weakly studied mechanisms of the disease development, lack of sufficient evidence about efficacy and safety of the therapy as well as insufficient data about long-term predictions for patients, official recommendations or protocols for diagnosis and treatment are not developed. The active research in molecular allergology opens new perspectives for diagnosis. The usage of A. fumigatus antigen components makes it possible to differentiate ABPA from asthma with hypersensitivity to fungal allergens, and also to select the most specific vaccine for ASIT in future. Therefore, the efficiency and expediency of these diagnostic and treatment methods need to be investigated in detail.

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