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Aspergilloma in atypical localisation in severe asthma patient — case report

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Abstract

Pulmonary aspergillosis is a condition caused by the fungi *Aspergillus*. The form of disease depends on the immunological condition of the host organism and other concomitant illnesses that influence the pulmonary tissue. Asthmatic patients, in particular with the severe form of disease, who require the use of systemic glucocorticoids, are predisposed to develop allergic bronchopulmonary aspergillosis. Development of aspergilloma in the lung is preceded by the formation of pathological cavity in the course of another illness. The study reports a case of a severe asthma patient who developed aspergilloma in atypical localisation, without the presence of predisposing anatomical changes and illnesses.

Key words: asthma, aspergilloma, pulmonary aspergillosis

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Introduction

Pulmonary aspergillosis is caused by a fungus of the genus *Aspergillus*, most frequently by *Aspergillus fumigatus*. This type of fungi is widespread in nature, therefore exposure to them is very common. Small size of spores, resistance to extreme environmental conditions together with high prevalence, enable them to reach the pulmonary alveoli [1–3]. Development of various pathological syndromes depends on mutual reaction of the fungus and immunological system of the organism. In the case of persons with impaired immunological system, patients with neoplasms of the haematopoietic system and cachectic patients, invasive aspergillosis may develop. Aspergilloma is a noninvasive form of infection with *Aspergillus*. It may complicate diseases in the course of which abnormal cavities in the lung form, such as tuberculosis, ankylosing spondylitis, bronchiectasis or bronchogenic cysts.

People with atopy and asthma, and those with cystic fibrosis develop allergic bronchopulmonary aspergillosis [1, 4–6]. Hypersensitivity to the antigen of *Aspergillus,* defined as immediate cutaneous reaction, occurs in approximately 28% of asthma patients. Among the persons with hypersensitivity to the antigen of *Aspergillus*, only 40% of people meet diagnostic criteria of allergic bronchopulmonary aspergillosis [7]. Hypersensitivity to the antigen of *Aspergillus* develops as a result of ciliary clearance disorders and impaired removal of conidia from the airways.

The literature reported patients in whom allergic bronchopulmonary aspergillosis preceded the occurrence of aspergilloma or the two conditions coexisted. Immunological reaction to the antigen of *Aspergillus* in patients with

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asthma and cystic fibrosis results in increased mucus production in the airways, which leads to obstruction of the bronchi and dilation of their lumen. Sporadically, such a process may finish in the development of aspergilloma in the cavity that was formed secondarily [8–10].

The present paper reports the case of the patient with severe bronchial asthma, in whom in the left lower lobe aspergilloma was detected, but no anatomical changes predisposing to developing cavities in the lungs were observed earlier. The criteria required to diagnose allergic bronchopulmonary aspergillosis were not met.

Case report

A male patient, 51 years of age, with diagnosed 10 years earlier asthma, was admitted to the pulmonological ward in June 2015 due to failure to achieve control of the disease in outpatient setting. Since diagnosis of asthma, the patient remained under the care of the outpatient clinic of lung diseases. He had 2–3 asthma exacerbations during the year that required hospitalisation and the systemic use of glucocorticoids. In order to control symptoms and reduce the number of exacerbations, he used oral prednisone and methylprednisolone at the doses corresponding to 30 mg of prednisone. The use of glycocorticosteroids was complicated by cataract of both eyes — the patient underwent phacoemulsification and implantation of artificial lens to the left and right eyeball 6 years ago — and osteoporosis together with fracture of lumbar and costal vertebrae. Moreover, one year ago the patient underwent ischaemic stroke of the left cerebral hemisphere with retreating right-sided paresis. In the course of neurological evaluation chronic inflammatory changes in the maxillary sinuses were discovered.

At the admission to the ward the patient reported cough with expectoration of purulent sputum and dyspnoea attacks with wheezing despite the use of inhaled budesonide and formoterol at the doses of 320 ug and 9 ug respectively twice a day, theophylline at the dose of 300 mg per day, montelukast at the dose of 10 mg daily and methylprednisolone at the dose of 4 mg daily. In addition, during exacerbations of the disease the patient noticed that expectorated sputum was periodically stained with blood.

Physical examination identified the following deviations: weaker sensation on the right side of the body, weaker muscle strength on the right side to 4/5 in the Lovett scale and increased tendon and periosteal reflexes at the right side.

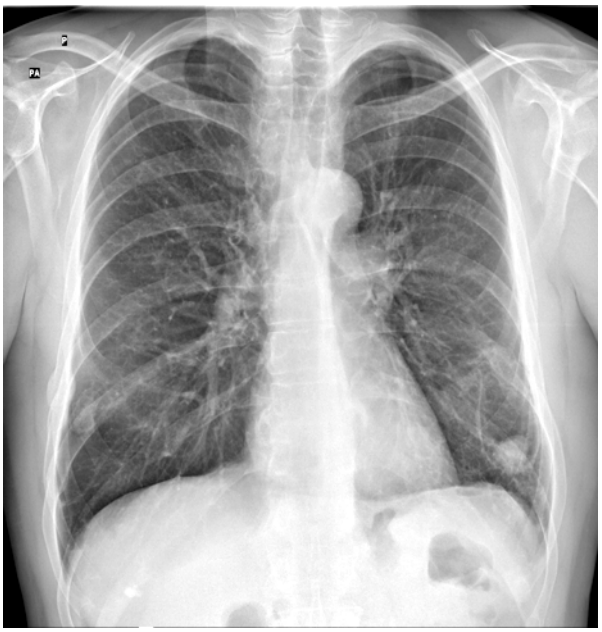

Figure 1. Chest radiograph — 25 × 23 mm focal lesion in the lower, left lobe

Laboratory tests showed as follows: morphology with no significant deviations from the norm, liver and kidneys function was within the normal levels, parameters of inflammatory state (CRP, leucocytosis) were normal. IgE concentration was determined > 2500 IU/ml. Scatoscopy did not reveal parasites. Spirometry discovered obstruction, FEV_1/FVC after the use of beta-mimetic was 52% of predicted with FEV_1 amounting to 44% of predicted. Arterial blood gases did not show features of respiratory failure.

Skin prick tests showed allergy to dog and cat hair, tree and weed pollen.

Chest radiograph was performed revealing oval focal lesion measuring 25 × 23 mm in the left lower lobe (Fig. 1). Computed tomography of the chest was carried out (June 22, 2015) showing in the left lower lobe a cavity measuring 31 × 39 mm in the transverse plane, within which soft tissue structure measuring 17 × 25 mm, which could correspond to aspergilloma, was detected (Fig. 2). Computed tomography performed 5 years ago had not shown pathological lesions in the mentioned site (Fig. 3). CT scans did not reveal bronchiectasis or infiltrations in the lung tissue.

As radiological image corresponded to aspergilloma, bronchofiberoscopy was performed. No pathology was visualized except reddening of the mucous membrane. Specimen was taken from the left lower lobe for mycological, cytological and bacteriological testing, including tests targeted at tuberculosis. Cytological examination of

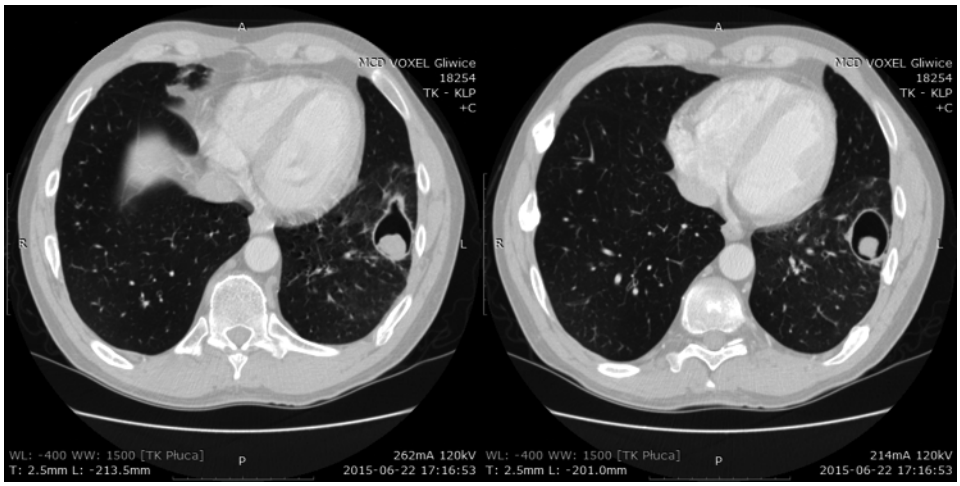

Figure 2. Chest computed tomography — 31 × 39 mm cavity with 17 × 25 mm soft tissue structure in the lower, left lobe

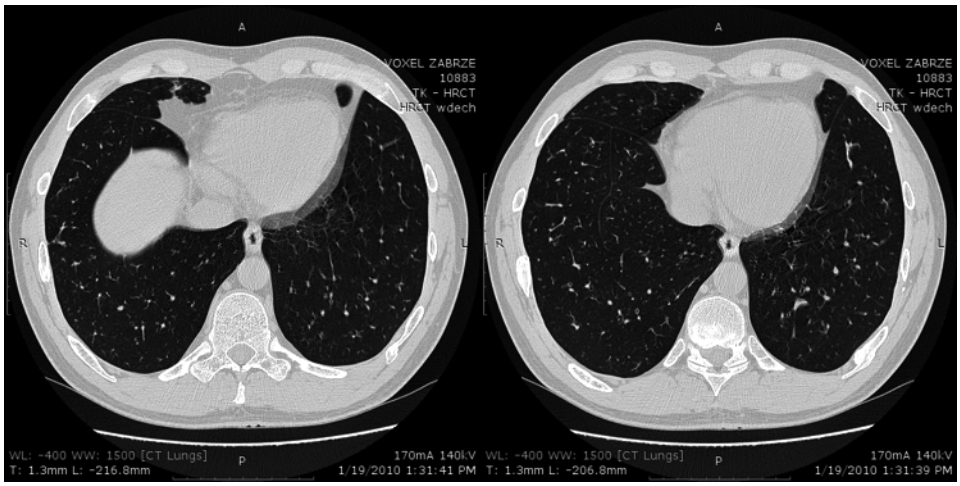

Figure 3. Chest computed tomography — no changes in region corresponding to Aspergilloma cavity in Figure 2

bronchial washings discovered purulent exudate. Bacterioscopy and PCR testing did not confirm mycobacteria in the collected material. They were not found neither in cultures using BACTEC MGIT 960 system nor the Lowenstein-Jensen medium. Quantiferon test gave a negative result.

Mycological examination of bronchial washings showed the presence of filamentous fungi of morphological features of *Aspergillus sp.* Mycological diagnosis was supplemented with determination of circulating antigen of *Aspergillus,* giving a positive result. Moreover, with the help of the 5 moulds panel, allergen-specific immunoglobulin E was determined. For *Aspergillus fumigatus* it was 4.69 kU/L. The levels of allergen-specific immunoglobulin E for the remaining moulds (*Alternaria tenuis, Penicilium notatum, Cladosporium herbarum, Candida albicans*) were below 0.1 kU/L.

Due to diagnosis of aspergillosis, blood serum was checked for HIV infection markers (4^{th} generation test). Anti-HIV antibodies and p24 HIV antigen were not detected.

Pharmacotherapy with itraconazole at the dose of 200 mg daily was introduced. The patient was referred to a thoracic surgery clinic in order to be evaluated for surgical treatment.

Discussion

Aspergillus fumigatus is a pathogen that causes a series of syndromes ranging from saprophytic to invasive forms, which are defined by the influence of the pathogen and immunological reaction of the organism. Depending on the actual condition of the immunological system, the form of disease may change. Aspergilloma is a noninvasive form of aspergillosis that develops in the cavities in the lung parenchyma in persons without immunity disorders. One of the most frequent conditions leading to for-

mation of cavities colonized by *Aspergillus sp.* is tuberculosis. In the Portuguese study, half of the subjects with aspergilloma reported the history of tuberculosis, whereas in the group studied by the Japanese authors, tuberculosis was diagnosed in 72% of patients [1, 11–13] In the reported patient, imaging examination including chest computed tomography performed during the current stay in hospital and the one carried out during the previous stay did not detect changes suggesting active tuberculosis or post-granulomatous changes. Imaging examinations conducted prior to hospitalization did not reveal pathological cavities, bronchodilatation or radiological features that could lead to the development of such changes. Bacteriological investigations, genetic tests or Quantiferon test did not show infection with *Mycobacterium tuberculosis*.

Tuberculosis most often involves the upper lobes, therefore the most frequent localisation of post-tuberculous cavities which aspergilloma colonizes, are the upper lobes [14]. Thus localisation of changes in the reported patient is atypical, as the focal change on chest radiograph is visible in the lower lobe.

The presence of aspergilloma is also typical of another disease entity — chronic necrotising aspergillosis, also called semi-invasive pulmonary aspergillosis. In this form of disease, although invasion does not affect vessels, in moderately immunosuppressed persons or those with chronic lung disease or with systemic disease such as diabetes or rheumatoid arthritis, which disturb immunity topically, the lung parenchyma is damaged. The patients complain about fever, chronic productive cough, haemoptysis with varying intensity and weight loss. In the reported case, fever or weight loss were not observed. Over time, in 50% of patients with semi-invasive pulmonary aspergillosis, due to destructed lung parenchyma, the cavities and aspergilloma may occur, although initially there were no anatomical predispositions towards aspergilloma. Imaging examinations show consolidation, the thickened pleura and cavernous lesions, which, similarly to pulmonary tuberculosis, have predilection for the upper lobes [15, 16]. Denning et al. proposed that, apart from the above mentioned physical and radiological symptoms, it is necessary to confirm the presence of the fungus *Aspergillus*, the existence of elevated inflammatory markers in laboratory tests, and to exclude the presence of other pathogens and immunosuppressive diseases. All six criteria have to be met concomitantly. The reported patient did not fulfill radiological or laboratory criteria [17].

In asthmatic patients, in particular with steroid-dependant form of asthma, as in the reported patient, due to hypersensitivity to the antigen of *Aspergillus sp.*, aspergillosis has the form of allergic bronchopulmonary aspergillosis [18]. This form is suspected basing on clinical symptoms in individuals with a predisposing illness. The patients complain about wheezing, fever and pleural pain. Expectoration of secretion with black and brown plugs is observed in 31–69% of patients [8]. In imaging examinations, transient infiltrations in the upper and central parts of the lung fields and symptoms of inflammatory thickening of the bronchi predominate. In computed tomography, first of all bronchiectasis and the presence of mucous plugs in the lumen of the changed bronchi are visible. They were not present in the reported patient neither on examination carried out during hospitalisation, nor in the previously performed computed tomography. Typical of this form of aspergillosis is elevated total immunoglobulin E concentration, which may be helpful in monitoring of the course of disease. Furthermore, as it was showed in the reported patient, the level of immunoglobulin E specific for *Aspergillus sp*. is elevated. It is worth emphasising that immunoglobulin E concentration remained above 2500 IU/ml in spite of long-term therapy with steroids. There is no unambiguous cut-off point, above which concentration of specific immunoglobulin E should be treated as diagnostic for allergic bronchopulmonary aspergillosis [19–22]. According to diagnostic and classification criteria proposed by Agarwal et al. in 2013, the reported patient has a predisposing condition (asthma), meets both required immunological criteria (elevated immunoglobulin E concentration specific for *Aspergillus* and total concentration of immunoglobulin of this class > 1000 IU/ml), but does not present with typical radiological changes or eosinophilia in the period prior to steroid therapy [8].

Patients with aspergilloma usually do not present any symptoms. In symptomatic patients, the most frequent symptom is haemoptysis being the result of local damage to the blood vessels done by mycelium and the substances it produces [13, 23, 24]. Depending on its intensity, haemoptysis may even lead to death. Therefore, due to burden related to haemoptysis, it is necessary to take into account surgical treatment, in particular in high-risk groups, i.e. people with sarcoidosis, immunosuppressed patients or those with increasing antibody titres against *Aspergillus* [14, 25]. The presented patient reported periodical expectoration of reddish secretion, which he

related to the periods of asthma exacerbations. Moreover, reported dyspnoea and cough are also attributed to infection with *Aspergillus sp*., and it is difficult to differ direct relation to infection with *Aspergillus sp*. from the symptoms of other concomitant lung diseases [12]. Pharmacotherapy in aspergilloma remains controversial. The use of intravenous amphotericin B does not influence significantly the course of disease. In case of abundant haemoptysis, good effects are brought about by the appliance of amphotericin B to the aspergilloma cavity. The use of oral itraconazole is associated with radiological and clinical improvement but the optimal dose and treatment period were not determined. Newer antifungal drugs such as voriconazole have not yet been sufficiently tested [11–13].

Due to underlying disease and its severity, the reported patient was predisposed to have allergic bronchopulmonary aspergillosis. Despite this fact, aspergilloma developed in atypical localisation, without predisposing anatomical pulmonary changes. Therefore in diagnostic and differential process of steroid-dependant and severe asthma, it is necessary to take into account various forms of aspergillosis.

Conflict of interest

The authors do not declare conflict of interest.

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