VIA MEDICA

CASE REPORT

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Allergic bronchopulmonary aspergillosis mimicking lung cancer in a non-asthmatic female patient: a case report

Alergiczna aspergiloza oskrzelowo-płucna imitująca guz płuca u chorej bez astmy oskrzelowej — opis przypadku

Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease caused by a hypersensitivity reaction to antigens of the *Aspergillus* species (most frequently *Aspergillus fumigatus*), with a variable radiographic appearance. ABPA most commonly affects patients with steroid-dependent asthma (1–2%) and patients with cystic fibrosis (5–15%). ABPA is very rarely diagnosed in non-asthmatics. We report a case of ABPA in a 45-year-old female initially evaluated for suspected cancer of the left lung with hilar lymphadenopathy, who had never been diagnosed with asthma. After the diagnostic investigation was complete, the diagnosis of ABPA was established and appropriate treatment was instituted leading to clinical, radiological, and serological improvement (IgE decrease).

Key words: allergic bronchopulmonary aspergillosis (ABPA), asthma, lung cancer

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a disorder caused by a hypersensitivity reaction to antigens of the *Aspergillus* species (most frequently *Aspergillus fumigatus*). ABPA was first described in 1952 by Hinson et al. [1]. The pathogenesis of ABPA is complex with immune and genetic factors on the part of the host being implicated. ABPA most commonly affects patients with allergic diseases, including steroid-dependent asthma (1–2% of ABPA patients) or cystic fibrosis (5–15% of ABPA patients) [2]. As ABPA is very rarely diagnosed in patients without a history of asthma, no data on the incidence of the disease in the general population are available [3]. Patients usually complain of paroxysmal dyspnoea, productive cough with expectoration of brownish purulent plugs and-less frequently-general symptoms, such as fever, weight loss, and asthaenia. ABPA is characterised by a considerably variable radiographic appearance with the most common findings being atelectasis, transient pulmonary infiltrates, proximal bronchiectasis, and signs of mucoid impaction.

We report a case of a previously healthy female referred to our Department with suspected tumour of the left lung.

Case presentation

A 45-year-old female never-smoker with a long-standing history of allergy, receiving no long-term medication, an ENT specialist, was admitted to our Department in December 2009 for diagno-

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stic evaluation of a left lung tumour. Since July 2009 she had been complaining of a cough with expectoration of mucopurulent sputum without haemoptysis, dyspnoea, or fever. Despite several courses of antibiotics (clarithromycin, cefuroxime, metronidazole) the cough kept returning after periods of temporary improvement. In November 2009 a chest X-ray revealed partial atelectasis of the upper lobe of the left lung with sparing of the lingula, suggestive of a lung tumour (Figure 1). The chest CT scan performed at that time confirmed atelectasis of the upper lobe of the left lung. The patient underwent diagnostic evaluation for cancer at an outpatient oncology facility, where she underwent flexible bronchoscopy revealing infiltration of the bronchus and the carina leading to segment 1–2 of the left lung, pus filling the bronchus, and infiltration of the bronchus leading to the lingula. Histopathological examination of the tissue samples collected from the left upper lobe bronchus revealed massive inflammatory changes with necrotic masses with signs of low-degree dysplasia focally in the metaplastic epithelium. Neither cytological examination of the bronchial washings nor bronchial brushing revealed tumour cells. Microbiological examination of the bronchial washings revealed a confluent growth of *Aspergillus fumigatus* and the presence of numerous Charcot-Leyden crystals. The patient was then admitted to the Institute of Tuberculosis and Lung Diseases in Warsaw for continuation of the diagnostic evaluation.

On admission the patient was in a good general condition without cough, any other respiratory symptoms, or fever. She said she had lost about 5 kg in the past month. Chest auscultation revealed crepitations over the anterior chest wall in the midclavicular line and anterior axillary line on the left. Differential blood cell count revealed an eosinophilia of 1.6×19^9/l (16.4%) and a marked elevation of immunoglobulin E (IgE) to 1400 IU/ml. A chest X-ray revealed a widened outline of the left hilum with atelectasis of the lingula (Figure 2). A chest CT scan revealed proximal bronchiectasis in segment 3 of the upper lobe of the left lung and the lingula with retention of discharge, causing partial atelectasis of the lingula and fine intralobular nodules consistent with retained discharge in the small airways with reactively enlarged lymph nodes in the mediastinum (Figure 3). Compared to the previous radiograms, based on the variable presentation of the pulmonary changes, a suspicion of ABPA was raised. Flexible bronchoscopy revealed severe inflammatory changes with purulent discharge and plugging of the bronchus

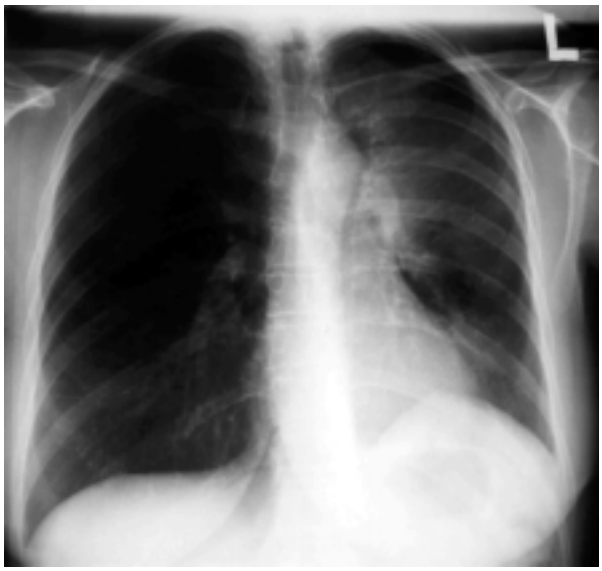

Figure 1. Postero-anterior X-ray of the chest — left upper lobe atelectasis sparing lingula

leading to the lingula. Microbiological examination of the bronchial discharge revealed isolated fungal hyphae, and the cultures revealed numerous *Aspergillus fumigatus* colonies and isolated *Candida albicans* colonies. No acid-fast bacilli were detected. The immediate aspergillin skin test was positive (5 × 5 mm) and the delayed test was negative. A positive result was obtained in the serological test for aspergillosis (IgG) and no IgE antibodies specific for *Aspergillus fumigatus* were detected. Spirometry did not reveal signs of airway obstruction, although upon the administration of a short-acting β_2-agonist a marked improvement of forced expiratory volume in one second (FEV_1) was observed, which was considered a sign of bronchial hyperreactivity. All these diagnostic investigations allowed us to rule out lung cancer and confirm the diagnosis of ABPA (the patient met 6 out of 8 major diagnostic criteria proposed by Rosenberg and Patterson) [4, 5]. The patient was started on glucocorticosteroids at the dose of 0.5 mg/kg/day, which were tapered off after 6 months, and on itraconazole at a dose of 200 mg BID for 2 months (due to the massive fungal growth).

A radiological improvement and a reduction in serum IgE was observed during the follow-up after the initiation of treatment.

Discussion

Aspergillus is a common mould which accounts for 0.1–22% of all fungal spores in air samples. Although about 250 species of this fungus have been described so far, only some of them are

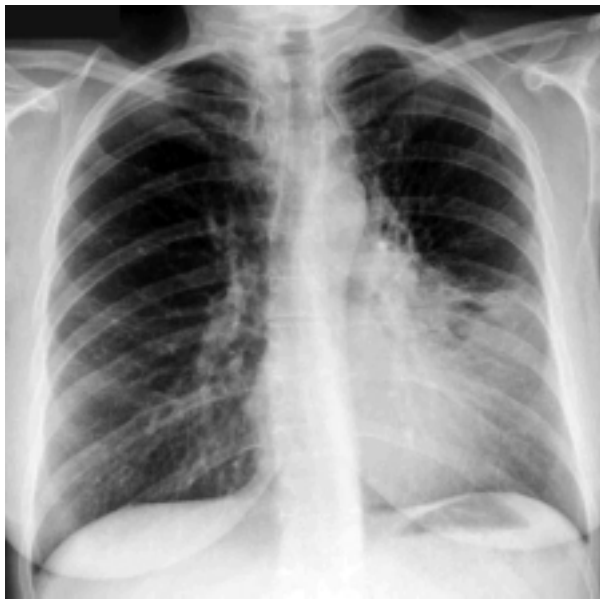

Figure 2. Postero-anterior X-ray of the chest — partial regression of the upper lobe lesions, atelectasis of lingula appeared

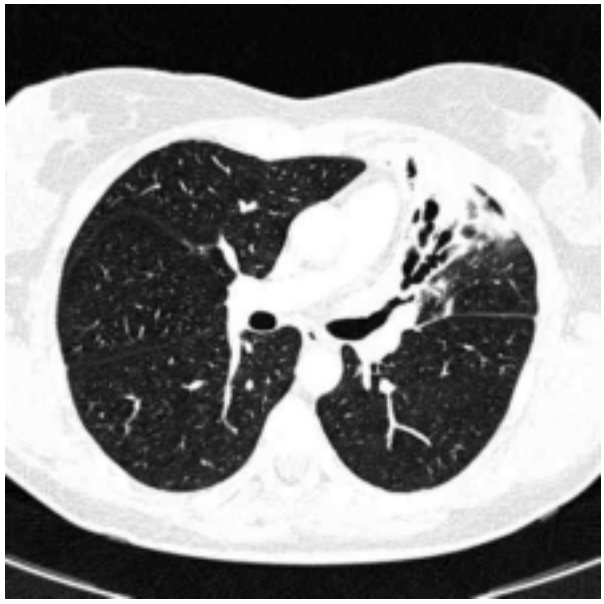

Figure 3. High resolution computed tomography of the lung — bronchiectasis within atelectatic lingula

human pathogens, e.g. *Aspergillus fumigatus* (90%), *Aspergillus flavus*, *Aspergillus niger*. They do not cause disease in all the people. Depending on the individual's immune status, the diseases caused by *Aspergillus* may be saprophytic (aspergilloma), allergic (ABPA, allergic aspergillosis of the paranasal sinuses, allergic alveolitis) or invasive (invasive aspergillosis) [6].

ABPA is a disease caused by hypersensitivity to antigens of moulds, most commonly to antigens of *Aspergillus fumigatus*, which usually develops in patients suffering from asthma or cystic fibrosis, usually in the presence of atopy. The increased viscosity of the mucus in the respiratory tract in some of the patients with asthma and cystic fibrosis combined with impaired mucociliary clearance in cystic fibrosis disrupts the process of effective removal of the fungal spores from the bronchi. The susceptibility to the development of ABPA is also a result of genetic factors that determine inflammatory response in atopic patients, which determines activation of T and B cells specific for *Aspergillus* [7, 8]. Five stages of the disease, which may develop in various orders, are distinguished: stage I (acute), stage II (remission), stage III (exacerbation), stage IV (steroid dependent), and stage V (fibrotic). The disease may be insidious with periods of exacerbation and periods of remission, and early diagnosis may prevent the progression of the disease, damage to the pulmonary interstitium, and pulmonary function deterioration [7].

The major diagnostic criteria of ABPA include [4, 7, 8]: (1) asthma, (2) pulmonary infiltrates on radiograms, (3) positive immediate aspergillin skin test (type I hypersensitivity), (4) peripheral blood eosinophilia (> 1000/mm^3), (5) serum precipitins (IgG) to *Aspergillus fumigatus*, (6) total serum IgE exceeding 427 IU/ml (1000 ng/ml) [9, 10], (7) central bronchiectasis, and (8) serum IgE and/or IgG specific for *Aspergillus*. The minor diagnostic criteria of ABPA include the presence of *Aspergillus* in the sputum, expectoration of brownish plugs and a positive delayed aspergillin skin test (type III hypersensitivity). The diagnosis of ABPA may be confirmed if at least 6 major criteria are met, although it is also acceptable to confirm the diagnosis based on the minimum criteria (without the presence of peripheral blood eosinophilia and antibodies specific for *Aspergillus fumigatus*). ABPA is also divided into seropositive ABPA, ABPA without central bronchiectasis, and ABPA with central bronchiectasis [2, 4, 6]. The disease usually affects patients with asthma or cystic fibrosis. In our case the patient had never been diagnosed with asthma but she had allergies to inhalation allergens and fulfilled 6 out of the 8 diagnostic criteria of ABPA.

In 1981, Glancy et al. described a group of 11 patients with ABPA without a previous diagnosis of asthma but half of whom were atopic (allergic rhinitis, hay fever). During the follow-up some of them developed asthma 2–10 years later [3]. In 1982, Berkin et al. described a group of 5 patients with ABPA without asthma, with only 1 patient presenting manifestations of hay fever [11]. Allergic aspergillosis has also been reported in isolated

cases of hyper IgE syndrome, bronchocentric granulomatosis and chronic granulomatous disease, bronchiectasis secondary to past tuberculosis, Kartagener's syndrome, and chronic obstructive pulmonary disease [2, 6]. Until 2009 a total of 36 cases of ABPA without asthma had been described. It is believed that due to the low frequency of this phenomenon these patients are usually evaluated for lung cancer or diagnosed with pulmonary tuberculosis, so the actual number of patients with ABPA is in fact underestimated [6].

A characteristic feature of ABPA is the variable radiographic appearance. The most common X-ray features include transient pulmonary infiltrates (mainly in the upper and lower lobes), atelectasis, band-like opacities (the gloved finger sign), bronchiectasis and — less frequently — areas of poor vascular pattern, cavities, and signs of fibrosis. The most common findings on chest CT include: bronchiectasis with a predominance of proximal changes, signs of atelectasis, mucoid impaction, local areas of consolidation and — less frequently — changes of an air trap nature, cavities, fibrosis, and pleural thickening [2]. Our patient was initially evaluated for suspected cancer of the left lung with hilar lymphadenopathy. Although such a manifestation of allergic aspergillosis is rare, several cases of ABPA have been reported in English-language journals. In 1982, Berkin et al. described 4 patients with complete or partial atelectasis without a history of asthma in whom the final diagnosis was ABPA [11]. In 2001, Sanchez-Alcaros et al. described a 65-year-old male smoker without a history of asthma who had undergone thoracotomy due to suspected lung cancer, which revealed the presence of dilated bronchi filled with mucus. The patient was eventually diagnosed with ABPA a year later [12]. In 1998, Cote et al. described a case of a 51-year-old female with mild asthma who was being evaluated due to haemoptysis and a peripheral tumour of the right lung. This patient was also eventually diagnosed with ABPA [13]. In 2006, Agarwal et al. described a case of a 60-year-old female evaluated due to the widening of the left hilum on a chest X-ray. A high resolution computed tomography (HRCT) scan revealed proximal bronchiectasis and numerous bronchocele, which mimicked hilar lymphadenopathy on a chest X-ray, as was the case with our patient. After additional investigations had been carried out, the diagnosis of ABPA was confirmed [14].

In the case of our patient, the first flexible bronchoscopy performed in an outpatient setting revealed infiltration of the bronchus and the carina leading to segment 1–2 and the bronchus leading to the lingula and the presence of pus filling the bronchi, and the histopathological examination of the sections of the bronchial mucosa revealed epithelial metaplasia with signs of low-degree dysplasia, which worried the doctors performing the examination. Usually, flexible bronchoscopy in patients with ABPA reveals severe inflammation with a thickened mucosa, bronchiectasis, ample amounts of purulent discharge, and the presence of pus plugs blocking the bronchi. Glucocorticosteroids, usually given at a dose of 0.5 mg/kg/day, are the treatment of choice in ABPA. They suppress the immune response to the fungus and exert an anti-inflammatory action. There is no consensus as to the duration of glucocorticosteroid treatment. It is, however, known that the use of lower doses is associated with more rapid relapses and the development of steroid dependence. Treatment is usually given for 6 months, although extending the duration of treatment to 12 months and increasing the dose (to 0.75 mg/kg/day) is associated with a higher rate of remissions and a lower rate of steroid dependence. After 6–8 weeks of treatment a decrease in IgE and a radiological improvement should be seen. The treatment goal is to reduce the baseline IgE levels by 35–50%, although it should be remembered that after treatment IgE levels need not be normal. In each patient the baseline serum IgE level should be determined, as a 100% increase suggests a risk of relapse. Each patient in the initial phase of treatment should be monitored every 6–8 weeks for the first year, followed by every 6–12 months [2, 6]. Our patient, due to the nature of her work, did not return for follow-up assessments, although about 8 months after treatment completion her IgE levels were found to have decreased by 50%, but the infiltrates in the right lung are still present and require follow-up. Publications on the management of ABPA do not unequivocally report on the justifiability of antifungal treatment. It is believed that antifungal treatment may suppress the growth of fungi colonising the patient's airways and at the same time reduce the exposure to *Aspergillus* antigens. It is believed that the addition of itraconazole to glucocorticosteroids at a dose of 200 mg BID for 16 weeks, followed by 200 mg QD for the next 16 weeks allows, in nearly half of the patients, a reduction of the dose of glucocorticosteroids, improves exercise tolerance, decreases total IgE, and improves FEV_1 [9, 15]. However, due to the insufficient number of studies, it is not recommended to combine glucocorticosteroids with antifungals as a standard course of action in the basic treatment of ABPA; this option is reserved for patients with recurrent disease. Despite the fact that the patient was

started on two-month antifungal treatment due to the confluent growth of fungi in bronchial washing cultures and considerable exposure at the workplace, the treatment resulted in elimination of the fungus from the bronchi.

In conclusion, it should be emphasised that ABPA is a frequently underdiagnosed condition associated exclusively with the presence of asthma or cystic fibrosis. It may, however, also develop in patients without atopy and may sometimes suggest other, much more common disease entities including tuberculosis and lung tumours, which should always be included in the differential diagnosis. Also, not all the diagnostic criteria are always fulfilled, which makes establishment of the final diagnosis difficult. However, the disease should be detected as soon as possible because prompt initiation of treatment may prevent irreversible pulmonary fibrosis and disability.

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