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Aspergillosis: from Allergic Bronchopulmonary Aspergillosis to Invasive Aspergillosa

Aspergillozis: Allerjik Bronkopulmoner Aspergillus'tan İnvazif Aspergillozis'e

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Abstract

Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex hypersensitivity reaction that develops in response to the colonization of the airways with Aspergillus fumigates. Aspergillus species are found in many places in nature, and while the inhalation of infectious conidia is a common occurrence, tissue invasion is rare, occurring most frequently in patients undergoing immunosuppressive therapy for hematological malignancy or solid organ transplantation. A 58-year-old male patient presented with dyspnea, cough and hemoptysis that had started 1 week earlier. The patient had been started on oral corticosteroid and itracanazole treatment following a diagnosis of ABPA 11 months previously. Computed tomography and laboratory findings were evaluated as invasive aspergillosis. Aspergillus fumigatus was identified in bronchial aspiration, and intravenous voriconasole was started. The patient's general condition worsened during follow-up and was transferred to intensive care, but died on the 3rd day of ICU hospitalization. Systemic corticosteroids applied for the treatment of many diseases should be used with caution due to their immunosuppressive properties, and the use of systemic corticosteroids in the treatment of ABPA must be carefully managed.

Key words: *Allergic Bronchopulmonary Aspergillosis, Invasive Aspergilosis, Steroid.*

Özet

Allerjik Bronkopulmoner Aspergillozis (ABPA), hava-yollarının Aspergillus fumigates ile kolonizasyonuna yanıt olarak gelişen kompleks bir hipersensitivite reaksiyonudur. Aspergillus türleri doğada pek çok yerde bulunur ve enfeksiyöz konidyumların inhalasyonu sık görülen bir olaydır. Ancak, doku invazyonu nadirdir. Doku invazyonu en sık olarak hematolojik malignite ya da solid organ transplantasyonu için immünsüpresif tedavi alan hastalarda görülür. Elli sekiz yaşında erkek hasta 1 hafta önce başlayan, dispne, öksürük ve hemoptizi şikâyeti ile başvurdu. On bir ay önce ABPA tanısı ile oral kortikosteroid ve itrakanazol tedavisi başlanan hastanın, bilgisayarlı tomografisi ve laboratuvar bulguları, invazif aspergillozis olarak değerlendirildi. Bronş aspirasyonunda aspergillus fumigatus üreyen hastaya intravenöz vorikanozol başlandı. Takiplerinde genel durumu kötüleşen hasta yoğun bakıma nakil verildi. Fakat yoğun bakım yatışının 3. gününde exitus oldu. Birçok hastalığın tedavisinde kullanılan sistemik kortikosteroidler, immünosupresif özellikleri nedeniyle dikkatli kullanılmalıdır. Bu nedenle, ABPA tedavisinde sistemik kortikosteroid kullanımı, dikkatle yönetilmesi gereken bir tedavi şeklidir.

Anahtar Sözcükler: *Allerjik Bronkopulmoner Aspergillozis, İnvazif Aspergillozis, Steroid.*

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Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disorder characterized by recurrent episodes of wheezing, fleeting pulmonary opacities and bronchiectasis. It is a hypersensitivity reaction that develops in response to the colonization of the airways with Aspergillus fumigates, and is usually seen in patients with asthma or cystic fibrosis (1,2). The diseases referred to as "aspergillosis" includes those that take the form of allergies, airway or parenchymal disease, cutaneous infection or extrapulmonary spread with Aspergillus species (mostly *A. fumigatus*, *A. flavus*, and *A. terreus*). Aspergillus species are found in many places in nature, and the inhalation of infectious conidia is a common occurrence, while tissue invasion is rare, being most common in patients undergoing immunosuppressive therapy for hematological malignancy or solid organ transplantation (3).

Glucocorticoids have pleiotropic and suppressive effects on immune response, and play a therapeutic role in inflammatory, allergic, immunological and malignant diseases (4). Glucocorticoid toxicity is one of the most common iatrogenic disorders associated with chronic inflammatory diseases. The present study emphasizes the relationship between this case and the effect of glucocorticoids used in the treatment of ABPA, and the risk of invasive aspergillosis.

CASE

A 58-year-old male patient presented with complaints of dyspnea, cough, sputum, and half a tea glass of bloody sputum a day. His medical history indicated the use of inhaler corticosteroid + long-acting β2 agonist treatment due to a diagnosis of asthma 9 years earlier. There was no smoking history, and no points of interest in his family history. His hemogram eosinophil level was measured as 2400 μL. The patient had high eosinophil levels in his blood and sputum, and his IgE level was 3256 (N: 0-165). An Aspergillus skin test was positive, and the patient was started on oral corticosteroid and itracanazole with a diagnosis of ABPA.

The patient developed dyspnea, cough, sputum and hemoptysis in the 11th month of treatment, and a fever of 38.5°C, respiratory rate 20/min, blood pressure 100/75 mmHg and pulse 110/min. A respiratory examination revealed bilateral rales and expiratory rhonchi.

A posteroanterior (PA) chest X-ray revealed a bilateral diffuse reticulonodular density increase (Figure 1). The ABPA patient was hospitalized with a pre-diagnosis of pneumonia. The patient's blood leukocyte level was 21900/uL and CRP was 12.33 mg/dL. The patient was started on piperacillin-tazobactam as a broad-spectrum antibiotic therapy.

Itracanazole treatment was continued, and on the 3rd day of hospitalization, leukopenia (2000/Ul) developed and the patent's CRP level (31.4) increased. Oxygen therapy was started after the patient developed hypoxemia, and his oxygen level increased to 60 mmHg from 50 mmHg with 3 L/min nasal oxygen therapy in his arterial blood gas. A PA chest X-ray showed a bilateral diffuse heterogeneous density increase (Figure 2), the galactomannan antigen was 1.82 (positive), and a Thoracic computed tomography (CT) revealed bilateral fibrocavitary lesions, increased diffuse homogeneous density, nodularity and ground-glass opacity, bronchiectasis areas and the "Halo" sign (Figure 3a and b)

The patient had hypotension (79/50 mmHg) and tachycardia (126/min), and his arterial blood gas showed (pO_2: 54 mmHg) hypoxemia. When the patient's lactate level reached 3.4, and thrombocytopenia (64,000/mm^3), anemia and leukopenia (2000/uL) developed, he was transferred to the intensive care unit with a diagnosis of sepsis and invasive aspergillosis.

Aspergillus fumigatus was reproduced in the bronchial aspiration obtained during an intensive care fiberoptic bronchoscopy (FOB). No bacterial growth was observed in the sputum culture, but the blood galactomannan antigen level was noted to increase. The patient was consulted for infectious diseases, and intravenous voriconazole treatment was started. The patient's general condition worsened during follow-up and was subsequently intubated, but died on the third day of intensive care treatment due to sepsis secondary to invasive aspergillosis.

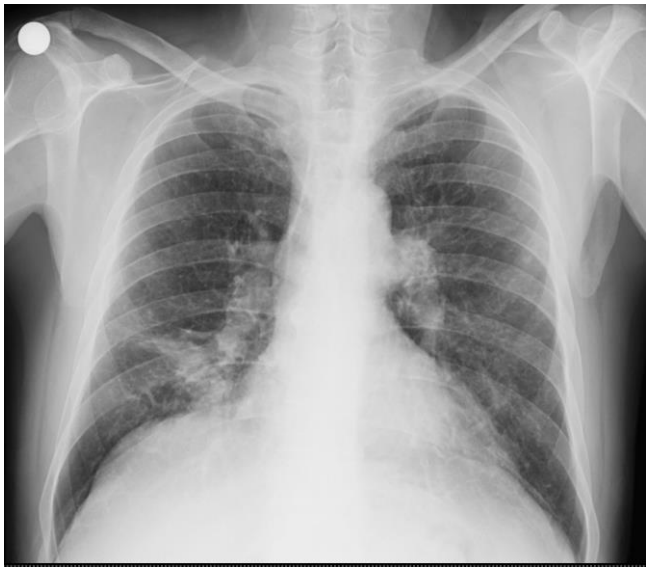

Figure 1: *A PA chest X-ray revealed a bilateral diffuse reticulonodular density increase*

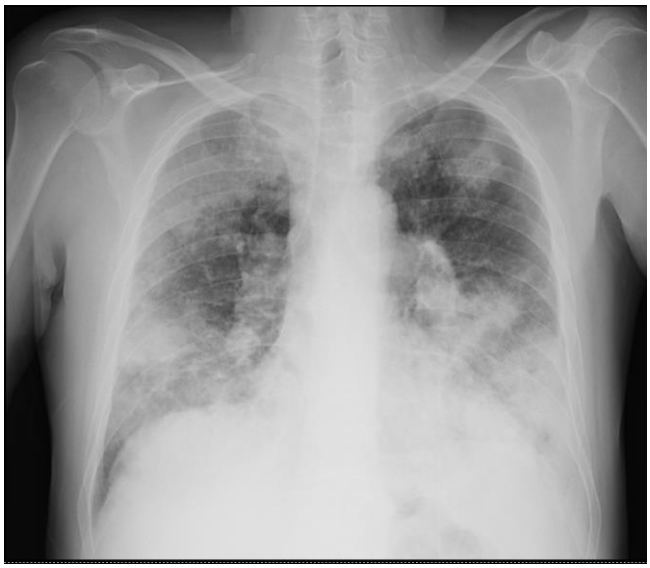

Figure 2: *A PA chest X-ray showed a bilateral diffuse heterogeneous density increase*

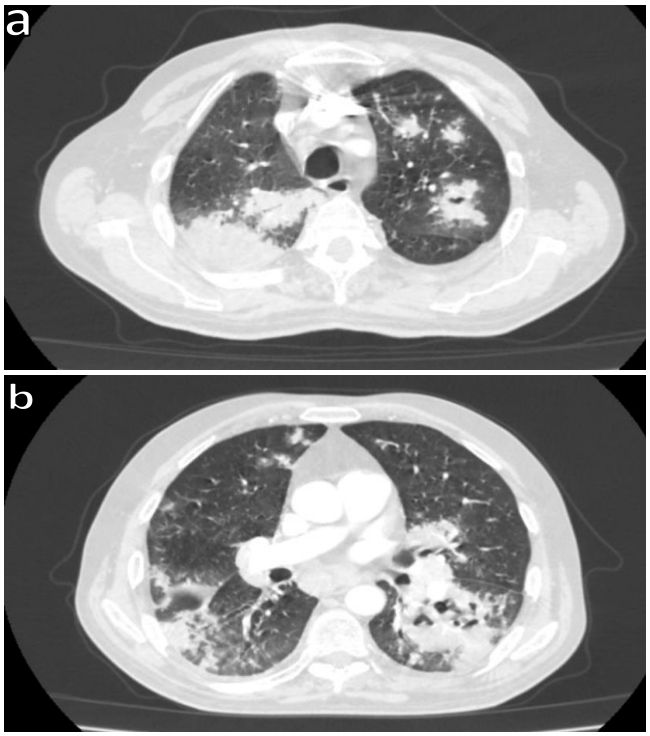

Figure 3a and b: *A Thoracic CT revealed bilateral fibrocavitary lesions, increased diffuse homogeneous density, nodularity and ground-glass opacity, bronchiectasis areas and the "Halo" sign*

DISCUSSION

Aspergillus species have emerged as an important cause of life-threatening infections in immunocompromised patients. The numbers of individuals who are immunocompromised is increasing day by day, and are primarily those with long-term neutropenia, advanced HIV infection, those with hereditary immune deficiency, and those who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) and/or lung transplantation (5). Infections related to aspergillus species and aspergillus pneumonia are an important cause of mortality and morbidity in all immunosuppressed groups, especially in patients with HSCT (6-8).

The degree of infection of Aspergillus in the body varies depending on the immune response of the host (9). Allergic, saprophytic and invasive forms of aspergillus infections may be seen. Aspergillus hifa, when taken into the lungs via inhalation, may cause angioinvasion in the host as a result of failure of the immune response (10).

The most important criterion in diagnosis is the visualization of aspergillus reproduction in a culture analysis. While aspergillus reproduces easily in sputum cultures, its reproduction is rare in blood cultures. Bronchoalveolar lavage, transthoracic percutaneous needle aspiration or video-assisted thoracoscopic biopsy are standard procedures for the diagnosis of invasive pulmonary aspergillosis. The presence of septa with hives in direct microscopy in the samples obtained using these methods is sufficient for diagnosis (2,5,11). Aspergillus hives were observed in bronchial aspiration obtained with FOB performed in the intensive care unit, however, other interventional procedures could not be performed due to the general condition of the patient.

Chest radiographs can reveal upper-lobe tubular branching opacities radiating out from the hilum in a bronchial distribution, classically referred to as the 'finger-in-glove' radiologic sign (12). CT plays an important role in the diagnosis of invasive pulmonary aspergillosis, with CT features to look out for being central or proximal upper lobe pre-dominant cystic or varicose bronchiectasis, tree-in-bud nodules, bronchial wall thickening and air-trapping (13). All of the radiological findings that may be seen in invasive aspergillosis were observed in the thorax CT of the presented case.

The Galactomannan antigen (GMA) test can also contribute significantly to the diagnosis of invasive aspergilosis, and can be studied from cerebrospinal fluid and bronchoalveolar lavage fluid. GMA is used not only for early diagnosis, but also for the evaluation of treatment response by serial follow-up. In the present case, the galactomannan antigen was found to be high, and was observed to have continued to increase at follow-up.

Invasive aspergillosis can lead to mortality without adequate treatment, and sometimes even with adequate treatment. In the treatment of invasive aspergillosis, starting antifungal treatment early is the most important step (13-15). Oral or intravenous voriconazole has been the most commonly used antifungal medication applied for the treatment of invasive aspergillosis (16), although

posaconazole, itraconazole, caspofungin and micafungin may also be used (5). In the present case, as soon as invasive aspergillosis was suspected, the patient was started on voriconazole. However, invasive aspergillosis is a lung infection that is associated with high mortality rates, and that may have a poor prognosis despite treatment. Our case died on the 3rd day of treatment.

The systemic corticosteroids used in the treatment of many diseases should be used with caution due to their immunosuppressive properties. Accordingly, the use of systemic corticosteroids in the treatment of ABPA must be carefully managed.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - D.S.U., A.A., G.P., G.K., Ö.S.U., F.D.Ü.; Planning and Design - D.S.U., A.A., G.P., G.K., Ö.S.U., F.D.Ü.; Supervision - D.S.U., A.A., G.P., G.K., Ö.S.U., F.D.Ü.; Funding - D.S.U., G.P., G.K.; Materials - F.D.Ü., G.K.; Data Collection and/or Processing - D.S.U., A.A., Ö.S.U.; Analysis and/or Interpretation - Ö.S.U., A.A., G.P.; Literature Review - Ö.S.U., D.S.U., G.K.; Writing - D.S.U., A.A., Ö.S.U.; Critical Review - F.D.Ü., G.P., G.K.

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