Chronic Necrotizing Pulmonary Aspergillosis in a Patient with Asthma: Case Report

Astımlı Bir Olguda Kronik Nekrotizan Pulmoner Aspergillozis

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ABSTRACT Chronic necrotizing pulmonary aspergillosis is a rare fungal infection that is characterized by slow progression and local invasion. It is most commonly seen in patients with impaired lung parenchyma and mild immunodeficiency. A 81 years old female patient with an established diagnosis of asthma for 5 years was admitted to our clinic with complaints of cough and sputum. Posteroanterior chest radiograph showed an irregular opacity at the right middle zone. Thorax CT revealed an irregular pleural based lesion with central cavitation. Histopathological examination of the transthoracic biopsy specimen showed aspergillus hyphae with tissue invasion. The patient was treated with voriconazole. At the end of a total of 6 months therapy, control CT revealed no lesion. We reported this case to emphasize that the chronic necrotizing pulmonary aspergillosis may develop in the immunocompetent patients with asthma resistant to the treatment. Early diagnosis of aspergillus infection in these particular patients is essential for the control of the disease to decrease mortality.

Key Words: Aspergillosis, asthma

ÖZET Kronik nekrotizan pulmoner aspergillozis, invaziv pulmoner aspergillozisin aksine, yavaş seyirli, genellikle lokal invazyon gösteren ve sıklıkla akciğer parankim hasarı varlığında gelişen, hafif immün yetmezlikli hastalarda görülebilen nadir bir fungal enfeksiyondur. Beş yıldır astım tanısıyla takip edilmekte olan 81 yaşındaki kadın hasta öksürük ve balgam yakınması nedeniyle kliniğimize başvurdu. Çekilen postero-anterior akciğer grafisinde sağ orta zonda düzensiz sınırlı dansite artışı saptandı. Bilgisayarlı toraks tomografisinde sağ alt lobda tabanı plevraya oturan kavitasyon içeren düzensiz sınırlı lezyon izlendi. Yapılan transtorasik akciğer biyopsi örneğinin histopatolojik incelemesinde doku invazyonu gösteren aspergillus ile uyumlu mantar hifaları gözlendi. Hastaya vorikonazol tedavisi başlandı. Tedaviden sonraki 6. ayda çekilen kontrol tomografisinde lezyon kaybolmuştu. Olgumuz, astım tedavisine dirençli immünkompetan hastalarda kronik nekrotizan pulmoner aspergillozisin gelişebileceğini vurgulaması yönünden önemlidir. Bu hastalarda aspergillus infeksiyonunun erken tanınması hastalığın kontrol altına alınabilmesi için gereklidir.

Anahtar Kelimeler: Aspergillosis, astım

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Pulmonary aspergillosis infections develop after inhalation of *Aspergillus* spores which are found widespread in nature. The disease presents with variable clinical pictures depending on the patients' immunity and underlying lung diseases.[1] Aspergilloma develops in preexisting cavities. Hypersensitivity pneumonia and allergic bronchopulmonary aspergillosis are seen in atopic patients while invasive pulmonary aspergillosis with high mortality occurs mostly in patients with immuno-

suppression. Chronic necrotizing pulmonary aspergillosis (CNPA) is a rare clinical condition which was first defined by Gefter in 1981.[2] Since it is a subacute disease, seen in patients with chronic lung diseases and mild immunosuppression, diagnosis is often delayed and mortality may occur due to delayed treatment.

CASE REPORT

Eighty-one years old female patient was followed with the diagnosis of severe persistant asthma for 5 years. She was hospitalized before with acute exacerbation while she was on inhaled corticosteroid and beta mimetic therapy. She was non-smoker and had no comorbidity. During routine out-patient clinic visit, the patient complained of cough and recently developed purulent sputum. Her physical examination was as follows; blood pressure: 130/80 mmHg, pulse rate: 86/min., respiratory rate: 20/min., temperature: 36.6 °C. Expiration was prolonged and bilateral sibilant rhonchi were heard on auscultation. Physical examination of other systems was normal.

Laboratory findings were as follows; leukocyte: 6.120/mm^3, hemoglobin: 10.6 g/dl, thrombocyte: 254.000K/mm^3, eryhtrocyte sedimentation rate: 49 mm/hr, C-reactive protein: 9 mg/dl. There was no significant finding in the microscopic examination of sputum and it was negative for acid-resistant bacilli. Pulmonary function tests revealed severe airway obstruction.

Heterogenous opacity with irregular margins was seen in the intermediary region of the right middle zone in the chest x-ray. Computerized tomography (CT) of the thorax revealed a pleural based mass lesion sized 50 x 31 mm with irregular margins and a central cavitation in the lower lobe of right hemithorax (Figure 1). Transthoracic trucut biopsy was performed to this peripheric lesion. Histopathologic examination of the biopsy specimen revealed hyalinized tissue, branching septations between the hemorrhagic areas and *Aspergillus* hyphae (Figure 2).

Depending on these clinical and laboratory data, the patient was diagnosed as CNPA. Voriconazole at a dose of 6 mg/kg/day in the first day was started and followed as 4 mg/kg/day in the subsequent days. The therapy was ceased in the third day because of hallucination, and restarted upon disapperance of the complaint. CT in the second month of the treatment showed near-complete remission of the lesion. The patient had this therapy for 4 months. CT, performed 6 months after the treatment, was normal except for atelectatic and fibrotic lesions (Figure 3). The patient is still

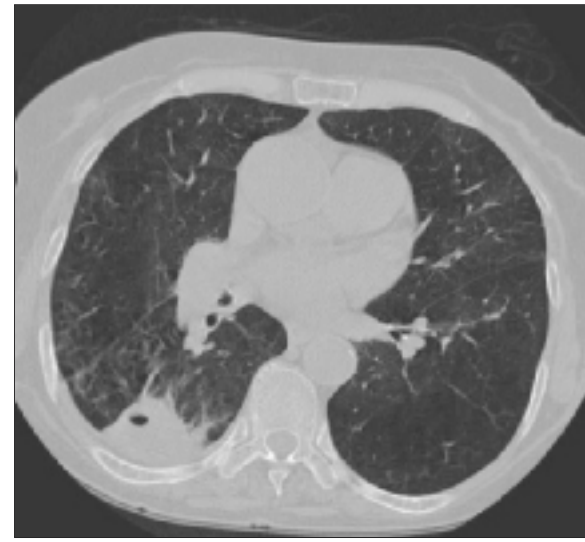

FIGURE 1: Chest computed tomography, a pleural based mass lesion with irregular margins and a central cavitation in the lower lobe of right hemithorax.

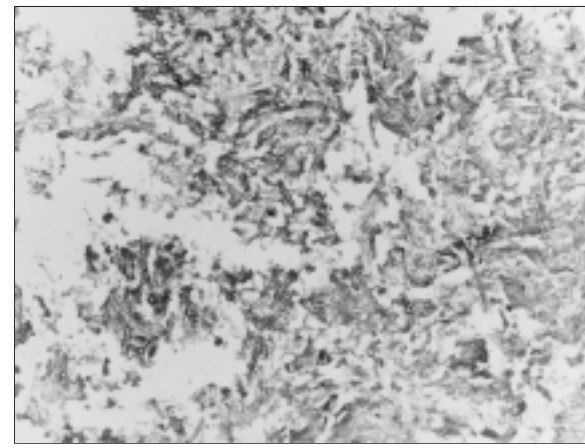

FIGURE 2: Histopathologic examination of the biopsy specimen, narrow angled branching *Aspergillus hyphae*, surrounding by inflamatory cells. PAS (periodic acid-Schiff) stain, x400.

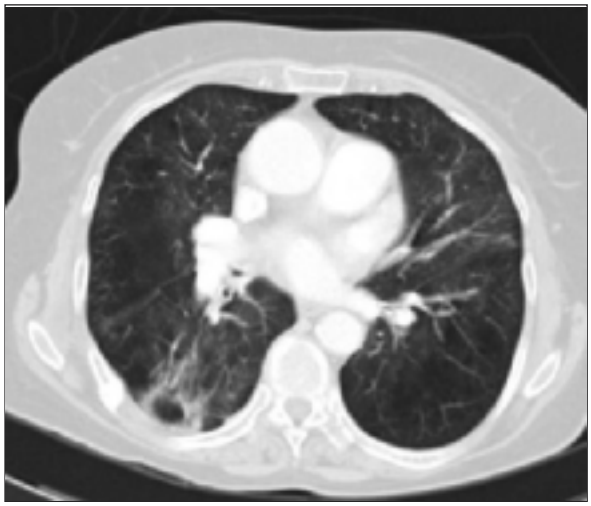

FIGURE 3: Chest computed tomography, 6 months after the treatment.

on our follow up without any evidence of recurrence.

DISCUSSION

CNPA, also called semi-invasive aspergillosis, is a fungal infection destroying the lungs by slow progression. The diagnosis is made by isolating *Aspergillus* sp. in sputum or biopsy specimen in the presence of the clinical and radiological findings and by excluding tuberculosis, atypical mycobacterial infections, chronic cavitary histoplasmosis, coccidiomycosis. The pathogen is generally *A. fumigatus*. Difference between CPNA and other *Aspergillus* infections is that CPNA neither necessitates a preexisting cavity nor invades vascular tissues or other organs.[1,3]

This clinical condition is generally seen in middle-aged and elderly people. The diseases with impairment in lung tissue such as chronic obstructive lung disease, inactive tuberculosis, damage due to radiotherapy, pneumoconiosis, cystic fibrosis and sarcoidosis ease the development of CPNA.[1,3,4] In addition, conditions causing mild immunosupression such as diabetes mellitus, malnutrition, low dose corticosteroid usage facilitate development of the disease.[1,4] Our patient did not have a systemic disease or a parenchymal lung disease, whereas she was an elderly asthmatic requiring short term corticotherapy during exacerbations.

Patients with CPNA generally admit with cough, sputum and weight loss, however few of them are asymptomatic. CPNA usually involves upper lobes or superior segments of lower lobes. Fungus ball is seen in half of the cases; accompanying pleural thickening is a characteristic feature and early indicator of local invasion.[2-4] The lesion in our case was located in the superior segment of right lower lobe and thickening in adjacent pleura suggests that this is an early diagnosis. Diagnosis is made by showing the fungal invasion in the bronchoscopic or transthoracic biopsy specimens or by isolating the fungus in sputum, bronchial lavage fluid or tissue.[1-3] Thoracoscopy or lung biopsy with thoracotomy are rarely required.[5] Serological tests used to support the diagnosis in recent years have high sensitivity and specificity.[6]

Diagnosis of CNPA requires urgent antifungal therapy. Amphotericin B is the first choice agent, but must be used carefully due to its nephrotoxic side effects. In the recent years, non-nephrotoxic orally used agents are preferred in the *Aspergillus* infections; voriconazole is one of these. The most important side effects are transient visual loss (33%) and hepatotoxicity (13.4%).[7] Only side effect seen in our patient was hallucination which developed in the third day of the treatment; this complaint disappeared upon cessation of the drug and did not recur when the drug was restarted. There is only one report about hallucination caused by voriconazole requring cessation of the drug in the literature.[8] Surgical therapy is generally required in young patients with normal pulmonary functions and focal disease or in patients who do not tolerate antifungal therapy and in whom control of the disease is not possible with antifungal therapy.[9] Surgery was not required in our patient since response to medical therapy was good.

Although the data related to long term prognosis of the CPNA is not satisfactory, prognosis is poor due to delay in diagnosis. In original series, it was reported that 73% of the patients lived for 1-2 years after the diagnosis, and in mortality rate was found to be 39% (1.3). The cause of death is usually complications, developing during the course of the disease. In the literature, cases who died due to

massive hemoptysis and acute respiratory distress syndrome were reported and peripheric eosinophilia was suggested to be the indicator of poor prognosis.[10,11] We did not detect eosinophilia in our case.

The average delay in diagnosis ranged from 3 to 7 months.[3,10] Our patient is a rare case of early diagnosis; this period was only 6 weeks. Good response to therapy was due to early diagnosis in our case.

Newly developing respiratory complaints in an elderly patient with chronic lung disease without any immunosupression must be noticed. In case of suspicious radiological findings, mycological examinations must be done in sputum, bronchial lavage fluid and tissue specimens. In this way, mortality and morbidity may be reduced by diagnosing the disease in an early phase, starting the therapy early and preventing the development of the complications.

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