Semi-Invasive Aspergillosis in an Immunocompetent Host

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SUMMARY

A 54 year-old male patient was admitted to our clinic with dyspnea, dry cough and fever. Chest X-ray revealed pneumonic infiltration with air bronchograms involving all zones of right hemithorax. We observed radiological and clinical progress despite ceftriaxone, clarithromicin and bronchodilator for chronic obstructive pulmonary disease. The gram staining of bronchoalveolar lavage showed fungal septate hyphae. Cultures of sputum yielded Aspergillus fumigatus. The specimen of transthoracic fine-needle aspiration depicted tissue invasion by fungal hyphae and spores. Liposomal amphotericin B 150 mg/day was started and 40 mg/day metilprednisolone was initiated for bronchospasm. Under this treatment, patient's clinical findings were improved. On the 21st hospital day, chest X-ray revealed abscess formation at the right upper and middle zones. Surgical treatment was not considered because of high postoperative high complication risk. Intracavitary 50 mg/day amphotericin was administered three times by a bronchoscopic catheter. On the 48th hospital day, respiratory distress, hypotension, bradycardia and juguler venous distension developed and patient was died.

Key Words: *Aspergillosis.*

ÖZET

İmmün Yeterli Kişide Semi-İnvaziv Aspergillozis

Ellidört yaşında, memur, erkek; nefes darlığı, kuru öksürük ve ateş şikayetleri ile kliniğimize başvurdu. Akciğer grafisinde sağ üst zonda pnömonik gölge koyuluğu izlendi. Seftriakson, klaritromisin ve kronik obstrüktif akciğer hastalığı için bronkodilatatör tedavisine rağmen, klinik ve radyolojik bozulma oldu. Tanısal bronkoalveoler lavajı Gram boyanmasında septalı mantar hifaları izlendi. Balgam kültürlerinde Aspergillus fumigatus raporlandı. Torakal bilgisayarlı tomografi rehberliğinde yapılan iğne aspirasyon sitolojisinde doku invazyonu gösteren mantar hifaları ve sporları görüldü. Hastaya 150 mg/gün lipozomal amfoterisin B ve ciddi bronkospazmı için 40 mg/gün metil prednizolon başlanıldı. Bu tedaviyle klinik olarak düzelme oldu. Yatışın 21. gününde çekilen akciğer grafisinde üst-orta zonda apse görüntüsü izlendi. Cerrahi sonrası yüksek komplikasyon riski nedeniyle cerrahi tedavi düşünülmedi. Bronkoskopik kateter ile kavite içine 50 mg/gün amfoterisin B 3 günde 3 kez uygulandı. Yatışının 48. gününde solunum sıkıntısı, hipotansiyon, bradikardi ve juguler venöz dolgunluk belirtileri sonrasında hasta kaybedildi.

Anahtar Kelimeler: *Aspergillozis.*

Semi-invasive aspergillosis is a subacute infection that develops in an alreday abnormal lung with severe structural damage, such as in bullous disease, fibrosis, cavitation. Partial degrees of immunosupression also play an important role. The patient is presented, because semi-invasive aspergillosis is very rare in immunocompetent hosts and has a poor prognosis.

CASE REPORT

A 54 year-old male was admitted to our clinic with dyspnea, dry cough and fever. One year before admission chronic obstructive pulmonary disease had been diagnosed and one month before admission he experienced a worsening of exertional dyspnea with the subsequent onset of coughing.

The patient had a history of heavy alcohol consumption and 35-pack-year smoking which he had discontinued one month before admission. There was not any other history of systemic disease.

On physical examination; the temperature was 39.5°C, the pulse was 106 per minute, the respirations were 30 per minute, bilateral diffuse rhonchi and on the right hemithorax rales were heard. The white cell count was 16300 per cubic milimeter. Analysis of blood gases revealed; pH: 7.52, PaO_2: 57.1 mmHg, $PaCO_2$: 26.4 mmHg. Chest X-ray revealed pneumonic infiltration with air bronchograms involving all zones of right hemithorax (Figure 1).

Bronchodilator medications, ceftriaxone and clarithromicin were administered. The Gram staining of sputum which was taken before treatment revealed fungal septate hyphae (Figure 2). Bronchoscopic examination showed mucosal edema and purulent secretions in the right lung. The Gram staining of bronchial and bronchoalveolar lavage yielded gram-negative bacilies and fungal hyphae. After 72 hour of treatment the patient was still febril. Treatment was changed as cefepime with amicasin. Despite this treatment, clinical and radiological progression was observed. Thoracal computed tomography (CT) was performed. Thoracal CT revealed consolidation with air bronchograms in the right upper lobe, right middle lobe and in the superior

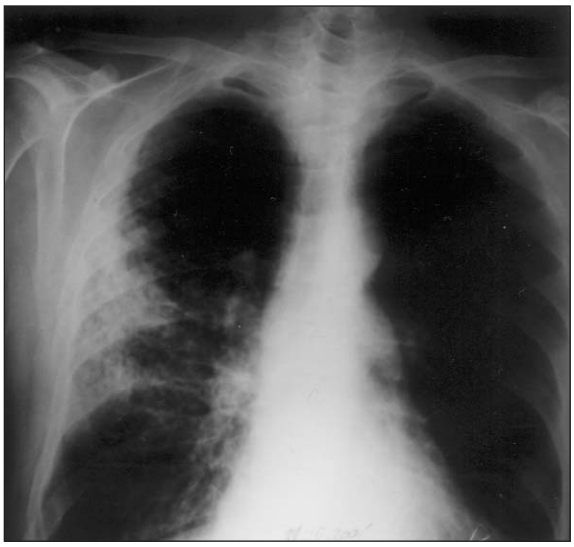

Figure 1. Chest radiography taken on the first hospital day revealing pneumonic infiltration.

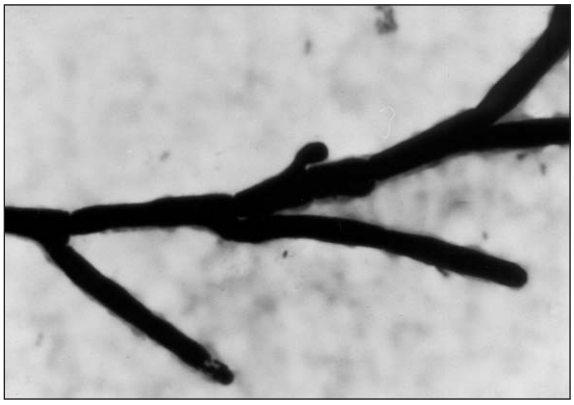

Figure 2. The Gram staining of sputum revealing septate hyphae.

segment of lower lobe, emphysema in both of lungs, subpleural micronodules and reticular shadowing in the right middle and lower lobes, bilateral minimal pleural effusion. Cranial and abdomen CT showed no abnormalities. A CT guided transthoracic fine-needle aspiration was performed and specimen depicted tissue invasion by fungal hyphae and spores (Figure 3). Culture of sputum yielded *Aspergillus fumigatus*. Cefepime and amicasin was discontinued and on the 8th hospital day liposomal amphotericin B 150 mg/day and 40 mg/day metilprednisolone were administered for bronchospasm. When metilprednisolone was discontinued, it was started again due to worsening symptoms and clini-

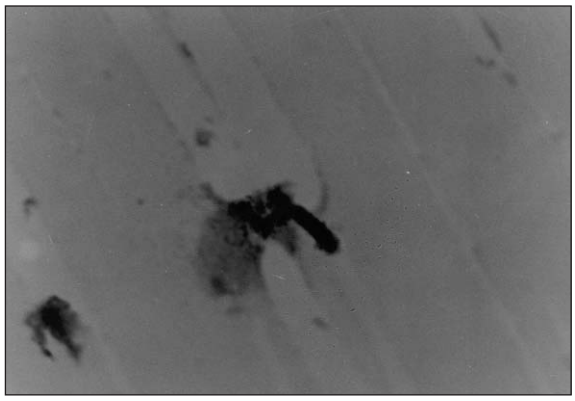

Figure 3. The Gram staining of specimen of transthoracic fine-needle aspiration revealing septate hyphae.

cal findings. During hospitalization, 5 sputum cultures yielded *A. fumigatus,* 2 blood cultures remained sterile. Microscopic examination of three specimens of sputum and bronchoalveolar lavage showed no acid-fast-bacilli and cultures of sputum for acid-fast-bacilli were negative.

Cytolgical examination of bronchoalveolar lavage, bronchial lavage and sputum showed no tumor cells.

On the third treatment day of amphotericin B, the temperature was 37°C. Under this treatment, patient's clinical findings were improved. On the 21st hospital day chest X-ray revealed abscess formation at the right upper zone (Figure 4). Thorax CT was consistent with abscess formation (Figure 5). Surgical treatment was not considered due to postoperative high complication risk. Bronchoscopy was performed and a cavity drainage oriphis was seen in the right main bronchus. Intracavitary 50 mg amphotericin B was administered three times by bronchoscopic catheter in addition to the systemic amphotericin.

On the 48th hospital day, respiratory distress, hypotension, bradycardia and juguler venous distension developed and patient was died.

DISCUSSION

Different members of *Aspergillus* genus can induce lung disease in human, but particularly two species *Aspergillus flavus* and *A. fumigatus* which was responsible pathogen in out patient are usually involved (1). *Aspergillus* species are

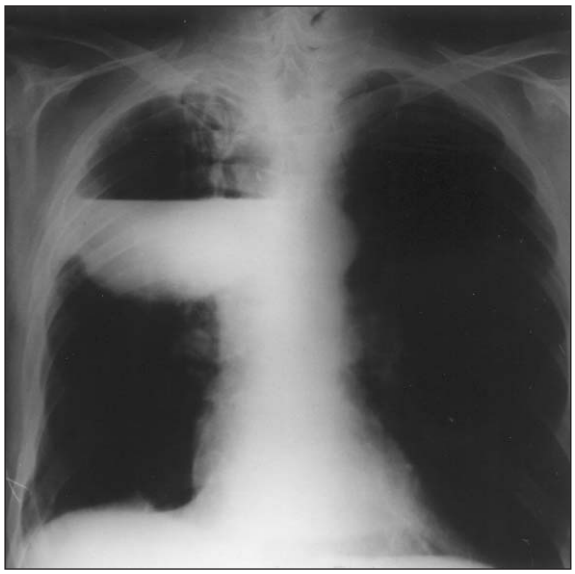

Figure 4. Chest radiography revealing abscess formation.

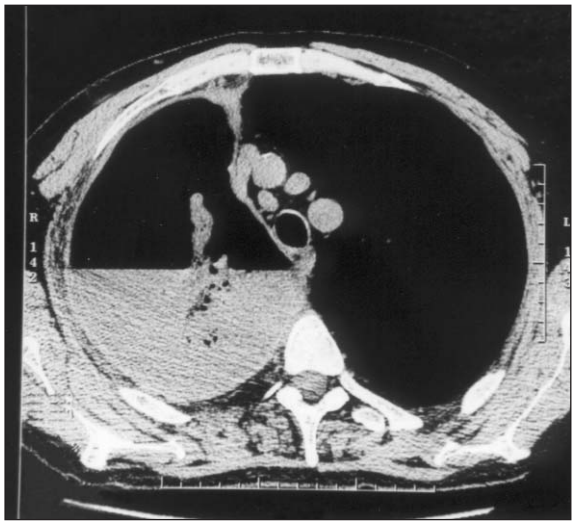

Figure 5. Thorax CT revealing abscess formation.

found worldwide. Characteristically, the hyphae are septate and have finger-like branching.

The spectrum of *Aspergillus*-induced disease in the human lung is extensive, ranging from allergic asthma, hypersensitivity pneumonitis, colonization and chronic infection of bronchi (allergic bronchopulmonary aspergillosis) colonization of preexisting lung cavities (aspergilloma), invasive aspergillosis and chronic necrotising pneumonia like in our patient.

Chronic necrotising aspergillosis is a semi-invasive, subacute infection that develops in an already abnormal lung with severe structural damage, such as in bullous disease, fibrosis and cavitation. Partial degrees of immunosupression also play an important role. Despite these predisposing factors, semi-invasive aspergillosis is very rare in immunocompetent hosts. Our patient was not neutropenic or hypogamaglobulinemic, had no underlying malignancy and HIV antibody was negative. Because of high incidence in alchololic cirrhosis in a review of 25 nonimmunocompromised patients, it has been suggested that ethanol-induced impairment of pulmonary alveolar macrophage function or depressed granulocyte bactericidal activity may predispose aspergillus-induced disease (2). Hence, history of alcoholism was accepted as a possible risk factor for our patient.

A. fumigatus also produce several antiphagocytic factors. Murayama et al studied in vitro effects of *A. fumigatus* culture filtrates on the functions of human alveolar macrophages and polymorphonuclear leucocytes and they demonstrated that *A. fumigatus* produce several antiphagocytic factors which can be responsible for the colonization of *A. fumigatus* in the bronchopulmonary tissues and allow this species to invade surrounding lung tissues in pulmonary aspergillosis by supressing local host defences (3).

Clinical symptoms are not specific. Fever and productive cough usually are present and other symptoms caused by underlying chronic disease (dyspnea, malaise) usually worsen.

The diagnosis of pulmonary aspergillosis must be considered in patients with a chest radiography revealing diffuse infiltrates or new cavitation and we considered *Aspergillus* as a pathogen, because our patient's radiographic findings was consistent with this definition. Because of it's low incidence in immunocompetent host, the diagnosis is usually delayed. Clancy et al reported 11 patients with acute community-acquired pneumonia due to *Aspergillus* who were immunocompetent. The diagnosis was delayed for all patients and mortality was 100%. They concluded that increased recognition and more timely diagnosis in future cases will improve the outcome of this rare but fatal infection (4). We thought that, mediastinal vascular and/or pericardial invasion by cavity were causes of death for our patient because suddenly juguler venous distension and hypotension developed.

Definitive diagnosis is based on the exclusion of other possible infections such as tuberculosis, atypical *Mycobacteria* or histoplasmosis as well as on the isolation of aspergilli in samples such as sputum or obtained by bronchoscopic procedure and transthoracic needle aspiration. In our patient five sputum cultures were positive for *A. fumigatus*. In our patient, diagnosis was achieved by positive sputum cultures in addition to the positive gram staining of CT guided fine-needle aspiration specimen for *A. fumigatus*.

Surgical resection usually is not possible because of the severe respiratory impairment caused by underlying respiratory disease (1).

The treatment efficacy of available therapeutic agents for pulmonary aspergillosis is poor (5). Amphotericin B has been considered the alternative treatment for chronic necrotising aspergillosis when surgery is not possible. Oral itraconazole for several months appears to be the treatment of choice (1).

Amphotericin B has a high toxicity that is decreased by liposomal capsulation (6). Itraconazole is a triazole antifungal agent with broad-spectrum that is available as a capsule or oral suspension. It's safety and therapeutic index are superior to those of amphotericin B. Itraconazole has fungicidal activity against *Aspergillus* species in vitro (7).

The efficacy and safety of combination therapy of aspergillosis have not been determined. Although it has been reported that, treatment by amphotericin B combined with itraconazole produce antagonistic effects in animal models, Adrian et al demonstrated that itraconazole and amphotericin B given together are not clinically antagonistic and the addition of itraconazole to amphotericin B in the management of aspergillosis may be useful therapeutic measure (8).

Although mycotic infections are rare cause of lung abscess, it has been reported that *Aspergillus* species may cause lung abscess like in our patient. The main goals of therapy are rapid eradication of the causative pathogene with appropiate therapy and monitoring and prevention of complications. Surgical treatment is indicated in a nonresolving lung abscess or for relieving an underlying anatomic disturbance. Surgical treatment was not considered for our patient because of postoperative high complication risk. As an alternative to surgery, intracavitary instillation by fiberoptic bronchoscopy or percutanous administration of antifungal can be performed (9). We administered intracavitary amphotericin B by a bronchoscopic catheter in addition to the systemic amphotericin B. Although satisfactorily high intracavitary concentration of the antifungal agent can be achieved by the intracavitary instillation, the rate of roentgenographic improvement is variable (8). We observed partial radiologic improvement after intracavitary administration.

Although treatment with high doses of amphotericin B may improve survival among some patients with pulmonary aspergillosis, the mortality from this infection remains unacceptablly high. We present this patient, because this from of pulmonary aspergillus infection is extremely rare in immunocompetent patients and has a poor prognosis.

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