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A Case of Septic Pulmonary Embolism due to *Candida Ciferrii*

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Septic pulmonary embolism (SPE) is a rare disease difficult to treat characterized by an acute onset, respiratory system symptoms, fever and bilateral pulmonary nodules. Bacterial, viral or fungal agents play a role in the etiology of septic pulmonary embolism. Candida species are important agents which are widely available in nature and lead to severe nosocomial infections. Candida species-related septic pulmonary embolism is rare. Being aware in risky patients is important for diagnose of fungal invasion.

Candida ciferrii related septic pulmonary embolism has been reported at 70-year-old female patient with type 2 Diabetes Mellitus in this paper.

Although the pathogens of SPE may differ depending on the primary focus of the infection, early diagnosis, prompt antimicrobial therapy, radiologic or surgical intervention can lead to a successful treatment outcome.

Key Words: *Septic pulmonary embolism, Candida ciferrii, invasive candidiasis*

Candida Ciferrii ile Gelişen Bir Septik Pulmoner Emboli Olgusu

Septik pulmoner Emboli (SPE) akut başlangıçlı solunumsal belirtiler, ateş ve bilateral akciğer nodülleri ile karakterize, nadir gözlenen ve tedavisi güç bir hastalıktır. Bakteriyel, fungal ve viral ajanlar septik pulmoner embolinin etyolojisinde rol oynar. Doğada geniş ölçüde bulunabilen kandida türleri önemli ajanlardır ve ciddi nozokomiyal enfeksiyonlara yol açarlar. Kandida türleri ile ilişkili SPE nadirdir. Fungal invazyonun tanısı için riskli hastalarda uyanık olmak son derece önemlidir.

Bu yazıda, Tip 2 Diyabet mellitusu olan 70 yaşında bayan hastada görülen *Candida ciferrii* ilişkili septik pulmoner emboli olgusu sunulmuştur.

Her ne kadar SPE'ye sebep olan patojenler, primer odağa bağlı olarak değişiklik gösterebiliyorsa da, erken tanı, erken antimikrobiyal tedavi, radyolojik ve cerrahi müdahaleler ile tedavi başarısı sağlanabilir.

Anahtar Kelimeler: *Septik pulmoner emboli, Candida ciferrii, invazif kandidiyazis*

Introduction

Septic pulmonary embolism (SPE) is a rare disease difficult to treat characterized by acute onset, respiratory system symptoms, fever and bilateral pulmonary nodules. It is radiologically seen as multiple, peripheral, round and/or wedge shaped opacities. In SPE, the embolic blood clot that leads to an infarction in the pulmonary vasculature also contains microorganisms that incite a focal abscess (1). Opacities are asymmetrical and frequently bilateral (2).

Bacterial, viral or fungal agents play a role in the etiology of septic pulmonary embolism. Fungal infections consist 8% of all nosocomial infections and species are responsible for 80% of them (3). *Candida* species are important agents which are widely available in nature and lead to severe nosocomial infections (4).

Many pathogenic *Candida* species which commensally exist in gastrointestinal tracts, oropharynx and vagina in immunocompromised individuals may lead to opportunistic infections in immunosupression conditions like hematological or solid organ neoplasms, hepatic failure or gastrointestinal surgery, catheterization and wide spectrum antibiotic use. A significant increase has occurred in the prevalence of *Candida* species-related infections within the recent two decades. Although *C. albicans* is responsible in most of the cases in whom candidemia is detected, non-candida albicans prevalence has been observed to increase recently (5).

Although mortality rates are suggested to decrease if quick and correct diagnosis is made in *Candida* infections, the current diagnostic tests are inadequate for this.

Therefore the use of clinical parameters and knowing the risk factors well is important for diagnosis and treatment of invasive candidiasis cases.

Candida ciferii is a new fluconazole resistant strain of *Candida* (4). But, fluconazole sensitive *Candida ciferii* cases have been determined (6). We aimed to present this case as diagnosis and treatment of *Candida ciferii*-related septic pulmonary embolism is difficult and a rare disease.Informed consent was taken from the patient.

Case Presentation

A 70-year-old female patient with type 2 DM was admitted to the emergency room with complaints of altered consciousness, speech disorder, vomiting and loss of power in the left. On her physical examination, she was confused, she had pupillary isocoria, deep tendon reflexes (DTR) and direct light reflex (DLR) were (++/++) and she had left hemiplegia. Laboratory findings revealed WBC: 16.14x 10^3/µL (86% PNL), Hgb: 12.0 g/dL, Htc: 38%, PLT: 319x 10^3/µL. Biochemical tests and PTZ-INR values were normal. An intracerebral hematoma was detected on the right parietal-occipital region on computed tomography of the brain. She underwent an urgent operation and hematoma was evacuated.

She was transferred to the Intensive Care Unit. Her laboratory tests which were repeated on postoperative day 0 were as follows: WBC: 15.40x 10^3/µL (86% Ne) Hgb: 11.0 g/dL, Htc: 35% PLT: 326x 10^3/µL. Biochemical tests were in normal limits. C-reactive protein (CRP) was detected as 2.13 mg/dL. No pathogenic microorganisms were detected in tracheal aspirate and urinary cultures. Cefamezine 1 gr tid and gentamicin 80 mg bid treatment was started empirically. Her fever was 38.5°C on postoperative day 7. A purulent drainage was observed at the operation site (parieto-occipital region) on her physical examination. Wound culture, blood, and urinary culture were obtained. Whole blood count results were as follows: WBC: 8.5x 10^3/µL (86 Ne%) Hgb: 9.2 g/dL, Htc: 28% PLT: 174x 10^3/µL. Biochemical tests and INR values were in normal limits. CRP was 15.8 mg/dL. Pulmonary examination findings and chest x-ray were interpreted as normal (Figure 1). Tigecycline treatment was started with 100 mg initially and maintained with 50 mg bid empirically with prediagnosis of superficial surgical site infection as fever, purulent drainage continued. *Enterococcus faecalis* growing was detected in wound culture. The microorganism was susceptible to tigecyclin and treatment was continued. Low dose of enoxaparin (2000 IU-1x0.2cc) was started as she developed deep venous thrombosis (DVT) in her left leg on postoperative day 15. Her fever was elevated to 39^{o}C on day 10 of treatment (postoperative day 17). Her general condition deteriorated and respiratory rate was 30 /min, blood pressure was 100/60 mmHg and heart rate was 120 bpm. Respiratory amplitude was low and inspiratory rales were heard on basal parts of both lungs on her respiratory system examination. Her laboratory tests were as follows: WBC: 10.4x 10^3/µL (86% Ne) Hgb: 11.2 g/dL, Htc: 35% PLT: 286x 10^3/µL, CRP: 20.8 mg/dL. Liver and renal function tests were normal. Blood and urinary cultures were obtained and no growing was detected. A chest x-ray was obtained and interpreted as normal. Computed tomography of the thorax was obtained as widespread nodular densities of which contours could not be clearly discriminated from the lung parenchyma were detected on chest x-ray (Figure 2). Scattered nodular and cavitary images were observed together with bilateral minimal pleural effusion. Septic pulmonary embolism was suggested due to the coexistence of nodular images and supplying vessels. Thrombus was not detected in the branches of the main pulmonary artery and subpulmonary branches. Electrocardiography findings were interpreted as normal. Echocardiography was performed for differential diagnosis of infective endocarditis and vegetation was not detected. Almost complete subacute thrombus was observed in bilateral lower extremity veins on control Doppler ultrasonography.

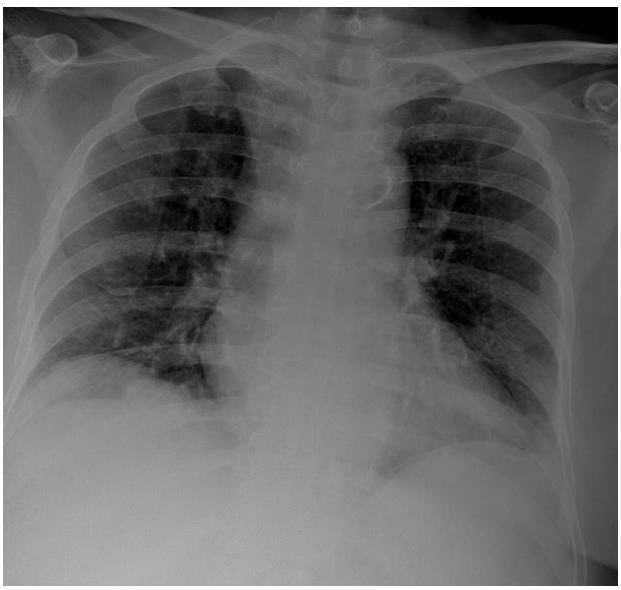

Figure 1. Septic pulmonary embolism. Fields showing wedge style density increase are observed.

Based on these findings, meropenem 1 g tid + vancomycin 500 mg qid treatment was started. Enoxaparin dose was gradually increased to 0.4 cc bid for prevention of a potential haemorrhage. Patient's fever reached 40°C once daily and continued for four days despite this treatment. So vancomycin treatment was discontinued and linezolid 600 mg bid was added to the treatment. Blood cultures were obtained every day regularly. *Candida ciferri* grew on her blood, and urinary cultures obtained on the fourth day following embolism. Isolates were identificated by VİTEK 2 automated system. Isolates were then tested for drug sensitivity by determining minimal inhibitory concentrations (MIC) of fluconazole with macrobroth dilution technique by VİTEK 2. After that the blood cultures were obtained every other day.

Anidulafungin treatment (200 mg daily loading dose and 100 mg daily maintenance dose) was added. Central venous catheter was removed. Urinary catheter was changed. *Candida ciferri* grew also on her blood culture obtained on the sixth day following pulmonary embolism in the patient who had persistent fever of 39°C every day. Susceptibility to fluconazole was observed as the result of antifungal susceptibility testing. Her fundus examination revealed normal findings. Embolism-related pathology was not detected in another organ. Her fever regressed on day 7 of antifungal treatment. Her general condition improved. Meropenem and linezolid treatment discontinued.

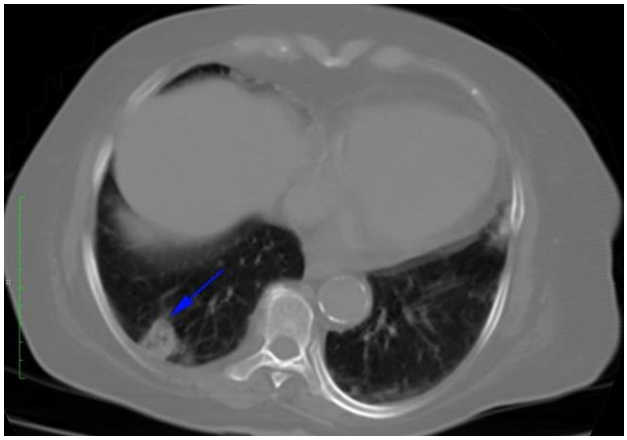

Figure 2a. Septic pulmonary embolism image at thorax CT on admission.

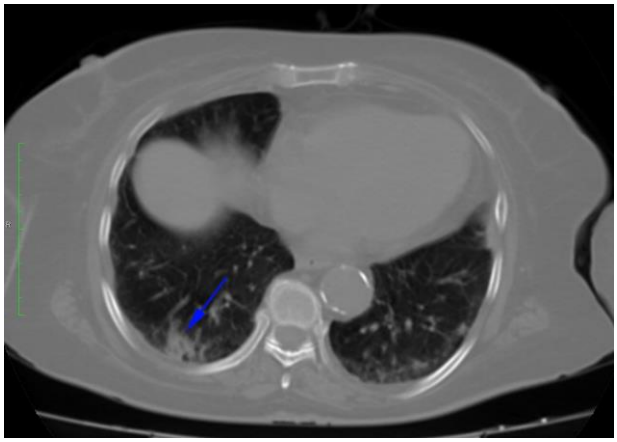

Figure 2b. Regression is observed in the wedge-shaped consolidation area on thorax tomography obtained with two weeks of intervals.

Clinical and laboratory findings improved. Near-complete improvement was observed on chest x-ray and computed tomography of the thorax obtained with 15 days of intervals (Figure 3). Although fluconazole suspectibility was determined, the intravenous anidulafungin treatment applied for four weeks due to delayed improvement and persistant fever. After that, her treatment was discharged with 400 mg fluconazole according to antifungal susceptibility test which was performed and determined sensitive by VİTEK-2 and she used it for two weeks. She was recommended to continue enaxaparin treatment for six months. She was invited for periodic monitoring. Radiological findings were observed to completely resolve on thorax tomography obtained two months later. Detection of widespread pulmonary nodules in both lungs, the coexistence of these nodules with feeding vessels, detection of deep venous thrombus in the lower extremities, *Candida ciferri* growing twice in blood culture and once in a urine culture, responding to antifungal treatment verified the diagnosis of invasive candidiasis-related septic pulmonary embolism.

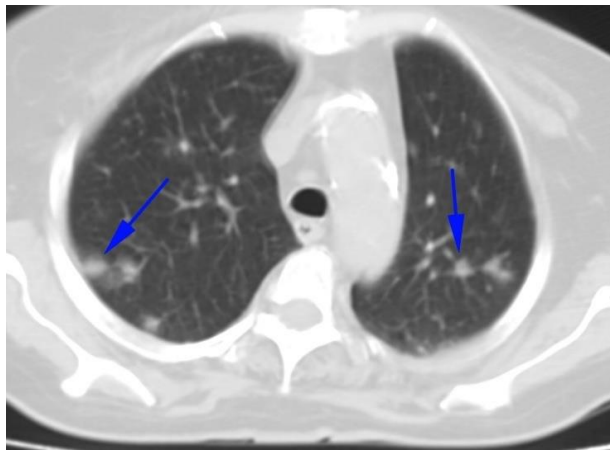

Figure 3a. Multiple septic pulmonary embolism image at thorax CT on admission.

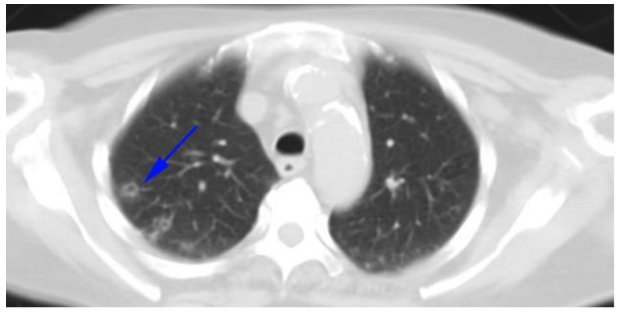

Figure 3b. Improvement in the infiltrations in the left upper lobe together with the regression in nodular infiltration fields on thorax tomography obtained with two weeks of intervals.

Discussion

SPE is an uncommon disorder that generally presents with an insidious onset of fever, respiratory symptoms and lung infiltrates. Clinical and radiologic features at presentation are usually nonspecific, and the diagnosis of this disorder is frequently delayed (1-5).

The most common causes for SPE include intravenous drug use, infective endocarditis of the tricuspid valve, septic thrombophlebitis, suppurative angina, periodontal abscess, purulent infection of skin

and soft tissues, pelvic thrombophlebitis, intravascular catheters, pacemakers, liver abscess and hemodialysis (2).

In SPE, the embolic blood clot that leads to an infarction in the pulmonary vasculature also contains microorganisms that incite a focal abscess. Chest radiography may reveal poorly marginated peripheral lung nodules that cause a tendency to cavitate but are more often nonspecific in appearance. CT of the thorax can be more helpful in demonstrating peripheral cavitary lesions (2).

Many risk factors have been discovered in the pathogenesis of fungal infections. Being aware of the risk factors and being careful in risky patients is important for the clinicians in the diagnosis of fungal invasion. These risk factors include disease severity (being on a ventilator for longer than 48 hours), wide spectrum antibiotic use, presence of an intravenous catheter, malnutrition, immunosupression and burns (4, 5). Our patient was in high risk groups as she underwent an operation due to intracerebral hematoma, having diabetes, being followed up in intensive care units, using wide spectrum antibiotics.

Candidal identification is required phenotypical and genotypical tests. Samples which were collected from clinical specimens, identified by using physiological and morphological tests, including some of the following: morphology on a cornmeal agar, assimilation of sugars in commercial kits, fermentation of several carbon sources, growth on nitrogen sources, growth at various temperatures, and ability to hydrolyze urea. Now these phenotypical and morphological determinations can be offered by automated systems. For molecular identification, genomic DNA was made right away from a single yeast colony (7).

In a serial composed of 17 SPE cases published by Carriago et al (8), fever was the most common symptom (88%) followed by chest pain and cough. Fever was in the foreground also in our patient. Okada et al. (9) has been reported a case report related to septic pulmonary emboli caused by urinary tract infection.

In a study of Sakuma et al. (10) from Japan, they stated that the fungal embolism incidence is higher than bacterial agents in case of presence of an underlying risk factor. Our patient had the risk factors like presence of diabetes, intensive care unit stay, antibiotic use.

Takahasi et al. (11) reported an SPE case caused by *C. albicans* in a patient who was immunocompromised due to continuing bladder cancer.

Diagnosis may frequently hold up due to nonspecific clinical and radiological features. SPE should be suspected in high-risk patients with a history of intravenous drug use or underlying disease, if they have fever, dyspnea, chest pain and other clinical manifestations and their lung images suggest multiple nodules or plaques with or without pleural effusion. Enhanced chest CT examination should be done to identify the emboli and blood culture, liver ultrasound, echocardiography and other tests should be performed to find the origin of the emboli (12).

The prediagnosis of septic pulmonary embolism should be restrained in mind in patients who have fever, bilateral peripheral infiltrates on chest x-ray, whose clinical condition gradually deteriorates, differential diagnoses should be omitted and the principal focus should be investigated.

The primary treatment is antimicrobial chemotherapy and removal of the infected source. In our patient, CT revealed specific findings such as multiple nodular lesions, feeding-vessel sign, cavitation of nodules, and pleural effusion. *Candida* superinfection of the thrombus can occur, especially in patients on long-term antibiotic therapy and on parenteral nutrition. Removal of the catheter, thrombolytic therapy, anticoagulation, and antifungal therapy will usually eradicate the candidemia and restore venous patency (13).

Candida ciferrii is a newer strain of Candida, which has been seldom described as a case of human infection. All the same, in immunocompromised host it can cause human infection (5).

In conclusion; although the pathogens of SPE may differ depending on the primary focus of the infection, early diagnosis and prompt antimicrobial therapy with radiologic or surgical intervention can lead to a successful treatment outcome.

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