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Is Pulmonary Aspergillosis Common in Diabetes Mellitus Patients?

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ABSTRACT

Aspergillosis is a rapidly progressive, often fatal infection that occurs in severely immunosuppressed patients, including those who are profoundly neutropenic, recipients of bone marrow or solid organ transplants and patients with leukemia, lymphoma, advanced AIDS or phagocytic disorders such as chronic granulomatous disease. Patients with severe liver disease are at a higher risk for infections. Immunocompetent individuals rarely develop this infection and do so only in the presence of pulmonary and systemic abnormalities such as fibrotic lung disease, suppurative infection or when they are on corticosteroids.

We present 2 cases of pulmonary aspergillosis in diabetic patients. They presented with cough and dyspnea. Aspergillus was found in obtained respiratory samples. Pulmonary aspergillosis was confirmed in our first case by transbronchial lung biopsy (TBLB) and Galactomannan assay. In the second case, diagnosis of pulmonary aspergillosis was established by thoracic CT guided biopsy plus Galactomannan assay.

These patients had none of the suggested risk factors for Aspergillus infection but they had uncontrolled diabetes mellitus. This report highlights that pulmonary aspergillosis can occur in individuals with diabetes mellitus even in the absence of other risk factors such as corticosteroid use, severe granulocytopenia or other associated immunosuppressive factors.

It is; therefore, valuable to recognize that in patients with diabetes mellitus pulmonary aspergillosis should be considered as an important differential diagnosis for respiratory problems. ***(Tanaffos2010; 9(3): 69-74)***

Key words: *Aspergillosis, Diabetes mellitus, Pulmonary aspergillosis*

INTRODUCTION

Aspergillus species are ubiquitous molds found in organic matter and only intense exposures (e.g., during construction work, handling of moldy bark or hay, or composting) can cause disease in healthy immunocompetent individuals (1-3).

Aspergillus may cause a broad spectrum of diseases in a human host, ranging from hypersensitivity reactions to direct angioinvasion. Aspergillus primarily affects the lungs, causing four main syndromes, including allergic broncho-

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pulmonary aspergillosis (ABPA), chronic necrotizing aspergillus pneumonia (or chronic necrotizing pulmonary aspergillosis [CNPA]), aspergilloma, and invasive aspergillosis. However, in patients who are severely immunocompromised, aspergillus may hematogenously disseminate beyond the lung, potentially causing endophthalmitis, endocarditis, and abscesses in the brain, myocardium, kidneys, liver, spleen, soft tissues, and bones (2).

Invasive aspergillosis typically develops in patients with compromised immune status and is rarely found in immunocompetent individuals.The most common type of immune system problem that causes this infection is a very low white blood cell count over a long period. People who use glucocorticoids or have had chemotherapy or a bone marrow transplant sometimes have this type of problem. Many patients have some evidence of prior pulmonary disease typically a history of pneumonia or chronic obstructive pulmonary disease (3).

More than 80% of cases of invasive aspergillosis involve the lungs.The most common clinical features are no symptom, fever, cough, chest discomfort, trivial hemoptysis, and shortness of breath.The keys to early diagnosis in at-risk patients are a high index of suspicion, screening for circulating antigen, and urgent CT of the thorax (3).

We present two diabetic cases with pulmonary aspergillosis with no other important risk factor for pulmonary aspergillosis.

Case 1:

A 46 year-old woman was transferred to the hospital because of chronic productive cough and dyspnea. She had experienced exertional dyspnea with productive cough since one-month ago .Her past medical history included a poorly-controlled diabetes mellitus since 16 years ago and hypertension for 15 years. She was living with her husband and 2 children who were healthy. Her drug history included atenolol and metformin .On clinical examination, there was generalize wheezing and coarse crackles in the lungs. Other findings were normal. Her blood pressure was 145/95 mm Hg, temperature: 36.9ºC, pulse rate: 82 beats/min., and respiratory rate was 13/min.

All laboratory findings including levels of serum electrolytes, complete blood cell count, coagulation tests and renal as well as liver function tests were normal except for elevated ESR (126 mm/ 1st h) and fasting blood sugar: 229 mg/dl. Sputum for acid fast bacilli (AFB), bacteriology and PPD test were also performed which were all negative. Chest x-ray showed cavitary formation in the right upper lobe (RUL). Spiral CT-scan of thorax with intravenous contrast revealed large cavitation in anterior segment of right upper lobe(RUL) (Fig.1). Galactomannan level in serum was: 1.7 (highly positive).

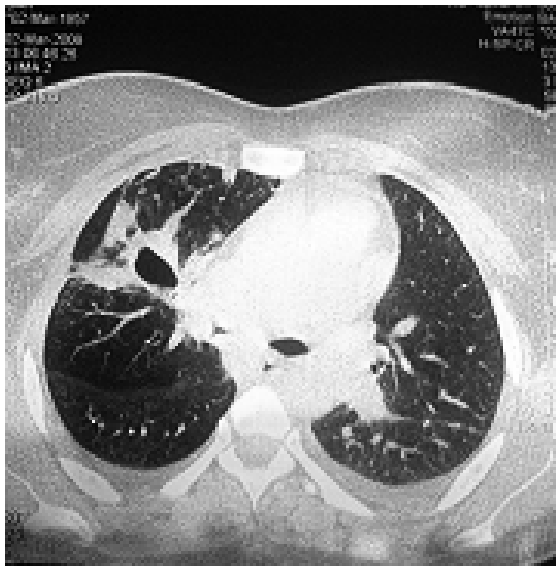

Figure 1. Computerized tomography scan of thorax with intravenous contrast shows large cavitation in anterior segment of RUL.

Bronchoscopy detected whitish membranous mass in the orifice of right upper lobe and the specimen obtained by transbronchial lung biopsy (TBLB) revealed chronic nonspecific inflammation

associated with presence of fungal hyphae suggestive of Aspergillus (Figure 2 A,B).

Treatment with Itraconazole was started. The patient was on medication without any complication. One month later, she expectorated gum like mass by a cough attack which in pathologic examination revealed to be degenerated Aspergillus hyphae with some bronchial cartilage fragments (Figure 3).

CT-scan of thorax with intravenous contrast after treatment showed no abnormality (Figure 4).

Abdominal sonography and brain CT scan were normal.

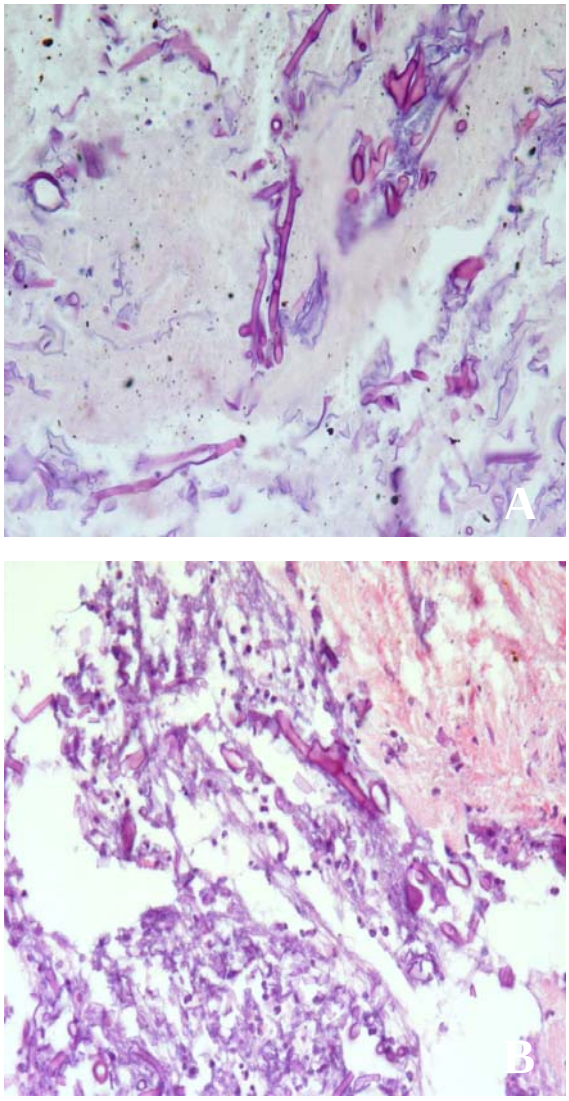

Figure 2 (A,B).Transbronchial lung biopsy (TBLB) shows fungal hyphae of Aspergillus

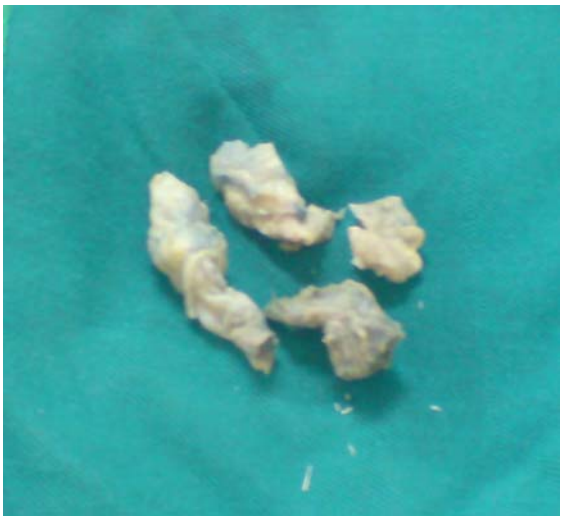

Figure 3. This figure shows gum like mass expectorated from this patient

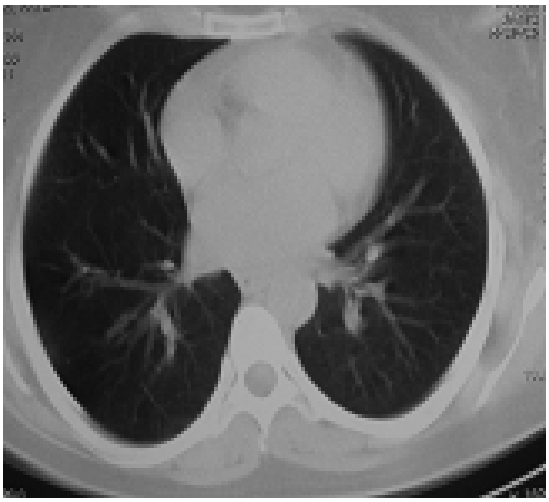

Figure 4. After treatment, CT scan of thorax with intravenous contrast shows no abnormality.

Case 2:

A 46-year-old man was evaluated because of dyspnea and dry cough with intermittent fever since one month ago. Recently, his symptoms exacerbated with night sweats and weight loss of about 8kg and exertional dyspnea during the last 2 weeks. He was a driver, smoker (20 pack/year) and was living with his wife and 3 children who were healthy. He had poorly-controlled diabetes mellitus since 4 years ago.

He was consuming glibenclamide .On clinical examination coarse crackles were detected in both lungs. Other findings were normal .He was normotensive, his temperature was 38º C, pulse rate: 92 beats/min., and respiratory rate: 23/min.

Laboratory tests were all normal except for elevated ESR (66 mm/1sth), white blood cells:18,700/mm^3, Neut.:88% and blood sugar :380 mg/dl. Sputum for acid fast bacilli (AFB), bacteriology and PPD test were performed which were all negative. Diffuse bilateral parenchymal nodules with cavitation in upper lobe nodules were detected on chest x- ray and CT-scan of thorax with contrast (Figure 5).

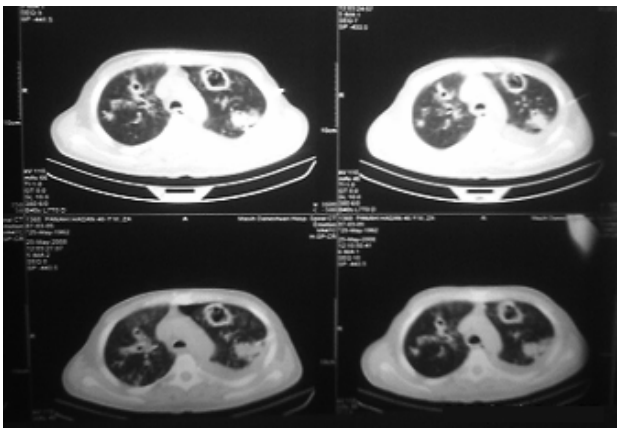

Figure 5. CT-scan of thorax with contrast shows diffuse bilateral parenchymal nodules with cavitation in upper lobe nodules.

Galactomannan level in serum was 1.8 (highly positive). CT-guided biopsy from cavitary mass showed chronic inflammation associated with the presence of fungal hyphae suggestive of aspergillus. CT-scan of paranasal sinuses showed nasal septal mucosa irregularity with suspicious bone lesion. CT-scan of the brain was normal.

DISCUSSION

Aspergillosis is a rapidly progressive, often fatal infection that occurs in patients who are severely immunosuppressed, including those who are profoundly neutropenic, recipients of bone marrow or solid organ transplants and patients with advanced AIDS or phagocytic disorders such as chronic granulomatous disease. Patients with severe liver disease are at a higher risk for infections. Immunocompetent individuals rarely develop this infection and do so only in the presence of pulmonary and systemic abnormalities such as fibrotic lung disease, suppurative infection or when they are on corticosteroids (2,4,5).

Our patients had none of the suggested risk factors for aspergillus infection but they had uncontrolled diabetes mellitus.

The diagnosis of invasive pulmonary aspergillosis is often difficult. Sputum cultures may be negative. In most cases, the diagnosis is made following tissue isolation of a single species in an appropriate clinical setting. Histological evidence requires invasive methods to obtain diagnostic samples. Common diagnostic procedures include CT-guided percutaneous needle aspiration, which can be both sensitive and specific for diagnostic evaluation. Bronchoscopy or bronchoalveolar lavage with washing is safe and sensitive and particularly useful in high-risk patients. Transbronchial biopsy via fiberoptic bronchoscopy has moderate sensitivity but is highly specific. Lung biopsy with video-assistance or thoracotomy is useful in providing samples large enough to provide tissue diagnosis (1,6-8).

In this study, histological evidences were obtained by CT- guided percutaneous needle aspiration and transbronchial biopsy. However, a negative fungus result from culture of sputum or BAL fluid does not exclude pulmonary aspergillosis because Aspergillus is cultured from sputum in 8-34% of patients and from BAL fluid in 45-62% of patients. The remaining cases are eventually found by biopsy or autopsy to have invasive disease.

An assay is available to detect Galactomannan, a major component of the Aspergillus cell wall (9,10).

The presence of an elevated Galactomannan level in BAL fluid may also be helpful in the diagnosis of pulmonary aspergillosis in patients in whom compatible radiographic changes are present and BAL testing is performed in the suspicious area (7). The patients in this study had elevated Galactomannan level in their serum samples.

In invasive aspergillosis, chest radiographic features are variable, with solitary or multiple nodules, cavitary lesions, or alveolar infiltrates that are localized or bilateral and become more diffuse as disease progresses. CT-scan images may be very helpful in the early diagnosis of aspergillosis because they may demonstrate a characteristic halo sign (i.e., an area of ground-glass infiltrate surrounding nodular densities)(11). Later, disease may show a crescent of air surrounding nodules, indicative of cavitation. Because Aspergillus is angioinvasive, infiltrates may be wedge-shaped, pleural-based, and cavitary, which is consistent with pulmonary infarction (12). Pulmonary aspergillosis in above patients was diagnosed based on lung CT-scan findings, elevated Galactomannan level and tissue samples.

The specificity of the morphologic identification of Aspergillus in tissue was based on the regular hyphae with dichotomous branching at 45° angles and distinct cross-septa .Histopathology and silver staining for patients with invasive aspergillosis demonstrate the characteristic septate hyphae, branching at acute angles, and acute inflammatory infiltrate and tissue necrosis with occasional granulomas and blood vessel invasion (2).

When high-risk patients develop a compatible clinical picture, empirical treatment for aspergillosis should be initiated as diagnostic testing is undertaken. Voriconazole is usually the first-line therapy, sometimes in combination with other agents such as caspofungin. Amphotericin may sometimes be used in cases with treatment failures. Oral Voriconazole or Itraconazole (sometimes chosen because of cost) is administered until clinical and radiographic resolution (13- 16).

Outcome is better if patients have well-controlled underlying disease. Surgical resection is a consideration for a localized disease that has failed to respond to anti-fungal therapy (17- 19).

This report highlights that pulmonary aspergillosis can occur in individuals with DM even in the absence of other risk factors such as corticosteroid therapy, severe granulocytopenia and other known predisposing factors.

It is therefore valuable to recognize that, in patients with diabetes mellitus, pulmonary aspergillosis should be considered as an important differential diagnosis for respiratory problems.

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