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AN UNUSUAL PATHWAY IN DIAGNOSIS OF IMMUNE DISORDER THROUGH INVASIVE PULMONARY ASPERGILLOSIS WITH HEMOPTYSIS: CASE PRESENTATION

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ABSTRACT

Invasive pulmonary aspergillosis is a fungal infections caused by aspergillus fumigates that transmitted through inhalation of air conidia in most cases.

Since these conidia will removed by phagocytes, they cause rarely any diseases in people who are not immunocompromised; therefore normal and also sufficient function of macrophages and neutrophyles are necessary to prevent aspergillosis. On the other hand immunocompromised patients like CGD (Chronic Granulomatous Disease) can easily involved in such fungal infections through exposure to high amounts of these conidia.

In this article we will introduce a girl with interesting history of BCGitis, after awhile presented by hemptysis discovered as a begin sign of invasive pulmonary aspergillosis. Finally out evaluations showed immune disorder in this neglected child.

Regarding high mortality of invasive aspergillosis as 30-50% ; effective management is achieved by on time suspicion to fungal infection associated by finding risky hosts and also early initiation of antifungals for reduction of invasive aspergillosis .

CASE PRESENTATION

Our patient was a 10 years old girl living in rural area of Khorasan (at the east of Iran) who was referred to our lung ward in Dr.Sheikh hospital in Mashhad in November 2014 with massive hemoptysis suspected to lung tumors especially due to huge mass in her thorax CT scan. She has had cough and hemoptysis from 20 days before our first visit. She has not had some symptoms like fever, headache, rhinorea and flu like ones. In past medical history she had notable points. First she had some erythematous exfoliating lesions on extensors regions of her limbs at age of 2 that they are recovered now. Pathologic investigations at that time showed atopic and exematous disorders. Secondly she had a history of several lymphadenitis in neck in infancy and childhood several years ago as a result of BCG vaccine during routine Iranian vaccination which they were fistulated spontaneously without any treatment and their scar are seen in right lateral of her neck just now. Her last episode of lymphadenitis was related to September 2014 that one large lymphadenopathy like a mass was found in right axillary region. Through different assessment her PPD test (purified tuberculin test) was negative in addition to a positive acid-fast smear for tuberculosis .It is necessary to say that although the most important factor for diagnosis of tuberculosis in children is close contact, her family history for tuberculosis was negative and her chest imaging was normal at that time. Therefore with a suspicion to BCG lymphadenitis the large node was resected .Finally tuber colisis was reported via pathologic assessment of lymph node. After excision of lymph node standard treatment for tuberculosis including isoniazide, rifampin, ethambotol and streptomycin were started for 2 months and has been continuing by isoniazid and rifampin for 4 months. Unfortunately she suffered from hemoptysis under 2drugs treatment after 2 months which had not responded to outpatient treatment. While she was referred to us in physical exam she looks pale and hepatomegaly was revealed .Laboratory evaluations results showed normal liver and kidney function test, anemia (hemoglobin:7.6 gr/dl)with normal ranges for the other items in cell blood count, high erythrocyte sediment rate (ESR : 60) and high C- reactive protein (CRP : 3+). It was notable that a huge mass in chest CT scan was found (see figure 1); so in order to roll out of malignancies she was undergone fibropic bronchoscopy and also whole body scan (see figure2). It was notable that pathological evaluation of biopsy via bronchoscopy showed aspergilosis surprisingly.

Pathologist described acute , granulomatouse and suprative infiltration .Fungal hyphee was seen in **Periodic acid–Schiff** (**PAS**) staining method.

Regarding to her unusual history we decided to evaluate her immune system. The level of serum immunoglobins were normal unless a high level of IgE .

Our assessment demonstrated that although NBT test (**Nitro blue tetrazolium**) was normal for 2 times, through Dihydrorhodamine (DHR) flow cytometry test Chronic Granulomatous Disease (CGD) was approved. In fact this poor girl was a kind of immunocompromised patient with a history of BCG adenitis who was susceptible for opportunistic fungal infections Acute invasive pulmonary aspergillosis.

INTRODUCTION

Invasive pulmonary aspergillosis is a fungal infections caused by aspergillus fumigates that transmitted through inhalation of air conidia in most cases.

The disease in humans is caused mainly by Aspergillus fumigatus, Aspergillus flavus and Aspergillus niger. Other species, for example, Aspergillus terreus or Aspergillus nidulans are quantitatively less prevalent (1).

Since these conidia will removed by phagocytes, they cause rarely any diseases in people who are not immunocompromised; therefore normal and also sufficient function of macrophages and neutrophyles are necessary to prevent aspergillosis. On the other hand immunocompromised patients like CGD (Chronic Granulomatous Disease) can easily involved in such fungal infections through exposure to high amounts of these conidia.

Filamentous fungi (moulds) are ubiquitous soil inhabitants whose conidia are inhaled into the respiratory tract, where they may cause life-threatening infections. Among these infections is invasive aspergillosis, which is a major cause of morbidity and mortality in the severely immunocompromised (2). Mortality from invasive aspergillosis has increased by several-fold in the 1980s and 1990s in the U.S (3).

There is also a growing appreciation of invasive aspergillosis in persons with less severe levels of immunocompromise. For example, chronic necrotizing pulmonary aspergillosis (CNPA) generally occurs in with patients pre-existing structural lung diseases such as prior tuberculosis or lung abscess or modest immune impairment, such as occurs with diabetes, poor nutrition, chronic obstructive pulmonary disease, or low-dose corticosteroids. Fungal disease is slowly progressive over months to years, and may require life-long therapy (3).

Invasive aspergillosis has also been diagnosed in normal hosts after massive exposure to fungal spores. Chronic pulmonary aspergillosis affects patients without obvious immune compromise, but

with an underlying lung condition such as COPD or sarcoidosis, prior or concurrent TB or non-tuberculous mycobacterial disease (3).

As it was mentioned previously our patient had hemoptysis from 20 days before our first visit. Hemoptysis is the expectoration of blood originating from the lower respiratory tract. It is a common alarming symptom accounting for 10 to 15% of all pulmonary visits.
In less than 5% of the cases, hemoptysis may be a life-threatening event with a mortality rate reaching 50 to 80% in the absence of adequate and early management that may reduce substantially the mortality below 20%.

More than 100 causes of hemoptysis have been described including infections, malignancies, inflammatory diseases. Among infections fungal ones are challenging. *Mycetoma* (fungal ball) is defined as a conglomerate of fungal mycelia, inflammatory cells, fibrin, mucus and tissue debris usually developing in a preformed lung cavity. *Aspergillus* spp is by far the most common etiologic agent; although tuberculosis is the main cause of cavitary lesions. This mass is separated from the wall of the cavity by airspace of variable size, which is often in the shape of a crescent. Therefore, the diagnosis should be confirmed by the sputum examination that may reveal *Aspergillus* spp in half of the cases and the serum IgG antibodies to *Aspergillus* spp, which are positive in approximately 90% of the cases. Hemoptysis is the cause of death in up to 26% of patients with mycetoma. Minor hemoptysis has been usually reported in up to 60% of patients with invasive pulmonary aspergillosis. The risk of fatal hemoptysis is particularly high during the phase of marrow recovering (4).

Acute invasive pulmonary aspergillosis is a pulmonary disease occurs in 80-90% of patients with invasive aspergillosis. Fever, dyspnea, nonproductive cough, mild hemoptysis, and pleuritic chest pain are the cardinal clinical manifestations of invasive pulmonary aspergillosis. Severely immunocompromised patients may have no initial symptoms but diagnosis warrants a high index of suspicion. (5). Since our patient has not had absolute or definite manifestications of immunocompromission.

Chronic invasive pulmonary aspergillosis usually occurs in patients with underlying diseases (eg. advanced AIDS, chronic granulomatous disease, sarcoidosis, and diabetes mellitus). Patients usually complain of chronic nonproductive cough, often with hemoptysis. Low-grade fever, weight loss, and malaise are also common (5).

There are also some variable organ involvements by Invasive aspergillosis like: Tracheobronchitis, sinusitis, involvement of the skin, endophthalmitis and cerebral involvement. Cerebral involvement

almost always occurs in patients who are severely immunocompromised usually present with altered mentation and seizures; prognosis is dismal (5).

Some type of noninvasive aspergillosis are also described like ABPA. Patients with allergic bronchopulmonary aspergillosis (ABPA) often have histories of worsening respiratory symptoms in association with asthma or cystic fibrosis (CF). ABPA occurs in approximately 11% of patients with CF, the main complaints of these patients are wheezing and cough. As the disease progresses, patients may expectorate mucous plugs containing eosinophils, and they may develop bronchiectasis.

Exacerbation and remission characterize the natural history of disease. Progression to respiratory failure may occur occasionally because of irreversible airway obstruction and pulmonary fibrosis. It may mimic pneumonia with mucopurulent bloody sputum, fever, and respiratory distress. Predominant wheezing may be the only manifestation suggesting an exacerbation of bronchial asthma. Aspergillomas may remain asymptomatic until hemoptysis occurs (5).

In addition to previous issues aspergilloma is usually found in patients with previously formed cavities in the lung, whereas allergic bronchopulmonary aspergillosis, a hypersensitivity reaction to Aspergillus antigens, is generally seen in patients with atopy, asthma or cystic fibrosis (6).

DIAGNOSIS

Diagnosis of invasive aspergillosis is difficult.

Certain invasive aspergillosis is approved by existence of invasive hyphae histologically or a positive culture from a normally sterile environment (e.g., pleural fluid); Whil probable invasive aspergillosis requires a combination of host factors that predispose to invasive aspergillosis (e.g., prolonged neutropenia, transplantation) and clinical (e.g., evidence of pneumonia) and mycological criteria. It is notable that in neutropenic patients, persistent fever may be the only sign of invasive fungal disease (4). A high index of suspicion is required in patients without the classical risk factors as early presentation is usually silent and non-specific, pyrexia uncommon and timely treatment is crucial for survival (7).

As it seems in figure1our patient had some abnormalities in her chest imaging. A chest CT scan is more sensitive than radiographs for detection of early pulmonary aspergillosis. The earliest radiological sign of invasive aspergillosis is a nodule. A halo sign defined as a macronodule surrounded by a perimeter of ground-glass opacity corresponding to alveolar hemorrhage, is suggestive of invasive aspergillosis in patients with compatible host factors and initiation of

treatment based on this sign has been associated with a better response compared to when therapy was initiated for more advanced fungal disease. However it is not pathogonomic for aspergillosis. Other radiographic findings associated with invasive aspergillosis are consolidation, wedge-shaped infarcts, and cavitation. In contrast to adults, children with invasive pulmonary aspergillosis frequently do not manifest cavitation or the air crescent or halo signs (4).

Mycological criteria require either isolation of *Aspergillus* species from the sinopulmonary tract or positive antigen-based laboratory markers. Bronchoalveolar lavage fluid (BALF) cultures have at best 50% sensitivity in focal pulmonary lesions (4).

Galactomannan detection and radiological diagnostic images complement the limitations of microbiology cultures in patients (8).

There are causes of false-positive results, including concomitant piperacillin/tazolbactam, other beta-lactam antibiotics, and gluconate-containing intravenous fluids. Cross-reactivity with other fungi (e.g., *Histoplasma capsulatum*) with similar cell wall galactomannan to *Aspergillus* can cause positive results (3).

Galactomannan detection in BALF appears to be more sensitive than serum detection, and can be used to support a diagnosis of probable aspergillosis. As an alternative to bronchoscopy, percutaneous lung biopsy may be attempted for peripheral nodules. Thoracoscopic lung biopsy should be considered in a deteriorating patient when less invasive procedures produce negative results (3).

In addition to serving as a diagnostic adjunct for invasive aspergillosis, a falling or rising serum galactomannan level may be useful as an early marker of therapeutic success or failure, respectively, in invasive aspergillosis (3).

PCR-based diagnosis of invasive fungal diseases, although promising, is currently investigational (3).

Multi-detector row helical CT (MDCT) angiography is essential for both the diagnosis and the treatment (4). Fiberoptic bronchoscopy (FOB) may be helpful for several reasons. The operational value of FOB in identifying the site of bleeding may range from 34 to 93% when performed early, as opposed to 11 to 50% when performed later. Conversely, the operational value is decreasing in massive hemoptysis (4).

TREATMENT

Major progress for the management of invasive aspergillosis has come from the introduction of new antifungals since the late 1990s (9).

Prophylaxis makes sense, since diagnosis and treatment of invasive aspergillosis remain difficult. The introduction of non-culture based tools for the diagnosis of invasive aspergillosis is an important step forward for early and sensitive diagnosis of invasive aspergillosis. Early treatment is the cornerstone of a successful management of invasive aspergillosis. Because mortality of invasive aspergillosis remains up to more than 50%, prophylaxis, early diagnosis and early initiation of antifungal therapy are of utmost importance for the reduction of invasive aspergillosis related mortality (10).

Voriconazole and liposomal amphotericin B are the gold standard in patients requiring therapy, and posaconazole, itraconazole, caspofungin and other echinocandins are effective alternatives (8) . Evidence based treatment of invasive aspergillosis has become safer and more effective within the last ten years through the introduction of the new azoles and the echinocandines (1).

Amphotericin B-desoxycholate is associated with definite side-effects in intravenous therapy. On the grounds of its substantial toxicity, the North American Infectious Disease Society's (IDSA) Guidelines of 2008 recommend amphotericin B-desoxycholate for regions with restricted resources only, which could be the case in underdeveloped countries (1).

Voriconazole was more effective than amphotericin B deoxycholate (AmB-D) as initial therapy for invasive aspergillosis and was associated with significantly improved survival (71% vs. 58%, respectively) in a randomized trial .The rate of successful outcomes was superior in voriconazole compared to AmB-D recipients (53% versus 32% respectively). The poorest prognosis occurred in extrapulmonary aspergillosis and in allogeneic HSCT recipients (3).

Voriconazole exhibits non-linear elimination in adults. It is estimated that increasing the oral dose of voriconazole from 200 mg Q12h to 300 mg Q12h leads to a 2.5-fold increase in exposure, and increasing the intravenous dose from 3 mg/kg Q12h to 4 mg/kg Q12h results in a 2.3-fold increase in exposure (package insert). In contrast, clearance of voriconazole in children is linear, necessitating higher dosing per kg of body weight in children to achieve comparable exposure as adults (3).

Therapeutic drug monitoring for voriconazole should be considered, particularly in cases of refractory fungal disease or drug toxicity. For patients with invasive aspergillosis refractory to

voriconazole or who are intolerant of voriconazole, a lipid formulation of amphotericin B or an echinocandin can be used. Lipid formulations are generally preferred over amphotericin B deoxycholate for invasive aspergillosis, because of less nephrotoxicity (3).

Caspofungin, micafungin and posaconazole have recently been under study. Both the echinocandines and posaconazole have proven effective in daily clinical practise. In refractory cases of invasive aspergillosis a combination therapy has been employed clinically (1).

Of the echinocandins, caspofungin is approved by the U.S. FDA as salvage therapy for invasive aspergillosis. Caspofungin monotherapy led to a successful outcome in 37 (45%) of 83 patients with invasive aspergillosis, 86% of whom had disease refractory to standard antifungal therapy (3).

There is significant interest in combination antifungal therapy pairing an echinocandin with either an azole or amphotericin B formulation as therapy for invasive aspergillosis (2).

Posaconazole is recommended for prophylaxis against aspergillosis in patients treated for acute myelogenous leukemia, myelodysplastic syndrome or patients with graft versus host disease after allogeneic transplantation.While oral voriconazole resportion is reduced when taken with food, posaconazole has to be taken with fatty food for optimal intestinal resorption (9).

On the other hand some accessory suggestion have been described recently like reduction or even discontinued of immunosuppressive therapy (e.g., corticosteroids),using adjunctive myeloid colony-stimulating factors (G-CSF or GM-CSF) in neutropenic patients with severe infections(such as aspergillosis) and adjunctive recombinant interferon-γ (3).

Although marrow recovery is critically important for host defense against aspergillosis, myeloid recovery may lead to the liquefaction of pulmonary foci and increase the risk of pulmonary hemorrhage and may increase pulmonary consolidation as part of an immune reconstitution syndrome in patients with invasive aspergillosis (3).

The role of host genetics in selecting patients that may benefit from more aggressive antifungal prophylaxis or treatment practices remains unclear but is likely to guide therapeutic choices as newer data become available (11).

DISCUSSION AND FUTURE PROGNOSIS

Since invasive pulmonary aspergillosis is a life threatening opportunistic infection especially in immunocompremised patients; it seems it is necessary to detect some children who are in risk to be involved in this fungal infection particularly in whom with a history of unusual or disseminated infections like BCGitis. As discussed in our case Chronic Granulomatous Disease (CGD) was diagnosed in a invert pathway after an invasive pulmonary aspergillosis. In fact if previous suspicion to immune disorder had been considered by medical team at the earliest stage of disease, it would be prevented from more morbidity and invasive process in a little girl.

Despite significant progress having been made in the treatment and diagnosis of invasive aspergillosis, it is still a devastating complication in children with immunocompression disorders. New antifungal therapies and strategies are promising, but objective data are still lacking (12).

Although mortality of invasive aspergillosis remains as high as 30-50%. Backbone of management are prophylaxis, early diagnosis and early initiation of antifungals for reduction of invasive aspergillosis related mortality (9).

Future progress will likely involve the development of more refined diagnostic tools, new classes of antifungal agents, and greater knowledge of pathogen and host factors that predispose to aspergillosis (13). Despite all advances in the management of invasive aspergillosis important questions remain unresolved (10).

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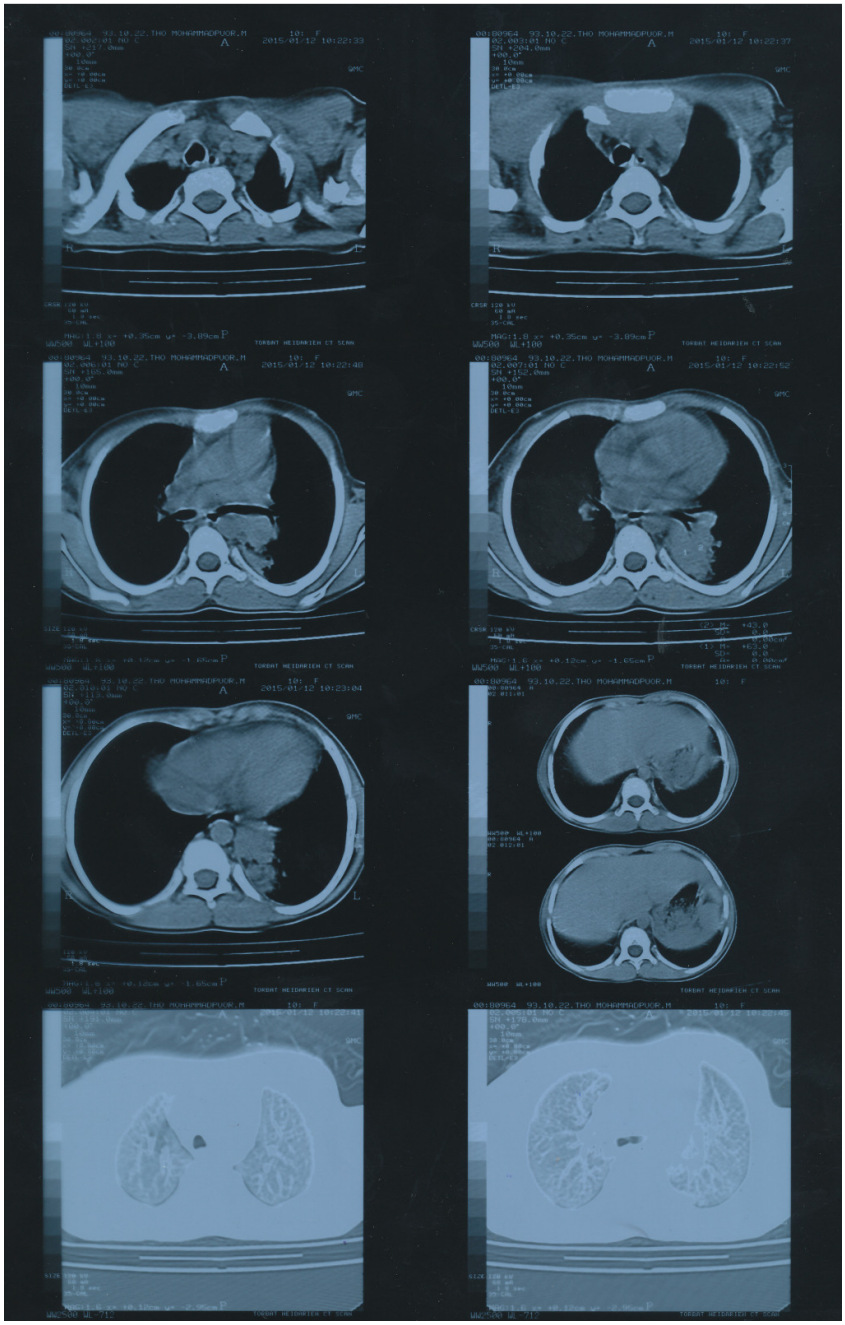

Figure 1: chest CT- scan

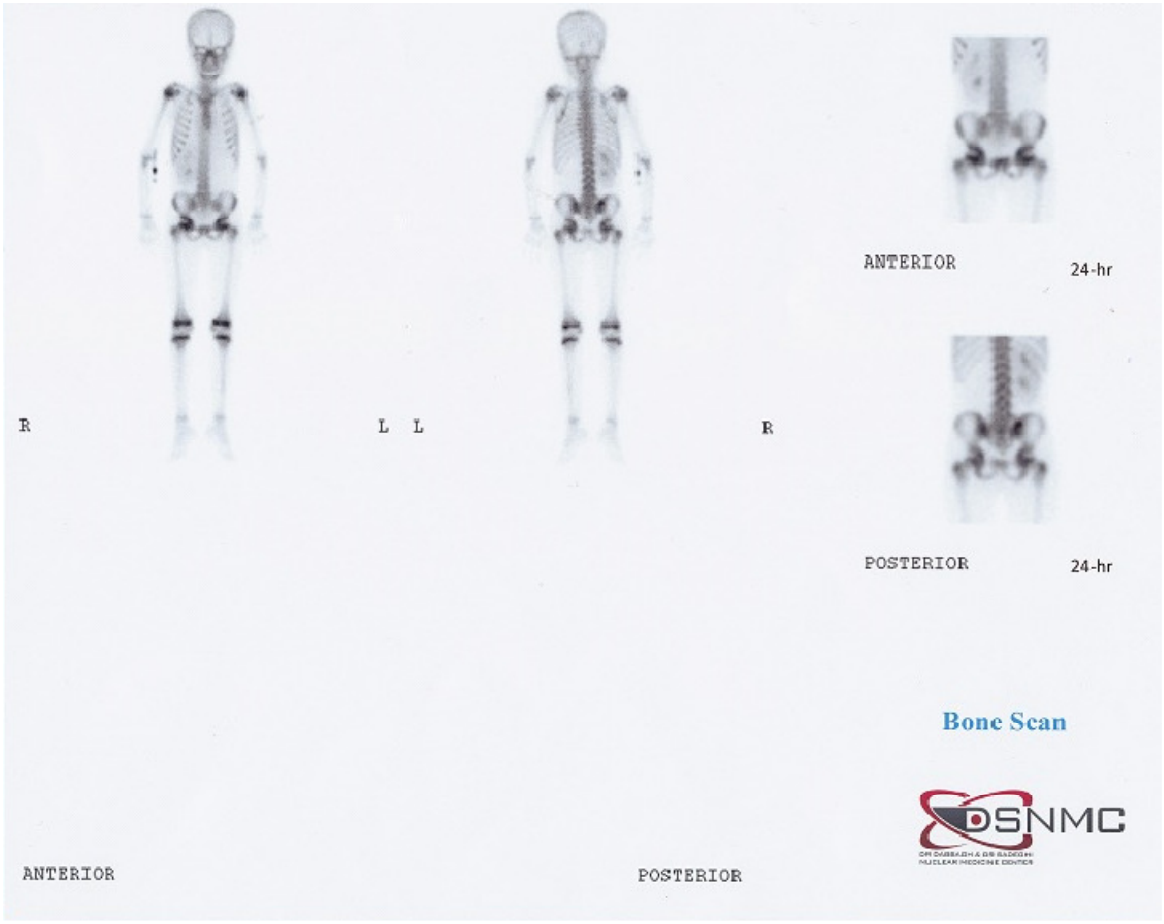

Figure 2: total body bone scan