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Radio-Biological Confrontation in the Diagnosis of Invasive Aspergillosis: About Two Cases and Review of Literature

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Abstract **Case Report**

Invasive pulmonary aspergillosis due to *Aspergillus fumigatus* is an often serious mycosis, usually occurring in severely immunocompromised patients. It is accompanied by a high mortality rate due to its often difficult and late diagnosis. Diagnosis is based on early chest computed tomography and mycological examination of respiratory samples. Both patients had presented with acute respiratory distress, developing in a context of fever and deterioration of the general condition despite the initiation of broad-spectrum empirical treatment. In each of them, a chest CT scan was performed, objectifying atypical cavitary images not suggesting pulmonary aspergillosis. Cytobacteriological examination of sputum and search for Mycobacterium tuberculosis were negative. Serology for aspergillus antigens and a sample of bronchoalveolar lavage fluid for a mycological study were requested. Direct examination of bronchoalveolar lavage fluid was negative, but culture allowed the identification of *Aspergillus fumigatus*. Galactomannan testing was positive. Given these results, treatment with injectable voriconazole was initiated in our two cases. The evolution was marked by a clinical improvement of one patient and the death of the other patient. Invasive pulmonary aspergillosis is a major concern due to the frequency of its complications. Its diagnosis must be early to ensure adequate management for a better prognosis.

Keywords: Invasive Aspergillosis, *Aspergillus Fumigates*, Pneumonia, Voriconazole.

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INTRODUCTION

Invasive pulmonary aspergillosis is defined by a more or less distal bronchial aspergillus involvement with invasion of the pulmonary and/or vascular parenchyma, causing a risk of visceral dissemination [1]. *Aspergillus fumigatus* is the most isolated species and is responsible for 80 to 90% of cases of invasive pulmonary aspergillosis. Other species such as *Aspergillus flavus*, found mainly in hot countries, as well as *Aspergillus nidulans*, *Aspergillus terreus* and *Aspergillus niger* are also causal agents of the invasive form. The existence of a possible association of two or more Aspergillus species in the same sample is possible [2]. Invasive aspergillosis is responsible for significant morbidity and mortality, particularly in certain immunodeficiency conditions such as profound neutropenia, malignant hemopathies, long-term corticosteroid therapy, as well as in patients with solid organ transplants, those hospitalized in intensive care and patients suffering from chronic respiratory diseases [3].

Early diagnosis of this pathology determines the response to treatment and the survival of patients. Here we report two cases of invasive aspergillosis with atypical imaging, in which *Aspergillus fumigatus* involvement was confirmed by mycological diagnosis.

OBSERVATION 1

67-year-old diabetic woman on insulin, followed for diffuse large B-cell lymphoma, who presented an episode of chemotherapy-induced aplasia (agranulocytosis for more than 10 days) and who was admitted to the emergency room for worsening dyspnea, associated with a productive cough with mucopurulent sputum and chest pain, all evolving in a context of fever.

Her haemogram showed neutropenia (PNN < 450/mm^3 for more than 10 days), with an inflammatory syndrome (CRP at 162). A chest CT scan was performed, showing the presence of diffuse and bilateral pulmonary nodules (figure 1). The bacteriological study of the

sputum was negative as was the search for *Mycobacterium tuberculosis*. The patient was put on broad-spectrum antibiotic therapy based on imipenem (500 mg x 3/day) and teicoplanin (300 mg/day).

Given the lack of improvement, a mycological examination of the bronchoalveolar lavage fluid was requested. A fresh preparation and staining with lactic blue were performed. The microscopic examination objectified the presence of mycelial filaments, hyaline, septate and presenting acute angle ramifications. The culture made on medium of Sabouraud Chloramphenicol and incubated at 35 ° C, objectified after 48 hours powdery colonies of blue green color at the beginning, then grayish with age with the reverse in yellowish brown (figure 2). Microscopic examination of the culture using lactophenol blue allowed the identification of uniseriate aspergillus heads in a column, the phialides were inserted directly on the vesicles. The conidia were globular and echinulate and the conidiophores were short, smooth and colorless (figure 3).

Given all these clinic-biological data, the diagnosis of invasive aspergillosis due to *Aspergillus fumigatus* was retained. Treatment with voriconazole (800 mg on day 1 then 400 mg/day) was initiated. The outcome was favorable, marked by an improvement of the patient.

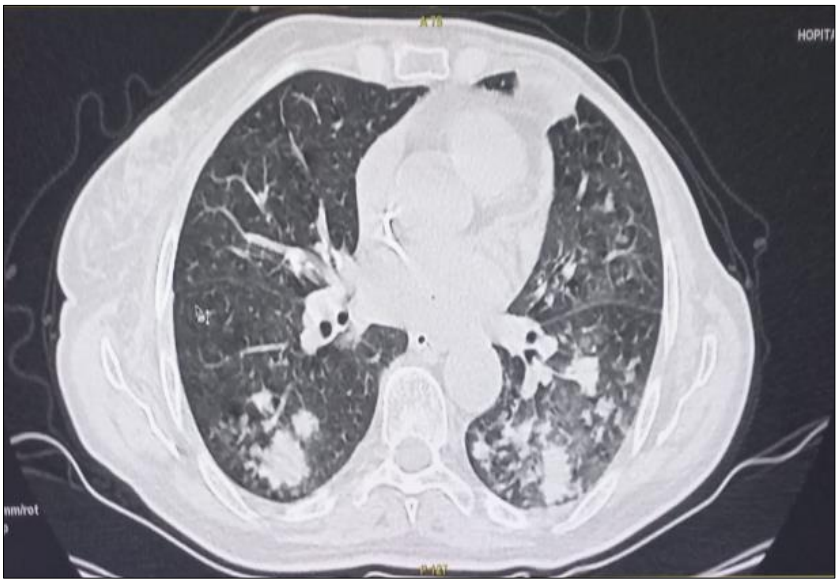

Figure 1: Cross-section of a chest CT scan showing pulmonary nodules

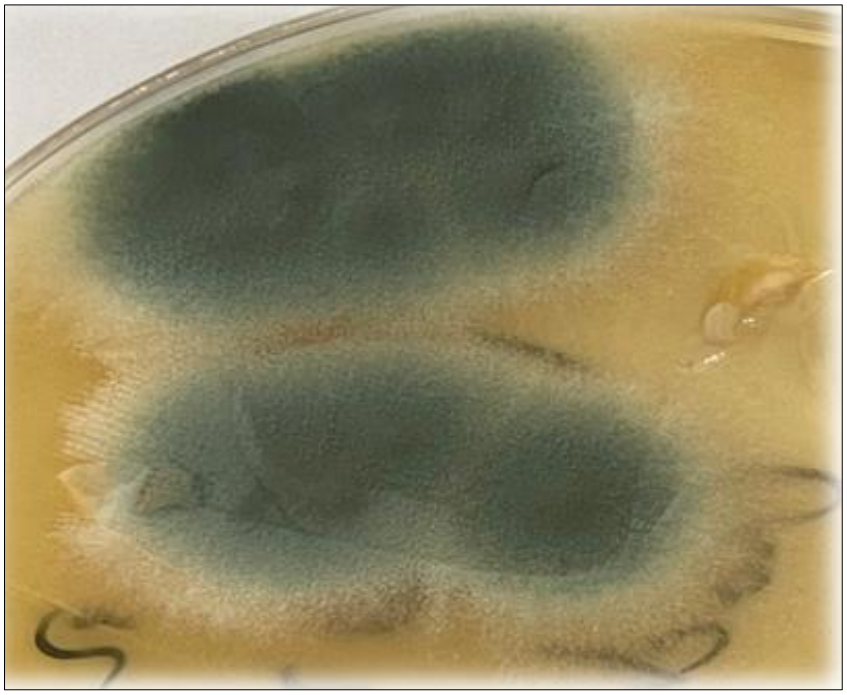

Figure 2: Macroscopic appearance of *Aspergillus fumigatus* colonies

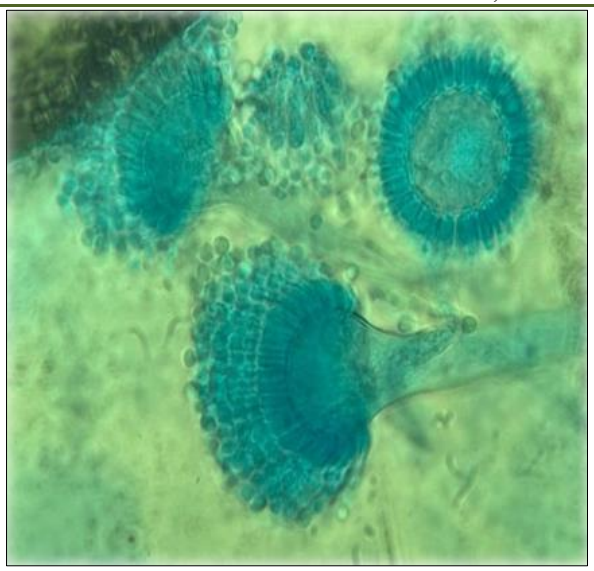

Figure 3: Microscopic appearance of an *Aspergillus fumigatus* colony

OBSERVATION 2

a 62-year-old patient, a smoker, being monitored for chronic obstructive pulmonary disease, who was admitted in the intensive care unit for acute respiratory distress syndrome with haemoptysis, all developing in a context of fever and deterioration of general condition despite the establishment of broad-spectrum empirical treatment.

A CT scan was performed, revealing an atypical cavitary image not suggestive of pulmonary aspergillosis (figure 4). The cytobacteriological examination of sputum and the search for Mycobacterium tuberculosis in the sputum were negative. At day 15, a serological sample for aspergillus Ag and a sample of the bronchoalveolar lavage fluid for a mycological study were requested. Direct examination by optical microscopy did not show the presence of spores, mycelial filaments or pneumocystis juroviceii cysts. The culture revealed colonies of *Aspergillus fumigatus* after 48 hours, and the search for galactomannans was positive. The evolution was unfavorable and the patient died following severe sepsis with respiratory distress despite the initiation of treatment including injectable voriconazole.

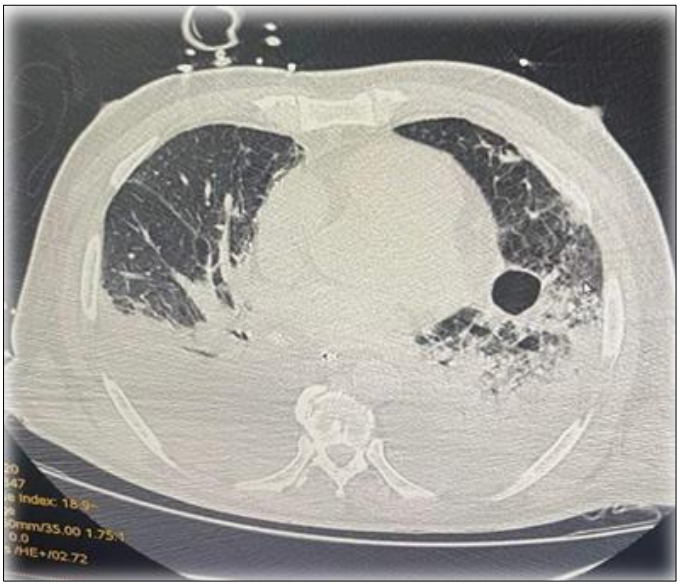

Figure 4: Cross-section of a chest CT scan showing an atypical cavitary image

DISCUSSION

Aspergillus species remain an important cause of life-threatening infection in immunocompromised patients. This at-risk population includes patients with prolonged neutropenia, allogeneic hematopoietic stem cell transplantation, solid organ transplantation, hereditary or acquired immunodeficiency, corticosteroid use, etc. [4]. In case of immunodeficiency, particularly in case of neutropinia, the patient will have a high risk of

developing an invasive fungal infection, firstly candidemia followed by invasive aspergillosis [5]. The risk of aspergillus infection increases depending on the term of neutropenia and its duration [6, 7]. In our patients, constant and profound neutropenia was a recognized risk factor for invasive fungal infection.

The clinical presentation of pulmonary aspergillus pathology is determined by the interaction between the fungus and its host. In addition to neutropenia, aspergillosis develops in the presence of environmental contributing factors related to the richness of the environment in aspergillus spores, chronic bronchopulmonary disease and related factors such as intercurrent viral or bacterial infection, low-dose systemic corticosteroid therapy by general route, assisted ventilation on intubation [8-10]. In the second patient, the involvement of chronic obstructive pulmonary disease may explain the colonization of the tracheobronchial tree by Aspergillus.

The clinical symptomatology of invasive aspergillosis is not specific, which complicates the diagnostic approach and can delay the therapeutic management of cases in this pathology where antifungal treatment must be initiated as early as possible [11, 12]. The clinical presentation classically includes a persistent fever under broad-spectrum antibiotic therapy, a cough and dyspnea. The final stage of vascular invasion can manifest itself by revealing complications with pleuritic pain linked to a pulmonary infarction, bronchospasm or hemoptysis of varying severity [13, 14]. These symptoms were found in our two cases.

Thoracic CT scan plays a central role in the diagnosis of invasive aspergillosis by allowing the detection of suggestive images, but the diagnosis must be supported by mycological arguments [15]. In the study by Feki *et al*., 80% of cases presented bilateral pulmonary nodules. Although these signs are not pathognomonic, their association with the clinical context strengthens the diagnosis [16]. In our patients, we did not find any correlation between the CT appearance and the severity of the clinical presentation, hence the use of other diagnostic methods.

Due to the ubiquitous nature of Aspergillus, its isolation in nasal or proximal bronchial samples has no absolute value, however, the recommended examination is bronchial fibroscopy with bronchoalveolar lavage and sometimes bronchial biopsies in case of macroscopic lesions during endoscopy and/or sometimes guided by CT [17]. bronchoalveolar lavage fluid allows for better quality samples and also to obtain a large quantity of secretions distributed between the alveolar and bronchial fractions. Sputum analysis can also be used and has the advantage of being easy to perform and non-invasive, but its major disadvantage is the risk of oropharyngeal contamination [18]. A blood sample can also be taken in the event of suspected blood dissemination. Aspergillus galactomannan antigen is a polysaccharide antigen released by Aspergillus but also by other fungi such as Cryptoccocus and Fusarium. It can be searched for in serum or from a bronchoalveolar lavage fluid and is one of the tests useful for the diagnosis of invasive aspergillosis [19]. Our two patients had undergone bronchoalveolar lavage fluid examination and a search for aspergillus antigens, the results of which were in favor of Aspergillosis due to *Aspergillus fumigatus.*

Currently, the first line of treatment consists of anti-aspergillary monotherapy, with recommendations based solely on studies conducted in immunocompromised patients. A French consensus conference in 2004 issued recommendations for invasive aspergillosis in adults [20]. The leading triazole, voriconazole (V-Fend®), was compared to amphotericin B deoxycholate in an open randomised study. An overall improvement in survival at 12 weeks was observed in the group of patients receiving voriconazole [21]. As a result, the first-line treatment recommended in immunocompromised patients is currently intravenous voriconazole. However, in the management of patients with chronic pulmonary disease, caution should be exercised in applying these recommendations. In our patients the treatment of choice was voriconazole with an improvement in the first patient and the death of the second patient which was due to the delayed diagnosis of *Aspergillus fumigatus.*

CONCLUSION

Invasive pulmonary aspergillosis is a major concern due to the frequency and severity of its complications, particularly in immunocompromised subjects. Optimization of diagnostic management and recent therapeutic advances have led to an improvement in prognosis.

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