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Case Report

Importance of Galactomannan Dosage in Bronchoalveolar Lavage for Diagnosing Bronchopulmonary Aspergillosis: A Case Report

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Abstract: Invasive pulmonary aspergillosis is a life-threatening condition that predominantly affects individuals with weakened immune systems. We report the case of a 70-year-old patient with a history of immunosuppression, diagnosed with invasive bronchopulmonary aspergillosis based on a positive galactomannan test. The diagnosis was supported by a combination of clinical history, predisposing factors, and characteristic findings on biological and radiological assessments. Confirmation relied on direct detection of the fungus through culture, antigen testing, and molecular methods. Early initiation of antifungal therapy was critical. The identification and management of this condition are often complicated by the diversity of underlying clinical contexts and nonspecific diagnostic indicators, emphasizing the need for a high index of suspicion and prompt intervention.

Keywords: Invasive pulmonary aspergillosis, Immunosuppression, Galactomannan, *Aspergillus fumigatus*, Antifungal therapy, Dyspnea.

INTRODUCTION

Invasive bronchopulmonary aspergillosis (IPA) is an opportunistic fungal infection that is primarily severe in immunocompromised individuals, including organ transplant recipients, neutropenic patients, and those on prolonged immunosuppressive therapy. It is also observed in intensive care patients with severe influenza or COVID-19 infections [1].

IPA represents the most critical form of pulmonary aspergillosis with a poor prognosis and high mortality rate exceeding 50% [2]. Of note, Aspergillus fumigatus is the most frequently incriminated species in IPA [1]. Common and definitive diagnostic methods include direct examination, culture, galactomannan antigen (GA) detection and polymerase chain reaction (PCR) to detect the germ. Concerning therapeutic management, antifungal treatment should be started early [1-3].

We report the case of a patient hospitalized for IPA, with a background of immunosuppression by prolonged corticosteroid therapy. Through this observation, we aim to highlight the epidemiological, clinical and biological elements enabling an effective diagnosis of IPA.

CASE PRESENTATION

This is the case of a 70-year-old female patient, a housewife and former wool weaver, with history of chronic exposition to wood smoke. Her medical history includes hypertension, diabetes, with nonadherence to medication, chronic dyspnea stage II of SADOUL since 2014 and chronic bronchitis since 2022. The patient also reports self-medication with short-term corticosteroids on several occasions.

One month before her admission, following a cold episode, she presented rapid worsening of her dyspnea, progressing to SADOUL stage IV, associated with a productive cough bringing up whitish sputum with atypical right chest pain in the context of fever and night sweats with deterioration of her general condition.

On admission, the patient was conscious, apyretic, hypertensive (14/09 cmHg), tachycardic (127 beats/minute), polypneic (28 cycles/minute) with oxygen saturation of 84% that increased to 93% under O2. The pleuropulmonary examination showed a condensation syndrome of the right lung.

Chest X-ray show A dense homogeneous triangular opacity in the right upper lobe with regular

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contours, attraction of the elements of the mediastinum, elevation of the homolateral hemidiaphragm, and a stop image on the right main bronchus. There was a second dense heterogeneous round irregular opacity with spiculated contours occupying the middle part of the right hemifield associated with confluent nodular and alveolar images in places occupying the entire lower third of the right lung. Additionally, we note confluent reticular, micronodular and alveolar images occupying the middle part of the left lung. Figure 1

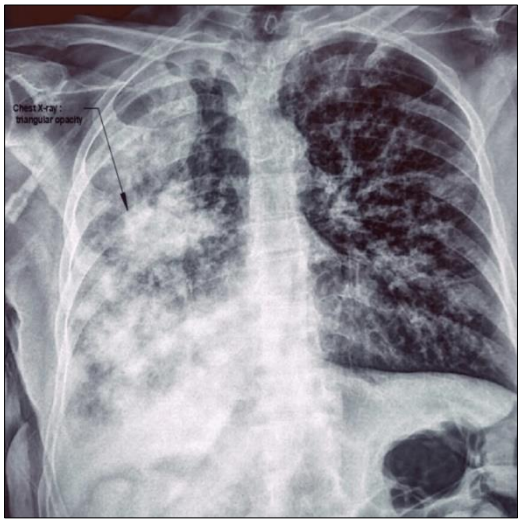

Figure 1: Chest X-ray showing a dense, homogeneous triangular opacity in the right upper lobe with regular contours. Also visible are a second heterogeneous spiculated opacity in the mid-right lung field and confluent nodular and alveolar opacities in the lower third of the right lung, with additional interstitial changes in the left mid-lung zone

Thoracic CT scan show Nodular and micronodular bilateral opacities, more marked on the right, dense with clear contours, measuring 8 * 8 mm for the largest (at the left apical lobe), surrounded by a ground glass area creating the appearance of the halo sign, suggesting an infectious origin in favor of aspergillosis. It a It also demonstrates the presence of homolateral attraction of the mediastinal elements and lingular foci of atelectasis in the right upper lobe, right mid-basal and in the right inferior lobe. Aditionally, there is a peri bronchial thickening visible at the right basal and lingula lobe. And finally, a low-abundance pericardial effusion. Figure (2et 3)

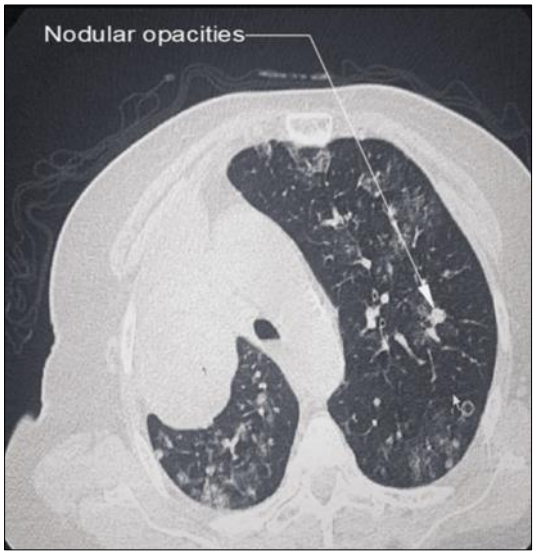

Figure 2: Thoracic CT Scan: Nodular opacitie

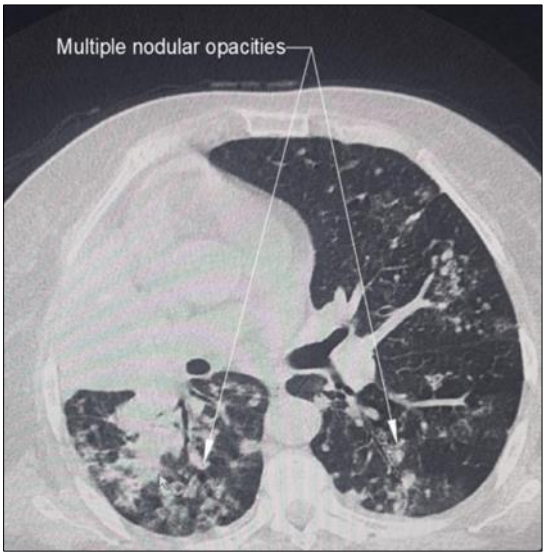

Figure 3: Thoracic CT Scan: multiples nodular opacities

Urine test strips found glucosuria (1 cross) with no ketonuria. Biological tests highlighted hyperglycemia (3.47 g/l), elevated CRP (221.5 mg/l), The complete blood count revealed leukocytosis with a WBC count of 13,350/µL, predominantly neutrophilic (9,770/µL, normal Hemoglobin (13.9 g/dl) and platelet (261.10^3/uL) levels. Renal function was preserved. Serological tests for viral hepatitis C HVC and HIV were negative. The search for Koch's bacillus by GeneXpert® on bronchial aspirates was negative. (Table *1*)

Table 1: Patient's Laboratory Test Results Compared to Normal Values

Parameter	**Patient's Result**	**Normal Range**	**Interpretation**
Blood glucose	3.47 g/L	0.70 – 1.10 g/L	hyperglycemia
Urine glucose (dipstick)	+ (1 cross)	Negative	Glucosuria present
Urine ketones	Negative	Negative	Normal
C-reactive protein (CRP)	221.5 mg/L	< 5 mg/L	Severely elevated
White blood cell count (WBC)	13,350/µL	4,000 – 10,000/µL	Leukocytosis
Neutrophil count	9,770/µL	1,500 – 7,000/µL	Neutrophilia
Hemoglobin (Hb)	13.9 g/dL	Male: 13 – 17 g/dL	Normal
Platelet count	261 × 10^3/µL	150 – 400 × 10^3/µL	Normal
Renal function	Preserved	—	Normal
HCV serology	Negative	Negative	Normal
HIV serology	Negative	Negative	Normal
Mycobacterium tuberculosis (GeneXpert® on bronchial aspirate)	Negative	Negative	No evidence of TB

Mycological examination of the bronchial aspiration in fresh state revealed the presence of fragments of filaments, and MGG staining highlighted the presence of hyaline septate mycelial filaments. However, the culture remained sterile.

The search for Aspergillus galactomannan antigen was performed twice on serum and once on bronchoalveolar lavage fluid (BAL). It was conducted by chemiluminescence (CLIA) on the VirClia Lotus automated system and was positive, with an index of 0.269 then 0.313 in the serum, and 1.712 in the (BAL), all exceeding the positivity threshold set at 0.2.

Based on all clinical, radiological, biological and mycological data, particularly the presence of mycelial filaments in direct examination, a reversed halo sign on imaging, as well as serological results in favor of aspergillosis with a positive serum galactomannan antigen twice (index of 0.269 then 0.313) and marked positivity in BAL (index of 1.712), the diagnosis of probable angio-invasive bronchopulmonary aspergillosis was made. This diagnosis was based on an evocative clinical symptomatology, in the context of immunosuppression, in a poorly controlled diabetic patient.

An urgent therapeutic management was initiated, including intravenous administration of voriconazole according to the recommended protocol (400 mg twice a day on the first day, then 200 mg twice a day for maintenance), high-flow oxygen therapy, preventive anticoagulation, as well as strict blood glucose control. Despite this multidisciplinary care, the evolution was quickly unfavorable, with a progressive worsening of respiratory distress. The patient died after 14 days of hospitalization, in the context of acute respiratory failure.

DISCUSSION

Aspergillus is a ubiquitous, opportunistic filamentous fungus, saprophytic in the external environment (air, soil, water, etc.) and feeding on the decomposition of organic matter, favored by humidity. In cases of immune deficiency, Aspergillus can cause localized or disseminated infections, mainly affecting the lungs [2-4], producing several clinical forms. The most severe manifestation is invasive pulmonary aspergillosis, which is represented in the case of our patient.

In our patient, the notion of chronic respiratory disease can explain the colonization of the tracheobronchial tractus by Aspergillus, while diabetes, advanced age and long-term corticosteroid therapy constitute factors of immune vulnerability.

The clinical presentation of the patient was nonspecific, with fever, cough, and sputum. However, the underlying immunocompromised state of the patient should prompt early consideration of IPA, which will then be supported by early chest CT scan, mycological examination of respiratory samples, and the search for galactomannan antigen.

The clinical presentation of IPA is determined by the interaction between the fungus and the host. Thus, aspergillosis only develops in the presence of factors that promote its adhesion. Local factors include epithelial damage, such as alteration of the mucociliary layer by smoking or chemoradiotherapy treatments, presence of cavities within the pulmonary parenchyma in the case of tuberculosis and chronic bronchopulmonary disease, facilitating aspergillus graft [2-5].

General factors include immunosuppression, classically in neutropenic patients (neutrophil counts below 500 elements/mm3 for more than 10 days), organ transplantation and taking immunosuppressants, hospitalization in intensive care units, high-dose of corticosteroids (up to 0.3 mg/kg/day or more, during more than 3 weeks), hematological malignancies, allogeneic hematopoietic stem cell transplant recipients, congenital or acquired immune deficiencies, and immunomodulatory biotherapy [1-6].

Chest CT plays an important role by showing suggestive images such as the Halo sign, as in the case of our patient. Despite technological advancement, IPA remains a difficult diagnosis and is commonly classified as "possible", "probable" or "certain", depending on clinical, radiological and biological arguments [5].

Identifying aspergillosis through direct examination and culture on biological samples from sterile sites confirms the diagnosis of invasive infection [7]. However, interpreting findings from sites prone to colonization, such as the bronchi is delicate to interpret and necessitates consideration of clinical context and diagnostic criteria [5-7].

Bronchoscopy-guided bronchoalveolar lavage (BAL) is the recommended diagnosis method, with sometimes bronchial biopsy in the case of macroscopic lesions [7].

Direct examination of BAL samples reveals mycelial filaments, hyaline, septate and sometimes branched. Fungal wall staining technics increase the sensitivity of direct examination [3].

Culture of BAL samples is done on Sabouraud medium with antibiotics without cycloheximide. It allows us to specify the genus and the species of the fungus. Its positivity alone has a positive predictive value of only 50%. Therefore, the positivity of the direct examination increases sensitivity and specificity when combined with positive culture.

If the BAL study is negative, CT-guided biopsy is indicated but should be discussed in severely immunocompromised patients. The anatomopathological examination can identify septate or non-septate mycelial filaments and can demonstrate a process of tissue invasion, particularly vascular invasion [1].

Aspergillus antigen testing in BAL samples is strongly recommended [7]. Galactomannan is a major component of the Aspergillus cell wall, it is released into the circulation in cases of invasive infection [1]. It is also recommended to look for the pan-fungal biomarker B 1-3 D-glucan present in the cell wall of all fungi [1-4].

Galactomannan and/or B 1-3 D-glucan positivity in serum/plasma and/or galactomannan positivity in BAL have a high positive predictive value for diagnosis in exposed patients. It can be positive even before the appearance of radio-clinical signs [1]. Therefore, it also has a preventive interest in exposed

patients, by dosing once or twice a week, provided that the patients are not taking any prophylactic medication [3]. It should also be used for therapeutic monitoring, as a positive rate under treatment is considered as a poor prognostic factor.

The sensitivity and specificity of galactomannan on serum is variable. However, it is more significant when tested in BAL samples [7]. A positive exam may need confirmation by a second sample, justified by the existence of false positives induced by technical contamination, certain medications or foods [1].

The diagnosis of IPA sometimes requires more relevant paraclinical examinations in difficult cases. Molecular technics such as aspergillus PCR are recommended using serum or BAL samples for some cases. However, these technics are not yet widely integrated into routine IPA diagnosis [3]. The gold standard for the diagnosis of invasive pulmonary aspergillosis remains culture because it highlights the fungus and specifies its sensitivity to antifungals.

The EORTC-MSGERC (the European Organization for Research and Treatment of Cancer and Mycosis Study Group and Education and Research Consortium) has defined the probable, possible and certain diagnosis of IPA in immunocompromised patients on several criteria: host factors, the clinical, radiological and mycological signs [3].

Indirect method for diagnosis includes the detection of circulating antibodies reflecting a normal immune response in an immunocompetent person, and this is a major argument for the diagnosis of chronic pulmonary aspergillosis, localized aspergillosis and immuno-allergic aspergillosis. But in the case of invasive pulmonary aspergillosis, the reference method remains the search for precipitating antibodies by immunoprecipitation; however, interpretation can be difficult in immunocompromised patients due to the absence of the humoral response [1].

An anti-Aspergillus treatment must be initiated urgently, starting with voriconazole on first line, a fungicide against A. fumigatus (day 1: 6 mg/kg per day at 12-hour interval; day 2 : 4mg/kg per day every 12 hours, dose to be adjusted according to pharmacological therapeutic monitoring), or isavuconazole (200 mg of isavuconazole every 8 hours for the first 48 hours, then 200 mg per day) [1-5] .In second line, liposomal amphotericin B (3 mg/kg per day) intravenously is indicated [4].

These molecules offer the advantage of availability for intravenous and oral use. Their main adverse effect is hepatotoxicity, which is more pronounced in patients treated with voriconazole than in those treated with isavuconazole. Its occurrence sometimes requires treatment interruption, but it is most often reversible [3-5].The total duration of treatment will be defined based on host factors, in addition to clinical and biological evolution [1].

Caspofungin acetate at a dose of 70 mg on the first day (then 50 mg per day on subsequent days) intravenously, or micafungin at a dose of 100 mg per day or posaconazole are indicated in cases of intolerance or therapeutic failure of other antifungals [1, 2].

Surgery may be indicated mainly to prevent hemorrhagic complications [1].

Empirical treatment with liposomal amphotericin B and caspofungin is reserved for suspected IPA while awaiting mycological evidence, in cases of persistent febrile neutropenia unresponsive to broad-spectrum antibiotic therapy.

Primary chemoprophylaxis can be initiated to prevent IPA, and currently several molecules can be used: posaconazole, voriconazole or micafungin.

Secondary prophylaxis is indicated in patients who have had an episode of IPA with favorable response to treatment, in order to limit the risk of relapse in case of new courses of chemotherapy or hematopoietic stem cell transplant. Chemoprophylaxis with posaconazole is then proposed [1-5].

CONCLUSIONS

Invasive pulmonary aspergillosis is a serious infection where A. fumigatus is the most isolated species. It is an opportunistic infection with a poor prognosis; diagnosis is based on a combination of clinical, radiological, and mycological arguments. Treatment must be initiated urgently (voriconazole as first-line treatment), however, despite all the therapeutic procedures considered, the mortality rate remains high.

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