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PULMONARY ASPERGILLOSIS WITH HEMATOLOGIC DISSEMINATION TO THE CENTRAL NERVOUS SYSTEM: CASE REPORT

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Abstract: Aspergillosis is an opportunistic infectious disease that affects the lower respiratory tract through the inhalation of spores of the fungus genus Aspergillus, most commonly by individuals with reduced immunity. With this in mind, the aim of this study is to describe a case report of an adult patient diagnosed with pulmonary aspergillosis that evolved into a hematogenously disseminated disease with central nervous system involvement. The patient was 65 years old, female, with a history of severe osteoarthritis of the right and left knees, taking corticosteroids and suffering from prosthetic infection. She had undergone bilateral arthroplasty and had negative general cultures. During hospitalization, the patient developed a high fever with no focus and no response to conventional antibiotic therapy, and was referred to an infectious disease specialist. A laboratory test for the enzyme galactomannan was carried out, with a positive result, and together with the CT scan findings, the hypothesis of pulmonary aspergillosis was raised. Variconazole was started, but other complications followed with asystole and death. However, the diagnosis of invasive aspergillosis is difficult due to the lack of a test with high specificity and the absence of a pathognomonic sign/symptom. However, it is essential to determine a rapid and effective diagnosis to ensure better recovery and patient survival.
Keywords: Aspergillosis; Pulmonary Aspergillosis; Central Nervous System; Neuroaspergillosis.

INTRODUCTION

Aspergillosis is an infection caused by fungal species of the genus *Aspergillus*, which have a high sporulation capacity and are normally present in soil, water and various decomposing organic materials (LATGÉ J et al., 2019).

The most common entry point for these fungi is through the inhalation of spores, with the lungs being the main organ involved. There, the fungus initially lodges in the paranasal sinuses and lower airways. However, the fungus may be able to invade and occupy other organs and tissues (brain abscess, disseminated infection) and is usually associated with immunosuppression of various etiologies (LAMOTH et al., 2022). It has been observed that there is greater involvement of the nervous system in immunocompromised patients with aspergillosis infection. (Shamim MS, Enam SA, Ali R, et al., 2010).

Aspergillosis presents itself in various ways, whether through allergic diseases (allergic fungal rhinosinusitis, allergic bronchopulmonary aspergillosis, severe asthma with hypersensitivity to fungi and extrinsic allergic alveolitis), chronic cavitary forms (common in immunocompetent patients with respiratory problems) or it can also manifest as an invasive disease via the hematogenous route in the central nervous system after traumatic brain injury or repeated lumbar punctures for intrathecal treatment or after neurosurgical manipulation. (WINGARD; HSU, 2010).

Research has shown that there is a concern about the aggravation of aspergillosis in immunocompetent patients, having a high importance at the level of intensive care units in hospitals, presenting higher levels of mortality and morbidity (PAULUSSEN et al., 2016). Aspergillosis has a severe involvement of 75% to 100% death (WINGARD; HSU, 2010). According to Bokhari, the mortality rate of Aspergillus infection in the immunocompetent population is approximately 10% to 20%, while in immunocompromised patients it can reach 85% to 100% (Yubao et al, 2020 apud Bokhari et al, 2014).

Confirmation of the diagnosis is made by the presence of culture and histology-based methods (Abby P. Douglas et al, 2021).

However, the diagnosis of aspergillosis in the ICU is not simple and can take several days due to a lack of clinical suspicion. This is because imaging tests are usually non-specific, showing consolidation, irregular infiltrates, cavitation or nodules, and can be complicated by coexisting findings such as pleural effusion, atelectasis or adult respiratory distress syndrome. (Hangyong He1. et al.,2011)

With this in mind, the aim of this study is to describe a case of an adult patient diagnosed with pulmonary aspergillosis, immunocompromised with hematological dissemination in the central nervous system, and to discuss her diagnosis and treatment.

CASE DESCRIPTION

This is a 65-year-old female patient with a history of severe osteoarthritis of the right and left knees, who underwent bilateral arthroplasty 20 days ago. She was admitted to hospital complaining of severe knee pain and the immediate suspicion was prosthetic infection.

Patient with previous rheumatoid arthritis associated with the use of metrotexate for immunosuppression.

The patient was admitted for investigation and osteomyelitis was confirmed and teicoplamine was started. However, the cleaning approaches showed negative general cultures and a negative blood culture. The patient did not respond as expected to the initial antibiotic therapy, evolving with clinical worsening, associated with respiratory complaints and persistent fever.

A non-contrast chest CT scan was then performed, which showed bilateral parenchymal consolidations associated with thickening of the peribronchovascular interstitium, with centrilobular opacities in between and bilateral pulmonary nodules, some of which were excavated. In conclusion, a fungal infection was suggested.

A fiberoptic bronchoscopy was performed, which came back positive for galactomannan in bronchoalveolar lavage, and other pathologies were ruled out in the other cultures. Due to the aspergillus infection, voriconazole was started.

Due to the neurological worsening associated with the pulmonary diagnosis and compared to the initial admission where the patient was previously normal in the clinical neurological examination and, now, with a lowered level of consciousness, disorientation, excessive drowsiness, with an initial Glasgow Coma Scale (GCS) of 15 and now a GCS of 10 (AO2, VR 3, MR 5), no focal motor deficits, no nystagmus and a cranial CT scan showing no acute lesions or bleeding, central nervous system involvement was suspected due to the spray and a puncture for cerebrospinal fluid culture was carried out.

During hospitalization, the patient presented with chest pain with enzymatic alterations and an electrocardiogram with dynamic alterations (ST depression in the infero-lateral wall). IAMSSST was identified and catheterization was performed with angioplasty of the anterior descending artery with placement of 01 drug-eluting stent. The patient is currently stable and not taking VADs

72 hours after the AMI, the patient's respiratory condition worsened, progressing to shock in less than 24 hours and then multiple organ dysfunction. Noscomial pneumonia was identified and meropenem was started. At this point, the patient was still taking teicoplamine and the decision was made to switch from voriconazole to amphotericin B and other measures for septic shock.

Despite new measures, the patient evolved with refractoriness to the therapy adopted and died 48 hours after the onset of shock.

DISCUSSION

The most devastating form of Asepergilus infection is Invasive Aspergillosis, a life-threatening condition especially for immunosuppressed individuals

In more serious cases, the fungi can travel through the bloodstream and cross the blood--brain barrier to reach the brain and meninges, causing severe inflammation with accumulation of cerebrospinal fluid, with a consequent increase in intracranial pressure. The mortality rate varies from 40-90%, depending on factors such as: immune status, the site/organ affected and the treatment applied, both in terms of time and the correct drug (Lin et al, 2001).

The diagnosis of Meningeal Aspergillosis is challenging, as there is no pathognomonic symptom or sign, nor even a test that is 100% specific (Segal BH. Aspergillosis. N Engl J Med. 2009;360(18):1870-84). Therefore, in these cases the diagnosis is made by exclusion.

It is estimated that meningeal aspergillosis occurs in between 10 and 20% of all cases of invasive aspergillosis among immunocompromised patients (Patterson T, 2015). Imaging tests such as magnetic resonance imaging (MRI) or computed tomography (CT) can reveal signs of inflammation or lesions in the brain and spinal cord, but are not specific for this infection (Miceli,M, 2019). A more assertive diagnosis could be obtained by taking samples of cerebrospinal fluid (CSF) for laboratory analysis (fungal culture). However, immunocompromised patients taking corticosteroids and antibiotics tend to have lower or undetectable titres (Thompson, TF et al) and cross-reactions with histoplasmosis, blastomycosis and paracoccidioidomycosis can occur. Molecular tests (such as PCR - Polymerase Chain Reaction) can be carried out to detect the DNA of the Aspergillus fungus in CSF samples, but these types of assay should not be recommended for routine use in clinical practice to date, due to the lack of conclusive validation for commercially available assays, the variety of methodologies in the literature and questions about the extent to which the results relate to diagnosis (Patterson, et al).

Generally speaking, diagnosis consists of clinical examinations, a medical history and laboratory tests, which may include taking samples of cerebrospinal fluid (CSF) via a lumbar puncture. The CSF can be examined for the presence of inflammatory cells, such as leukocytes, and can also be cultured to identify the fungus.

However, CSF examination is not always useful for diagnosis, as confirmed cases may have negative CSF cultures (Kourkoumpetis et al., 2012; Antinori et al., 2013). This is because the isolation of Aspergillus in cerebrospinal fluid is difficult and may require repeated testing with large-volume samples. In addition, other CSF examination findings, such as cell count and protein level, are also non-specific (Kourkoumpetis et al., 2012).

In this case, a prosthetic infection was initially suspected, but the patient did not respond well to antibiotic therapy. A non-contrast chest CT scan was then requested, which showed bilateral parenchymal consolidations, with slight thickening of the peribronchovascular interstitium and centrolocular opacity, suggestive of infection by Aspergillus. The investigation was followed by bronchoalveolar lavage, which confirmed the suspicion due to the presence of galactomannan. The treatment of choice with Voriconazole was started, but the patient's condition continued to deteriorate.

Due to the worsening of the patient's neurological condition, the possibility of infection disseminated to the CNS was considered, and a CSF culture was requested, which was negative. This negative result, however, does not rule out the diagnosis of meningeal aspergillosis since, according to the literature, only 1/3 of all cases of meningeal aspergillosis have a positive CSF culture result (Spinello A et al, 2012).

In addition, the patient suffered from rheumatoid arthritis and had been using corticosteroids for several years, a type of immunosuppressive medication that is a major determining factor in opportunistic diseases such as meningeal aspergillosis. Immunosuppressed patients do not have adequate levels of granulocytes and so the lesions are not easily localized, which encourages them to spread to multiple organs (Ma Y et al, 2020).

In addition, cultures of synovial fluid and CSF were carried out which were not positive for Aspergillosis, but which were also not compatible with infection by virus (increased lymphocytes, normal or decreased proteins, normal glucose) or bacteria (increased neutrophils, increased proteins, highly consumed glucose, purulent appearance).

Another important factor was the occurrence of non-ST-segment elevation myocardial infarction (STEMI). Although it is very rare to find Aspergillosis in the heart, there is one reported case in which the infection involved all four chambers of the heart and the tricuspid and mitral valves (Soman S et al, 2014). In that case, a biopsy stained with hematoxylin and eosin showed multiple non-caseous granulomas and fungal hyphae and Schiff's stain with periodic acid showed septate fungi, and the diagnosis of Aspergillus was made as the cause of the granulomatous lesion.

Thus, considering the patient's clinical condition, the positivity for galactomannan, the worsening of the neurological condition and ISST and the negative CSF culture, the diagnosis is made by exclusion.

The main treatment for Meningeal Aspergillosis is antifungal drugs, usually drugs such as Liposomal Amphotericin B or Voriconazole (Denning, D.W., Clinical Infections Diseases, Volume 26, Issue 4, Apr. 1998). The choice of drug and duration of treatment depend on the severity of the infection, the patient's response to treatment and other medical factors. In some severe cases, surgical drainage of brain abscesses or removal of infected tissue may be necessary to control the infection. Patients may also need symptomatic support to deal with symptoms such as headache, nausea, fever and fluid therapy to prevent dehydration.

CONCLUSION

Aspergillus infection can develop extrapulmonarily, especially in severely immunocompromised patients. Dissemination can affect other organs such as the brain and other tissues via the hematogenous route, with rapid evolution and a high mortality rate.

Diagnosing invasive aspergillosis is difficult, either because of the lack of a test with high specificity or because there is no pathognomonic sign/symptom. However, it is essential to determine a rapid and effective diagnosis in order to guarantee better recovery and patient survival. This is why it is important to consider invasive aspergillosis when the patient has an infection that is refractory to antibiotic treatment and the characteristics of the imaging and laboratory tests do not point to infection by bacteria or viruses. Diagnosis by exclusion is necessary in these situations.

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