Arch Bronconeumol. 2015;51(12):647–653

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Review

Updates on *Aspergillus*, *Pneumocystis* and Other Opportunistic Pulmonary Mycoses☆

José Curbelo,[a] José María Galván,[a] Javier Aspa[b,*]

[a] *Servicio de Medicina Interna, Instituto Princesa de Investigación IIS-IP, Madrid, Spain*
[b] *Servicio de Neumología, Instituto Princesa de Investigación IIS-IP, Madrid, Spain*

ARTICLE INFO

Article history:
Received 22 October 2014
Accepted 20 February 2015
Available online 4 October 2015

Keywords:
Opportunistic pulmonary mycoses
Aspergillus
Invasive pulmonary aspergillosis
Mucormycosis
Cryptococcus
Pneumocystis jirovecii

ABSTRACT

Mycoses are serious diseases with potentially fatal outcome. The introduction of immunosuppressive treatments and life support techniques has led to a growing prevalence of different degrees of immunosuppression. Compromised immune response is the primary risk factor for the development of opportunistic mycoses. Early diagnosis and treatment are crucial for improving prognosis. However, isolation in cultures or identification using antigen detection techniques cannot distinguish between colonization and invasive infection, and the clinical status of the patient often prevents biopsy sampling. Clinicians thus find themselves in an uncertain position, requiring them to quickly recognize clinical and radiological signs and interpret microbiological results in context. The aim of this review is to provide a general overview of the profile of patients susceptible to these infections, the role of the immune system and, in more detail, the major diagnostic developments that have gained most acceptance and recognition among the scientific community.

Actualización sobre *Aspergillus*, *Pneumocystis* y otras micosis pulmonares oportunistas

Palabras clave:
Micosis pulmonares oportunistas
Aspergillus
Aspergilosis pulmonar invasiva
Mucormicosis
Cryptococcus
Pneumocystis jirovecii

RESUMEN

Las micosis son enfermedades graves y potencialmente letales. Con el desarrollo de terapias inmunosupresoras y técnicas de soporte vital, la inmunosupresión en sus diferentes grados es cada vez más prevalente. El deterioro de la respuesta inmune es el factor de riesgo principal para el desarrollo de las micosis oportunistas. El diagnóstico y tratamiento precoces son factores cruciales para mejorar el pronóstico de estas enfermedades. Sin embargo, los aislamientos mediante cultivos o las técnicas de detección antigénicas no son capaces de distinguir entre colonización e infección invasiva, y las biopsias rara vez se pueden realizar por la situación clínica. Ello sitúa al médico en una situación de incertidumbre en la que debe reconocer precozmente los signos clínicos y radiológicos e interpretar los resultados microbiológicos en su contexto. El objetivo de esta revisión es aportar una visión general del perfil de paciente que sufre estas infecciones, el papel de su sistema inmune, y de forma más detallada, los principales avances diagnósticos más reconocidos y recomendados por la comunidad científica.

Introduction

Fungi form a huge kingdom of eukaryotes, of which only a few are pathogenic. This review focuses on fungi which can cause respiratory disease by tissue invasion in situations of immunosuppression. Thus, diseases resulting from a disordered immune response (e.g. allergic bronchopulmonary aspergillosis) and endemic mycoses (less common and less dependent of the immune status) are not considered in this review.

☆ Please cite this article as: Curbelo J, Galván JM, Aspa J. Actualización sobre *Aspergillus*, *Pneumocystis* y otras micosis pulmonares oportunistas. Arch Bronconeumol. 2015;51:647–653.

* Corresponding author.
E-mail address: jaspa@separ.es (J. Aspa).

1579-2129/

Table 1
Risks Factors for Opportunistic Mycosis.

- Disrupted natural barriers: mucositis, venous access lines, surgical wounds, intubation
- Prolonged neutropenia
- Blood cancers, whether associated or not associated with stem cell transplantation or graft-versus-host disease
- Disseminated malignant solid tumors
- Solid organ transplants
- HIV infection, especially with CD4 counts < 200 cells/mm^3
- Chronic lung diseases
- Connective tissue disease
- Immunosuppressive drugs, primarily corticosteroids. Other immunosuppressants associated with anti-TNFα drugs and alemtuzumab

Opportunistic mycoses are caused by ubiquitous fungi, including those present in commensal flora. Mycotic invasion is controlled by intact skin and mucous membranes, neutrophil activity, and cell-mediated immune response led by CD4 cells and macrophages. There is no common response to all fungi, and distinguishing clinical features have been identified: low CD4 levels are associated with pathogens such as *Pneumocystis* and *Cryptococcus*, while neutropenia can lead to *Aspergillus* and Mucoralean infections.

Types of immunosuppression associated with these mycoses are listed in Table 1. It is worth noting that many of the risk factors mentioned are associated with the chronic use of high-dose corticosteroids, underlining the need for careful adjustment of immunosuppression and consideration of therapeutic alternatives.

Clinical manifestations of pulmonary mycoses are not specific, and while it is easy to suspect mycosis in the context of known immunosuppression, the opposite approach must not be forgotten: a diffuse, slowly progressing pulmonary syndrome should alert to a possible fungal infection and lead to an investigation of any possible underlying immunosuppression. Detailed history and examination may guide diagnosis: involvement of paranasal sinuses may be suggestive of *Mucor*, skin lesions in disseminated disease may be a good source for biopsy, etc.

With regard to diagnosis, chest X-ray may be normal, so computed tomography is the imaging test of choice. Diffuse bilateral infiltrates with areas of ground glass and/or multimodal patterns are common, but not specific,[1] and microbiological culture or the detection of fungal antigens may be positive in a colonization setting, reducing their diagnostic value for invasive disease. The yield of serological testing in immunocompromised patients is poor. Biopsy has been conventionally considered as the unequivocal test for demonstrating invasive fungal proliferation, but in many cases, the clinical status of the patient prevents sampling. Moreover, the extreme seriousness of these diseases means that appropriate empirical treatment must be started as soon as possible.

The European Organization of Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) has defined invasive mycoses as: proven (consistent histological results or positive culture in sterile medium); probable (lower grade microbiological evidence in a patient with risk factors and consistent clinical syndrome); and possible (patients with clinical syndrome and risk factors, despite absence of microbiological confirmation).[2] These guidelines reflect the effort made in unifying criteria to assist the clinician in dealing with diagnostic uncertainty.

It is important to point out that treatment does not depend exclusively on the administration of antifungals. Immunosuppression must also be addressed and reduced or reversed to achieve a level of balance that remains poorly defined. In a situation of irreversible immunosuppression, there will be little response to antifungal treatment, while recovery of the immune response may be associated with clinical worsening, due to the inflammatory response. This phenomenon is well established in HIV patients, but has also been described in non-HIV patients.[3]

Aspergillosis

Aspergillosis is the primary pulmonary mycosis among critically ill patients,[4] the most common species being *A. fumigatus*, *A. flavus*, *A. niger* and *A. terreus*. They are acquired by inhalation of conidia, which in an immunocompetent individual are eradicated by alveolar macrophages and neutrophils. Disease develops when this line of defense breaks down, or, more rarely, in situations of excessive inhalation of conidia, such as occurs during landslides or great catastrophes.[5] Several clinical pulmonary forms have been described, the most important of which are invasive pulmonary aspergillosis (IPA), chronic aspergillosis, and aspergilloma.[6] The type and severity of aspergillosis is determined by the characteristics of the patient (Fig. 1). Severe, generalized immunosuppressive states, such as prolonged neutropenia, are associated with acute invasive disease, while moderate, localized immunosuppression, such as preexisting cavities, favors the development of forms such as aspergilloma.

Invasive Pulmonary Aspergillosis

IPA is the most severe form of aspergillosis, with a mortality of around 50%. It is caused by massive proliferation of *Aspergillus*, with tissue invasion and high vascular tropism, promoting ischemia and dissemination.

Serious risk factors include prolonged neutropenia in patients with hematological malignancies, hematopoietic stem cell (HSC) and solid organ transplants, particularly lung and heart. Other factors thought to be intermediate include intensive care unit admission, chronic obstructive lung disease (COPD) treated with inhaled or systemic corticosteroids, chemotherapy and radiation therapy, AIDS, etc.[5,7] Despite the varying importance of each risk factor, IPA in critically ill patients mostly occurs in association with COPD and prolonged corticosteroid use,[4] due to their higher prevalence.

IPA progresses with fever, cough, expectoration, hemoptysis, dyspnea, and pleuritic pain. Tracheobronchial involvement may be observed, particularly in lung transplantation.[8] If it disseminates, the skin, central nervous system (CNS), liver and kidneys may be affected.[5]

CT reveals areas of ground glass opacities with multiple nodules and cavitated lesions. Nodular lesions may be associated with perinodular hemorrhage, producing the typical "halo" sign. Subsequently, as the disease progresses, peripheral necrosis and

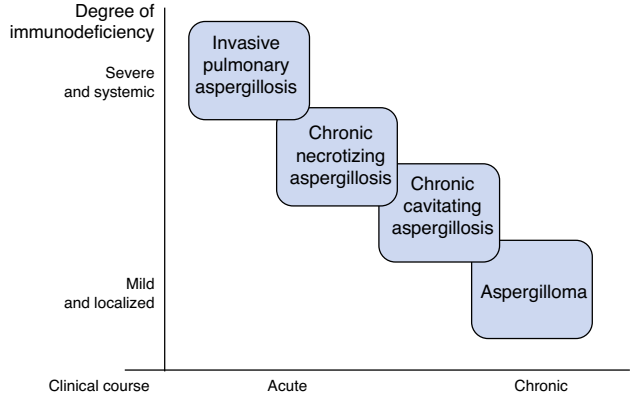

Fig. 1. Association between degree of immunodeficiency and type of pulmonary aspergillosis.