Disponible en ligne sur
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com
Médecine et maladies infectieuses 44 (2014) 89–101

General review

Diagnosis of invasive pulmonary aspergillosis: Updates and recommendations

Diagnostic de l'aspergillose pulmonaire invasive : actualités et recommandations

G. Desoubeaux [a,*,b], É. Bailly [a], J. Chandenier [a,b]

[a] *Service de parasitologie–mycologie–médecine tropicale, pôle de biologie médicale, hôpital Bretonneau, CHU de Tours, bâtiment B2A, 1er étage, 2, boulevard Tonnellé, 37044 Tours cedex 9, France*

[b] *CEPR–UMR Inserm U1100/EA 6305, faculté de médecine, université François-Rabelais, 37032 Tours cedex 1, France*

Received 8 April 2013; received in revised form 15 September 2013; accepted 18 November 2013
Available online 16 February 2014

Abstract

Invasive pulmonary aspergillosis is an opportunistic mycosis, difficult to diagnose, due to the environmental fungi of the genus *Aspergillus*. The diagnostic tools, even if more are available, are still limited in number and effectiveness. The current recommendations issued by the EORTC/MSG (European Organization of Research and Treatment of Cancer/Mycoses Study Group) and the ECIL (European Conference for Infection in Leukemia) suggest collecting epidemiological, radio-clinical, and biological data to support the diagnosis of aspergillosis with a strong presumption. Thus, medical imaging and serum galactomannan antigen currently constitute the basis of the screening approach, although they both have some limitations in specificity. (1→3)-β-D-glucans are pan-fungal serum markers with a very good negative predictive value. Real-time PCR lacks standardization, and fungal culture from respiratory specimens is sometimes not sensitive enough. Histology allows proving the diagnosis of aspergillosis, but biopsy is not always possible in immunodepressed patients. We present the various arguments for the diagnosis of invasive aspergillosis, with a particular emphasis on recent exploration techniques.

Keywords: Invasive aspergillosis; Recommendations

Résumé

Mycose opportuniste invasive dues aux champignons environnementaux du genre *Aspergillus*, l'aspergillose pulmonaire demeure une entité infectieuse délicate à diagnostiquer. Même s'ils tendent à s'étoffer, les outils aujourd'hui à notre disposition sont en nombre et en efficacité limités. Les recommandations actuelles des experts de l'EORTC/MSG (European Organization of Research and Treatment of Cancer/Mycoses Study Group) et de l'ECIL (European Conference for Infection in Leukemia) préconisent de rassembler des arguments épidémiocliniques, radiologiques et biologiques afin d'étayer le diagnostic d'aspergillose avec une forte présomption. Ainsi, les techniques d'imagerie et la recherche sérique de l'antigène aspergillaire galactomannane constituent la base de la démarche de dépistage, même si elles se heurtent à quelques problèmes de spécificité. Les (1→3)-β-D-glucanes sont des marqueurs sériques pan-fongiques avec une très bonne valeur prédictive négative. La PCR en temps réel souffre d'un manque de standardisation et la culture mycologique à partir des prélèvements respiratoires est parfois peu sensible. L'anatomopathologie permet de poser le diagnostic de certitude, mais le geste biopsique n'est pas toujours envisageable chez des patients fragilisés. Nous présentons les différents éléments concourant au diagnostic d'aspergillose invasive, en insistant notamment sur la place des dernières techniques d'exploration.

Mots clés : Aspergillose invasive ; Recommandations

* Corresponding author.
E-mail addresses: guillaume.desoubeaux@univ-tours.fr, guitoon007@hotmail.com (G. Desoubeaux).

0399-077X/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.medmal.2013.11.006

1. Introduction

Acute or chronic aspergillar infections account for a large number of mycoses due to environmental fungi of the *Aspergillus* genus [1]. Invasive pulmonary aspergillosis (IPA) has the most severe prognosis among these various clinical presentations [2]. This opportunistic mycosis usually occurs in immunodepressed patients: allogeneic hematopoietic stem-cell transplantation (ASCT), patients presenting with cancer and hematological diseases or treated by anticancer chemotherapy, solid organ transplantation recipients [3–5]. The incidence of IPA has considerably increased in recent years in new populations at risk, especially in individuals presenting with lymphoproliferative syndromes [3], and in medical ICU patients, especially those treated by corticotherapy [6,7].

Despite progress in understanding the disease, and the availability of new fungicidal agents such as voriconazole (V-Fend®) in 2002, or posaconazole (Noxafil®) in 2007 [4], the global death rate remains superior to 30% [8,9]. The causes of this high death rate are related partly to the severity of comorbidities, but also to the difficulty to make a diagnosis both sensitive and specific. The delay before diagnosis has an obvious impact on how early treatment is initiated, and consequently on the prognosis [10].

We will describe the currently available diagnostic approaches, focusing on the assets and limitations of each. We will later explain how confronting these various diagnostic approaches allows classifying the IPA according to its degree of confidence, according to EORTC (European Organization for Research and Treatment of Cancer) criteria [11] and ECIL (European Conference for Infection in Leukemia) recommendations [12,13].

2. Physiopathological definition of IPA

IPA is a severe mycosis characterized by the acute invasion of bronchi, then of the pulmonary parenchyma, by *Aspergillus* filaments.

The contamination usually occurs by the respiratory tract since each individual inhales several dozens to hundreds of naturally airborne aspergillar spores daily [14]. These are first blocked mechanically then ejected by mucociliary clearance. Finally, the innate immune defenses, *via* alveolar macrophages then PMN, destroy any remaining conidiae. The aspergillar spores escape these natural defenses in patients weakened by immunodepression or another risk factor, and may settle in the pulmonary alveoli to bud, and take a filamentous form.

Recently, an particular distinction was made between so-called angioinvasive IPA usually observed in severely immunodepressed patients usually occurring *via* a vascular invasion, and broncho-invasive IPA usually observed in patients without severe neutropenia or acute leukemia, and mostly limited to destruction of the bronchial wall [15].

3. Populations at risk of IPA and diagnostic contexts

IPA, more frequently observed in immunodepressed patients of hematology and oncology units and ASCT centers, is the most severe clinical presentation of *Aspergillus* spp. infections [4,5,9].

Aspergillosis is the most frequent invasive fungal infection occurring in hematopoietic stem-cell transplantation recipients. Neofytos et al. reported 59.2% of cases among invasive mycosis occurring in this clinical context [16], and Kontoyiannis et al. in his Transnet multicentric study reported a rate of 43% [9]. The incidence of IPA is estimated at between 7 to 13% in the specific case of ASCT recipients with myeloablative conditioning, with 2 peaks of onset [17]: the first during the early post-allograft phase after the second week of aplasia, and the second, later, during treatment for GvH (*Graft* versus *Host* disease) by corticosteroids and immunosuppressors, around the third month [3,9]. IPA seems to occur more frequently if the hematopoietic stem-cell donor is not family related or in case of mismatch (hazard ratio = 1.5; IC95% [1.1–2.0] *versus* family related donor with matching) [18]. But the incidence of IPA is significantly lower in case of peripheral ASCT rather than bone marrow, because the former induces shorter periods of neutropenia, from 6 to 8 days [2]. The incidence of IPA is estimated at between 0.5 and 8% in case of hematopoietic stem-cell autograft, according to authors, and is directly related to the duration of neutropenia [2,19].

Besides cases occurring in a context of allogeneic or auto-hematopoietic stem-cell transplantation, IPA also occurs in the hematology unit, most frequently in patients presenting with acute myeloblastic leukemia (AML, accounting for 66% of leukemia cases), and especially during induction chemotherapy (68% of reported cases during AML), often intensive in this type of indications with aplasia beginning in 3 to 5 days and lasting 15 to 25 days or more [3]. The average duration of neutropenia, before aspergillosis occurs, is 16 days in this context [4]. Recently cases of IPA occurred in a new context, in patients treated outside of usual hospitalization: for example, in patients presenting with long-term myelodysplastic syndromes and treated in ambulatory care, or in patients presenting with chronic lymphoid leukemia treated in day-care with alemtuzumab (Mab-Campath®), an anti-CD52 depleting all lymphocytes [3].

The incidence is lower in solid organ transplantation recipients (1–6%), even if the pulmonary transplantation recipients are more at risk because of an early exposure of the graft to contaminating environmental spores [5].

Patients treated by long-term corticosteroid therapy, or new anti-inflammatory drugs such as anti-TNFα (especially infliximab, Remicade®), for systemic diseases de system are also concerned [20].

IPA, besides the usual cases occurring during chemotherapy-induced immunodepression, may concern more rarely patients presenting with a genetic disease of the immune defense (chronic septic granulomatosis which is due to a deficit in NADPH oxidase) or an acquired immunodeficiency (AIDS, diabetes, cirrhosis, etc.) [3]. Likewise, a lesion of the mucociliary epithelium, or the presence of preformed cavities in case of chronic obstructive broncho-pneumonia, may be a terrain for sub-acute presentation of IPA [21].