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Correlation between high-resolution computed tomography and galactomannan antigenemia in adult hematologic patients at risk for invasive aspergillosis

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Abstract

Objectives: To analyse the predominant radiological pattern of pulmonary lesions in adult hematologic patients at risk for invasive aspergillosis (IA) together with the results of serial serum *Aspergillus* galactomannan antigen testing (GM).
Material and methods: In a prospective study for patients at high risk of aspergillus pulmonary infection, serum GM were performed 2–3 times per week during the periods of high risk for IA and high-resolution CT (HRCT) was performed in case of abnormal chest X-ray (CXR) and/or persistent fever after 5 days of antibiotic treatment. Changes on HRCT scan were classified as airway IA and angioinvasive IA. IA was classified as proven or probable in accordance with the definitions stated by the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC-MS). Positive GM testing was not considered as microbiological criterion.
Results: 38 hematological patients were diagnosed of probable ($n=28$) or proven ($n=10$) IA. 55% patients had a neutrophil count less than 500 mm^{-3} ($n=21$), and 37% patients $\geq$2 risk factors for IA. All probable IA were diagnosed by bronchoalveolar lavage (BAL). Proven IA was reached by positive histopathologic and culture results of samples obtained by autopsy ($n=4$), percutaneous ($n=3$) or transbronchial biopsy ($n=3$). 18 patients had airway IA, and 60% had a GM level $\geq$1.5. 20 patients were diagnosed of angioinvasive IA from which 80% had a GM level $\geq$1.5.
Conclusion: Serum GM levels may be lower in patients with airway IA than in those with an angioinvasive form. HRCT and serum GM are complementary tests in the diagnosis of IA.

Keywords: Lung infection; Galactomannan; Computed tomography

1. Introduction

Invasive aspergillosis is a serious opportunistic infection in patients with hematological malignancies. Its incidence has been estimated around 10–15% and, nowadays, establishing an early diagnosis still remains an important challenge [1,2]. Current methods for its diagnosis with a high level of certainty, as radiological tests and invasive procedures to identify organisms in affected tissues, provide an early diagnosis for only a small proportion of patients with invasive aspergillosis (IA) [3,4]. Recent studies focus on establishing an earlier diagnosis with new non-invasive diagnostic tools, mainly high-resolution computed tomography and serum *Aspergillus* galactomannan antigen testing (GM) detection. HRCT often reveals characteristic but not pathognomonic findings of invasive pulmonary mould infections (the halo-sign and the air-crescent sign) earlier than by chest radiograph [5,6]. A halo-sign on a CT scan has been reported to be the first reliable sign of infection in neutropenic patients, with a high specificity (93%) but a low sensitivity (33%) [7]. Cavitations or air-crescent formation usually occur later in the course of the disease, after hematologic recovery. However, a significant proportion of patients has non-specific pulmonary lesions, such as airway invasive aspergillosis [8].

On the other hand, prospective monitoring of high-risk patients for serum GM, may allow an earlier diagnosis in two-thirds of patients when compared with conventional diagnostic methods [9,10], although numerous variables interact in

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explaining the broad range of sensitivities (29–94%) but high specificities (85–99%) reported [11–13].

To our knowledge, the correlation between the pattern of HRCT findings and the results of serum GM have been rarely studied [3,14,15]. We designed a prospective study in hematological patients who developed a probable or proven IA (high level of diagnostic certainty), to analyse the predominant radiological pattern of pulmonary lesions in IA (airway or angioinvasive patterns) together with the results of serial serum GM testing in each case.

2. Material and methods

2.1. Selection of patients and study design

We performed a prospective, single-cohort study that included adult patients admitted to the Clinical Hematology Division of Sant Pau's Hospital in Barcelona, Spain, from January 2000 to January 2007. Our institutional committee for medical research ethics approved the study and written informed consent was obtained from all patients. All patients (inpatients) suffered from acute leukaemia or had received hematopoietic stem cell transplantation (HSCT), and had one or more predisposing risk factors to develop an IA, according to established criteria (European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC), see below) [16]. Clinical symptoms and routine laboratory tests were recorded daily for each patient. When fever (defined as a temperature of $\geq$38 °C) appeared during the neutropenic phase, with or without clinical findings, blood samples were obtained for culture and an initial (CXR) was performed. At this moment, broad-spectrum empirical antibiotic treatment was started, according to standard recommendations. In case of abnormal CXR and/or persistent fever after 5 days of antibiotic treatment, a HRCT was performed and an empirical antifungal drug was added. If HRCT showed any typical or atypical infiltrate/s, bronchoscopy with BAL was performed, when clinically possible, and the antimicrobial treatment was adjusted. Serum GM was performed 2–3 times per week during the periods of high risk for IA.

2.2. Definitions

2.2.1. High-risk patients for IA

Patients had one or more of the following factors: 1. Neutropenia (less than 500 neutrophils/mm^3 for at least 10 days) and persistent fever for more than 96 h, refractory to appropriate broad-spectrum antibacterial treatment; 2. Body temperature either >38 °C or <36 °C and any of the following predisposing conditions: prolonged neutropenia (>10 days) in previous 60 days, recent or current use of significant immunosuppressive agents in previous 30 days, or an invasive fungal infection (proven or probable) during previous episodes of neutropenia; 3. Signs and symptoms indicating graft-versus-host disease (GVHD), particularly severe acute (grade 2 or higher) or chronic extensive GVHD; 4. Prolonged (>3 weeks) use of corticosteroids in the previous 60 days.

2.2.2. Proven and probable IA (according to accepted criteria [16])

A proven pulmonary IA was referred to the histopathologic evidence of tissue invasion by filamentous fungi and positive results of culture for *Aspergillus* species, or the isolation of *Aspergillus* species from a sample (excluding BAL fluid and sinus aspirate) from a normally sterile but clinically infected body site obtained by a sterile procedure. Probable pulmonary IA implied the presence of positive culture results or cytologic evidence for *Aspergillus* species from a lower respiratory tract specimen, together with 1 major ("halo sign" or "air crescent" sign on CT scan) or at least 2 minor clinical findings (symptoms of lower respiratory tract infection, pleural rub, and presence of any new infiltrate in a patient who did not fulfil the major criterion but for whom no alternative diagnosis was available).

Positive GM testing was not considered as a conclusive microbiological criterion by itself in the current study, in order to have patients with a very high level of certainty of having an IA.

2.3. Radiological methods and definitions

The patients were examined with either a Toshiba 900 CT unit or Asteion CT scanner (Toshiba Medical Systems, Tokyo, Japan) or a Tomoscan SR 7000 scanner (Philips Medica Systems, Best, The Netherlands). The scans were obtained at end inspiration using 1.0 or 2.0 mm collimation, performed at 10 mm intervals from the apex of the lung to the diaphragm, and reconstructed with an edge-enhancing algorithm. The scans were obtained using 120 kV and 200–320 mA. The lungs were viewed at a window width of 1000–15,000 HU and level of −600 to −700 HU.

A hard copy of the CT scans was retrospectively reviewed by two radiologists (X and Y.) with more than 10 years of experience in thoracic CT image interpretation. Findings and interpretations were based on consensus opinion. The CT examinations were performed an average of 6 days after the onset of symptoms (range, 5–8 days) and only one CT scan per patient was evaluated.

The CT images were assessed for the presence, extent and anatomic distribution of air-space consolidation, areas of ground-glass attenuation, centrilobular branching structures resulting in a tree-in-bud pattern, nodules with halo and the air-crescent sign. Ground-glass attenuation was defined as an area of hazy increased attenuation without obscuration of underlying vascular markings. Air-space consolidation was considered present when the opacities obscured the underlying vessels. Parenchymal nodules were assessed as to whether or not they were surrounded by a halo of ground-glass attenuation. The air-crescent sign was recognized as a crescent-shaped or circumferential area of radiolucency within a parenchymal consolidation or nodular opacity.

Based on previous reports [17,18], invasive aspergillosis was divided into airway and angioinvasive. Airway invasive aspergillosis was considered when the predominant CT find-