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Original article

Mortality risk factors in patients with zygomycosis: a retrospective and multicentre study of 25 cases

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ABSTRACT

Aim: To investigate mortality risk factors in patients with zygomycosis.
Patients and Methods: Retrospective case history review of patients diagnosed with proven zygomicosis in 17 centres in Spain. We compared demographics and risk factors in patients who survived, and in those who died.
Results: We identified twenty-five patients with proven zygomycosis. The primary site of infection was rhino-orbito-cerebral (28%) and disseminated (20%) or cutaneous/soft infections (20%) of the patients. Eleven patients (44%) received preemptive or empirical antifungal treatment; of these patients, 4 received liposomal amphotericin B, 1 received amphotericin B lipid complex, and 6 received other antifungals. The overall mortality rate was 72%. In the univariate analysis factors associated with an increased risk of death were the presence of a haematological malignancy (P = .03), neutropenia (P = .03) and monocytopenia (P = .008).
Conclusion: Our study supports previous research that has documented a high mortality rate among patients with invasive zygomycosis, especially among those with an underlying haematological malignancy, and the need for a rapid initiation of an effective antifungal treatment.

Factores de riesgo de mortalidad en pacientes con zigomicosis: un estudio retrospectivo y multicéntrico de 25 casos

Palabras clave:
Zigomicosis
Mortalidad
Factores de riesgo
Anfotericina B

RESUMEN

Objetivo: Investigar los factores de riesgo de mortalidad en pacientes con zigomicosis.
Pacientes & Métodos: Revisión retrospectiva de pacientes diagnosticados de zigomicosis documentada en 17 centros en España, comparando los datos demográficos y los factores de riesgo entre los pacientes que sobrevivieron y aquellos que fallecieron.
Resultados: Se identificaron 25 pacientes con zigomicosis probada. El lugar primario de la infección fue rino-órbito-cerebral (28%) e infecciones diseminadas o cutáneas / de tejidos blandos en el 20% de los pacientes cada una. Once pacientes (44%) recibieron tratamiento antifúngico anticipado o empírico; de estos pacientes, cuatro de ellos recibieron anfotericina B liposomal, un paciente recibió anfotericina B complejo lipídico y 6 pacientes recibieron otros antifúngicos. La tasa de mortalidad global fue del 72%. En el análisis univariado, los factores asociados a un mayor riesgo de muerte fueron la presencia de enfermedad hematológica maligna (p = 0,03), neutropenia (p = 0,03) y monocitopenia (p = 0,008).

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Conclusión: Los datos de nuestro estudio concuerdan con los de trabajos previos que habían documentado una elevada tasa de mortalidad en pacientes con zigomicosis invasiva, especialmente en aquellos con enfermedad hematológica maligna subyacente, y la necesidad de instaurar rápidamente un tratamiento antifúngico eficaz.

Introduction

Zygomycosis is a rare but devastating invasive fungal infection (IFI) caused by the agents of Zygomycetes, most commonly by those of the order Mucorales.[1] Zygomycosis is becoming increasingly important among certain populations, such as recipients of haematopoietic stem cell or solid-organ transplants and among patients with haematological malignancies.[1,2] In these populations, reports of zygomycosis have been increasing since the 1990 s,[2,3] and zygomycosis has become the third leading cause of IFI (following invasive aspergillosis and invasive candidiasis).[1,4] Although it has been proposed that this increase in the frequency of zygomycosis might be due to the introduction of voriconazole, an antifungal not active against Zygomycetes, for the prophylaxis of opportunistic fungal infections,[5,6] this association is not yet well-established.[3]

The clinical manifestations of invasive zygomycosis include tissue necrosis from invasion of blood vessels and subsequent thrombosis, and the most common clinical presentations are a rhinocerebral syndrome and pulmonary infection.[1] A definitive diagnosis of zygomycosis can be difficult to reach and requires histopathological confirmation.[1] The adequate management of zygomycosis requires a multifaceted approach that includes the control or reversal of the underlying risk factors (such as diabetic ketoacidosis or immunosuppression), surgical debridement, and the use of systemic antifungal therapy.[1,7] Amphotericin B, particularly the liposomal formulation, is the mainstay for the treatment of this IFI.[7-9] More recently, posaconazole has also been shown to be active against zygomycosis,[10] with some evidence of its clinical efficacy as a salvage therapy[11,12] but without the same spectrum of coverage as amphotericin B.

Zygomycosis has a poor prognosis. Despite the introduction of amphotericin B, mortality in patients with zygomycosis is high and has remained almost unchanged in the last four decades.[2] According to data from the largest series of patients with zygomycosis,[2] the current mortality rate is close to 40%, and it can be as high as 76% in cases of pulmonary zygomycosis.[2] However, a smaller study examined 16 cases of proven zygomycosis and found an overall mortality rate of only 25%.[13] These different mortality rates may be due to differences in the clinical characteristics of the cases or in their management. To better manage this serious infection, it is important to know what factors are associated with a greater risk of mortality.

Our study was aimed at investigating risk factors for mortality in a retrospective case series of patients with proven zygomycosis.

Patients and methods

We performed a retrospective review of the clinical history of all patients with zygomycosis who were seen in seventeen health centres in Spain between January 1, 2007 and June 30, 2008. Patients were included in the study only if they had no previous history of zygomycosis and had been diagnosed with proven zygomycosis according to the EORTC/MSG criteria.[14]

A standardised case report form was used to extract information from the medical records. Demographic information, including age and sex, and clinical data were recorded. The clinical information collected included (1) clinical outcome and, in cases of death, the relationship between this outcome and the IFI; (2) site of the infection (categorized as sinusitis, sinopulmonary, pneumonia, rhino-orbito-cerebral, disseminated, and cutaneous/soft-tissue infection); (3) underlying conditions and APACHE II at the time of diagnosis; (4) risk factors for zygomycosis within one month of the diagnosis (including type of bone marrow transplantation (BMT), graft-versus-host disease grade, use of immunosuppressive therapy, cytomegalovirus infection, diagnosis of diabetes mellitus, hyperglycaemia defined as a glucose level equal to or greater than 200 g/dL, neutropenia defined as a neutrophil count equal to or lower than 500 cells/mm^3, lymphopenia, monocytopenia, acidosis defined as a pH value lower than 7.35, malnutrition defined as a serum albumin level equal to or lower than 3 g/dL, use of corticosteroids, use of tumour necrosis factor inhibitors, serum iron level, serum ferritin level, and use of deferoxamine therapy); (5) use of an antifungal agent within three months of the diagnosis as either prophylactic, pre-emptive, empirical, or targeted therapy; and (6) whether or not the patient underwent surgical debridement.

Demographic and clinical characteristics were described using the mean, median and standard deviation for continuous measures and the frequency and percentage for categorical variables. The demographic information and risk factors of patients who survived were compared with the information of those who died in a univariate analysis using the Student's *t*-test, Chi-squared test, or Fisher's exact test where appropriate. In addition, a stepwise logistic regression analysis was planned to explore variables independently associated with mortality. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois). All analyses were two-tailed and were considered significant if $P < .05$.

Results

Throughout the 18-months study period, we identified twenty-five patients with proven zygomycosis. Patients were predominantly male (80%) with a median age of 46 years. The most common underlying conditions were haematological malignancies (52%) and diabetes mellitus (32%). At the time of diagnosis, nearly one third of the patients presented with rhino-orbito-cerebral infections; 20% of the patients presented with disseminated infections and 20% presented with cutaneous/soft-tissue infections. The median of the follow-up duration was 2 months (interquartile range 0.9 to 5.5) and the mean (SD) was 5.2 (7.1) months. Mean time between the beginning of the symptoms and the diagnosis, independently of patient outcome, was 8 days. In all cases, targeted antifungal treatment was started in the first 24 h after a confirmatory diagnosis. Patient demographics, underlying conditions, infection locations and case history are presented in Table 1.

Eleven patients (44%) received pre-emptive or empirical antifungal treatment; of these, 4 (16%) received liposomal amphotericin B (in one case, this treatment was combined with caspofungin), 1 (4%) received amphotericin B lipid complex, and 6 (24%) received other antifungals (Table 2). These other antifungals were not effective against zygomycosis. The rationale to start empirical or pre-emptive antifungal treatment was based on clinical suspicion by the clinician in charge of the patient. One patient did not receive any antifungal treatment, and the remaining thirteen patients (52%) commenced antifungal treatment after they were diagnosed with zygomycosis. The most common antifungals, used either alone or in combination as targeted treatment, were