Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007

A. Skiada[1], L. Pagano[2], A. Groll[3], S. Zimmerli[4], B. Dupont[5], K. Lagrou[6], C. Lass-Florl[7], E. Bouza[8], N. Klimko[9], P. Gaustad[10], M. Richardson[11], P. Hamal[12], M. Akova[13], J. F. Meis[14], J.-L. Rodriguez-Tudela[15], E. Roilides[16], A. Mitrousia-Ziouva[17] and G. Petrikkos[18] for the European Confederation of Medical Mycology Working Group on Zygomycosis*

1) *1st Department of Propaedeutic Medicine, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece,* 2) *Institute of Hematology, Catholic University, Rome, Italy,* 3) *Infectious Disease Research Program, Center for Bone Marrow Transplantation and Department of Pediatric Hematology/Oncology, Children's University Hospital, Münster, Germany,* 4) *Institute for Infectious Diseases, University of Bern, Bern, Switzerland,* 5) *Hôpital Necker, Maladies Infectieuses et Tropicales, Paris, France,* 6) *Department of Medical Diagnostic Sciences, K.U. Leuven, Leuven, Belgium,* 7) *Division of Hygiene and Medical Microbiology, Innsbruck Medical University, Innsbruck, Austria,* 8) *Department of Clinical Microbiology and Infectious Diseases, Hospital General 'Gregorio Marañón', Madrid, Spain,* 9) *Department of Clinical Mycology, Allergiology and Immunology, Saint Petersburg Medical Academy of Postgraduate Education, Saint Petersburg, Russia,* 10) *Institute of Medical Microbiology, Rikshospitalet University Hospital, Oslo, Norway,* 11) *Regional Mycology Laboratory, University Hospital of South Manchester, Wythenshawe Hospital and The University of Manchester, Manchester Academic Health Science Centre, School of Translational Medicine, Manchester, UK,* 12) *Institute of Microbiology, Palacky University, Faculty of Medicine, Olomouc, Czech Republic,* 13) *Hacettepe University School of Medicine, Section of Infectious Diseases, Ankara, Turkey,* 14) *Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands,* 15) *Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Madrid, Spain,* 16) *3rd Department of Pediatrics, Aristotle University School of Medicine, Hippokration Hospital, Thessaloniki, Greece,* 17) *Department of Microbiology, National and Kapodistrian University of Athens, Athens, Greece and* 18) *4th Department of Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, 'Attikon' Hospital, Athens, Greece*

Abstract

Zygomycosis is an important emerging fungal infection, associated with high morbidity and mortality. The Working Group on Zygomycosis of the European Confederation of Medical Mycology (ECMM) prospectively collected cases of proven and probable zygomycosis in 13 European countries occurring between 2005 and 2007. Cases were recorded by a standardized case report form, entered into an electronic database and analysed descriptively and by logistic regression analysis. During the study period, 230 cases fulfilled pre-set criteria for eligibility. The median age of the patients was 50 years (range, 1 month to 87 years); 60% were men. Underlying conditions included haematological malignancies (44%), trauma (15%), haematopoietic stem cell transplantation (9%) and diabetes mellitus (9%). The most common manifestations of zygomycosis were pulmonary (30%), rhinocerebral (27%), soft tissue (26%) and disseminated disease (15%). Diagnosis was made by both histology and culture in 108 cases (44%). Among 172 cases with cultures, *Rhizopus* spp. (34%), *Mucor* spp. (19%) and *Lichtheimia* (*formerly Absidia*) spp. (19%) were most commonly identified. Thirty-nine per cent of patients received amphotericin B formulations, 7% posaconazole and 21% received both agents; 15% of patients received no antifungal therapy. Total mortality in the entire cohort was 47%. On multivariate analysis, factors associated with survival were trauma as an underlying condition (p 0.019), treatment with amphotericin B (p 0.006) and surgery (p <0.001); factors associated with death were higher age (p 0.005) and the administration of caspofungin prior to diagnosis (p 0.011). In conclusion, zygomycosis remains a highly lethal disease. Administration of amphotericin B and surgery, where feasible, significantly improve survival.

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Corresponding author: G. Petrikkos, 4th Department of Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, 'Attikon' Hospital, Rimini 1 – Haidari, Athens 12464, Greece
E-mail: petrikos@hol.gr, petrikos@med.uoa.gr

*Members of the ECMMM Working Group on Zygomycosis are listed in the Appendix section.

Introduction

Although often described as a rare fungal infection, zygomycosis (mucormycosis) appears to be increasing in frequency [1]. It mainly affects immunocompromized patients, such as those with haematological malignancies, recipients of haematopoietic stem cell (HSCT) [2] or solid organ transplants (SOT) [3], patients with diabetes mellitus and ketoacidosis [4,5], and infants with prematurity [6]. Zygomycosis may also affect immunocompetent patients with trauma or burns, or patients with elevated serum levels of iron under treatment with deferroxamine. The increased frequency of this infection is attributed to the rising prevalence of diabetes mellitus, as well as to the increased use of immunosuppressive treatments. The introduction of newer antifungals, in particular voriconazole, has also been suggested to play a role in the increased incidence of zygomycosis [7]. Due to the relative rarity of the disease it is difficult to perform stringent epidemiological studies to estimate its exact incidence. Most of the available data stem from case series and pertain to haematological patients [8] or to patients who have undergone transplantation [9]. An active population-based surveillance in the Bay Area of San Francisco, USA, was published in 1998 [10].

While mortality approached 100% in the older literature depending on the patients' underlying disease and the type of zygomycosis [11], it has been reduced since amphotericin B has become available [12]. Since then, however, it has remained essentially unchanged. Nevertheless, with the availability of the less toxic lipid formulations, survival rates of up to 85% have recently been reported in select patient populations [13,14].

Taking into consideration the challenges related to epidemiology, treatment and outcome of zygomycosis, a working group on zygomycosis was formed by the European Confederation of Medical Mycology (ECMM). The aim of the group was to analyse the clinical characteristics, microbiology, treatment practices and outcome of zygomycosis in Europe through a voluntary case registry. We present here the results of the first 3 years (2005–2007) of this effort.

Patients and Methods

Study design

In each participating European country, a national coordinator was appointed, who prospectively collected zygomycosis cases, recorded by the treating physicians in standardized case report forms (CRFs), which were then sent either by e-mail or fax to the general study coordinator. The national coordinators were all experts in the field of zygomycosis and in most cases were appointed by the respective national Mycology Societies. The participating hospitals were selected by the national coordinator on the basis of their capacity to document all episodes of zygomycosis occurring during the study period.

Mucorales isolates were initially identified at the participating institutions by the routine methods used in each laboratory. Molecular identification was then performed either at a national centre (Institut Pasteur in Paris, Medical University in Innsbruck, etc.) or the isolates were sent to a central laboratory in Spain (National Centre for Mycology, Madrid) for sequencing. Furthermore, coordinators were informed that they could send paraffin-embedded tissue for PCR identification to a central laboratory in Germany [15].

In order to be included as a case in the registry, sufficient information regarding diagnosis, predisposing factors and clinical presentation had to be provided. The CRFs were reviewed by the principal investigators (GP and AS) and queries were sent to the national coordinators in order to complete missing data. After completing the database, a data review committee examined all the data. The study was approved by the Ethics Committee of the University of Athens 'Laikon General Hospital', in Athens, Greece, the institution of the principal investigators. In addition, approval was also obtained from local ethics committees of all collaborating countries according to local regulations.

Definitions

For the classification of each case as proven or probable, the revised definitions of invasive fungal disease of the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) were used [16], with the following modification: if the diagnosis was made by histology and there was PCR testing on tissue positive for zygomycetes (from the central laboratory described above), the case was classified as proven zygomycosis, even if there were no cultures available. In addition, diabetes mellitus was also included in the host criteria.

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