Epidemiology of Zygomycosis in Cairo, Egypt

Thesis

Submitted in Partial Fulfillment of the Requirement for the Degree of M.Sc. in Microbiology

By

Nadia El-Sayed Ahmed Mohamed El-Kady

(B.Sc. Microbiology, 2007)

DEPARTMENT OF MICROBIOLOGY

FACULTY OF SCIENCE

AIN SHAMS UNIVERSITY

2013

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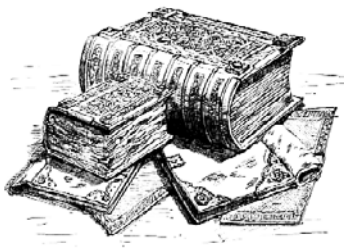
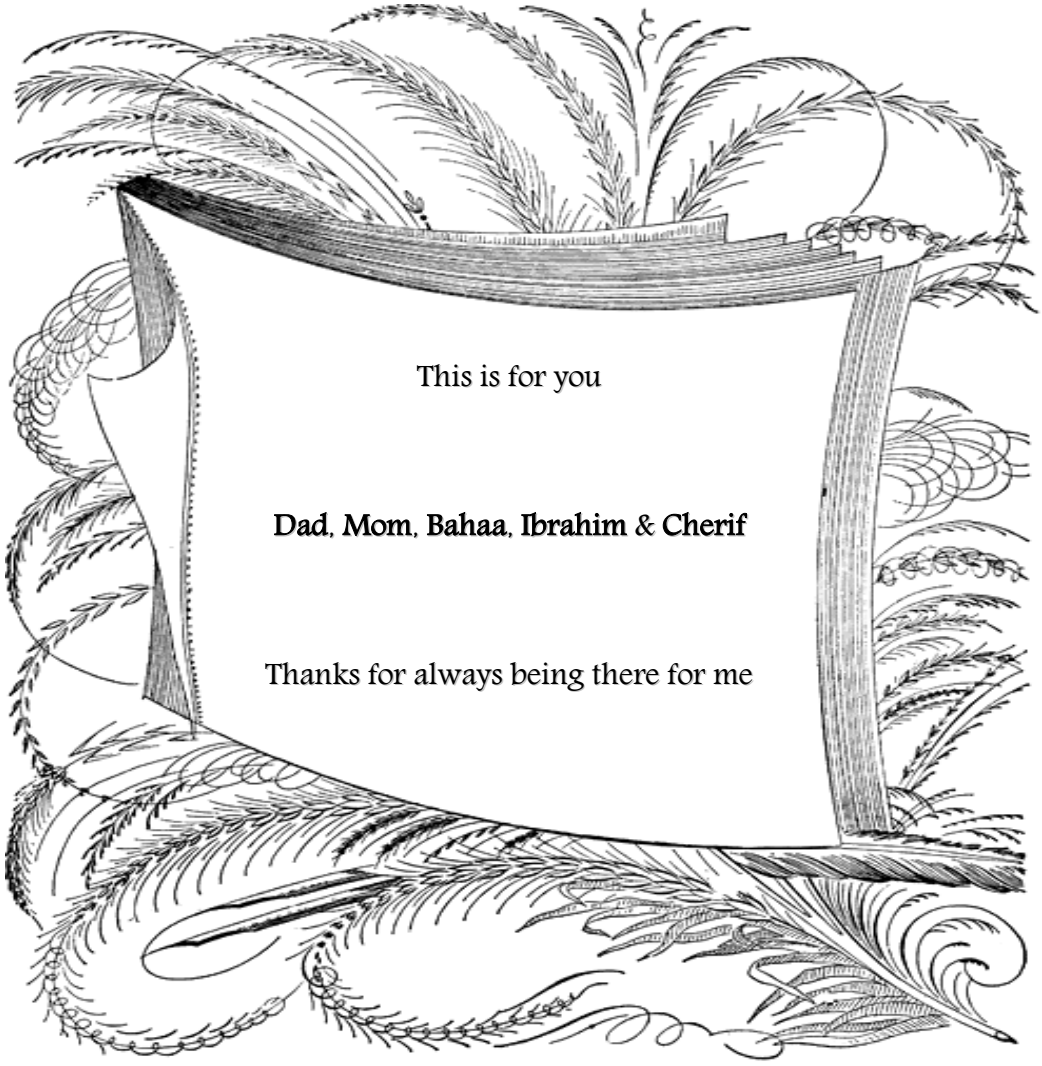
I certify that the thesis titled "*Epidemiology of Zygomycosis in Cairo, Egypt*" is my own work. The work has not been presented elsewhere for assessment. Where material has been used from other sources it has been properly acknowledged / referred.

Signed

Nadia El-kady





This is for you

Dad, Mom, Bahaa, Ibrahim & Cherif

Thanks for always being there for me

Acknowledgement

First and foremost, I thank Allah for all his blessings and for being my strength and guide through the good and bad times of my life.

I am forever grateful to my supervisors, **Prof. Dr. Khairya A. Youssef**, Prof. of Mycology and **Dr. Sherif M. Zaki,** Assistant Prof. of Microbiology, at Microbiology Department, Faculty of Science, Ain Shams University and **Dr. Iman M. Elkholy**, Assistant Consultant at Ain Shams University Specialized hospital; for their support, guidance and encouragement in time of difficulties and new ideas. Their discussions and comments have led to key insights and their sincere advice has been invaluable on both an academic and a personal level. I am also particularly grateful for the assistance given by **Dr. Samar Samir**, lecturer of Microbiology, Microbiology Department, Faculty of Science, Ain Shams University throughout this work. Thanks are also due to **Dr. Sahar Farouk**, Ain Shams University Specialized hospital and Dr. **Ahmed Moukhtar**, Wadi El-Nil Hospital, for their help and assistance.

Utmost gratitude is also due to all the members of Department of Microbiology, Faculty of Science, Ain Shams University for their support that kept me going on.

I thank my dearest and closest friends who did a significant part in making my life a fruitful and memorable one as well, especially **Noha Mohamed**.

Above all, I would like to thank my family for their unequivocal support throughout, as always, for which my mere expression of love and thanks likewise does not suffice.

شكر و تقدير

أولا و أخيرا، الحمد لله رب العالمين حمدا كثيرا على نعمه ظاهرة و باطنة.

كامل الشكر و التقدير للسادة الأساتذة الذين قاموا بالإشراف على هذه الرسالة حتى تظهر بصورة لائقة و هم: **أ.د. خيرية عبد الغنى يوسف،** أستاذ الفطريات المتفرغ، قسم الميكروبيولوجى، كلية العلوم، جامعة عين شمس، **د. شريف محمد زكى،** أستاذ الميكروبيولوجى المساعد، قسم الميكروبيولوجى، كلية العلوم، جامعة عين شمس، و **د.إيمان محمد الخولى،** الإستشارى المساعد بمستشفى عين شمس التخصصى جامعة عين شمس.

ثم أتقدم بخالص الشكر إلى كل من ساعدنى قولا أو فعلا أثناء قيامى بهذا العمل لإخراجه فى أحسن صورة و كذلك أشكر والدى و والدتى و إخوتى.

كما أتوجه بجزيل الشكرلأعضاء هيئة التدريس و الهيئة المعاونة و جميع العاملين بقسم الميكروبيولوجى، كلية العلوم، جامعة عين شمس على دعمهم المتواصل.

Abstract

To our knowledge, this is the first epidemiological study discussing the pattern of zygomycosis in Egypt. 1000 patients hospitalized at Ain Shams University Specialized Hospital and Wadi El Nil Hospital in Cairo, Egypt during the year 2010 were included in this study. The results obtained showed that 573 cases were positive for fungal infection, while 427 were negative. A total of 364 positive cases were male patients (63.5%) while 209 positive cases were female (36.5%). A total 246 positive cases were less than 50 years old (42.9%) while 327 positive cases were more than 50 years old (57.1 %). The highest number of patients positive for fungal infections was among cancer patients (174 cases, 17.4%) and the least number was among renal failure patients (46 cases, 4.6%). Pulmonary presentation was the most common clinical manifestation of fungal diseases (58.3%) while sinusitis and cerebral infections were the least encountered manifestations by 0.35% each. Yeast and yeast-like group were the most frequently encountered etiologic agents, where they were recovered from 82.5% of cases, followed by *Aspergillus* group which represented 15.5% of cases. Zygomycetes group

came next by 1.7% and finally *Fusarium* by 0.3%. Based on the criteria of The European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) for defining invasive fungal diseases, this study recorded 10 cases with mucormycosis among patients with a recent history of neutropenia, prolonged use of corticosteroids and treatment with immunosuppressants. The reported cases were categorized as 50% proven mucormycosis and 50% probable mucormycosis. No cases were classified as possible mucormycosis. The median age of the patients with proven and probable mucormycosis was 50 years (range 22 – 68 years), of which 80% were male and 20% were female. Uncontrolled diabetes with ketoacidosis was common in 60% of cases and liver transplantation comes next by 40% of cases. Pulmonary mucormycosis was the predominant presentation representing 80% of cases, while sinus involvement constituted only 20% of cases. *Lichtheimia* was the predominant genus seen in 40% of cases, while the genus *Rhizopus* was seen in 30% of cases. 20% of cases were infected with *Syncephalastrum* and 10% were infected with *Rhizomucor*. *L. ramosa* and *R. oryzae* were the predominant species; both of them were recovered from 30% each,

followed by *S. racemosum* which obtained from positive cultures of 20% of cases. Both *L. corymbifera* and *Rhizomucor pusillus* were the etiologic agents in 10% of cases. Liposomal formulation of amphotericin B (LAMB) has been successfully used to treat all the cases we reported. We concluded that the incidence of mucormycosis was relatively high during the study period. No cases of entomophthoramycosis were recorded during the study period. Further studies on the epidemiology, diagnosis and the control of zygomycosis in Egypt are required.

Introduction

Zygomycosis is known as a human disease for more than 100 years but has remained largely understudied partly due to the low frequency of the disease **(Dannaoui & Garcia-Hermoso, 2007)**.

The history of zygoymycosis dates back to the 19th century in 1855, when Kurchenmeister described a case of zygomycosis (*Mucor*) in a neoplastic lung. Fiirbringer in 1876 then described pulmonary zygomycosis caused by *Absidia*. In 1884, Lichtheim established the pathogenicity of the Mucorales in rabbits and described the two species: *Mucor* (*Absidia*) *corymbifera* and *M. (Rhizopus) rhizopodiformis* **(Espinel-Ingroff et al., 1987)**.

Paltauf described the first well documented case of systemic zygomycosis with gastric and rhino-cerebral involvement in a 52-year old white male cancer patient in 1885. His descriptions, in German, were detailed enough to suggest that this case was caused by *Absidia corymbifera* **(Espinel-Ingroff et al., 1987; Ribes et al., 2000; Antachopoulos et al., 2008** and **Meis & Chakrabarti, 2009)**.

In many of the cases reported thereafter the infection was identified as "mucormycosis" or *Mucor* infection based solely on histological findings of wide, rarely septate hyphae, without culture confirmation. This term, however ignored the important role that the Entomophthorales play in causing the disease **(Ribes et al., 2000** and **Antachopoulos et al., 2008)**.

Unlike most of the Mucorales which enjoy a worldwide distribution of both organism and human disease, disease due to Entomophthorales is mostly seen in tropical climates, primarily in India, South America, and Africa despite their occurrence as environmental organisms worldwide **(Ribes et al., 2000)**. Disseminated disease is uncommonly described with the Entomophthorales **(Kimura et al., 2011)**.

The degree of invasiveness of disease is also markedly different for the Mucorales and Entomophthorales. While the hallmark of infection for the Mucorales is invasion of blood vessels, thrombosis, tissue necrosis, acute inflammation, and dissemination, the Entomophthorales typically lack these features. Entomophthoramycosis is characterized by

slowly enlarging subcutaneous nodules that eventually ulcerate forming a chronic inflammatory response **(Ribes et al., 2000)**.

Disease caused by the Mucorales is summarized by the term "opportunistic infections". Disease in immunocompetent hosts represents a tiny minority of cases in the Mucorales. The exact reverse of this is true for Entomophthorales infections. Disease occurs primarily in normal, immunocompetent hosts, with relatively few cases currently seen associated with immunocompromised patients **(Ribes et al., 2000)**.

In recent years, not only has the geographic distribution of entomophthoramycosis expanded but also the etiology of the disease and the range of the infected hosts have broadened **(Ribes et al., 2000)**. Given their distinct clinical presentations, the term "mucormycosis" should be reserved for those infections caused by Mucorales, and the term "entomophthoramycosis" for those caused by Entomophthorales **(Prabhu & Patel, 2004)**.

The term of zygomycosis is broader and more relevant when fungal cultures are not available or the fungal identification is not known, so it

is currently preferable, reflecting all disease processes caused by the members of the class Zygomycetes, but unfourtunately, it ignores the diversity of the disease caused by the organism in these two orders **(Ribes et al., 2000; Sundaram et al., 2005** and **Chayakulkeeree et al., 2006)**.

For all of its benefits, medical progress has led to an expanding population of susceptible hosts with impaired immunological defenses against infection. Although the increasing use of invasive monitoring and aggressive therapeutic technologies in intensive care units has resulted in improved survival of individuals with life threatening illnesses, it has also contributed to an increase in the number of persons at risk for invasive fungal infections **(Warnock, 2007)**.

New diagnostic tools and improved therapeutic strategies are urgently needed and a better understanding of the biology of the pathogens and the epidemiology of the disease will be of particular importance in the coming years.

During the past several decades, there has been a steady increase in the frequency of opportunistic invasive fungal infections in immunocompromised patients. However, there is substanial controversy concerning optimal diagnostic criteria for these invasive fungal diseases. Therefore, members of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EROTC/MSG) formed a consensus committee to develop standard definitions for Invasive Fungal Disease (IFD).

These standard set of IFD definitions were approved in order to foster communication, for better understanding of the epidemiology and evolution of IFD and facilitating the ability to test the efficacy of therapeutic regimens and strategies. The approved definitions are as follows: a proven IFD case was based on a histopathologic, cytopathologic or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae are seen accompanied by evidence of associated tissue damage. Alternatively, recovery of a mould by culture of a specimen obtained by a sterile

procedure from a normally sterile and clinically or radiological abnormal site consistent with an infectious disease process. Probable IFD cases require presence of a host factor, clinical features and mycological evidence. Possible IFD cases require presence of appropriate host factors, clinical evidence consistent with IFD and absence of mycological support **(De Pauw et al., 2008)**.