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Incidence of zygomycosis in transplant recipients

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Abstract

Recently, a remarkable increase in the incidence of zygomycosis has been reported from institutions in the USA and Europe. The use of voriconazole for the treatment of aspergillosis and, less frequently, the use of echinocandins as empirical treatment for invasive fungal infections are thought to be responsible for the increase. In addition, an increased incidence of this infection has been observed in transplant recipients, including both haematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) patients. There are no global surveys on the prevalence or incidence of zygomycosis, but data from individual institutions and countries show that zygomycosis is an emerging infection. The increased incidence of zygomycosis most probably reflects a greater frequency of predisposing factors, such as higher numbers of patients undergoing HSCT and immunosuppressive chemotherapy. In addition, the emergence of rare pathogens as a result of the rise in the use of antifungal therapy against common species can be postulated. Further, the availability of antifungal agents with activity profiles that are more specific for selected fungi increases the necessity of identifying pathogenic fungi; the frequency of Zygomycetes infections may have been underestimated until now because therapeutic decisions did not depend on the precise identification of pathogenic fungi.

Keywords: Echinocandins, emerging diseases, invasive fungal infections, mucorales, voriconazole

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Introduction

The Zygomycetes are ubiquitous and thermo-tolerant microorganisms which are largely saprotrophic, feeding on decaying organic matter, including vegetables, fruits, seeds, bread, soil, compost piles and animal excreta. These species sporulate abundantly and spores are easily airborne [1].

In general, members of the Mucorales cause the more severe form of zygomycosis, also called mucormycosis, whereas the Entomophthorales cause more chronic disease of the nasal mucose and subcutaneous tissue. These infections are uncommon in immunocompetent patients, in whom they cause a localized infection that is easily treatable. However, mucormycosis in the debilitated patient may be the most fulminate opportunistic fungal infection known [2,3].

Mycoses caused by the Mucorales are emerging fungal infections which occur in immunocompromised patients. Recently, a remarkable increase in their incidence has been reported from single institutions in the USA and Europe [4,5]. The use of voriconazole for the treatment of aspergillosis and, less frequently, the use of echinocandins as empirical treatment for invasive fungal infections (IFI) are thought to be responsible for the increased incidence of zygomycosis [2,6,7].

An increased incidence of these fungal infections has also been observed in transplant recipients, including both haematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) patients. There are no global surveys of the incidence of zygomycosis, but data from individual institutions and countries show that zygomycosis seems to be a new and emerging concern in these groups of patients [2].

We reviewed reports and publications on the incidence of zygomycosis in transplant recipients and determined if the increase in its incidence can be considered significant from an epidemiological point of view. We undertook a MEDLINE search using the keywords 'zygomycosis', 'mucormycosis', '*Rhizopus*', '*Mucor*', '*Rhizomucor*', '*Absidia*', '*Cunninghamella*', 'transplant recipients', 'solid organ transplantation' and 'haematopoietic stem cell transplantation', as well as a text word search. We included reports published on MEDLINE from 1970 onward. The analysis was divided into two periods to include reports published during 1970–2005 and those

published during 2006–2008. We separated the reports according to these time periods because surveys showing an increase in the incidence of zygomycosis supposedly caused by the use of voriconazole were initially reported in 2005 and, if voriconazole represents a risk factor for outbreaks of zygomycosis, an increased incidence in reports should be observed from that year onward.

Analysis of Reports of Zygomycosis in Transplant Recipients During 1970–2005

As stated above, there are no global surveys of the prevalence of incidence of zygomycosis. Most published data consist of reports from single institutions and retrospective studies depicting the epidemiological status of zygomycosis in single countries. There are also a limited number of publications on multicentre prospective studies analyzing the incidence of zygomycosis in both SOT and HSTC recipients.

One of those prospective surveys was performed by RESITRA (Spanish Net for Research in Transplant Recipients), a research network formed by 16 transplant centres and three reference laboratories, which prospectively analyzed all SOT and HSCT recipients from 2003 to 2005. A total of 3487 patients were included (2615 SOT and 872 HSCT patients). The rate of IFI was 3.8% (133 cases). Only two cases of zygomycosis were described (2/133, 1.5%) and both occurred in allograft HSCT recipients.

Data from the USA can be accessed in the multicentre register TRANSNET, which has recorded infections in transplant patients since 2001. In 2003 the published rate of zygomycosis in liver and heart transplant recipients suffering from IFI in some American institutions was 5.7% [8]. Other American institutions have reported prevalences of zygomycosis in SOT and HSCT in the range of 0.2–3.5% [9–14].

Authors from other countries have published surveys with fragmentary data on the prevalence of zygomycosis in their institutions. Studies from Austria, Belgium, Italy and France have revealed infection rates in the range of 0.3–2.0% [15–19]. Non-European countries such as Japan, Brazil, Israel and Kuwait have reported similar figures of zygomycosis prevalence [20–23], but India and Iran have reported higher rates, particularly in kidney transplant recipients [24,25], and an Iranian centre reported a prevalence as high as 7.8% (4/51 cases) in orthotopic liver transplant recipients [26].

In addition, there are two exhaustive literature reviews on zygomycosis in transplantation which include cases reported up to 2005 [27,28]. These reviews report a total of 160 cases of zygomycosis in transplant recipients. Notably, 108 cases (65%) refer to SOT patients, of whom 73 underwent renal transplants, 19 underwent liver transplants and 16 underwent heart transplants. The most frequent clinical presentation was pulmonary infection, which occurred in 26% of transplant recipients with zygomycosis. Table 1 displays the most common presentations of zygomycosis in these groups of patients.

TABLE 1. Most common clinical presentations of zygomycosis in transplant recipients according to Davari *et al.* (2003) [26] and Almyroudis *et al.* (2006) [27]

Clinical presentation	Percentage (%) of zygomycosis cases
Pulmonary	26
Rhino-sino-orbital	20
Cutaneous	17
Rhinocerebral	15
Disseminated	12
Gastrointestinal	10

Analysis of Reports of Zygomycosis in Transplant Recipients During 2006–2008

Some anecdotal case reports published in 2004 and surveys published in 2005 indicate that an increased incidence of zygomycosis may be occurring as a result of the use of voriconazole to treat aspergillosis and other fungal infections [2,4–7,29–31]. This rise has been observed particularly in patients suffering from malignancies or in those who have undergone HSCT [4].

In the last 3 years, a significant increase in the incidence of breakthrough zygomycosis has been observed. This increase has occurred mainly in allo-HSCT patients on antifungal prophylaxis, but there have also been some reports of an increased incidence of zygomycosis in SOT [7,11,32–36].

In 2007 Trifilio *et al.* [37] published a cohort study on zygomycosis after voriconazole exposure in 13 oncological centres in the USA. Patients were enrolled after ≥5 days of voriconazole therapy and were diagnosed by culture or histology. A total of 58 cases were detected, of whom 56 (96.5%) had been treated with voriconazole. Among transplant recipients, a total of 36 of 58 cases (62%) referred to patients who had undergone HSCT [37].

Spanish institutions within RESITRA have detected ten cases of zygomycosis (data not published), of which seven occurred in HSCT and three in SOT patients. In addition, some Spanish institutions have reported an incidence of 0.62 cases per 100 000 hospital admissions [38].

Including surveys and case reports, the literature reports a total of approximately 200 cases of zygomycosis in transplant recipients, of which 160 occurred up to 2005 and 40

occurred during the subsequent 3 years [4,5,7,11,19,28, 32–37].

Discussion

At present, *Candida* and *Aspergillus* spp. are the most common causes of opportunistic fungal infection, but other rare emerging species belonging to several groups, such as the Zygomycetes, are increasingly reported as causes of lethal infection. Several factors have been proposed as causes of the increasing numbers of reports of opportunistic infections and the emergence of rare moulds. Environmental changes, antimicrobial pressure and an expanding population of immunocompromised hosts are the most commonly proposed. In addition, efficient control and eradication of more prevalent species can extend the niche of rare and more resistant fungi [3]. The use of voriconazole for the treatment of aspergillosis may be responsible for the increase in the incidence of zygomycosis because it is inactive against Zygomycetes [6, 37].

It could also be argued that the increase in the number of cases reported may not be as significant as it appears and that the incidence of zygomycosis has been underestimated for two reasons. Firstly, until recently there has been a shortage in the number of medical mycology experts with the capability to identify rare fungi. Secondly, there has been a lack of interest in the precise identification of pathogens as distinct alternatives for treatment were not available; thus, although it was essential to know if the patient was suffering from a fungal infection, it was not vital to identify the genus and species. Consequently, for many years there has been a lack of reliable epidemiological information with which to ascertain the prevalence and incidence of fungal infections that have been precisely identified.

Conclusions

We consider that there may be a combination of explanations for the increased incidence of reports of zygomycosis. The significant rise reflects a greater frequency of predisposing factors, such as higher numbers of patients undergoing HSCT and immunosuppressant chemotherapy. In addition, the emergence of rare pathogens as a result of the increased use of antifungal therapy against common species is plausible. However, it should also be accepted that the current availability of several antifungal agents with activity profiles that are more specific for selected fungal species increases the interest of identifying fungal species and that the prevalence of Zygomycetes may have been underestimated until now.

It should also be noted that emergent fungal infections will continue to increase in clinical settings in which experts such as microbiologists, haematologists and paediatricians are interested in precise fungal identification.

Transparency Declaration

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