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Mini review

A Fatal Case of Otomycosis due to *Lichtheimia* Spp in an Immunocompromised Patient with a Brief Review of *Lichtheimia*

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Abstract

The genus *Lichtheimia* consists of fungal species (Mucorales, Zygomycetes), which are ubiquitous soil inhabitants and represent important causative agents of mucormycoses in human and animals. Subsequent phylogenetic and physiological studies showed that Absidia-like fungi represent three separate lineages *Absidia, Lentamyces, Lichtheimia*. Only the last group has clinical relevance. Infection due to *Lichtheimia* spp is an infrequent opportunistic infection that can potentially be angioinvasive when affecting immunocompromised patient. In the present study we are discussing a case of A 68 yrs old male with type 2 diabetes, and chronic kidney disease, presented with right side otalgia with purulent discharge from right external auditory canal. This minireview throws light on fatal nature, various diagnostic modalities and treatment available for *Lichtheimia.*

Keywords: ***Lichtheimia, otomycosis, immunocompromised, mucorales, mucormycosis***

1. Introduction

Mucormycoses, i.e., infections caused by members of the Mucoromycotina subphylum, are uncommon but often dramatic, requiring immediate action on the basis of an accurate diagnosis [1]. The recently observed increase in case reports on mucormycosis can be ascribed to the growing number of patients with risk factors, such as diabetes, neutropenia, bone marrow transplantation, and the long-term use of steroids [1]. The Zygomycetes genus *Lichtheimia* was first named Mycocladus, typified by *Mycocladus verticillatus*. However, the type strain of that species turned out to represent a mixed culture of *Absidia sensu stricto*, and possibly, a *Lentamyces* species; thus, it was not congeneric with any of the thermotolerant species. Therefore, this group had to be renamed with the oldest available genus name, *Lichtheimia* [2]. *Lichtheimia* species are emerging opportunistic fungal pathogens in the Mucorales, causing serious skin and respiratory infections in immunocompromised patients [3].

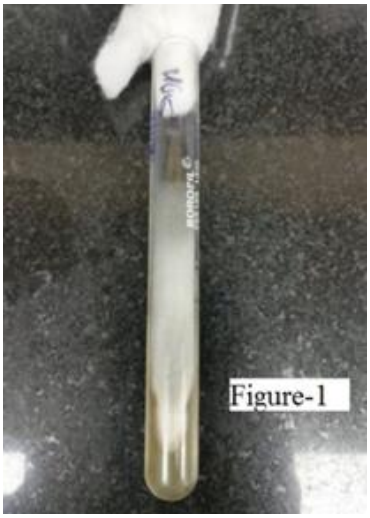
In post COVID era mycoses has been studied in depth by various broad specialities of Medicine. Every 150 million severe cases of fungal infections occur worldwide, resulting in approximately 1.7 million deaths per year [53]. Currently there is increase in patients with mycotic lesion of outer and middle ear due to significant increase in risk factors and uncontrolled use of antibacterial drugs [54].

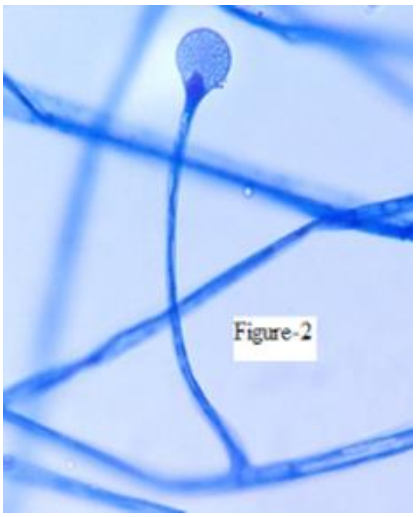
Otomycosis or fungal otitis externa is a superficial, subacute or chronic infection of External Auditory Canal (EAC) with irregular complications involving the middle ear [55]. It is characterised by inflammation, pruritus, scaling, otalgia, fullness of ear, tympanic membrane perforation, hearing impairment and ear discharge [55]. Habit of swimming, lack of ear hygiene, immunocompromised conditions, use of steroids without consultation are the main risk factors of otomycosis [56]. Special care has to be taken to prevent infection and treatment should be started as soon as possible [56]. If adequate treatment is not taken then there is a chance of recurrence of otomycosis [56]. This minireview throws light on fatal nature, various diagnostic modalities and treatment available for *Lichtheimia*

2. Case History

A 68 years old male patient admitted in the general medicine ward had complaint of pain in the right ear which was associated with purulent discharge from external auditory meatus and intermittent fever since 1 month. His past medical history included well-controlled type 2 diabetes mellitus since 24 years and Hypertension

since 25 years. Patient was on hemodialysis for chronic kidney disease since 6 years. There were no other physical examination findings of note. Patient was on antihypertensive drugs for chronic kidney disease and regular human Insulin for type 2 diabetes. Empirical antifungal was administered as ear drops which contains 5% clotrimazole and 1% beclomethasone and 0.025% lignocaine for his right ear pain. An ear swab sample from right external auditory canal was collected and sent to microbiology laboratory for routine fungal culture and potassium hydroxide (KOH) mount examination. On KOH mount no fungal elements were seen but within 4 days sabouraud's dextrose agar (SDA) showed coarse woolly gray surface which covered agar slant with fluff resembling gray cotton candy with white obverse(**Figure-1**). Lactophenol cotton blue mount revealed wide aseptate hyphae (6-15 mm in diameter) (**Figure-3**), the columella was typically shaped like a semicircle with a small, domelike projection on top. The sporangia are small (20–90 mm in diameter) and slightly pear shaped instead of round (**Figure-2**). The sporangiospores were round to oval (3–5 mm in diameter). Same growths were seen on both SDA tubes which were incubated at 25^0C and 37^0C.





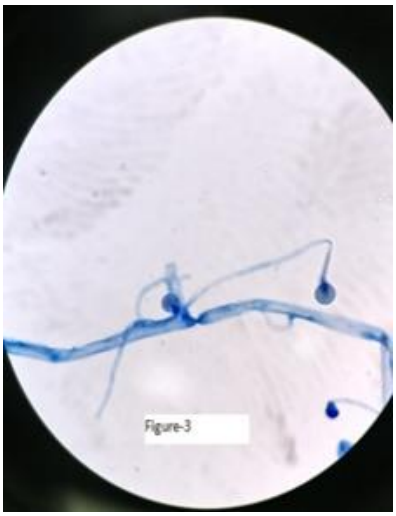


Figure 1: Growth of *Lichthemia spp* on SDA at 25ºC
Figure 2: LPCB Mount showing *Lichthemia spp* under 40x
Figure 3: LPCB Mount showing sporangiophore and aseptate hyphae *Lichtheimia* under 40x

Otomycosis is one of the common entities affecting the external auditory meatus and the ear canal. The presenting symptoms include: scaling, pain, pruritus and erythema [2]. The majority of cases caused by *Lichtheimia* species relate to patients that are severely debilitated due to malignancies, poorly controlled diabetes or solid organ transplantation [4]. *Lichtheimia* produces spectrum of infections which are cutaneous, pulmonary, rhino cerebral, renal and disseminated infections as well as otomycosis [4]. In the present case report we have presented a case of otomycosis due to *Lichtheimia* spp. The diagnosis was confirmed by SDA Culture. Our KOH and SDA Culture findings were concordant with study done by Mohanty A *et al* 2021 [57]. where it was found out that out of 186 samples 6 samples (3.22%) were only positive in Culture and an another study by Begari V et.al 2019 [58]. where also it was found out that out of 50 samples 3(6%) were only culture positive. Our patient was immunocompromised with type 2 diabetes and chronic Kidney disease. Type 2 diabetes is well known factor for mucormycosis [5]. According to a clinicomycological study by Ravinder Kaur *et al*, earache and ear discharge are the major complaints in 65.2% and 50.5% patients, respectively [5]. Their findings correlated well with the symptoms of the present case. Otomycosis has a worldwide distribution and it is estimated that approximately 10-20% of total external otitis cases are due to otomycosis [2]. Otomycosis is more frequent in adults and is less common among children [2].

In the present case, *Lichtheimia spp* caused local mucormycosis in an immunocompromised patient. In a case study published by Cecilia *et al*. necropsy report of the patient revealed that *Lichtheimia* can cause thrombotic mycosis of lungs, kidney,brain, thyroid, heart, spleen, liver, lymph nodes, bladder, ureter, and small bowel. Once the infection disseminates the most frequent locations affected are those near to the origin of infection [52].

4. Epidemiology

The exact incidence/prevalence of *Lichtheimia* infection is not known because there are few population-based studies, and they differ in capture periods, populations and definition or diagnostic procedures [6]. The most common source of mucoralean outbreaks was contaminated medical devices that are responsible for 40.7% of the outbreaks followed by contaminated air (31.3%), traumatic inoculation of soil or foreign bodies (9.4%), and the contact (6.2%) or the ingestion (6.2%) of contaminated plant material. Outbreaks of *Lichtheimia* species were transmitted by direct contact [7]. Uncontrolled diabetes mellitus was the most common risk factor for all forms of mucormycosis [8]. *Lichtheimia* accounts for 0.5-13% cases from India among which most are due to *Lichtheimia* ramose [9].

5. Predisposing Factors

In an Indian study done by Ashopa *et al* 2021 Ear Pricking was most common predisposing factor followed by oiling, swimming, use of local antimicrobials, and diabetes [55]. According to a study done by Schulze *et al* 2017, a murine pulmonary infection model was established, to study the predisposing factor leading to *Lichtheimia* Infection [9]. The study revealed that immunosuppression was essential for establishment of infection and ketoacidosis did not predispose to infection with *Lichtheimia corymbifera* or *Lichtheimia ramose* [9].

6. Pathogenesis

Lichtheimia is a less virulent and infrequent pathogen in comparison to *Rhizopus, Mucor* and other Mucorales [10]. The initial host defences against sporangiospores of Mucorales are intact barriers,

i.e. skin and respiratory as well as intestinal mucosa. Innate immune cells such as neutrophils, monocytes/macrophages and dendritic cells are important in the host defences against Mucorales [11]. There is different interspecies susceptibility to host responses exist within the order Mucorales however the exact mechanisms underlying such variable responses against Mucorales have not yet been elucidated. One of the critical characteristics of Mucorales is angioinvasion that leads to vessel thrombosis and tissue necrosis [12]. Infections are usually initiated by either inhalation of spores, or are associated with traumatic or surgical wounds, facilitating cutaneous or deep-tissue infections. Notably, infections can spread hematogenously and by direct invasion of adjacent tissue [13]. Although *Lichtheimia* species are known as pathogens since the 19th century, no comprehensive study about the pathogenic potential and pathogenesis of *Lichtheimia* species in humans exists till date [9].

7. Clinical Features

Spores enters the host through respiratory tract which manifest as pulmonary infection. Pulmonary infections with L. *corymbifera* have been reported in patients with different underlying diseases, including bone marrow and solid organ transplantation, uncontrolled diabetes and leukaemia [14]. Pulmonary *Lichtheimia* infections can disseminate to different internal organs, including the central nervous system, often associated with fatal outcome.

Another common clinical manifestation caused by *Lichtheimia* species is cutaneous and subcutaneous infections which are associated with contamination of wounds, either with plant material during accidents, or via non-sterile bandages or surgical dressings [15-21]. Superficial infections can occur in Immunosuppressive patients which are characterised by rapid tissue necrosis leading to purple to black discolouration of the skin [22-29]. In premature infants, *Lichtheimia* infections commonly affect the gastrointestinal tract often resembling necrotising enterocolitis [30-31]. Very less number of studies on mucormycosis have examined the infection to species specific level. Alvarez *et al*. included seven cases of *Lichtheimia* infections with pulmonary infection and infections of the sinuses as the most important presentations [32].

8. Laboratory Diagnosis

8.1 Specimen collection

The prompt diagnosis of any fungal infections is of paramount importance to guide appropriate treatment and to avoid adverse outcomes [33]. The clinical materials from infected area, nasal discharge or sputum may rarely contain fungal elements [34]. Biopsy of deeper tissue is required for appropriate diagnosis [35]. Blood cultures, while an appealing approach for angioinvasive disease, are essentially always negative [36]. Obtaining a sterile biopsy specimen involves cleaning the affected area with chlorhexidine or other antimicrobial cleanser to eliminate surface organisms, followed by obtaining a biopsy specimen under sterile technique and with prompt submission to microbiology, where direct examination and culture is performed [37].

8.2 Direct Examination

Microscopic examination of tissue biopsy specimen in potassium hydroxide(KOH) wet mount shows broad aseptate hyphae with wide angle branching at irregular interval. Mucorales are also very well seen in Hematoxylin & Eosin(H&E) stain [38].

8.3 Fluorescent Microscopy

Wide, sparsely septate hyphae can be seen when biopsy material examined by fluorescence microscopy using the optical brightener Blankophor [39]. By fluorescent microscopy broad aseptate hyphae can also be visualised in tissue slices with negative histopathological findings [40].

8.4 Culture

Yield of culture is greatly increased if whole tissue samples are minimally processed and placed directly onto cycloheximide-free culture media [41]. It is recommended not to homogenize tissue material and specimens must be directly inoculated on to culture media to keep viability of fungal cells [42]. Growth is seen usually within few days because mucorales are rapid growers. Obverse side shows coarse woolly gray surface which rapidly covers agar slant with fluff resembling gray cotton candy and white reverse [43]. Same appearance is seen in both the SDA tubes incubated at 25^0C and 37^0C after 24 hrs [44]. The isolates can be identified as *Lichtheimia sp*. based on the micromorphological features in the slide culture under Lactophenol Cotton Blue(LPCB) mount [45].

8.4.1 Micromorphological features of LPCB Mount

Broad non septate hyphae (6–15 mm in diameter), sporangiophores of *Lichtheimia* arise (often in small clusters) at points on the stolon that are between the rhizoids. The sporangiophores (up to 450 mm long) are branched and widen near the top, forming a conical apophysis just below the columella. The columella is typically semicircle in shape with a small, domelike projection on top. The sporangia are relatively small (20-90 mm in diameter) and slightly pear shaped. The sporangiospores are round to oval (3-5 mm in diameter) [41].

8.4.2 Matrix Assisted Laser Desorption Ionisation time of flight mass spectrometry (MALDI-TOF MS)

The technique involves extraction of proteins from the fungal cells, spotting of the specimen on a grid, and overlaying the spot with a matrix. The spectrum is generated rapidly and is compared with a reference database [42]. All five species of *Lichtheimia* can be easily distinguished from all other clinically important mucoralean genera by the help of MALDI-TOFF MS.

8.5 Molecular Methods

The molecular detection of Mucorales is currently restricted to the detection of deoxyribonucleic acid (DNA), as ß-D-glucan and galactomannan assays do not detect this fungal group. Due to the angioinvasive nature of Mucorales infections, the load of circulating Mucorales DNA in serum was found to be very high [43,44]. So blood samples are suitable for suspicion-independent screenings of high-risk patients and therapeutic monitoring [43]. Several Studies had been done for molecular diagnosis by different PCRs targeting different genes of *Lichtheimia corymbifera*, which were Multiplex PCR +Restriction Fragment Length Polymorphism (RFLP) targeting 18S rRNA gene [45], PCR+ Microarray targeting ITS 1/5.8S rRNA/ITS 2 gene [46]. Detection of *Lichtheimia spp* by the above-mentioned molecular technique were reliable and can be used as an effective alternative to the conventional identification methods.

9. Treatment

Whenever there is high suspicion of mucormycosis, emperical treatment should be started in patient because delay in treatment also increases the chances of mortality [48]. Intravenous liposomal amphotericin B should be started at 5 mg/kg daily with increase to 10 mg/kg as first line treatment along with aggressive debridement of infected tissue [49]. In patients that cannot tolerate amphotericin B, intravenous posaconazole can be used, although it is contraindicated in patients with end-stage renal disease [50] but incidence rates of invasive fungal diseases were successfully reduced by posaconazole

200 mg three times daily [47]. Intravenous or oral isavuconazole can be used in posaconazole-intolerant patients [51].

10. Conclusion

Patients infected by *Lichtheimia* more likely to acquire disseminated infections. It can be angioinvasive when affecting immunocompromised hosts. Early diagnosis and treatment is very important in a case of *Lichtheimia* infection. If diagnosis and treatment are delayed it may result in massive tissue destruction and, eventually death of patient. One need to clinically suspect mucormycosis in presence of associated risk factors. More comprehensive studies are required which can elucidate information about the epidemiology, risk factors, pathogenesis of *Lichtheimia* infections among humans

Conflicts of Interest

There is no conflict of Interest

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Authors' contributions

All authors contributed equally to this work.

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