Chapter 5
Chaetomium in Indoor Environment and Medically Important Species of *Chaetomium*

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5.1 Introduction

Fungal contamination in damp or water-damaged buildings has become an increasing problem worldwide (Andersen et al. 2011). After water damage (e.g., leaking water pipes, flooding, faulty building constructions, or severe and prolonged condensation), many building materials become good substrates for certain fungi. These growing fungi can cause adverse effects not only on the buildings but also to their occupants (WHO 2009; Samson et al. 1994; Samson et al. 2010; Flannigan and Miller 2011; Andersen et al. 2011; Miller and McMullin 2014). Members of the genus *Chaetomium* are capable of colonizing various substrates and are well-known for their ability to degrade cellulose and produce a variety of bioactive metabolites. More than 400 species have been described in *Chaetomium*. Some of these species have been reported to be important inhalant allergens. They contribute to the development of the symptoms of both rhinitis and asthma due to the production of mycotoxins and microbial volatile organic compounds as well as the liberation of ascospores and hyphal fragments in the indoor environment (Gonianakis et al. 2005; Apetrei et al. 2009; Polizzi et al. 2009; Mason et al. 2010; Andersen et al. 2011; Miller and McMullin 2014). *Chaetomium globosum* is the most common species of the *Chaetomiaceae* in the indoor environment (Vesper et al. 2007; Ayanbimpe et al. 2010; Straus 2011; McMullin et al. 2013; Miller and McMullin 2014), and this species can already be present in new gypsum wallboard (Andersen et al. 2017). *Chaetomium globosum* has been reported to produce a variety of toxic metabolites, such as chaetoglobosins, chaetomugilins, and chaetoviridins (Andersen et al. 2011; McMullin et al. 2013; Miller and McMullin 2014), while both *C. elatum* and *C. globosum* were able to produce cochliodones in pure cultures as well as on naturally contaminated building materials (Došen et al. 2017). Little is known about the other

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indoor *Chaetomium* species and their potential hazard to humans and buildings. Furthermore, *C. globosum* and several other *Chaetomium* species are reported as causal agents of onychomycosis or superficial infections (Naidu et al. 1991; Koch and Haneke 1965; Hubka et al. 2011; Aspiroz et al. 2007; de Hoog et al. 2013a), and some of them are capable of opportunistically causing deep or systemic infections (Hoppin et al. 1983; Guppy et al. 1998; Barron et al. 2003; Ahmed et al. 2016).

The genus *Chaetomium* is commonly recognized by having ostiolate ascomata with a membranaceous perithecial wall covered by relatively well-developed hairs, producing fasciculate and evanescent asci and single-celled, smooth, and pigmented ascospores with germ pores (Ames 1963; von Arx et al. 1986). *Chaetomium globosum*, the type species of the genus, was first described by Kunze (Kunze and Schmidt 1817). The taxonomy of *Chaetomium* has been studied by several authors (Corda 1840; Zopf 1881; Chivers 1915; Skolko and Groves 1948, 1953; Sörgel 1960; Ames 1963; Mazzucchetti 1965; Seth 1970; Dreyfuss 1976; Millner 1977; Millner et al. 1977; von Arx et al. 1984). von Arx et al. (1986) re-defined the taxonomic concept of *C. globosum*. They included species that produce globose to ovate or obovate ascomata with a wall consisting of textura intricata, covered by a diverse morphology of ascomatal hairs ranging from erect, flexuous to regularly coiled. The ascomata contain clavate (or slightly fusiform), evanescent asci, and the ascospores are limoniform and bilaterally flattened shaped and have an apical germ pore. Following this concept, 28 species were reduced to synonymy with *C. globosum*. The species concept of *C. globosum* sensu von Arx was not supported by a recent study (Asgari and Zare 2011). On the basis of phylogenetic inference of six loci and morphological characters, *C. globosum* was again revised by Wang et al. (2016), and six species that were treated as synonyms of *C. globosum* by von Arx et al. (1986) were resurrected. Furthermore, the non-ostiolate genus *Chaetomidium* was also synonymized with *Chaetomium* (Wang et al. 2016).

Melanized fungi are important causes of human infection, and about 70 genera representing hundreds of species have been implicated in human disease (de Hoog et al. 2013b; Guppy et al. 1998; Revankar and Sutton 2010; Revankar et al. 2002). Several main ecological groups can be distinguished. Members of *Chaetothyriales* exhibit pronounced virulence and cause deep and systemic infections in immunocompetent humans, e.g., chromoblastomycosis or brain infection (Badali et al. 2009; Revankar and Sutton 2010). Members of Pleosporales are preponderantly found as degraders of plants debris or as mild opportunistic pathogens; human infections mostly comprise traumatic inoculation of contaminated materials (Revankar and Sutton 2010). Recently, the significance of *Sordariales* was underlined (Badali et al. 2011; de Hoog et al. 2013a), particularly the *Chaetomiaceae*, whose prevalence has been underestimated because of diagnostic problems.

Phenotypically, the identification of clinical *Chaetomium*-like fungi has been difficult as a large proportion of them fail to produce typical diagnostic structures in culture (Najafzadeh et al. 2014; Vinod Mootha et al. 2012). Until recently, fungi lacking propagation in the form of conidia were treated in the clinical laboratory as unidentifiable 'mycelia sterilia'(Pounder et al. 2007; Santos et al. 2013; Vinod Mootha et al. 2012). Isolates forming clumps or bulbils were referred to as

Papulaspora, whereas filamentous strains from subcutaneous infection were known as *Madurella* (de Hoog et al. 2013a). With the application of molecular phylogenetic multi-gene DNA sequence analyses, such isolates were found to be of high diversity being distributed to many genera and families of ascomycetes. In addition, the species proved to comprise several sibling species that were previously thought to represent a single taxon.

Recently, more attention has been paid to the non-sporulating *Chaetomium*-like isolates that cause human infection (Najafzadeh et al. 2014; Vinod Mootha et al. 2012), such as keratitis or subcutaneous infection after trauma. Despite application of molecular phylogenetic methods, researchers were unable to identify these isolates down to species level in the genus *Chaetomium* because of the present state of morphological confusion and high phylogenetic divergence in the genus.

Chaetomium contains more than 300 described species and are generally cosmopolitan and reside in soil on cellulose-rich materials or on dung (Bell 2005; Carter and Khan 1982; Doveri 2008; von Arx et al. 1986). A certain prevalence of *Chaetomium*-like species was noted in desert soil subjected to conditions of dryness and extremely variable temperatures (Rodríguez et al. 2004). Members of the *Madurella* clade, phylogenetically located inside the genus *Chaetomium*, are typically confined to areas with arid climates. *Madurella* species are consistent agents of human subcutaneous mycoses, and the arid areas of northeastern Africa are endemic for human mycetoma (Ahmed et al. 2002, 2016). Most human infections by *Chaetomium*-like species concern traumatic inoculations into otherwise healthy humans and rarely occur as deep infections in severely immunocompromised hosts (Al-Aidaroos et al. 2007; Guppy et al. 1998; Hubka et al. 2011).

5.2 Clinical Features

Despite being saprophytic ascomycetes with only occasional involvement in human disease processes, *Chaetomium* are capable of inducing a broad spectrum of mycoses including onychomycosis, sinusitis, empyema, pneumonia, and fatal disseminated cerebral disease, especially in immunocompromised patients and intravenous drug users (Hoppin et al. 1983; Anandi et al. 1989; Yeghen et al. 1996; Aru et al. 1997; Thomas et al. 1999).

Chaetomium atrobrunneum is a notably invasive, neurotropic species, and its ability to grow at elevated temperatures may contribute to its neurotropism (Stiller et al. 1992; Guarro et al. 1995; Friedman 1998; Guppy et al. 1998; Rock 1998; Lesire et al. 1999).Thomas et al. (1999) described a case of fatal brain abscess due to *C. atrobrunneum* in a bone marrow transplant patient. The rapid progression of cerebral infection indicates that the brain tissue provides a favorable environment for growth and proliferation of the fungus. In 2019, Mhmoud et al. reported *C. atrobrunneum* for the first time causing human eumycetoma (Fig. 5.1).

Chaetomium strumarium is another invasive, neurotropic species. Abbott et al. (1995) reported three *C. strumarium*-related cases of fatal cerebral mycosis in males

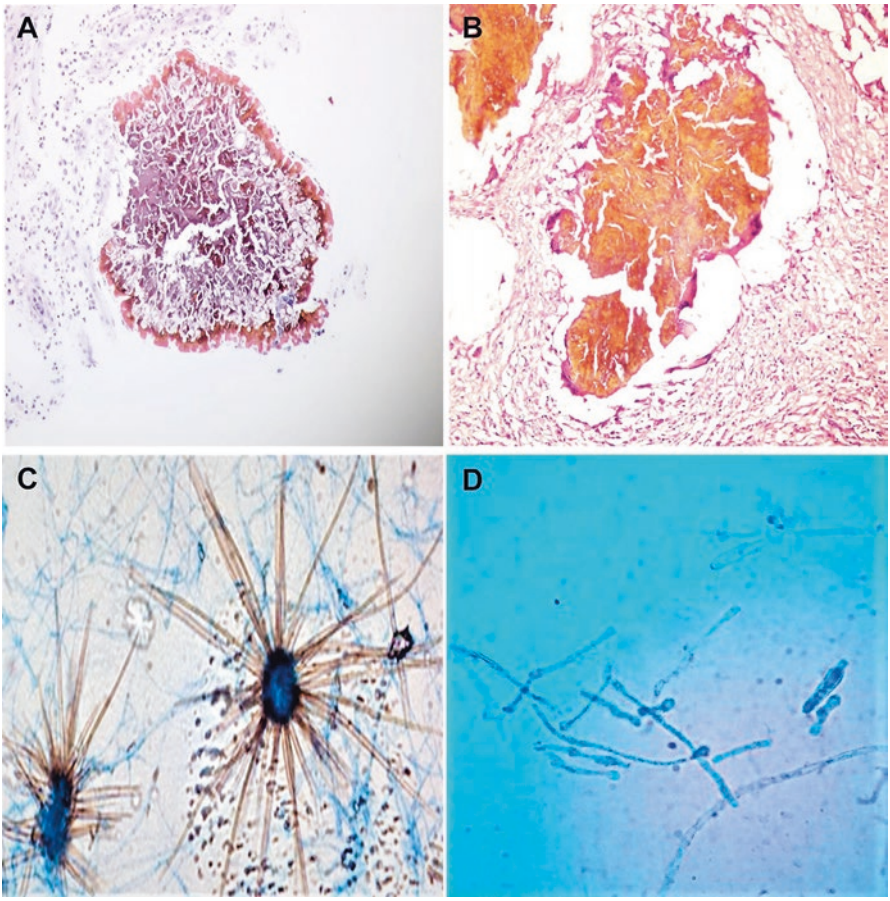

Fig. 5.1 Microphotograph showing multiple black grains surrounded by granulation tissue with marked histiocytic and mixed inflammatory cellular infiltrates (HE 10×). (**a**) Grains of *Chaetomium* spp. showed abundant extracellular matrix, which was yellow to brown in colour, and the fungus hyphae are located at the periphery of the matrix with short filamentous structure. (**b**) The filamentous pattern of *M. mycetomatis* grains consists of brown septate and branched hyphae at the centre and periphery with long filament. (**c, d**) Microphotograph of LPCB mount showing ascoma and ascospore cells resembling the typical *Chaetomium* spp. cells (**c**) and conidia of *M. Mycetomatis* (**d**). HE, haematoxylin–eosin; LPCB, lactophenol cotton blue (after Mhmoud et al. 2019)

with prior histories of intravenous drug use from the United States and Australia. *C. strumarium* was detected by histopathology and isolated from the brain tissue.

Chaetomium perlucidum is recently confirmed as a neurotropic species. Barron et al. (2003) documented the first two cases of invasive human mycoses caused by this phaeoid ascomycete. The first case concerned a 45-year-old female patient with acute myelogenous leukemia, who had an unrelated, 4/5 HLA-matched umbilical cord blood transplant. The patient became disoriented and febrile; computed tomography of the chest revealed a 3 × 2 cm mass in the right lower lobe. After suffering

a massive right-sided intraparenchymal hemorrhage, the patient died. Autopsy revealed disseminated invasive fungal infection in the lungs, brain, and myocardium; and cultures from the surgically obtained lung tissue yielded *C. perlucidum*. The second case involved a 78-year-old female with a history of asthma and chronic bronchiectasis. The patient underwent a lobectomy due to worsening symptoms, and cultures from the lung tissue grew *C. perlucidum*. The patient showed no further manifestations of disease after the lobectomy.

Chaetomium globosum is an occasional agent of onychomycosis (Stiller et al. 1992; Lesire et al. 1999). In addition, Teixeira et al. (2003) reported that *C. globosum* was responsible for a systemic infection with enlargement of the axillary and cervical lymph nodes in a chronic myeloid leukemia patient, who underwent an allogeneic sibling-matched bone marrow transplant. Culture of the aspirates from both lymph nodes resulted in the growth of *C. globosum*. The infection was successfully treated with amphotericin B.

5.3 Diagnosis

Considerable similarities exist between mycosis caused by *Chaetomium* and *Aspergillus* from radiographical and histopathological standpoints. A melanin-specific stain (i.e., the Masson-Fontana stain) is helpful reputedly for distinguishing the melanin-containing *Chaetomium* from most *Aspergillus* species. However, this is contradicted by reports of melanin from *Aspergillus* (e.g., *Aspergillus fumigatus*) (Youngchim et al. 2004), and so the information obtained may have limited value in differentiating the causal fungi.

In vitro culture techniques offer a slow but valuable way to isolate and propagate *Chaetomium* organisms for subsequent macroscopic and microscopic characterization. Inoculation of sterilized plant material with ascospore suspension may enhance induction of mature perithecia, leading to the production of well-developed ascomata on the surface of the substrate.

Molecular methods such as (i) PCRand (ii) sequencing analysis of the rRNA and internal transcribed spacer (ITS) regions provide an approach for the rapid and accurate identification of *Chaetomium* species from other fungi.

5.4 Methods

5.4.1 Sample Preparation

Clinical specimens are examined by microscopy with a melanin-specific stain (i.e., the Masson-Fontana stain). However, as mentioned above, a melanin stain may not be particularly useful. Portions of the samples are inoculated on Sabouraud glucose

agar with or without antibiotics. The resulting isolates are identified on the basis of macroscopical and microscopical features.

Genomic DNA of fungal pellets was extracted using a cetyltrimethylammonium bromide (CTAB) method described previously by Möller et al. (1992). Amplification and sequencing were performed for the internal transcribed spacer (ITS) and D1/D2 domains of the 28S rRNA gene, partial translation elongation factor 1-α (TEF1), β-tubulin (Btub), and DNA-dependent RNA polymerase II largest subunit (RPB1) and second largest subunit (RPB2). Primers used for amplification and sequencing are according to de Hoog et al. (2013b).

DNA sequences were assembled and edited using SEQMAN from the Lasergene package (DNASTAR, Madison, WI, U.S.A.). Sequences will be deposited in GenBank. To study the phylogenetic position of the unknown species, two alignments will be generated. Sequences will be aligned with the online version of MAFFT v.7 (http://mafft.cbrc.jp) and manually adjusted using BIOEDIT v.7.1.3 software (Hall 1999). Each gene will be aligned independently and concatenated matrices will be prepared using DATACONVERT v. 1.0. The first alignment consisted of ribosomal ITS and LSU sequences of representative species of *Chaetomium*, *Chaetomidium*, *Thielavia*, *Papulaspora*, *Subramaniula*, and *Madurella*. The second alignment consisted of the protein coding loci TEF1, Btub, RPB1 and RPB2 sequences of a selected number of strains. Alignments and trees will be deposited in TreeBASE database.

Phylogenetic analyses using maximum likelihood were performed in RAxML v. 8.0.24 (Stamatakis 2014). Bayesian analyses with default priori of MRBAYES v. 3.1.2 were conducted using the CIPRES Science Gateway server. Two simultaneous Markov chain Monte Carlo samplings were performed with four chains of which one was cold and three were heated.

The run was conducted for 30,000,000 generations with sampling every 100 generations and the 'burn in' was set at 25% of resulting trees. Convergence was evaluated from the two independent runs using AWTY and TRACER v. 1.5 (Nylander et al. 2008; Rambaut and Drummond 2007).

Phaeohyphomycosis and onychomycosis due to *Chaetomium* spp., including the first report of *Chaetomium brasiliense* infection, have been studied by Hubka et al. (2011). *Chaetomium* species have been rarely described as etiological agents of invasive and dermatomycotic infections in humans. The majority of cases have been reported within the last two decades. Treatment failed in most of these cases. In their study, they presented two cases in which *Chaetomium spp*. can be clearly identified as an etiological agent in pathological conditions. In the first report, they described a new etiological agent, *Chaetomium brasiliense*, which was implicated in a case of otitis externa in a patient with spinocellular carcinoma basis cranii. The patient had been repeatedly treated for relapsing otitis externa and had previously undergone surgery several times for otitis media. The fungal etiology was confirmed by repeated positive culture and histologic studies. The second case involved onychomycosis with strikingly brown nail discoloration due to *Chaetomium globosum* in an otherwise healthy patient. The nail lesion was successfully cured by oral terbin-

afine. The determination of both species was supported by sequencing of rDNA regions.

Eumycetoma is a traumatic fungal infection in tropical and subtropical areas that may lead to severe disability. *Madurella mycetomatis* is one of the prevalent etiologic agents in arid Northeastern Africa. The source of infection has not been clarified. Subcutaneous inoculation from plant thorns has been hypothesized, but attempts to detect the fungus in relevant material have remained unsuccessful. de Hoog et al. (2013a) tried to find clues to reveal the natural habitat of *Madurella* species using a phylogenetic approach, i.e., by comparison of neighboring taxa with known ecology. They found four species of *Madurella* were included in a large data set of species of *Chaetomium, Chaetomidium, Thielavia*, and *Papulaspora* ($n = 128$) using sequences of the universal fungal barcode gene rDNA ITS and the partial LSU gene sequence. Their study demonstrates that *Madurella* species are nested within the *Chaetomiaceae*, a family of fungi that mainly inhabit animal dung, enriched soil, and indoor environments. They hypothesized that cattle dung, ubiquitously present in rural East Africa, plays a significant role in the ecology of *Madurella*. If cow dung is an essential factor in inoculation by *Madurella*, preventative measures may involve the use of appropriate footwear in addition to restructuring of villages to reduce the frequency of contact with etiologic agents of mycetoma. On the other hand, they mentioned that *Chaetomiaceae* possess a hidden clinical potential which needs to be explored.

A consistent human pathogen is thus introduced in the family *Chaetomiaceae*. Traditionally, most species of the family were considered to be insignificant as agents of human disease. The majority of *Chaetomium* clinical strains analyzed in de Hoog et al. (2013a) study were probably transient colonizers or agents of mild superficial disorders. Twenty-seven were involved in onychomycosis or cutaneous and eye infections in otherwise healthy individuals. This matches with literature data (Hattori et al. 2000; Hubka et al. 2011). Data of de Hoog et al. (2013a) illustrated that *Chaetomium globosum* showed a definite bias toward superficial infection, with 17 out of 29 strains analyzed. The species is able to degrade keratin by production of extracellular keratinases (Kaul and Sumbali 1999). Fatal, disseminated, and cerebral infections by *Chaetomiaceae* have also been reported. In the literature, about 20 deep and disseminated cases were described, nearly all in immunocompromised and severely debilitated patients (Guppy et al. 1998; Badali et al. 2011). Several *Chaetomium*-like fungi thus show rather pronounced pathology, sometimes with species-specific predilections.

Grain formation in tissue by *Chaetomiaceae* other than *Madurella* is not known. A single case of chromoblastomycosis by *Chaetomium funicola* was reported by Piepenbring et al. (2007). The few subcutaneous cases (Lin et al. 1995) all showed hyphae in tissue rather than the compact grains of *Madurella mycetomatis*. In contrast to *Madurella*, none of the infecting *Chaetomiaceae* was exclusively clinical; all contained environmental strains as well. If agents of black-grain mycetoma have a relatively limited distribution in the phylogeny of *Sordariales*, i.e., are clustered within a single family, *Chaetomiaceae*, one may hypothesize that these fungi are predisposed to human infection and thus are likely to share a set of fundamental

virulence factors. Many members of *Chaetomiaceae* have their natural habitat in soil or on mammal dung. A possible explanation of their recurrent virulence may lie in physiological properties such as growth at the human body temperature of 37 °C and the production of secondary metabolites such as inhibitors of chemokines and TNF-a (Rether et al. 2004; Chan and Chu 2007). Particularly the fatal brain infections, which were repeatedly reported in *Achaetomium strumarium* (synonym of *Chaetomium strumarium*) (Abbott et al. 1995; Aribandi et al. 2005), in *C. atrobrunneum* (Hubka et al. 2011), and in *Thielavia subthermophila* (Badali et al. 2011), all belonging to the *Chaetomiaceae*, are remarkable. The hidden clinical diversity of *Chaetomiaceae* urgently needs to be explored. The role of mammal dung and dung-enriched soil is one of the prime ecological niches in the order *Sordariales*, and this also holds true for *Chaetomium* (Zhang et al. 2006). Some species in the current study exclusively grow in dung, such as *Chaetomium homopilatum*. Multiple *Chaetomium* and *Thielavia* species have been isolated in East Africa from different kinds of dung, ranging from cow and horse to more exotic types of dung such as that of elephant and wildebeest (Carter and Khan 1982). Conversely, the position of *Madurella* in *Chaetomiaceae* is informative for the natural habitat of this pathogen. In the highly endemic area in Sudan, *M. mycetomatis* has as yet not been cultured, whereas the isolation of other causative agents of mycetoma, *Nocardia brasiliensis, Actinomadura madurae*, and *Streptomyces somaliensis*, has been successful (Aghamirian and Ghiasian 2009).

In Sugiyama et al. (2008) described a case of erythematous epilation of a dog caused by *C. globosum*. A mixed-breed young dog, a 4-month-old male, weighing 7.25 kg, showed depilation, scales, and dermatitis with slight itchiness on his skin. The main symptom was an erythematous epilation on the left subocular skin, 7.5 cm in diameter, accompanied by elephantiasis-like hyperplasia and scales. Similar lesions were observed on the skin on both sides of the ear lobes, the heels, tail, and left angulus oris. The scales from the crusted lesion were cultured on chloramphenicol-added potato dextrose agar plates at the first visit; this was followed by ambulatory practices. The isolates at the first visit, 1 and 3 weeks after treatment, were identified as *C. globosum* by mycological study and the D1/D2 domain of the large subunit rRNA gene sequence.

Fungal keratitis is a common cause of corneal ulcers in developing nations, accounting for 44% of corneal ulcers in South India (Reddy et al. 2017). Fungi are opportunistic in the eye since they rarely infect healthy, intact ocular tissues. *Chaetomium* species is an uncommon etiological agent when it comes to causing keratitis in humans. A global review of the literature with search words "*Chaetomium*" and "keratitis" reveals only four reported cases of *Chaetomium* keratomycosis (Vinod Mootha et al. 2012; Kaliamurthy et al. 2011; Balne et al. 2012; Ghosh et al. 2016; Reddy et al. 2017). Two cases were identified by ITS sequencing to *Chaetomium*-like species (non-sporulating), *Chaetomium atrobrunneum*, and yet another morphologically as *Chaetomium* spp. *Chaetomium globosum* has also been reported as a causative agent in <1% cases of fungal keratitis in a series from North India (Ghosh et al. 2016).

In Plumlee et al. (2017) investigated equine hyphalmycotic encephalitis, characterize key histopathologic features, and classify causative organisms with molecular

diagnostic techniques. Seven cases were evaluated by histopathology. Panfungal PCR targeting the ribosomal RNA large subunit coding region and the noncoding internal transcribed spacer 2 region was performed on DNA extracted from formalin-fixed, paraffin-embedded sections of affected brain, and the resulting sequences were queried against published fungal genomes. Affected animals ranged from 8 to 22 years of age and presented with neurologic signs. Macroscopic lesions within affected brains included multifocal hemorrhage, focal swelling of the thalamus with red and yellow discoloration, and focal cerebral malacia. Major histologic findings included multifocal discrete foci of necrosis, neutrophilic to granulomatous inflammation, vasculitis, and intralesional fungal hyphae variably affecting the cerebrum, thalamus, and brainstem. DNA sequences in four cases showed >98% homology with species within the *Chaetomiaceae* family, including *Acrophialophora fusispora, Acrophialophora levis*, and *Chaetomium strumarium*. Histomorphologically, *Chaetomiaceae* fungi were 7–10 mm wide, septate, parallel walled, and nonpigmented, with dichotomous branching in affected horses. This case series is the first report of equine mycotic encephalitis caused by members of the *Chaetomiaceae* family, previously reported as rare emerging pathogens in humans.

5.5 Conclusion

The role of genus *Chaetomium* in human and animal disease has increased significantly in the last decade. *Chaetomium* infections and infections by species clustering in the *Chaetomium* phylogenetic tree, such as *Chaetomidium* and *Thielavia*, have been reported from the skin, hair, and nails. Moreover, several species of the *Chaetomiaceae* have been reported to cause serious opportunistic infections in immunocompromised patients. It seems that members of *Chaetomiaceae* indeed have an underestimated clinical potential, and re-evaluation of the role of the genus in human pathology is urgently required. The natural habitat of many species in arid climates and their survival at high temperatures probably enhance their survival in mammalian tissue. Due to identification difficulties on the basis of phenotypic criteria, some older cases of *Chaetomium* or *Subramaniula* species might have been erroneously disregarded or reported as cases of *Madurella* or *Papulaspora* infection. Moreover, antifungal susceptibility studies are scant, and treatment protocols are urgently needed.

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