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Review

Scedosporium apiospermum: changing clinical spectrum of a therapy-refractory opportunist*

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Current knowledge on the opportunist *Scedosporium apiospermum* (teleomorph: *Pseudallescheria boydii*), generated over a period of more than 120 years, is reviewed. The natural environmental habitat of the fungus is unknown; nutrient-rich, brackish waters like river estuaria have been suggested. The fungus is strongly promoted by agricultural and particularly by industrial pollution.

Keywords *Pseudallescheria boydii*, mycetoma, near-drowning, cerebral infection, pulmonary colonization, CF, multidrug resistance

Introduction

Scedosporium apiospermum – the anamorph (asexual state) of the ascomycete *Pseudallescheria boydii* – is a significant opportunist with very high levels of anti-fungal-resistance. Previously it was mainly known to be involved in traumatic, subcutaneous infections and in asymptomatic pulmonary colonization, but in recent years, new disease entities have emerged. The fungus has become recognized as a potent etiologic agent of severe infections in immunocompromised and occasionally also in immunocompetent patients. Currently *Scedosporium* infections are among the most common deep mould infections. With a frequency of c. 9%, *S. apiospermum* is among the most common filamentous fungi colonizing the lungs of cystic fibrosis patients [1]. The intrinsic clinical potency of *S. apiospermum* can be deduced from its extremely infrequent isolation from outside and indoor air but its high prevalence in the lungs of susceptible patients.

In general, the clinical significance of filamentous fungi can be inferred from the following data. In Europe around 18,000 patients will be diagnosed with acute leukemia alone and around 13,000 die of this disease each year. It is estimated that approximately 99,000 patients will be treated for a hematological malignancy and around 18,800 will be bone-marrow or organ transplanted. A significant share of the patients undergoing lung or allogenic bone-marrow transplantation and of the patients with acute leukemia will develop invasive mycoses [2]. Roughly estimated, 5000–6000 cases involve filamentous fungi, which mostly become the ultimate cause of death. *S. apiospermum* has been specifically listed as an important cause of death in transplant recipients, with a frequency of 1:1000 patients [3]. A comparable frequency (0.4%) was observed by Pagano *et al*. [4] in patients with hematologic malignancies. The role of *S. apiospermum* in the fatal infections may be underestimated due to the present lack of detailed diagnostics.

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Diagnosis of a *Scedosporium* infection is difficult, because clinical features and histopathology are similar to those of *Aspergillus, Fusarium* and other relatively common hyaline hyphomycetes [5,6]. Sporulation in culture is required for a correct diagnosis, but even then confusion with other morphologically similar species is possible [7].

Over the last 5 years numerous articles including some excellent reviews have been published on clinical aspects of this fungus [8–12], but these mostly elaborate on only a limited number of clinical manifestations. The aim of the present article is to review the currently available information on the fungus and to provide insight into recent developments.

Microbiology

Morphology

Thallus. Colonies are fast growing, greyish-white, suede-like to downy with a greyish-black reverse (Fig. 1). Despite the fact that cultures often are grey,

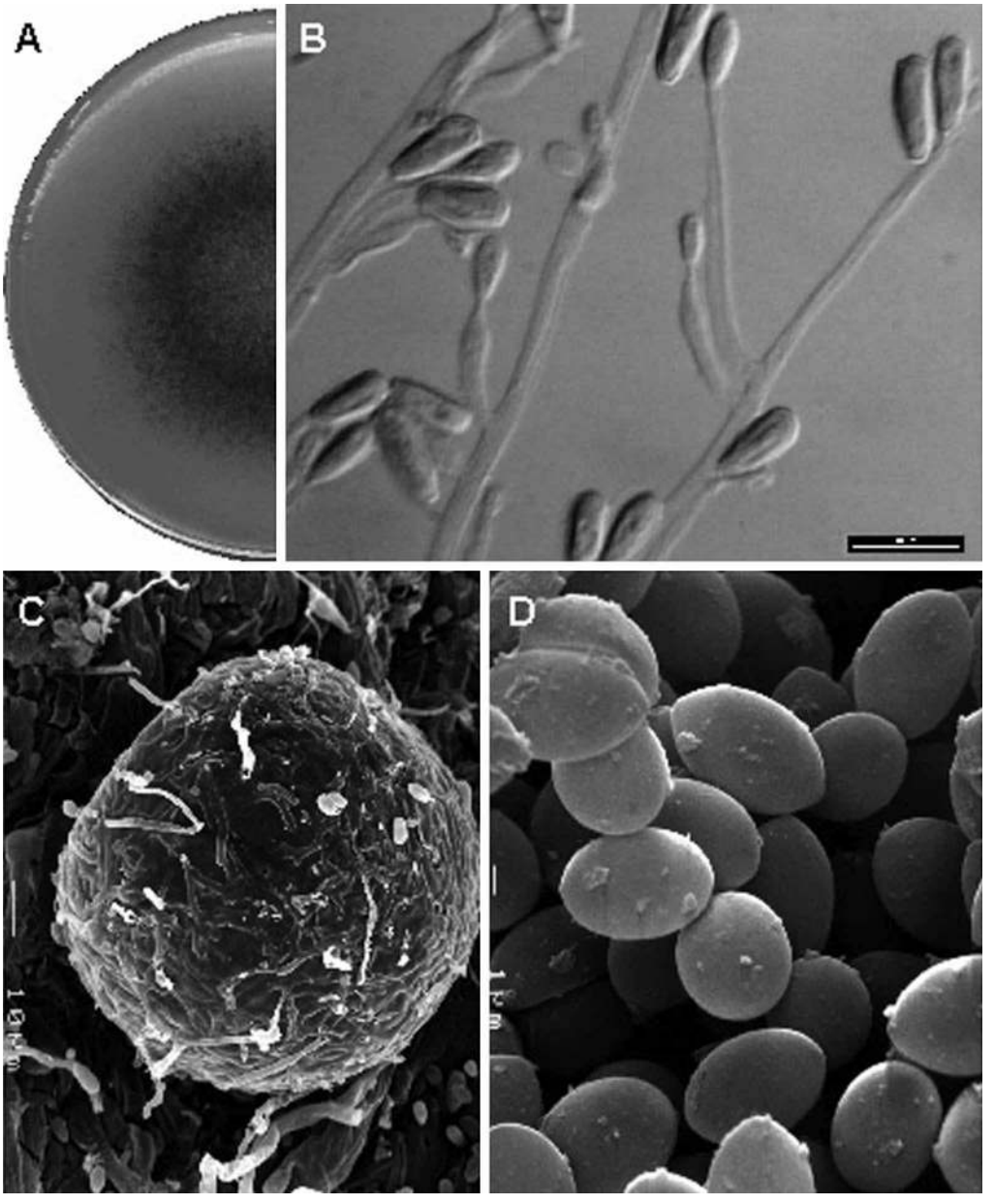

Fig. 1 *Pseudallescheria boydii*. (A) Colony on oatmeal agar at 15 days of incubation at 25°C. (B) Conidiogenous cells and conidia. (C) Ascoma. (D) Ascospores.

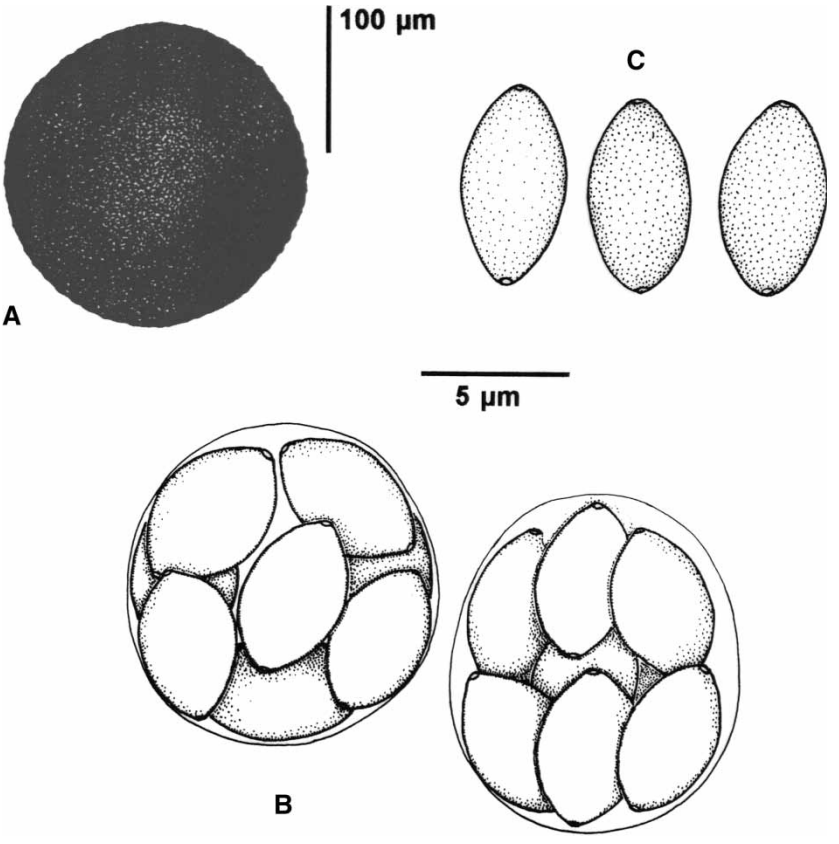

Fig. 2 *Pseudallescheria boydii* teleomorph. (A) Ascoma. (B) Asci. (C) Ascospores.

brown or almost black due to pigments or the production of brown conidia, the fungus has a colourless mycelium. Therefore it is not to be listed as a dematiaceous fungus, which, in contrast, is characterized by melanized hyphae. Fontana-Masson staining for melanin is negative [13]. Consequently, in histopathology the hyphae are hyaline ('hyalohyphomycosis') and the grains produced in cases of mycetoma are white.

Teleomorph. A small percentage of strains spontaneously produce ascigerous fruit bodies (Fig. 1 & 2). Ascocarp formation may be stimulated on cornmeal agar or other nutrient deficient media. The genus *Pseudallescheria* is characterized by the production of closed fruit bodies (cleistothecia) which are yellow-brown to black, spherical, 140–200 m in diameter mostly submerged in the agar and having thin, membranaceous walls composed of jig-saw-shaped cells [14]. When crushed under a cover slip, cleistothecia release numerous spherical, thin-walled, evanescent asci in unordered arrangement, which rapidly dissolve to release eight lemon-shaped, golden brown ascospores, 4–5 × 7–9 um in size [15]. Distinction from conidial Coelomycetes fruit bodies can be verified by crushing young ascomata, releasing spherical cells without ascospores; these are immature asci. Coelomycetes lack such structures in any phase of their development.

Anamorphs. Several types of asexual propagation are known. A *Scedosporium* anamorph is almost invariably present. This consists of hyaline cylindrical conidiogenous cells arising from undifferentiated hyphae, producing obovoidal, brown, sticky conidia (4–9 × 6–10 µm) from a short extension. Conidial development is annellidic (Fig. 3). The process of conidium production is clearly revealed in scanning electron microscopy [16,17], but scars are flat and are hardly visible in light microscopy; slide cultures are then essential to observe conidial arrangement (Fig. 4) [18]. A *Graphium* synanamorph (Fig. 3 & 5) may be produced in some cultures in a later stage at the edge of the colony. This consists of stiff, erect, olive-brown bundles of hyphae, terminating in a brush of slender conidiogenous cells. Conidiogenesis is similar to that of the *Scedosporium* synanamorph, but the cells are smaller and the conidia more slender and less pigmented [15]. Occasionally cultures are whitish and degenerate, having lost any

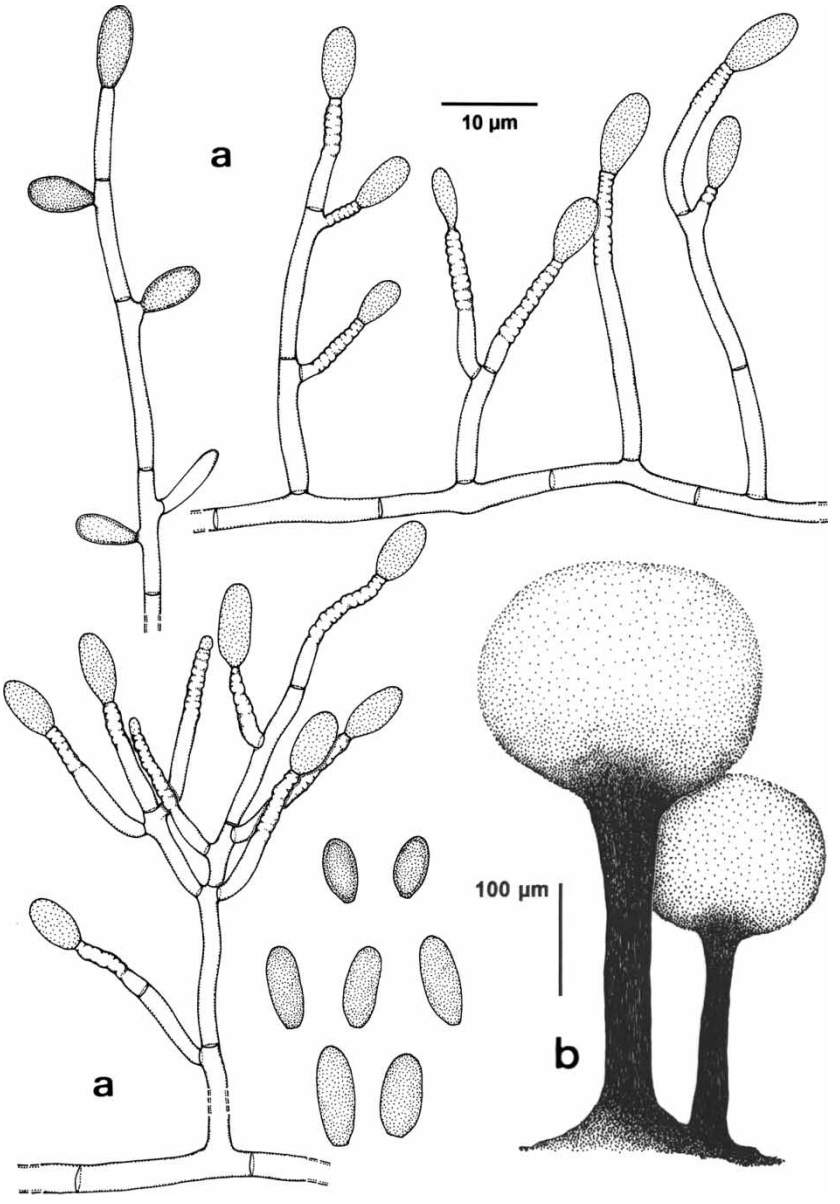

Fig. 3 *Pseudallescheria boydii* anamorphs. (A) *Scedosporium apiospermum*. (B) *Graphium*.

conidial production. Hyphal cells may then locally swell and disarticulate irregularly as multicelled arthroconidia. This form has been described under the generic name *Polycytella* [19], but molecular identity to *S. apiospermum* has been proven [20].

Phylogeny. Pseudallescheria is a genus of the ascomycete order *Microascales*, which contains other genera with potential agents of human disease such as *Scopulariopsis* and *Microascus*. *Petriella* is a related genus, differing by ascomata with preformed openings. Genera producing ascomata with preformed openings (perithecia) and without openings (cleistothecia) were shown to be members of a single family within the *Microascales*, the *Microascaceae*. This seems in conflict with Berbee & Taylor's [21] division of the Ascomycota on the basis of peri- vs. cleistothecia. However, true perithecia have an ordered centrum with asci in star-like arrangement, which is not the case in *Petriella* [22,23]. For this reason von Arx [24] regarded *Petriella* and *Pseudallescheria* as being closely akin and suggested that openings in fruit bodies produced by members of the genera could be influenced by culture conditions. This is confirmed by molecular phylogeny on the basis of rDNA SSU and LSU sequence data elaborated by Issakainen and co-workers [25,26]. The coherence of *Microascus* and *Pseudallescheria* was also shown by Okada *et al*. [27] with SSU rDNA sequences.

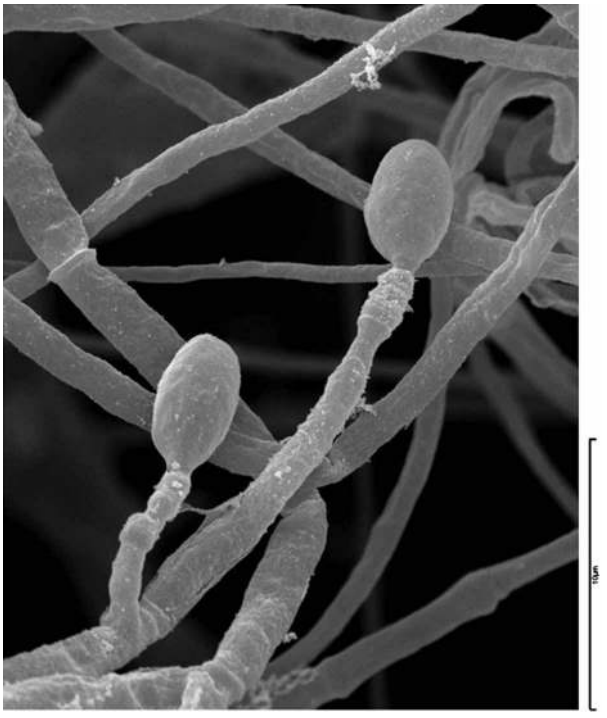

Fig. 4 *Scedosporium apiospermum*. Conidiogenous cells and conidia.

Both teleomorph genera share *Scedosporium*-like anamorphs, and frequently produce a *Graphium*-synanamorph characterized by large, erect bundles of hyphae terminating in a dense aggregate of conidium-producing cells. All propagules (ascospores as well as *Scedosporium*- and *Graphium*-anamorphs) are liberated in slime.

Biodiversity. *Scedosporium apiospermum* is highly variable at the molecular level [28]. A recent multigene sequence analysis has demonstrated that *P. boydii* is a complex that includes several phylogenetic species [29]. *Pseudallescheria angusta, P. ellipsoidea, P. fusoidea,* and the two recently proposed new species *P. minutispora* and *Scedosporium aurantiacum* are genetically and morphologically different from *S. apiospermum sensu stricto*, but there may be other species within the complex that are phenotypically undistinguishable from *S. apiospermum* [29]. Since the degree of involvement of each individual species in human infections has not been determined, the present review will maintain the name *S. apiospermum* in all disease entities.

The natural niche of *P. boydii* is not known, but the species is very common in heavily polluted environments (see below). The fact that the species has emerged from its original habitat in nature and now is successfully adapting to the human-dominated environment suggests that a process of competition between genotypes is currently taking place, with selection of those that are more suitable to survive in the new environment. This is reflected in the predominance of clinical strains that compose a more or less circumscribed entity within the species [30], with slightly higher degrees of thermotolerance [31].

Environmental occurrence and transmission

Scedosporium apiospermum is common in temperate climates and less frequently encountered in the tropics. Its natural niche is not known; all environments from which it is currently isolated being strongly influenced by human activity. It is a eutrophic fungus commonly found in soil [32–34]. Its occurrence is promoted in manure-enriched or polluted environments, such as agricultural and garden soil [35–37], sewer [38], or ditch mud and polluted pond bottoms [39,40]. It is also

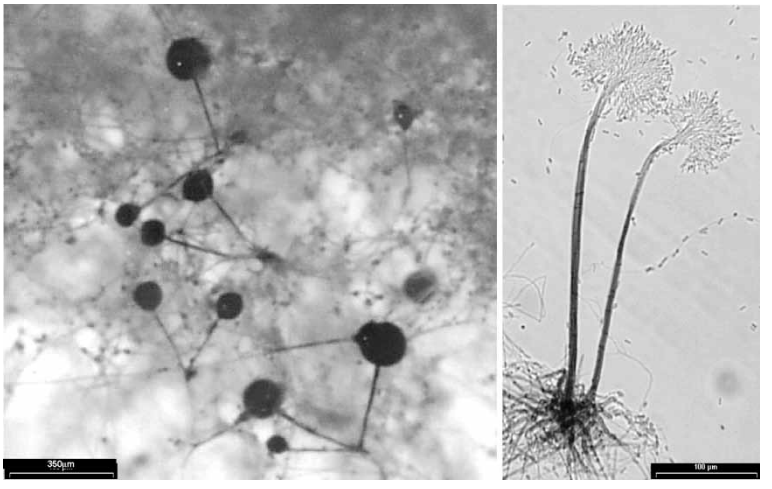

Fig. 5 *Graphium* synanamorph, synnemata.

found in hydrocarbon-contaminated soils [41], being able to assimilate natural gas [42,43] and aromatic compounds [44] and has therefore been suggested for use in bioremediation [45]. All these environments are poorly aerated; the fungus is able to grow at low oxygen tensions, and even shows activity under strictly anaerobic conditions [39]. Bell *et al*. [36] noted that it became the predominant species after prolonged incubation. *In vitro* it tolerates 5% additional salt [39]. This property enables the fungus to reside in somewhat osmotic environments such as dry bat faeces [46], chicken coops [47] and bird guano at their roosting sites [48]. It occurs in brackish and salt water, such as submerged wood in estuaria [49] and tide-washed areas and marine soil [50,51]. Its occurrence in low numbers in bathing facilities and swimming pools [52] are probably indicative for long-term pollution.

The selective medium based on benomyl [53] is useful for isolation from heavily contaminated materials. For soil samples, incubation of specimens for 2 h at 65°C prior to isolation has been recommended [54]. In case of liquid samples such as brackish water, enrichment using wooden blocks has proven successful [49]; abundant development of ascomata on the wood support was noted. Similarly, recovery from liquid medium is enhanced for clinical strains by the use of tooth picks that are immersed half-way in the broth, profuse mycelial growth being observed within a few days at the liquid-air interphase (R. Horré, unpublished data).

Physiology

Physiological profiles of this species were established by de Hoog *et al*. [39]. Most strains tolerate 37°C, and some still show growth at 42°C. Tolerance of magnesium chloride (5%) is higher than that of NaCl. Some strictly anaerobic growth is observed. Species are proteolytic and amylolytic. They assimilate urea, asparagine, potassium nitrate, and ammonium nitrate.

Molecular identification

PCR-based assays from infected tissue are useful for rapid diagnosis of *S. apiospermumi* infections, even before fungal cultures become positive [55]. Wedde *et al*. [56] developed specific primers based on Internal Transcribed Spacer (ITS) rDNA sequences. Given the large infraspecific variability of the species, a less variable region, such as the 26S rDNA operon [57] might also provide successful detection of *S. apiospermum*-like genotypes. Willinger *et al*. [58] used this marker for detection of *S. apiospermum* and similar organisms from fungus balls in the maxillary sinus.

Molecular epidemiology

Subspecific typing of *S. apiospermum* at population level is unproblematic because of the large degree of heterogeneity. Rainer *et al*. [28] found with M-13 fingerprinting that nearly all strains analyzed belonged to another genotype; several genotypes could be recovered from a single sampling site. The high degree of polymorphism enabled Zouhair *et al*. [59] to monitor dissemination of a strain colonizing the lungs of a patient with cystic fibrosis to cutaneous locations using multilocus enzyme electrophoresis and RAPD. In a longitudinal study, Defontaine *et al*. [60] analyzed nine patients with cystic fibrosis, none of which were found to share the same genotype. Five patients were colonized by a single genotype, but in four a predominant genotype was accompanied by one or two others with irregular presence. This demonstrates that the fungus may persist in CF lungs despite antifungal treatment.

Selection of reference strains

Given the high degree of diversity of the *Scedosporium* complex, calibration of research efforts using overlapping sets of strains and consistent inclusion of reference materials is mandatory. A list of essential isolates, based on nomenclatural types and strains previously used in labor-intensive methodologies, is presented in Table 1.

Laboratory diagnosis

Regarding the EORTC criteria, diagnosis of a *Scedosporium* infection should be based on histological and/or cytological evidence in samples from normally sterile body sites and isolation of the mould in culture. An overview of procedures enhancing the specific recognition of *S. apiospermum* is given below.

Direct microscopy and staining

Current histochemical staining methods include maceration in 20% KOH followed by fluorescence microscopy using Blankophor or Uvitek 2B [61,62]. These general mycological stains do not discriminate this fungus from other filamentous ascomycetes such as *Aspergillus* and *Fusarium*. Using polyclonal fluorescent antibodies, Kauffman *et al*. [63] successfully identified the species *S. apiospermum*.

Clinical specimens from mycetoma are serosanguinous fluids containing granules, or biopsy specimens. Grains can be broadly identified down to the genus level by characteristics of shape, colour and texture

Table 1 Selected reference strains.

Strain numbers	Status	Source	Used for	Reference
P. africana:				
CBS 311.72 = UAMH 4000	T of *Petriellidium africanum*	Sandy soil, Namibia, 1972		Gilgado *et al*. 2005
S. aurantiacum:				
CBS 116910 = FMR 8630 = IHEM 21147	T of *S. aurantiacum*	Ulcer, human ankle, Spain, 2004		Gilgado *et al*. 2005
P. boydii*/*S. apiospermum:				
CBS 101.22 = IHEM 15933 = IMI 015407 = IP 1975.91 = JCM 7441 = NCPF 2216 = UAMH 3982	T of *Allescheria boydii*	Human mycetoma, Texas, U.S.A., 1921	DNA reassociation group 1; shows anaerobic growth; MLST clade 5	Guého & de Hoog 1991; de Hoog *et al*. 1994; Gilgado *et al.* 2005
CBS 116892 = IHEM 21159 = IP 1945.90		Sputum of CF patient, France	DNA reassociation group 1	Guého & de Hoog 1991
CBS 591.90 = CDC A-495 = IHEM 21160 = NCMH 1169	T of *Pseudallescheria shearii*	Human mycetoma, Argentina, 1944		
ATCC 760 = ATCC 11600 = CBS 100.26 = IHEM 21161 = IP 1976.91 = MUCL 15755	T of *Acladium castellanii*	Human, 1926		
CBS 695.70 = IHEM 21162 = IP 1977.91 UAMH 3990 = VKM F-1474	T of *Acremonium suis*	Nasal cavity of pig, Ukraine, 1970	DNA reassociation group 2; shows anaerobic growth	Guého & de Hoog 1991; de Hoog *et al*. 1994
CBS 116779 = IHEM 21163 = IP 1946.90		Human sinus, France	DNA reassociation group 2	Guého & de Hoog 1991
CBS 948.87 = IHEM 21164 = IMI 239533 = NCPF 2230	T of *Polycytella hominis*	Human mycetoma, India, 1987		
CBS 108.54 = IHEM 21165 = IP 1987.91		Soil, Zaire, 1953	DNA reassociation group 3; shows anaerobic growth; strain producing teleomorph in abundance	Guého & de Hoog 1991; de Hoog *et al*. 1994
CBS 116894 = IHEM 21166 = IP 1742.88		Soil, Thailand	DNA reassociation group 3;strain producing teleomorph in abundance	de Hoog *et al*. 1994
CBS 418.73 = UAMH 3987	T of *Petriellidium ellipsoideum*	Soil, Tajikistan, 1973	MLST clade 5	Gilgado *et al*. 2005
CBS 116403 = IHEM 21167		Fatal cerebral infection after near-drowning, Germany, 1995		Rüchel & Willichowski 1995
ATCC 11657 = CBS 106.53 = CDC A-722 = UAMH 3997	T of *Petriellidium fusoideum*	Soil, Panama, 1973		
CBS 116895 = FMR 6694 = IHEM 21168		Cerebral abscess, Barcelona, Spain, 1999	Used in animal experiments; MLST clade 5	Ortoneda *et al*. 2002, Capilla *et al*. 2003, Capilla & Guarro 2004; Gilgado *et al*. 2005
CBS 116896 = FMR 6922 = IHEM 21169		Garden soil, Barcelona, Spain, 2000	Used in animal experiments; MLST clade 4	Ortoneda *et al*. 2002, Capilla *et al*. 2003, Capilla & Guarro 2004; Gilgado *et al*. 2005
CBS 116897 = FMR 4167 = IHEM 21170		Human otitis, Spain, 1992	Used in animal experiments; MLST clade 5	Ortoneda *et al*. 2002, Capilla *et al*. 2003, Capilla & Guarro 2004; Gilgado *et al*. 2005

Table 1 (*Continued*)

Strain numbers	Status	Source	Used for	Reference
CBS 116898 = IHEM 14263 = LMA 4 98 00204		Sputum of cystic fibrosis patient (1), Angers, France, 1998	MLEE and RAPD genotype 1; MLST clade 5	Defontaine *et al*. 2002; Gilgado *et al*. 2005
CBS 116899 = IHEM 14268 = LMA 4 98 00544		Sputum of cystic fibrosis patient (4), Giens, France, 1998	MLEE and RAPD genotype 6; MLST clade 4	Defontaine *et al*. 2002; Gilgado *et al*. 2005
ATCC 22956 = CBS 254.72 = IHEM 4429 = RV 57007 = TRTC 45321 = UAMH 3984	T of *Petriellidium angustum*	Sewage half digestion tank, Ohio, U.S.A., 1972	MLST clade 5	Gilgado *et al*. 2005
P. desertorum:				
CBS 489.72 = UAMH 3993	T of *Petriellidium desertorum*	Salt-marsh soil, Kuwait, 1973		
P. fimeti:				
CBS 129.78	T of *Petriellidium fimeti*	Goat dung, India		
P. minutispora:				
CBS 116911 = FMR 4072 = IHEM 21148	T of *P. minutispora*	River sediment, Spain		Gilgado *et al*. 2005
S. prolificans:				
CBS 467.74 = IHEM 5739 = IMI 188615 = MUCL 18141	T of *Lomentospora prolificans*	Greenhouse soil, Belgium, 1971		Hennebert & Desai 1974
CBS 114.90 = IHEM 21171 = IP 1974.91 NCMH 2365 = UAMH 5517	T of *Scedosporium inflatum*	Human bone infection, Maine, U.S.A., 1981		Malloch & Salkin 1984
CBS 116900 = FMR 3569 = IHEM 21172		Blood, Spain, 1990	Used in animal experiments	Ortodena *et al*. 2002ab, 2004
CBS 116901 = FMR 6721 = IHEM 21173		Soil, Spain, 1992	Used in animal experiments	Ortodena *et al*. 2002ab, 2004
CBS 116902 = FMR 6654 = IHEM 21174		Blood, Spain, 1998	Used in animal experiments	Ortodena *et al*. 2002ab, 2004
CBS 116903 = FMR 6802 = IHEM 21175		Air, Spain, 2000	Used in animal experiments	Ortodena *et al*. 2002ab, 2004
CBS 116904 = FMR 6649 = IHEM 21176		Blood, Spain, 1998	Used in animal experiments	Ortodena *et al*. 2002ab, 2004
CBS 116905 = FMR 7252 = IHEM 21177		Frontal sinus, USA, 1996	Used in animal experiments	Ortodena *et al*. 2002ab, 2004
CBS 116906 = IHEM 14076 = LMA 1286		Sputum of cystic fibrosis patient, Pontivy, France, 1998		
AZN7912 = CBS 116908 = IHEM 21178		Blood, Spain	MIC testing	Meletiadis *et al*. 2002

Abbreviations used: ATCC = American Type Culture Collection, Manasas, U.S.A.; AZN = Academisch Ziekenhuis Nijmegen St. Radboud, Nijmegen, The Netherlands; CBS = Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands; CDC = Centers for Disease Control and Prevention, Atlanta, U.S.A.; FMR = Facultad de Medicina, Reus, Spain; IHEM = Scientific Institute of Public Health, Mycology Section, Brussels, Belgium; IMI = International Mycological Institute, Egham, U.K.; IP = Institut Pasteur, Paris, France; JCM = Japanese Collection of Microorganisms, RIKEN, Saitama, Japan; MUCL = Mycothèque de l'Université Catholique de Louvain, Louvain-la-Neuve, Belgium; NCPF = National Collection of Pathogenic Fungi, London, U.K.; NCMH = North Carolina, Memorial Hospital, Chapel Hill, N.C., U.S.A.; RV = Raymond Vanbreuseghem Collection at IHEM; TRTC, now UTCC = University of Toronto Culture Collection, Department of Botany, University of Toronto, Ontario, Canada; UAMH = University of Alberta, Microfungus Collection and Herbarium, Edmonton, Canada; VKM = All-Union Collection of Micro-organisms, Moscow, Russia.

[64]. Grains of *Scedosporium apiospermum* are 1–2 mm large, soft, irregularly lobed, and are white when sectioned. They are frequently surrounded by a prominent eosinophilic fringe which is absent from grains of other white-grain agents of mycetoma [65].

Culture from clinical specimens

For reliable identification, culturing of the organism is recommended. Tissue specimens are macerated in 0.9% NaCl. Optimum temperature for growth for all strains

is between 30 and 35°C; not all strains are able to grow at 37°C. The fungus grows well on routine mycological media such as Sabouraud's glucose agar, blood agar and chocolate agar. A selective medium modified Leonian's agar with 10 μg/ml benomyl was introduced by Summerbell [53]; however, this medium is not commercially available. Growth is also observed on media with a high concentration (8 mg/ml) of cycloheximide [64] which is inhibitory for clinical *Aspergillus* species. Salkin *et al*. [66] and Dixon and Polak-Wyss [67] distinguished *S. apiospermum* from *S. prolificans* by growth responses on cycloheximide-based Mycosel agar, although de Hoog *et al*. [39] noted that strains of *S. apiospermum* are variably susceptible when tested in liquid medium.

Scedosporium apiospermum has been cultured from spinal or ventricular CSF, brain tissue, meninges and from other deep tissues. Culture of CSF from infected patients may be negative [68–71], positive [72–74], or delayed with up to three weeks [72]. CSF culture negative results might be attributed to the capsulated nature of the abscesses caused by the fungus residing in the brain. The fungus can also be isolated from whitish material that filled the shunt [69], from aspirated pus [75–78], from fluid obtained by ventriculostomy [79], or by cisternal tap [80].

Culture of sputum or bronchoalveolar lavage (BAL) or secretions from trachea or external ears, particularly in CF patients, may be hampered by their mucoid consistency. In addition, a competing fungal flora of rapidly growing *Aspergillus* and *Candida* species is frequently present. Isolation using benomyl agar [53] or cycloheximide containing agar [1] is then recommended.

Histopathology

In contrast to the regular, dichotomous branching pattern characteristic for *Aspergillus* in cytologic smears and tissue sections, *Scedosporium* hyphae usually show a slightly more irregular branching pattern [81,82]. Hyphae with multiple branching at acute angles [83] or dichotomously [73] have been reported. Other typical elements commonly observed in cytologic smears and tissue sections of *Scedosporium* infection are terminal or intercalary, globose chlamydospores [82], thick-walled structures of up to 20 μm in diameter [71,81,82,84], which might be confused with yeasts. Hayden *et al*. [85] developed an *in situ* hybridization technique based on rDNA probes to distinguish between *Aspergillus* and *Scedosporium* in tissue.

Purulent CSF revealing heavy infiltrate with PMNs, multinucleate giant cells and highly elevated WBC counts were reported in cases of meningitis [86–88] as well as in cases of cerebral granulomata [83]. Microscopical examinations revealed mostly granulomatous inflammation with multinucleate cellular tissue reaction in brain tissue [74]. Microscopically, abscesses can be detected in brain and hyphae may be seen to penetrate cerebral blood vessels [68,89].

Radiology

In most pulmonary or cerebral cases the lesions are multiple and have low density. The fungal mass is not separated from the wall of the cavity by an airspace. The 'air-crescent' appearance is more likely to indicate invasive pulmonary aspergillosis [9,90–92]. The difference between the CT may be explained by rapid and fatal evolution of *Scedosporium* infections [93].

Serology

Immunodiffusion may be useful in the diagnosis of *Scedosporium* infections, but reagents are not commercially available and antigenic extracts have to be made in the laboratory. Lupan and Cazin [94] used indirect passive hemagglutination based on rabbits immunized with *P. boydii* polysaccharide antigens. Tests were positive in humans with proven *P. boydii* infection: titers were up to 1:512, while healthy individuals have serum levels of max. 1:32. Using mouse experiments Lupan and Cazin [95] noted highest, dose-dependent response after injection of viable conidia. Tests are reliable for diagnosis and to monitor the prognosis of the infection [96]. Ouchterlony tests have classically been used for identification of the species, while intracutaneous inoculation may suggest invasion [97]. Antigen used is a peptidorhamnomannan from mycelium. Cross reactivity with *Sporothrix schenckii* [98] and with *Aspergillus* [96] have however been noted. A case of *S. apiospermum* encephalitis in a child whose CSF specimen revealed repeatedly highly positive cryptococcal antigen titre (1:4000) was reported by Rüchel and Willichowski [87]. Cimon *et al*. [99] applied antibody detection by counterimmuno-electrophoresis for *S. apiospermum,* which was found positive in 27 of 128 (21.1%) CF patients. This number was significantly higher than found with culture of sputum samples. The discrepancy between the mycological and serological results might be related to immune cross-reactions with *Aspergillus*, but are more likely to indicate that the frequency of colonization of patients with CF by *S. apiospermumi* is largely underestimated.

Host defense mechanisms

Macrophages are capable of phagocytosing conidia, while human mononuclear leukocytes and polymorphonuclear leukocytes (PMNs) damage hyphae in a concentration-dependent manner [100]. These effects can be enhanced by treating PMNs with interferon gamma and granulocyte-macrophage colony-stimulating factor [101], or in combination with amphotericin B lipid complex or the triazoles itraconazole, voriconazole or posaconazole [102,103]. While human interleukin-15, which acts on key cells of the innate immune system, enhances PMN-induced hyphal damage of *S. prolificans* and *Fusarium* species, it remarkably is not active against hyphae of *S. apiospermum* [104].

In vitro antifungal susceptibility

Numerous studies have proven that antifungal drugs such as amphotericin B (AMB), nystatin (NYS), liposomal nystatin (L-NYS), itraconazole (ITC), flucytosine (5FC), fluconazole (FLC), terbinafine (TBF) and ketoconazole (KTC) show low *in vitro* activity against *S. apiospermum* [105–116]. However, in some studies, ITC has shown some activity [117–119]. Some new triazoles are promising: voriconazole (VRC) has shown MICs 90 of 0.25 μg/ml [105] and 0.5 μg/ml [112] and ravuconazole of 0.125 μg/ml [105]. Posaconazole (PSC) has shown variable activity [105,112,120].The *in vitro* activity of echinocandins against *S. apiospermum* has generally been considered to be modest. The geometric mean MIC of caspofungin (CAS) for 6 isolates of *S. apiospermum* was of 1.3 μg/ml [108], the median MIC of anidulafungin for 5 strains was of 4 μg/ml [114] and the geometric mean MICs against 19 strains was 39.7 μg/ml (data not shown). However, it is important to exercise caution in interpreting *in vitro* susceptibility results [120], because clinical improvement of *S. apiospermum* infections with AMB treatment has been reported despite apparent *in vitro* resistance to this drug [122].

Considering the poor activity obtained with single agents, some attempts have been made to determine whether the activity of some drugs improves when combined with others. Walsh *et al*. [119] determined the *in vitro* antifungal activity of AMB alone and in combination with various azoles. They found that some strains were susceptible to AMB and that the combinations tested displayed additive or synergistic interactions against an important number of isolates, and no antagonism. The combination AMB/FLC displayed the greatest synergy; mean fractional inhibitory concentration index (FICI) = 0.61 [119]. According to those authors simultaneous exposure of the fungus to both antifungals resulted in increased permeability to the azole with increased inhibition of fungal ergosterol synthesis and thus greater antifungal activity. However, these results must be interpreted with caution because recently the criteria for evaluating interactions have changed and FICI values over 0.5 are now considered to be indicative of no synergy [123]. Li and Rinaldi [124] demonstrated that the combination of the nucleoside-peptide antibiotic nikkomycin Z, which is a chitin synthase inhibitor, with ITC resulted in moderate *in vitro* growth inhibition of *Scedosporium* spp. The combination AMB/micafungin (MFG) shows *in vitro* synergistic effect against *S. apiospermum* [125]. The mechanism of this synergy is unclear. The echinocandin MFG exerts antifungal activity via inhibition of (1,3)-β-D-glucan synthase, interfering with fungal cell wall synthesis and probably causes some structural alteration at the cell wall level which facilitates the action of AMB on the cell membrane at lower concentration.

Animal models of infection

In a limited number of older studies using murine models, virulence appeared to be low after intraperitoneal inoculation. Although the fungus was reisolated within several weeks after inoculation, no evidence of lesion was found [32,126,127]. Inoculating the fungus with gastric mucin, Ajello [32] was nevertheless able to obtain consistent mortalities. Other authors used similar protocols but could not reproduce these results [128,129]. This is probably explained by the use of strains with different degrees of virulence, as virulence of *S. apiospermum* is strain dependent [37,130]. Bell [37] indicated that human isolates of *S. apiospermum* are considerably more virulent than soil or feedlot manure strains.

The route of inoculation and the immune status of the animals play important roles in invasive abilities. Several authors were unsuccessful to produce lesions in guinea pigs via eyes, lungs, footpads, and peritoneum [126,127,130]. Subcutaneous inoculation [132] resulted only in small, localized abscesses. Recently, a model of disseminated infection was proposed using neutropenic guinea pigs [133]. The mortality rate correlated with inoculum density; some strain-dependent differences were observed. The two highest inocula (2×10^6, 7×10^5) produced 100% mortality with mean survival times of c. 3–4 days. With the lowest inoculum (3×10^5) mortality was 50% for one strain and 100% for the other, and the mean survival times were 12.5 and 5.25 days, respectively. Kidneys and brain were extensively

infected by both strains. Intraperitoneal (i.p.) and intranasal (i.n.) inoculation have proven to cause less morbidity than intracerebral (i.c.) or intravenous (i.v.) inoculation [130], the i.v. route being the most effective [130–134]. In immunocompetent animals, Schmitt *et al*. [126] proved that doses of 1.4×10^4 CFU were unable to kill mice when they were administered i.p. Lupan and Cazin [130], testing doses of 10^7, obtained mortality rates of up to 30%. Killing rates of inocula of 10^5 in immunocompetent mice ranged between 25% in 30 days [135] and 62.5% in 25 days [136]. The use of immunosuppressive drugs renders the animals highly susceptible to infection. Inocula of 10^4 and 10^5 CFU caused the death of all immunosuppressed mice within 6 [136] to 10 days [137], respectively. In general, mortality correlates with the dose of the inoculum and with the degree of immunosuppression [136]. Gonzalez *et al*. [136] made mice neutropenic with one injection of cyclophosphamide at 200 mg/kg reaching the most severe neutropenia on day 4. Other authors used the same drug at the same dosage but added 150 mg/kg of 5 fluorouracil one day before the infection [137]. With this dosage mice were maintained severely neutropenic from day 4 to day 7 after infection [138]. These models of disseminated infection in immunosuppressed mice have proven to be reproducible and are very useful for testing new therapeutic regimens and/or studying pathogenesis and immune response in *Scedosporium* infection. The i.c. route is more suitable for studying cerebral *Scedosporium* infection in immunocompromised humans [134].

Infected mice show considerable hyperirritability during early stages of infection. Torticollis is one of the most common symptoms. This is thought to be due to damage to the 11th cranial or spinal accessory nerve because conidia get lodged in the choroids [64]. The animals eventually become lethargic and die. Infected animals undergo marked weight loss due to dehydration and decreased food intake. The time of onset of neurological symptoms appears to be related to inoculum size [130] and at autopsy hyphae, conidia and conidiophores were found in most internal organs [64].

Few animal studies have been conducted to evaluate the effectiveness of drugs. AMB [134] and ITC appeared to be ineffective in murine models, while PSC was slightly more effective than FLC in survival and fungal burden reduction [139]. The efficacy of VRC was demonstrated in both murine and guinea pig models [133,137].

Clinical appearance

History of the disease

Pseudallescheria boydii was discovered in 1889 as an agent of human otitis [140]. Saccardo [141] described the *Scedosporium* anamorph from a case of human mycetoma. Since then the reported clinical spectrum of the fungus has changed over time, from prevalently chronic subcutaneous in otherwise healthy patients between 1911 and 1970, to more often systemic opportunistic after 1980 (Fig. 6). Fisher *et al*. [40] were the first to describe the near-drowning syndrome by *S. apiospermum*, while the species' neurotropism was stressed by Berenguer *et al*. [72]. Although Creitz and Harris [142] already noted the occurrence of *S. apiospermum* as a colonizer of the lungs of patients with pulmonary disorders, its consistent occurrence in the lungs of patients with cystic fibrosis has only recently received proper attention [99]. Guého and de Hoog [30] were the first to observe that infraspecific entities within *S. apiospermum* differed slightly in clinical predilection.

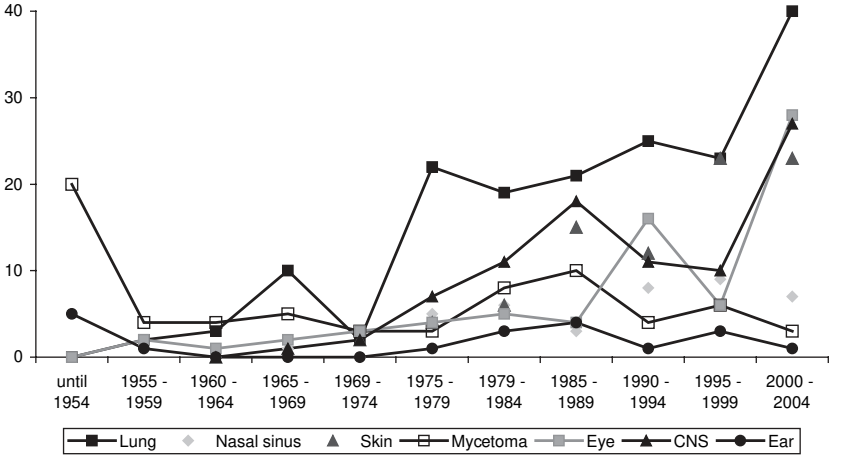

Fig. 6 Number of case reports of *Scedosporium apiospermum* infections in 5-year intervals listed according to body site. Y-axis = number of case reports.

Disease nomenclature

On the basis of previous synonyms of the fungus, systemic disease entities were referred to as allescheriasis [35], graphiosis [143], monosporiosis [144], petriellidiosis [145], pseudallescherioma [146], pseudoallescheriosis [147], pseudallescheriasis [64] or scedosporiosis [148]. Naming of disease entities after the fungus has three serious drawbacks. First, the nomenclature of the fungus has changed several times in the course of history, due to taxonomic developments. Given the fact that *S. apiospermum* is genetically heterogeneous [28,30] a further subdivision of the species is expected in the future, which might lead to changes in clinical nomenclature. Second, *S. apiospermum* is polymorphic, synanamorphs being differentially expressed and indicated with separate anamorph names, leading to different clinical names for the same entity. Finally, the species is a typical opportunist, thus the clinical appearance is largely dependent on the portal of entry and the patient's immune status, and thus very different clinical entities would be referred to with a single disease name. Therefore, it is strongly recommended to apply a general, strictly clinical disease name, with indication of the respective etiologic agent, as recommended by Odds *et al*. [149]. In general mycology the teleomorph name is applied, as this is a microbiological umbrella term for the entire organism. However, given the genetic heterogeneity of *P. boydii*, there is no absolute proof that this teleomorph belongs to every asexual strain (anamorph). Use of the invariably present *Scedosporium* name is therefore optimal, for example: endophthalmitis due to *Scedosporium apiospermum*.

Characteristics of disease

A major problem of recognition of *S. apiospermum* infections is the fact the fungus is a typical opportunist. Therefore, none of the clinical entities is fully characteristic for the species. Three basic clinical syndromes can be distinguished: (A) localized disease after trauma, (B) largely asymptomatic or symptomatic colonization of cavities, and (C) systemic invasive disease. Traumatic infections (A) are found in otherwise healthy persons. Pulmonary cases (B) are observed in patients with predisposing pulmonary disorders. Systemic disease (C) occurs if the immune status of the patient is severely impaired or in victims of near-drowning. The fungus then shows marked neurotropic behavior. Secondary cutaneous manifestations are infrequent with severe dissemination.

(A) Localized disease after trauma

(i) Mycetoma. This is one of the classical entities of *S. apiospermum*. Mycetoma is a chronic, suppurative infection of subcutaneous tissue and contiguous bone in otherwise healthy patients after traumatic inoculation of fungal elements (Fig. 7). Most cases start out as a small, hard, painless nodule which over time begins to soften at the surface and ulcerates to discharge a viscous, purulent fluid containing grains. A subsequent phase of proliferation may involve muscles and intramuscular layers [150] The infection slowly spreads to adjacent tissue, including bone, often causing considerable morbidity. Sinuses continue to discharge serosanguinous fluid containing the granules which are very large, lobed, and white on sectioning [64].

The first extensive report of a *S. apiospermum* mycetoma was that of Shear [14]; numerous cases have been described since then. Mainly the lower limbs are involved, the feet accounting for at least two-thirds of the cases. Other sites include the lower legs, hands, head, neck, chest, shoulder and arms. The clinical features are fairly uniform, regardless of the organism involved. Yücel *et al*. [151] reported a rapidly developing mycetoma of the hand due to *S. apiospermum* in a previously healthy male patient who had a long history of alcoholism and cigarette smoking. The patient was a cartwright living with poor hygiene on straw near his horses. On his admission after a 7-month history, his hand had severely swollen, with involvement of muscles and bones (Fig. 8). In patients treated with immunosuppressive agents, subcutaneous inoculations do not lead to grain formation, but the fungus produces scattered hyphae [152].

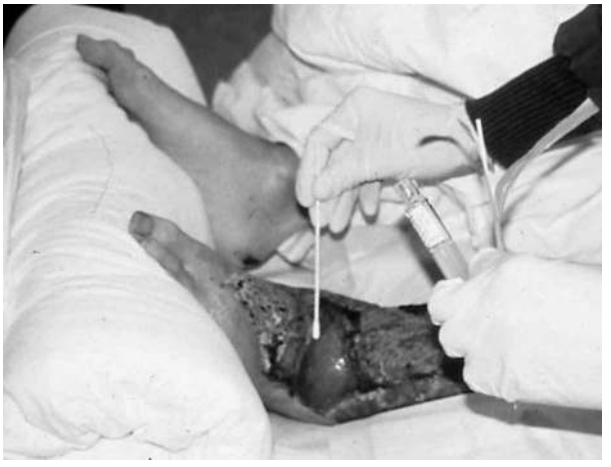

Fig. 7 Mycetoma of the foot by *Scedosporium apiospermum* during surgery.

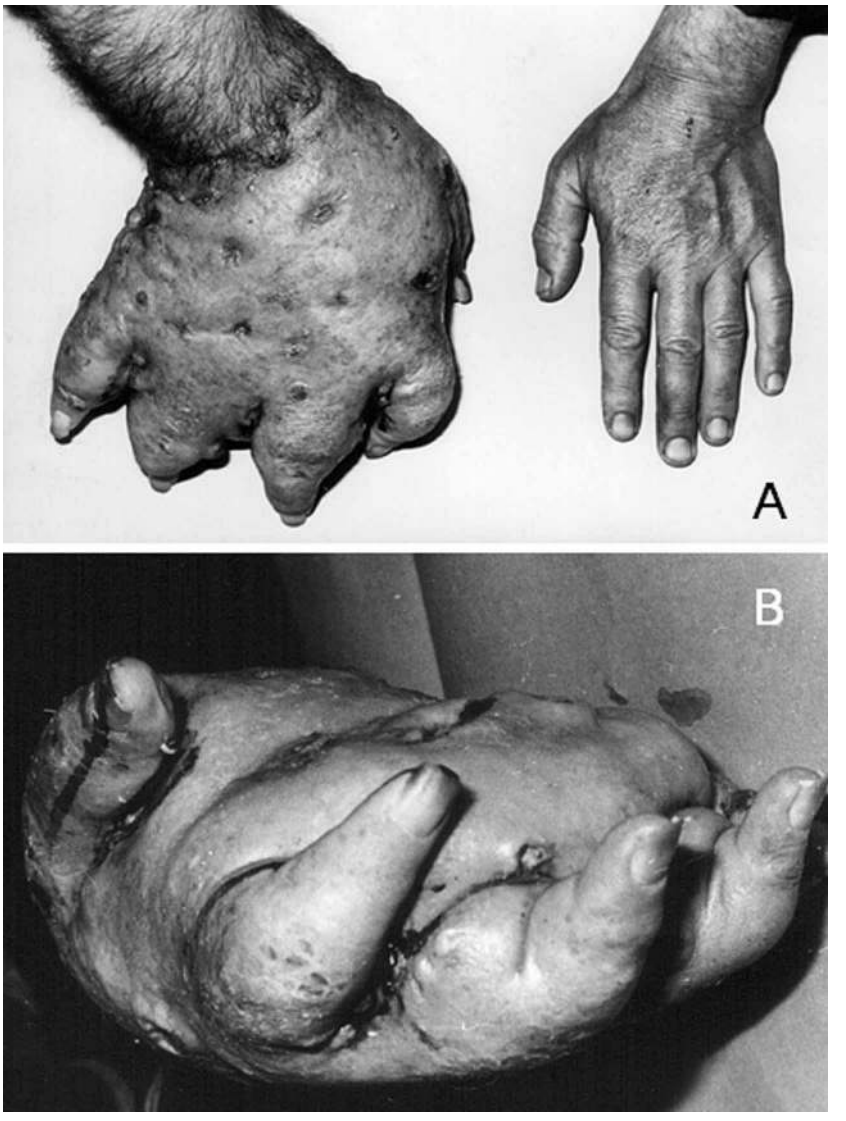

Fig. 8 Mycetoma of the hand caused by *Scedosporium apiospermum* showing multiple foci of suppuration and nodulation with sinus tract formation. (A) Superficial view. (B) Frontal view (courtesy of A. Yücel, Cerrahpasa Medical Faculty, Istanbul, Turkey).

Infections are found world wide, *S. apiospermum* being the most prevalent agent of mycetoma in temperate, moist climate zones [153]. In Europe and the USA it is therefore the only type of eumycetoma which can be acquired locally, all eumycetomata by remaining agents being import mycoses. In arid climates such as India [154] and North Africa [155] the species seems to be rare. Cultures from cases of mycetoma prevalently show an abundance of the *Scedosporium* anamorph and rarely exhibit *Graphium* or ascomata [30]; occasionally they are degenerate, with detaching hyphal elements [19].

Deep localized erosive infections are sometimes incorrectly referred to as mycetoma, e.g., scalp mycetoma [156]. Such infections do not drain and/or there is no grain formation, but hyphae are present in abscesses [75]. Cavitation and grains may be present in cases of pulmonary mycetoma; see below under pulmonary fungus ball.

(ii) Arthritis. With known traumatic inoculation, *S. apiospermum* frequently exhibits a predilection for joints, leading to arthritis of, e.g., knee and elbow [157–160]. Histopathologically, hyaline hyphal elements are observed rather than grains. Dirschl [162] reported a knee involvement in a six-year-old boy who had received a small puncture wound over the right patella nine months previously. Arthritis of the knee was noted two years after a compound patellar fracture contaminated with soil [163]. A concurrent bilateral knee involvement has been reported [164], and a case of arthritis by *S. apiospermum* in a previously healthy

female patient after an intra-articular steroid injection [157]. The disorder develops slowly over several months [159]. Local destruction of cartilaginous tissues is observed [9,165] which may lead to suppurative infections without grains [161], but more often also discharge remains absent [163]. Fever is noted only in children [166]. Infections may take a fatal course despite antifungal therapy when the patient has immunosuppression [167] or other diseases interfering with immunity [168].

In early stages, symptoms are present but the fungus may not readily be observed nor cultured [166]. Haapasaari *et al*. [169] cultured *S. apiospermum* from synovial fluid but not from aspirate. Occasionally fungal structures were reported to be absent; this may be due to the fact that most such diagnoses were by fine needle aspiration of synovial fluid which is followed by repeatedly positive culture [158].

(iii) Osteomyelitis. Subcutaneous infection may lead to severe local bone destruction [9,164,165,170,171]. Most cases arise after deep puncture wounds, particularly in the lower extremities [172]. Symptoms can be severe and may reactivate months [156] or even years [170]] after probable inoculation. Also hematogenous osteomyelitis is known. Vertebral osteomyelitis [173] may occur in patients with impaired innate immunity [174], drug abusers [175] as well as in immunocompetent individuals [171]. Severity may be promoted by immunosuppression [176]; also the risk of further dissemination increases [164]. Cultures are commonly negative [177].

(iv) Eye infection and endophthalmitis. This clinical picture [178] is observed with painful corneal ulceration and hypopyon (Fig. 9) [179] after introduction of a foreign body [144] or without overt injury [180,181]. Infection may be noted years after eye surgery [182]. Traumatic cases are more frequent in developing countries [183]. Non-traumatic cases may indicate severe septicaemia [184]. Ocular symptoms include pain, decreased visual acuity, lacrymation, redness and photophobia [185]. Hyphae are abundantly present in tissue; detection is enhanced by Calcofluor white staining [183]. For treatment, repeated surgical debridement of necrotic tissue may be necessary [186,187]. Numerous cases only could be cured by enucleation or evisceration of the infected eye. Köhler [188] described a lacrymal duct infection.

(v) Onychomycosis. *Scedosporium* may occasionally be isolated from cases of onychomycosis, but its pathogenic role has insufficiently been established [189]. In an extensive review of non-dermatophyte skin and nail infections [190], *S. apiospermum* was not listed.

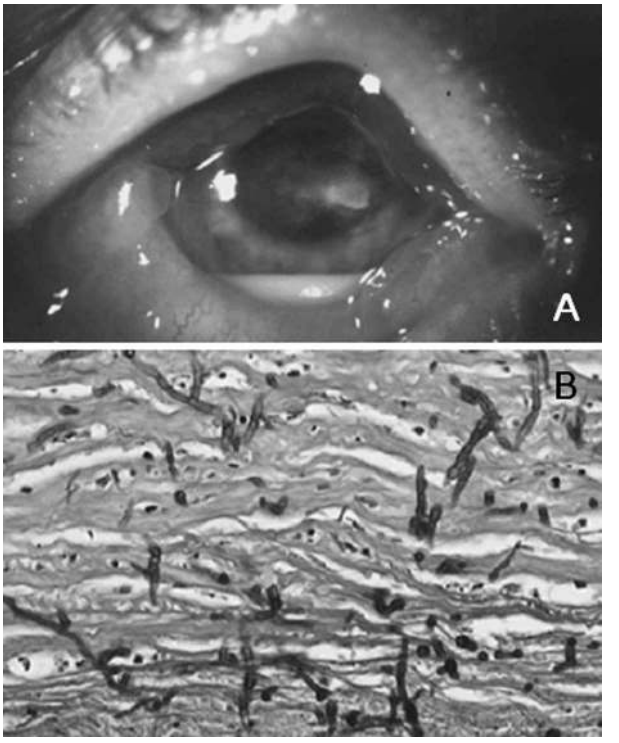

Fig. 9 Keratitis by *Scedosporium apiospermum*. (A) Left eye of the patient with an infiltrate in the central part of the cornea and a hypopyon in the anterior chamber. (B) Cornea section showing numerous fungal elements, PAS stain, ×400. Reprinted from reference 326 with the permission of the publisher.

(vi) Lymphocutaneous infection. Cutaneous infections are infrequent and mostly are associated with immunodepression [55,191], e.g., in solid transplant recipients [192]. An interdigital case was reported by Karaarslan *et al*. [193]. Cases of asymptomatic soft tissue abscess without sinus drainage were reported in immunosuppresssed [194] and also in previously healthy subjects [195,196]. Most cutaneous infections disseminate locally by lymphatic spread [197–199], leading to lesions similar to those due to *Sporothrix schenckii*, but easily distinguished from this clinical entity by histopathology. Skin lymphadenitis has also been reported in an immunocompetent patient [200]. Manifestations include draining ulcerations [201], erythema and folliculitis-like eruptions, with or without subcutaneous nodules [96].

(B) Asymptomatic or symptomatic colonization of cavities

(i) Sinusitis. Gluckman *et al*. [202] demonstrated that the sinuses and nasal septum may be a portal of entry

for infection. Chronic, extramucosal as well as invasive sinusitis is occasionally observed in patients with or without other underlying disorders [203–205]. The invasive form is mostly limited to patients with hematologic malignancy, neutropenia, or receiving broad-spectrum antibiotics [206]. A paranasal sinus mycetoma was described in a 92-year-old patient [207]. In otherwise healthy patients the bony margin of the sinus is invaded or extension into contiguous brain is noted, causing a purulent abscess in the frontal lobe [74,208,209]. The process may evolve for weeks without fever and with little pain. Mostly the maxillary sinus is involved [204,210] (Fig. 10). Predominant clinical findings are slight swelling of the face over the infected sinus, followed by nasal hypesthesia, pallor, and bleeding. The disorder is more common in arid climates [211]. Presence of fungus balls may lead to bone erosion due to pressure necrosis [212]. Cases are mostly treated by surgical removal of the fungal mass and diseased mucosa, with adjuvant antifungal therapy in case of deep invasion. Radiographs are not relevant to diagnose infections of the nasal sinuses, but MRI and CT can be useful.

(ii) Otitis. Already in the 19th century *S. apiospermum* was observed to be involved in cases of otitis [140], but this disorder is infrequent [213]. A case was reported in an immunocompetent child [214]. Chronic infection of the external auditory meatus is characterized by scaling, pruritus and inflammation [215]. Chronic colonization by *S. apiospermum* is accompanied by recurrent earache and enlargement of tonsils. This leads to perforation of ear drums, with production of greenish

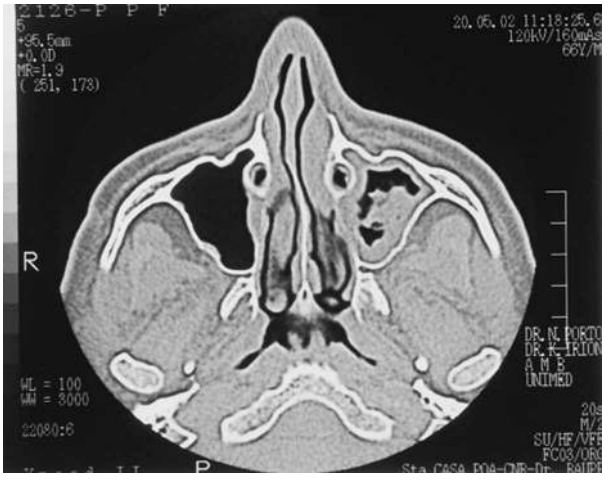

Fig. 10 A computed tomographic scan of a case of sinusitis by *Scedosporium apiospermum*. Notice the partial opacification of the left maxillary sinus. Reprinted from reference 222 with permission of the publisher.

purulent discharge and ear draining [216]. Slack *et al*. [217] reported mastoiditis secondary to ear infection. Yao and Messner [218] reviewed malignant otitis by *S. apiospermum*.

(iii) Pulmonary fungus ball. This disorder has been described in detail by several authors [210,219,220]. Susceptible patients are those with a chronic pulmonary infiltrate from a previously or underlying disorder, such as sarcoidosis or tuberculosis [97,221–223], but the fungus may also be the primary cause of disease [220] and occur in otherwise healthy patients [224–226]. Przyjemski [227] suggested that fungus balls begin as 'tissue balls' infiltrated by fungus. Colonization typically leads to a mass consisting of loose hyphal strands or a conglomeration of intertwined fungal hyphae admixed with mucus and cellular debris within a preexistent pulmonary cavity or ectatic bronchus (Fig. 11). The ball is the extreme consequence of colonization, where the mass of fungus has become large enough to be visible radiologically [8,90,97,146,170,216,219–221,225–231]. On radiography the fungus ball is characterized by the presence of a solid, round or oval mass with soft tissue opacity within a lung cavity. Explanted fungus balls usually fail to grow on laboratory media [90,219,221,232–234].

Mixed infections can be present. In a case reported by Rosen *et al*. [232], *S. apiospermum* was repeatedly isolated from sputum and intracavitary exudates of a human with cavitary bronchiectasis and *A. fumigatus* was found at autopsy. In a further case [97] the diagnosis was made by precipitin test, which reacted strongly with *S. apiospermum* and weakly with *Aspergillus versicolor*. Neither of the two fungi was cultured from sputum. However, both were isolated from cavity contents obtained by thoracotomy.

Presence of fungus balls stimulates chronic inflammation and elicits a marked vascular granulation tissue response. *S. apiospermum* fungus balls often associated with thickening of the cavity wall and adjacent pleura [233]. Fungal balls may be compact and spherical or become irregular. Concentric rings of hyphae, which represent waves of growth as the fungus ball enlarges, can be seen to radiate from a central area. In addition, conidia are frequently present at the surface where the mass is in contact with an air space [216]. Similar conidiation in air is commonly found in *Aspergillus* fungomas. The air meniscus may be absent on chest radiographs [81,220].

(iv) Allergic bronchopulmonary Scedosporium pneumonia (ABSP). Although most allergic bronchopulmonary mycoses have been attributed to *Aspergillus* species or

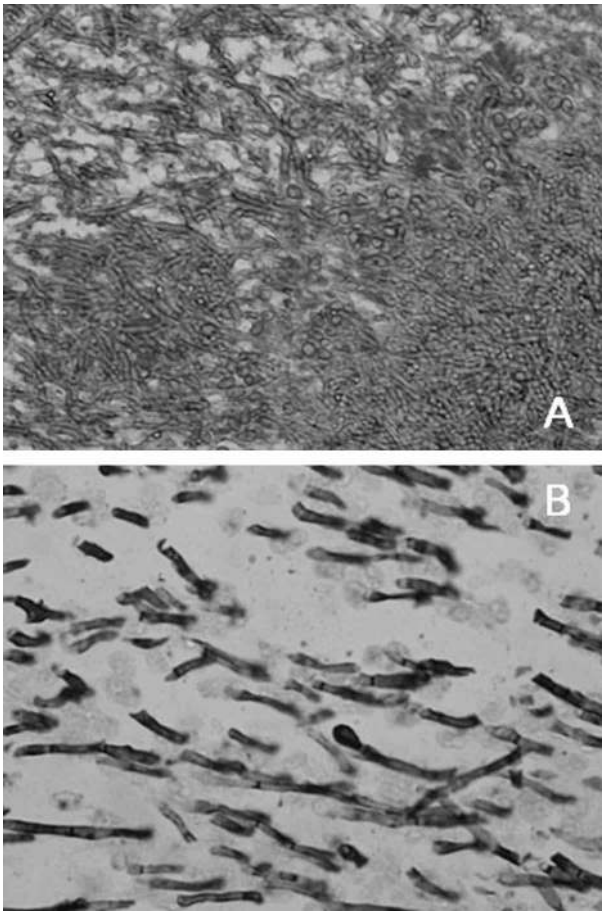

Fig. 11 Histopathological section of a pulmonar fungus ball by *Scedosporium apiospermum*. (A) Numerous hyphae and conidia, PAS stain, ×400. (B) Hyphae, and a conidium emerging from a conidiogenous cell, GSM stain, ×400.

dematiaceous fungi, this syndrome can also be caused by *S. apiospermum* [99,146,235]. Colonization may trigger an inflammatory response leading to allergic bronchopulmonary disorder [99]. The disorder is characterized by the presence of obvious plugs in sputum containing *S. apiospermum* cells. Clinical features are asthma, perpherial blood eosinophilia, infiltrates on chest radiography, raised IgE levels, precipitating antibodies and immediate cutaneous reactivity to the etiologic agent [236]. Precipitating antibodies to *P. boydii* were reported in several cases in which the fungus proliferated in the airway lumen [97,99,216,219,237–239]. However, after resection [219,238] or antifungal treatment [239] antibodies were not found. In general no reaction was detected with extracts of other fungi including *A. fumigatus*. Eosinophilia was noted in only one patient [238]. Of the three patients reported by Reddy *et al*. [230], one was skin tested with an extract of *S. apiospermum*, but gave no response. Rippon and Carmichael [216] reported a case of transient endobronchial colonization. Several sputum specimens were positive for *S. apiospermum*. Radiology showed diffuse interstitial infiltrates and precipitins against *S. apiospermum*.

(v) Pulmonary colonization in cystic fibrosis. Cystic fibrosis (CF) is a chronic, progressive, and frequently fatal genetic disease of the mucus glands that affects many organs including the lungs, plugging them with mucus that severely interferes with breathing. If the mucus is not cleared, it may trap bacteria and fungi, leading to transient or chronic colonization. Colonization of the respiratory tract is usually asymptomatic in patients with CF [35,243]. Dehydration of respiratory secretions contributes to defective mucociliary clearance and provides a suitable environment for growth of selected organisms [244]. *S. apiospermum* is among the regular agents [99,245]. Cimon *et al.* [99] recovered *S. apiospermum* from sputum samples in 8.6% of CF patients, ranking as the second most frequent filamentous fungus identified after *Aspergillus fumigatus*. Airways of CF patients are commonly colonized with fungi; the fungal flora increases with age. Pulmonary insufficiency is particularly caused by inflammation [244].

The regular occurrence of *Scedosporium apiospermum* in the lungs of patients with CF is remarkable, given its infrequent isolation from air. For example, *Scedosporium* was found in less than 1% of indoor sites analyzed in Belgium, ranking 49th among the 52 genera identified [240]. Nevertheless an appreciable percentage of CF patients are colonized by two or even three genotypes of *S. apiospermum* [99]. Such discrepancy is intriguing and raises questions about how patients are contaminated and about mechanisms that select this fungus from the high biodiversity of environmental molds. It is possible that the organism may be more common in the indoor environment, but methods used to isolate it are inadequate, or perhaps it is concealed by fast growing organisms upon culture. There seem to be large regional differences. *Scedosporium apiospermum* seems to be nearly absent from CF patients in Spain [241], where *S. prolificans* is prevalent. Potted plants may consitute a reservoir of the fungus (B. Cimon, unpublished data).

It has been supposed that the sticky conidia of *S. apiospermum* may hitchhike with dry, easily aerosolized *Aspergillus* conidia and be dispersed aerogenously. The presence of the fungus is often noted after the concurrent presence of *Aspergillus* in the bronchial

secretions of CF patients. Mixed allergic bronchopulmonary disease due to *S. apiospermum* and *Aspergillus* was described by Lake *et al*. [242] in an asthmatic female, and two further cases by Miller *et al*. [235]. *Scedosporium* frequently occurs after transient or cured *Aspergillus* infections. For example, Cimon *et al*. [1] analyzed sputum samples of a large series of adult and pediatric patients and revealed the presence of *S. apiospermum* in seven individuals (3.3%), six of these previously having bronchial secretions positive for *A. fumigatus*.

Defontaine *et al*. [60] typed sequential and multiple isolates from nine different CF patients, eight with bronchial colonization or transient infections, and one with bronchopulmonary infection defined by clinical or radiological signs associated with culture-positive sputum. No common genotype was found among the patients. Their results did not reveal any clustering according to geographic origins of isolates, and clonality of the *S. apiospermum* isolates was demonstrated. Patients were colonized by one to three genotypes. The latter group usually exhibited a predominant genotype accompanied by one or two others that were genetically close to the predominant genotype. Infection of susceptible patient populations is remarkably efficient, judging from the persistence of the same colonizing genotype over a long period, despite antifungal treatment.

Cimon *et al*. [99] reported two cases of ABSP in a longitudinal monitoring of CF patients, both chronically being colonized by *S. apiospermum* and one with previous allergic bronchopulmonary aspergillosis (ABPA) treated with a combination of corticosteroids and itraconazole. In most cases analyzed, however, colonization with *S. apiospermum* was not associated with allergic disease. Fungal colonization of CF lungs evolves particularly during adolescence. Airways of young children are very rarely colonized by fungi and if so, only after previous infections by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Children younger than 6 years had no antibodies against *S. apiospermum*. In a prospective investigation of the incidence of airway colonization in 128 patients with CF over a 5-year period [99] *S. apiospermum* was first encountered during adolescence at a mean age of 14.5 years.

Presence of *S. apiospermum* in CF lungs is counterindicative for lung transplantation, which is a therapeutic option for severe cases. Castiglioni *et al*. [8] reported a fatal pulmonary *S. apiospermum* pleuritis in a lung transplant recipient. Lung and pleural fluid cultures grew *S. apiospermum*, while sputum samples grew *A. fumigatus*. *S. apiospermum* was again detected at autopsy. Lung transplant recipients may develop pulmonary *Scedosporium* infection 9–58 months after surgery [246]. The majority of patients had previously been treated with itraconazole (ITC) because *Aspergillus* had been detected in BAL.

(C) Systemic invasive disease

(i) Scedosporium pneumonia. 'Pulmonary mycetoma' [225,247] is characterized by the frequent occurrence of numerous intercommunicating cavities, fibrosis, and granules. The latter consist of closely intertwined hyphal masses and occasional swollen cyst-like chlamydospores [35,90,142,237,239,248]. There is no evidence of cementing substance between the hyphae or the grains, as is frequently observed in subcutaneous mycetoma [216,249]. Patients are mostly symptomatic with impaired respiratory function [248]. Hemoptysis is frequently observed. Other symptoms include cough, purulent expectoration, weight loss, respiratory insufficiency, fatigue, and dyspnea.

Nearly all cases had pre-existing pulmonary disorders, such as tuberculosis, sarcoidosis, lung transplant, rheuma, chronic bronchitis, bacterial pneumonia or cystic fibrosis. Frequently a history of corticosteroid treatment is noted. For example, Horré *et al*. [249] reported a fatal pneumonia in a patient who had a long history of corticosteroid therapy. Rippon and Carmichael [216] described a case in which the patient's bronchial lesions disappeared when steroid therapy was discontinued. Despite having a normal neutrophil count, affected patients have functional neutropenia because the function of the neutrophils is inhibited by high-dose steroids. These data suggest that discontinuation of steroids and immunomodulation of neutrophil functions are among the major treatment options.

S. apiospermum pneumonia may occur in otherwise healthy hosts. Tekavec [250] reported a case of a cleaning worker in a thermal bath, the bottom sediment of which was found to be positive for the fungus. Seale [251] noted occupational exposure to dust as a possible source of pneumonia, while also cigarette smoking has been suggested [252,253]. One patient with *Scedosporium* pneumonia was immunocompetent with a perforated chest wound [254]. Sometimes no predisposing condition or underlying disease is found [255–257]. *S. apiospermum* may cause empyema in the immunologically intact host [252].

(ii) Endocarditis. This is a rare complication after cardiac surgery [258], sometimes years after intervention [258]. Armin *et al*. [259] described a case in an intravenous drug abuser. Occasionally mixed infections

are concerned [260]. Fatal *S. apiospermum* contamination of a porcine valve replacement was reported by Roberts *et al*. [261]. With profuse fungal growth at the tricuspid valve orifice, the species can be isolated consistently from blood of the patient [258]. Infected heart valves were thickened with friable lobulated masses of vegetation [262].

(iii) Disseminated infection. The first case of disseminated *S. apiospermum* infection was reported by Zafiro [263] in which multiple abscesses developed in the skin, muscles, joints and bones. Since the fifties of the previous century, numerous cases have been reported. Deep invasive infection is nearly exclusively observed in patients with severe disorders in innate immunity, such as acute lymphocytic or myelogenous leukemia, solid cancer, chronic granulomatous disease, glioblastoma multiforme, systemic lupus erythematosus, or having received bone-marrow or solid organ transplants [264]. Patients frequently had received immunosuppressive therapy. Infections then may evolve rapidly. Bower *et al*. [265] reported the case of an 81-year-old male patient with subcutaneous nodules on his forearm who had been taking prednisolone for many years. The patient had a clear history of trauma two weeks before the onset of skin changes, which were probably the source of the fungal infection. Disseminated cases frequently lead to CNS involvement [8,155,266–270]. Two such cases with CNS were in previously healthy patients [268,271].

The route of dissemination is hitherto unclear, since blood cultures of *S. apiospermum* generally remain negative, with some exceptions [270], which possibly are linked to late stages of disease with massive fungal expansion. This is remarkable, since *S. apiospermum* is one of the very few fungi known to produce conidia in tissue [32,35,37,97,303] and thus is thought to be disseminated easily in bodily fluids. Culture is possible also from urine in case of genitourinary infection [272], but also after dissemination from a localized infection [273]. The species is microaerophilic, having an assimilative thallus in the absence of oxygen [39].

Campagnaro [274] described a disseminated *S. apiospermum* infection in a renal transplant patient whose symptoms were suggestive of reactivation of a latent infection. The authors concluded that the fungus might have spread hematogenously during the increased immunosuppression required by the episode of acute rejection, previously reported by Lopez *et al*. [275].

In severely debilitated patients dissemination to the brain from a local disease process can be observed [273]. Genetic identity of the strains colonizing the lungs and causing a non-traumatic keratitis after double lung transplantation in a patient with CF has been proven by RAPD (Symoens *et al*., manuscript in preparation). Deep extrapulmonary infections nearly always show multi-organ involvement, despite neurotropy of *S. apiospermum*. This is in contrast to the neurotropic black yeast-like fungus *Cladophialophora bantiana*, which also reaches the brain via a hitherto uncovered route of dispersal [276].

(iv) AIDS-related Scedosporium infection. *Scedosporium* infection is nearly absent from AIDS patients, the rare cases reported being co-infections with e.g., *Candida* and *Aspergillus* [277] or with concurrent corticosteroid application. CD4 T-cell counts are then less than 100/μl [278].

(v) CNS infection. The first report of a *S. apiospermum* CNS infection was that by Benham *et al*. [132]. Berenguer *et al*. [72] reported the clinical manifestations and underlying disease or predisposing conditions of a total of 21 cases. Further overviews have been presented by Wilichowski *et al*. [279] and Nesky *et al*. [10]. The portal of entry of *S. apiospermum* is supposed to be the lung. Several cases of CNS infection in immunocompetent individuals have been reported [75,268,273,280,281]. Meningitis occurred in an immunocompetent individual [282]. Although *S. apiospermum* has a high affinity for blood vessels [68,283], and hemorrhagic features have been reported in some CNS cases [68,268,284], cerebral aneurysms occur only rarely [76,285,286]. Further predisposing factors are of traumatic nature [75,273,280,281]. Meningitis occurred in immunocompetent hosts after excision of the pilonidal sinus cyst of the sacrum [86] and after spinal anesthesia [132,287].

Brain abscesses may be solitary masses or multiple lesions located in the cerebrum and/or cerebellum. Diffuse cerebritis, cranial infection, and intraventricular device-related ventriculitis have occasionally been reported. Schwartz *et al*. [288] reported the only case to date of a cerebral fungus ball caused by *S. apiospermum*. In most of the CNS-associated cases in immunocompromised hosts, mainly vascular organs, brain and thyroid are involved [160,235,270,289–292]. This may have been promoted by the extremely vascular nature of these organs in association with the angiotropism of the fungus [68,283].

The predominant neurological symptoms are headache, facial paresis, neck stiffness, dizziness, nausea, seizures, altered mental status, vomiting, back pain, skin rash, photophobia, weakness in the arms and legs, infarcts and hydrocephalus. Most cases are fatal if

untreated. In about half of the patients with systemic infections no site of *S. apiospermum* infection other than the CNS was found. Brain abscess is the predominant manifestation in otherwise healthy hosts, while widespread involvement of other organs has been described in immunosuppressed patients [78,274]. CNS invasion by *S. apiospermum* may follow extension from a source near the brain (e.g., paranasal sinuses, eye, ear), direct inoculation (e.g., with trauma or surgery), via an intravenous catheter [84], or probable hematogenous spread from the lung in cases of massive aspiration, e.g., after near-drowning in polluted water. Fessler *et al*. [83] reported a unique superior sagittal sinus infection in a patient who had neither evidence of sinusitis on physical and radiological examination, nor history of trauma. It was demonstrated that the infection originated within the vascular structures and extended into the CNS.

CSF specimens from cases of CNS infection had extremely high white blood cell counts and high percentages of polymorphonuclear leukocytes (PMNs). Large numbers of PMNs should be regarded with concern and are of diagnostic significance. A number of patients had a predominance of neutrophils [40,69,79,80,88,132,292], mostly with counts exceeding 10^7. In addition, CSF pleocytosis with an increase in lymphocytes (>1000 cells/mm^3) was noted in some cases [80,264].

(vi) Near-drowning. All of about 20 cases reported to date were diagnosed in young, otherwise healthy individuals who had a history of aspiration of sewage, or polluted, stagnant, or muddy water [280]. In almost all cases dissemination of *S. apiospermum* took place, with a marked predilection for the CNS in 18 of 20 cases. Although it is considered that infection should initiate in the lung before extending to the brain, exclusively pulmonary involvement without cerebral lesions are rare [293,294]. The hypothesis is allowed that *S. apiospermum* may also enter the CNS directly from the pharynx, through the sinuses close to the brain and ethmoid bone during submersion in contaminated water. The comparably short incubation period of a *S. apiospermum* CNS infection after aspiration supports this hypothesis.

Messori *et al*. [285] reported a case of *S. apiospermum* infection in a near-drowned child with brain abscesses who died after a subarachnoid hemorrhage caused by mycotic aneurysm of the basilar and posterior cerebral arteries. Rüchel *et al*. [87] reported a case of a nearly-drowned child whose clinical condition began to deteriorate one week after the accident. On day 21 a CT scan of the brain revealed hypodense foci suggestive of cerebral abscess. Another fatal case of primary neurological *S. apiospermum* infection [295] manifested with meningismus 15 days after near-drowning. Also victims of the Asian tsunami have been reported [296]. The incubation period for *S. apiospermum* CNS infection after aspiration of a sufficient inoculum is thus estimated to be about one to four weeks. The infection often becomes symptomatic with delay, when remaining disorders resulting from the accident have been cured. This is in contrast to comparable bacterial infections, where pulmonary symptoms are notable within 1–3 days. *S. apiospermum* is the prevalent fungus associated with near-drowning, and is exceptional among microorganisms in being neurotropic [297].

Animal cases

Many strains of *S. apiospermum* are thermotolerant, having a maximum growth temperature between 36 and 42°C, and the species is eutrophic [39]. It may be surmised that the natural niche involves warm-blooded animals. Indeed the species has been reported to occur asymptomatically in the lungs of rodents [298] and in the lower digestive tract of feral pigeons [299]. Also the lungs of cold-blooded animals proved to be infected [300]. Nevertheless the infections reported from wild animals are too rare to allow any conclusion on the habitat of *S. apiospermum*.

Most reported animal infections are of traumatic origin, such as keratitis in a horse [301] and a dog [302], as well as cases of mycetoma in dogs [302–304] and in horses [302,305,306]. Such cases can be severe and extending to deeper organs and bones in both host families [307]. In addition, there are occasional reports of sinus infection in dogs [308,309] and horses [310]. Invasive pulmonary infection is rare [311]. Remarkably there are recurrent reports of infections of the reproductive tract leading to abortion in horses [312,313], pigs [314] and cows [315]. This suggests a higher pathogenic potential of *S. apiospermum* than that of most other opportunists. It is able to cause systemic, disseminated infections in case of impairment of the general condition of the animal [316–318]. The marked predilection for the central nervous system as noted in humans is uncommon. One of the few reports with brain involvement is that of Haulena *et al*. [319] in an elephant seal.

Nearly all reports from animals are subcutaneous or systemic. The report of Kuwano *et al*. [320] is exceptional in describing onychomycosis in several horses.

Treatment regimens and outcome

Invasive *S. apiospermum* infections are difficult to manage because of their intrinsic resistance to many antifungal agents. The initial approach to treating deeply invasive infections was to administer high-dose AMB. However, the overall response rates in immunocompromised hosts were dismal. AMB did not prove to be effective in animal studies either [133].

Localized infections

In localized infections, whenever possible, surgical resection of infected tissues is the preferred treatment. MCZ has been used successfully in many cases even in some patients whose immune systems were impaired [250]. However, this drug is not commercially available for systemic use, and considering its high toxicity and the high rates of infection recurrence [161] it is not currently recommended.

(i) Arthritis and osteomyelitis. Optimal treatment for localized infections is as yet unknown because numerous approaches have been tested with very variable results. In the 39 reported cases of osteoarticular infections, one of the most common manifestations of *Scedosporium*-related disease, 17 different therapeutic regimens have been applied. Surgery alone [165,321] or combined with one [163,165,176,255] or more antifungals [161,168] were the most common treatments; although in numerous occasions the patients only received medical treatment with one drug, such as AMB [159,160], ITC [161,167,170,173], KTC [169,255], MCZ [160,176] or combinations of them [158,177]. With the exception of three cases [167,170,177] all these treatment regimens resulted in a partial or total recovery of the infection. A case of cranial osteomyelitis and subdural empyema following craniotomy was successfully treated with surgical debridement and VRC [322], while a case of tenosynovitis-arthritis was resolved with fluconazole (FLC) [323], an antifungal with very poor *in vitro* activity against this fungus. Most cases were partially or totally resolved using these divergent therapeutic regimens. Surgical removal of the lesions seems to be the optimal treatment for most localized infections, but when complete resection is impossible, prolonged antifungal therapy is necessary.

(ii) Sinusitis. Of 24 cases, 14 responded positively to treatment. Six of these were by surgery [204,231,321,324–326], and in two AMB was administered as monotherapy [202,209]. The remaining cases applied surgery supplemented by antifungal combination therapy of AMB plus KTC, MCZ plus ITC, or AMB plus MCZ and KTC. The cases with negative outcomes were therapeutically similar to the successful ones, so that the reasons for failure are as yet unknown.

(iii) Lymphocutaneous infection. Cases of lymphadenitis or lymphocutaneous infection mostly responded positively to antifungal treatment with ITC [195,199–201], FLC [327] and sulfa drugs [197]; MCZ treatment was unsuccessful [160].

(iv) Cutaneous and subcutaneous. Trauma with introduction of the fungus into the dermal or subcutaneous tissue usually results in mycetoma. For these infections, surgical debridement with accompanying antifungal therapy is recommended. Of 21 cases of cutaneous or subcutaneous infections reported in the literature, 11 patients responded positively to ITC [148,192,195,328,329], although treatment with this drug failed in two cases [152,330]. VRC was able to resolve three cases [41,264].

(v) Keratitis. In the treatment of keratitis antifungals tend to be less effective than in other types of infections, possibly because the etiologic agent was not recognized timely and aggressive treatment was delayed [332]. Penetrating keratoplasty or enucleation is a frequently applied therapeutic option [187]. The most commonly used drugs are MCZ and natamycin [333]. Wu *et al*. [333] calculated a success rate of 47% for MCZ. Although there is little experience in the use of other drugs, ITC has proven its effectiveness in a recent case [334]. VRC was effective in two cases [335,336] but it failed in one [332]. This failure was ascribed to poor corneal penetration of the systemic preparation [332], although the level of VRC in the aqueous humor was 53% of the level in plasma and exceeded the minimal inhibitory concentration (MIC) for the isolate by sevenfold. There is no clinical experience with TBF, but it has been suggested that it can be clinically used in combination with MCZ because of the high *in vitro* synergy demonstrated by this combination [336].

(vi) Endocarditis. Endocarditis is one of the rare infections caused by *S. apiospermum* and usually involves heart valve prosthesis. Nine cases have been reported [258,337], and practically all the patients died before the fungus was identified and antifungal therapy could be initiated. Antifungal treatment has been mentioned in only three cases: in one MCZ was administered in combination with ITC [258], while the other applied

MCZ plus AMB [338], and AMB plus ITC [337], respectively. In the three cases the infection was fatal.

(vii) Scedosporium pneumonia. In 61 cases reported in the literature, 27 different therapeutic approaches were applied, with very variable outcome and occasional relapse. Infections were fatal in 31 patients (50.8%). In an immunocompetent adolescent with preceding trauma treated with ITC, a reactivation occurred after 20 months of therapy, despite adequate serum concentrations. This patient was treated with oral TRF (500 mg/d) and after 4 months of therapy bronchoscopy showed no evidence of fungal infection [254,339]. Another relapse occurred in a patient who initially responded to KTC [255].

(viii) CNS infection. CNS infections are those with the poorest outcome: patients died in 51 out of 66 reported cases. Nineteen different therapeutic approaches were used. Surviving patients all underwent surgery and/or received systemic antifungal therapy with AMB [271], MCZ [84,222], and VRC [10,340], alone or in combination [74,280]. In most cases MCZ was inoculated into the CSF because of its poor meningeal penetration. Of meningeal cases reported, one survived with surgical treatment alone and six after receiving systemic antifungal therapy with MCZ, AMB and 5FC [341], VRC [86,342] or PSC [343,344]. Three died after changing to VRC [274,345] or PSC salvage therapy [343]. Recently, a patient with multiple intracerebral abscesses after a near-drowning episode was successfully treated with CSF drainage and antimycotic therapy which included TRF and intraventricular CAS in addition to VRC [346]. Current data suggest that surgical removal of the abscess is as important as antifungal therapy.

(ix) Pulmonary fungus ball. Of the 75 patients that suffered from pulmonary intracavitary colonization, nine cases (12%) were fatal. Eighteen patients were managed surgically, and all survived. These data suggest that surgery is the treatment of choice for a cavitary lesion containing a fungus ball. Recovery was also achieved with MCZ [146], ITC [60,243] or VRC [226,229], but also in patients that did not receive any therapy [225,347]. In one apparently successful case sputum cultures remained positive despite AMB treatment [35].

Disseminated infections

Outcome of disseminated infections tends to be very poor, irrespective of treatment regimens used. Of the 39 cases reported in the literature, only four patients responded successfully. A common factor in all the cases with a positive outcome was that immunoadjuvants were given to the patients in addition to antifungal drugs. Under these conditions it is difficult to ascertain the true role of antifungals in the resolution of the infection. For example, a patient suffering from asthma and receiving corticosteroid therapy developed a lung infection and noted the presence of multiple nodular subcutaneous lesions. VRC was administered in combination with granulocyte colony stimulating factor (G-CSF), which resulted in recovery from the infection [348]. Other cases in which antifungals (VRC and AMB plus ITC, respectively) proved to be effective were in patients with acute myelogenous leukemia (AML) receiving G-CSF [349,350]. A patient with chronic granulomatous disease (CGD) who suffered from a mixed infection by *Aspergillus fumigatus* and *S. apiospermum* and who was successfully treated with prolonged administration of AMB and MCZ combined with recombinant gamma interferon (r IFN-γ) [351]. In the cases that did not respond to treatment, the most commonly used drug was AMB. In 18 cases this drug was administered alone, once supplemented by surgery and in 12 cases it was combined with other drugs that were often changed because patients were failing to respond. Since VRC has been able to resolve different types of *S. apiospermum* infections it seems to be a promising drug for the treatment of *Scedosporium* infection. In addition, it has shown *in vitro* activity and efficacy in different animal models. However, recent studies evaluating the efficacy of VRC in six clinical cases showed contradictory results. In one of the studies, five patients had a successful outcome [352], while in another [353] only two patients responded positively to the therapy.

Systemic invasive infections by *Scedosporium* species have a very high mortality rate due to their neurotropism (Fig. 12). When untreated, CNS infections are invariably fatal. Due to the therapy-refractory nature of *S. apiospermum*, surgery remains necessary in case of life-threatening disease. In severe infections, restoration of immune competence is mandatory, while adjunctive therapy with IFN-γ or cellular immune-stimulating factors such as GM-CSF or G-CSF may be helpful. Most routinely applied antifungals are poorly effective or ineffective. Therapy with PSC or VRC has been recommended, although authors present variable results. Alternatively, combination therapy might be applied, such as ITC with TBF. It should be kept in mind, however, that these drugs are fungistatic rather than fungicidal, and a very high relapse rate (Fig. 12) is observed.

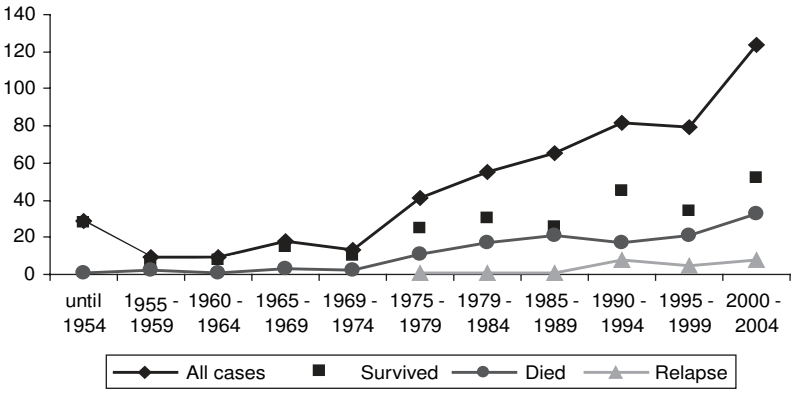

Fig. 12 Survival and relapse rates of *Scedosporium apiospermum* until today.

Epidemiology

Judging from currently available data, the species treated in this review appears to be a truly emerging environmental pathogen and to display a remarkable shift in its clinical spectrum. Our statistics are based on published cases, which number is likely to drop when a clinical syndrome has become routine. In addition, epidemiological studies of *Scedosporium* species have always been overshadowed by diagnostic problems. *S. apiospermum* in tissue is easily misidentified as *Aspergillus*, and even in culture the species is frequently not recognized due to its morphological plasticity. The species has been diagnosed particularly in Europe and the USA, while it seems to be nearly absent from other suitable climate zones. Within a single country, hospitals with comparable patient populations seem to encounter the fungus at very different frequencies. It is tempting to speculate that these highly diverging incidences are explained by underdiagnosis of the fungus. With this in mind, some striking observations can nevertheless be made.

From the point of view of localization (Fig. 6) it is apparent that otitis is the only disease category that has remained stable over the years, at a very low incidence. Outside this disease entity, nearly all infections reported before 1955 concerned mycetoma. Mycetoma is a subcutaneous infection in otherwise healthy hosts which elicits a strong innate immune response leading to fungal grain formation. Cutaneous infections, with hyphae present in tissue, typically are an emerging disease category that is observed in the immunocompromised patient population. Disseminated cases nearly exclusively occur in hosts with severe impairment of their immunity.

Sinusitis and CNS infection are fairly frequent today, but were unreported before 1970. Both disease categories are directly related to major disorders of innate immunity show a gradual increase in frequency. Systemic cases either tend to be pulmonary and cerebral with secondary cutaneous lesions, or are exclusively found in the brain (Fig. 13). Regarding predisposing conditions, particularly patients with bone marrow and solid organ transplant recipients are at risk [3] which is also reflected in the number of cases reported (Fig. 14). The infection frequently results after medical intervention and may therefore be a significant nosocomial disease entity. Given the sometimes very long incubation time, dissemination may also result from reactivation of previously acquired infections. In some cases, however, there was an obvious link to e.g. intraarticular injection, surgery, or use of catheters. Individuals with pre-existing defects, particularly in the lungs, are predisposed for infection. It is striking that neither AIDS, nor diabetes seem to be a risk factor for *Scedosporium*.

The emergence of near-drowning associated cerebral *Scedosporium* infection, known only since 1980, may be explained by the fact that these patients only rarely survived before that period. Alternatively, an increased prevalence of *S. apiospermum* in the manure-polluted

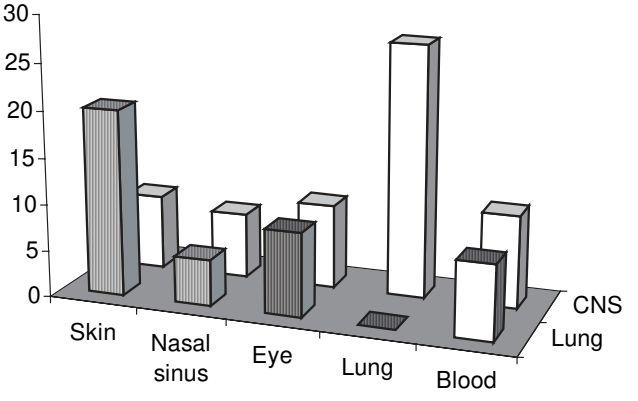

Fig. 13 Isolation of *Scedosporium apiospermum* from different body sites of single patients. Y-axis = number of case reports.

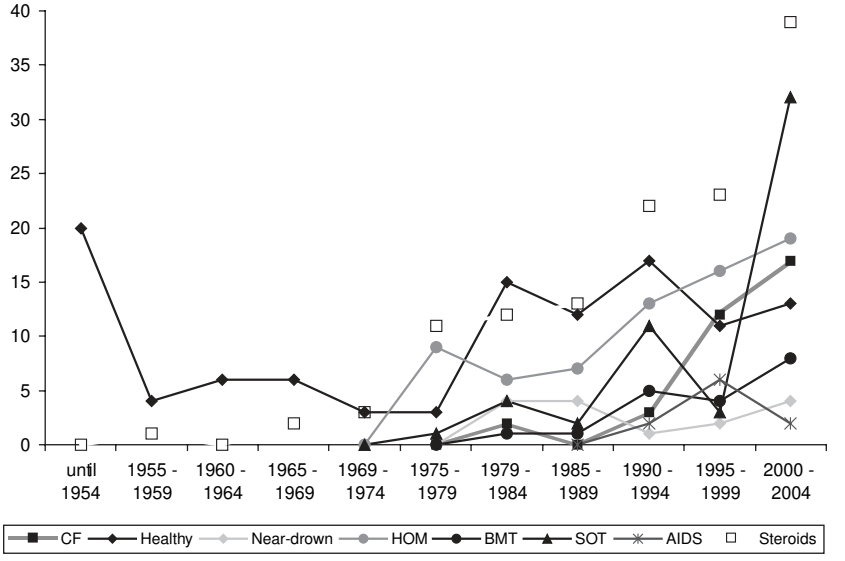

Fig. 14 Number of case reports of *Scedosporium apiospermum* infection in 5 year intervals listed according to underlying disorders, Y-axis = number of case reports. CF = cystic fibrosis, HOM = hemato-oncological malignancy, BMT = bone marrow transplant, SOT = solid organ transplant.

environment provides a possible explanation, given the fungus' eutrophic character [38–40]. *Aspergillus* CNS infections do occur but are rarely seen after near-drowning, despite the fact that *A. fumigatus* is commonly present in surface water [354]. Thus fungal infection after near-drowning is almost exclusively associated with *S. apiospermum*.

The increasing incidence of *S. apiospermum* in the lungs of CF patients in part certainly is linked to earlier problems of detection and identification, but is also explained by the fact that CF patients today survive much longer. *Scedosporium* generally only becomes apparent during adolescence. Older patients often carry more than one *S. apiospermum* genotype.

Infections were noted in patients of all ages between 2 and 92, but infections in neonates are strikingly absent (Fig. 15). The mean age was 42; no bias was noted with elderly individuals. Some patient groups were significantly younger than average, particularly BMT recipients and CF patients. Indeed these patient populations are known to be relatively young. Victims of near-drowning show three approximate peaks in relation to age. A first group concerns young children around the age of 2–3 years, a second group comprises reckless youth of 12–25, while a third, elderly group, is recognized having, e.g., cardiac arrest during swimming. All were previously in good health and frequently in the process of recovery from their accident

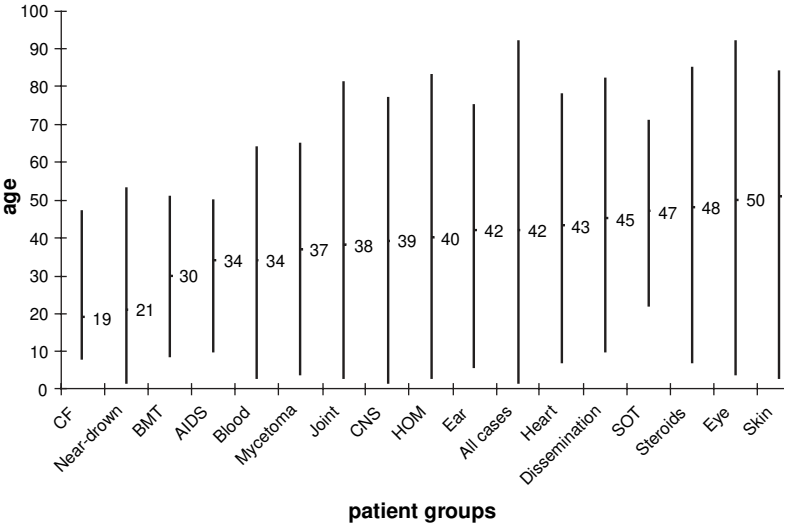

Fig. 15 Mean age and age range of *Scedosporium apiospermum* infections with respect to site of infection on underlying risk factor.

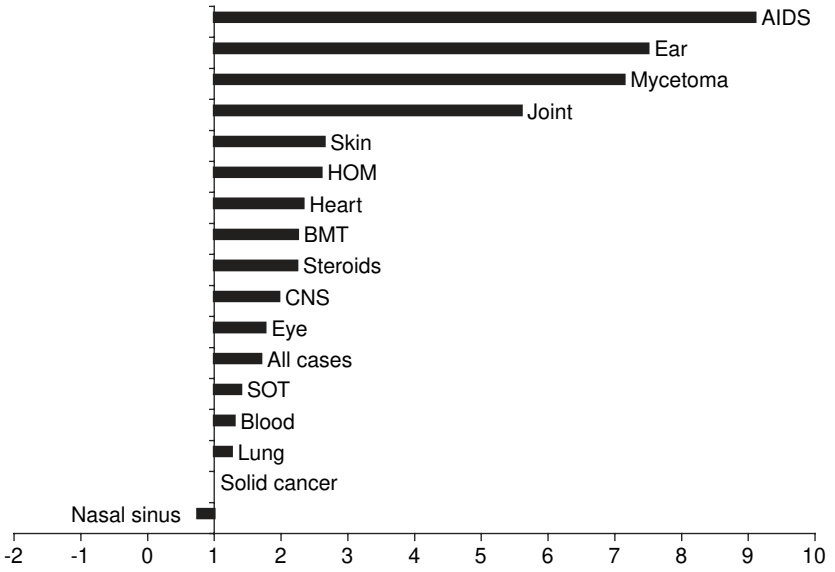

Fig. 16 Correlation between sex of patients and site or type (underlying disease) of *Scedosporium apiospermum* infection. Relative deviation from equal distribution female (left): male (right) = 1: 1, with percentage of cases on the X-axis. Abbreviations used: HOM = hemato-oncological malignancy; BMT = bone marrow transplant; SOT = solid organ transplant; CNS = central nervous system. HIV may be uncomparable due to the low number of cases.

when a cerebral *S. apiospermum* infection was noted. Given the rarity of this type of microbial infections, the syndrome can be listed as a characteristic disease entity for *S. apiospermum*.

Mycetoma has classically been associated with a higher incidence in males, alledgedly due to a higher exposure to the fungus due to outdoor labor [355]. Recently, however, the possibility of a higher degree of susceptibility of males has been put forward for *Madurella mycetomatis* [355]. Data supporting this thesis can be deduced from Fig. 16, where *S. apiospermum* is consistently more frequent in males, also when underlying disorders are non-occupational, such as immunosuppression or otitis.

Conclusions

In summary, *Scedosporium* infection is an emerging, potentially life-theatening disease category which is difficult to diagnose and treat. Infections have increased as a result of immunosuppressive therapy and of availability of older CF patient populations. *S. apiospermum*-related cerebral near-drowning syndrome is another emerging category, and the possibility exists that the frequency of such infections might augment as a result of increasing environmental pollution. Research on the development of reliable diagnostics, detection, and therapy is urgent. A Working Group with this aim has recently been founded by the European Confederation of Medical Mycology (ECMM). Its website (www.scedosporium-ecmm.com) provides an extended overview of all published cases where *S. apiospermum* was reported to be among the etiologic agents of disease. The *Scedosporium* network involving participants from 22 countries stimulates and co-ordinates research on all aspects of these significant environmental pathogens.

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