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Review

Clinical characteristics and epidemiology of pulmonary pseudallescheriasis

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ABSTRACT

Background: Some members of the *Pseudallescheria* (anamorph *Scedosporium*) have emerged as an important cause of life-threatening infections in humans. These fungi may reach the lungs and bronchial tree causing a wide range of manifestations, from colonization of airways to deep pulmonary infections. Frequently, they may also disseminate to other organs, with a predilection for the brain. In otherwise healthy patients, the infection is characterized by non-invasive type involvement, while invasive and/or disseminated infections were mostly seen in immunocompromised patients.
Aims: We reviewed all the available reports on *Pseudallescheria/Scedosporium* pulmonary infections, focusing on the geographical distribution, immune status of infected individuals, type of infections, clinical manifestations, treatment and outcome.
Results and conclusions: The main clinical manifestations of the 189 cases of pulmonary pseudallescheriasis reviewed were pneumonia (89), followed by fungus ball (26), and chest abscess (18). Some patients had more than one type of invasive pulmonary manifestations. Among patients with pneumonia, several cases of pneumonia associated with near-drowning (10/89, 11.2%) have also been reported in immunocompetent hosts. Major underlying conditions for non-invasive pulmonary infection were preexisting lung cavities and medical immunosuppression for invasive pulmonary infection. Saprobic airway colonization was mostly seen in patients with mucosal dysfunction, i.e. patients with cystic fibrosis. The mortality rate was closely related to the infection type, being 26.8% in non-invasive type (fungus balls) and 57.2% in invasive type.

Características clínicas y epidemiología de la pseudalescueriasis pulmonar

Palabras clave:
Bala fúngica
Pseudallescheria
Pseudalesquerioma
Infecciones fúngicas pulmonares
Scedosporium

RESUMEN

Antecedentes: Algunos miembros del género *Pseudallescheria* (anamorfo *Scedosporium*) están emergiendo como causantes de infecciones humanas graves. Estos hongos pueden alcanzar los pulmones y el árbol bronquial causando una amplia variedad de manifestaciones clínicas, desde colonizaciones de las vías aéreas hasta infecciones pulmonares profundas. Frecuentemente estos hongos pueden diseminarse a otros órganos, mostrando una marcada predilección por el cerebro. En pacientes por otra parte sanos la infección no suele ser invasora, mientras que en el paciente inmunocomprometido se caracteriza por su carácter invasor.
Objetivos: Se ha llevado a cabo una revisón de los artículos disponibles sobre infecciones pulmonares por *Pseudallescheria/Scedosporium*, destacando la distribución geográfica de las mismas, el estado inmunitario de los pacientes, el tipo de infección, las manifestaciones clínicas, el tratamiento y curso clínico de la enfermedad.
Resultados y conclusiones: La principal manifestación clínica de los 189 casos de pseudalescheriasis pulmonar revisados fue neumonía (89), seguido por la presencia de bola fúngica (46), y absceso pulmonar (18). En algunos casos de sujetos inmunocompetentes la neumonía fue debida a aspiración con agua contaminada (10/89, 11,2%). Los principales factores de riesgo para las infecciones pulmonares no invasoras fueron la preexistencia de cavidades pulmonares y el tratamiento inmunosupresor para infecciones pulmonares invasoras. La colonización saprofítica de vías aéras se observó principalmente en pacientes con alteraciones de la mucosa,

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como aquellos con fibrosis quística. La tasa de mortalidad estuvo estrechamente relacionada con el tipo de infección, siendo del 26,8% en las infecciones no invasoras (bola fúngica) y del 57,2% en las invasoras.

Currently, *Pseudallescheria/Scedosporium* infections are some of the most prevalent mould infections in humans, being the respiratory tract the most commonly infected site.[52] Recent molecular studies have demonstrated that *Pseudallescheria/Scedosporium* complex (PSC) includes several phylogenetic species,[46] but since the degree of involvement of each individual species in human infections has not been determined, the present review will maintain the name PSC in all disease entities. The species of that complex and relatives recovered so far from clinical samples are: *Scedosporium apiospermum* (teleomorph *Pseudallescheria apiosperma*), *Scedosporium aurantiacum*, *Scedosporium boydii* (*Pseudallescheria boydii*), *Pseudallescheria angusta* and *Pseudallescheria minutispora*.[46,47] Several types of respiratory system involvements of PSC have been described in both immunocompromised and immunocompetent individuals. Three general reviews, on a range of PSC infections[29,52] and central nervous system (CNS) infections,[68] have recently been published. In addition, a few more, shorter, reviews each covering a small number of previous cases[6,9,14,82,109,113,115] have also been published. The clinical spectrum of the disease associated with PSC was examined by Rippon, in 1980.[112] In the present study, the available case reports of PSC pulmonary infections have been reviewed chronologically to clarify many aspects associated particularly with these illnesses, including the risk factors and underlying conditions, clinical manifestations, diagnostic factors, treatment and outcome.

Methods

Literature search

A computerized search of the MEDLINE database (National Library of Medicine, Bethesda, Maryland, USA) was made for cases reported in the literature between 1955 and mid-2009, with (by cross-referencing) the terms: "*P. boydii*" and "*S. apiospermum*", "pulmonary", "pneumonitis", "lung abscess", "pulmonary nodules", "mycetomas", "fungomas", "respiratory system infection", "disseminated" and "near-drowning", "respiratory system colonization", "Pseudallescherial colonization", "fungal colonization" "cystic fibrosis", "allergic bronchopulmonary pseudallescheriasis", "scedosporiosis" and "pseudallescheriasis". Additional search terms included were "*Allescheria boydii*", "*Monosporium apiospermum*", and "*Petriellidium boydii*" as referring to prior or other nomenclature for this fungus. These key words were used alone and/or in combination with an "and" statement. Additional cases were found by scanning the references cited in the original articles. Original full texts of all the relevant articles were found via MEDLINE, TUBITAK-ULAKBIM (Turkish Academic Network and Information Center), and/or other international libraries and were used for the analysis or personal communication of the authors.

Definitions

A case was considered an invasive pulmonary infection when the presence of lesion and clinical syndrome consistent with pulmonary infection (involvement of lung parenchyma) was documented and any species of the PSC was recovered from the lesion, usually from lung tissue, mucosal biopsy, aspirate from an abscess or bronchoalveolar lavage fluid (BAL). Cases were included in the study as non-invasive involvement when the fungus grew in pre-existing lung cavities from a previous disease, i.e. tuberculosis or sarcoidosis, without invading the cavity wall. The mass may move within the cavity but does not invade the cavity wall.

Infection types that refer to a saprobic involvement, such as fungus ball or mycetoma were evaluated and categorized as reported by the authors. Duplicate publications were excluded and follow up reports were regarded as associated with a single case together with the previous report. The following data were recorded for each patient, if stated: age and sex, geographical location, predisposing factors (including underlying diseases and associated medical conditions), clinical symptoms, mode and time to diagnosis, other pathogens isolated or observed in specimens if any, antimicrobial agents administered, regimens and duration of antifungal therapy, invasive or surgical procedures, duration of hospitalization, and patient outcome.

Results

There were 231 case reports and records of isolation of PSC from pulmonary specimens identified from 1955 to end-2010. PSC was first reported as a cause of pulmonary disease in 1955 by Creitz and Harris,[30] although the organism was probably a secondary invader, being inhaled from the soil. Four cases were described twice,[22,67,74,84,85,109,134,145] due to the progression or reactivation of the disease. No details of the patients' histories were available in two case reports.[36,38] One case was summarized in a general report on brain abscesses following bone marrow transplantation,[36] and the presence of the fungus in sputum was mentioned in an environmental study.[31] In another case with bronchiectasis, in spite of PSC being repeatedly isolated from the patient's sputum it was not obtained in culture from the intercavitary mass, in which many *Aspergillus fumigatus* conidiophores were histologically observed.[109] Of these 231 published cases, 56 involved patients with cystic fibrosis (CF).[23,26,27,32,53,59,63,83,86,94,105,119,127,129,135,144,148] Twelve of these CF patients were reported to have invasive and two non-invasive pulmonary infection.[53,83,86,94,127,135,144] A total of 189 cases were invasive or non-invasive infections with isolation of PSC from lower respiratory tract specimens.

Overall demographic and geographic features

The majority of those 189 pulmonary pseudallescheriasis were reported from the USA (78 cases), followed by Australia (40 cases), Japan (14 cases), France (14 cases) and Germany (7 cases). Occasionally, there were cases reported from Argentina, Belgium, Brazil, Canada, China, Congo, Croatia, Finland, India, Spain, Mexico, The Netherlands, Poland, Spain, Taiwan and the UK [total = 80 female patients and 101 male, age range = 2–90 years].

Portals of entry and route of dissemination

Pulmonary involvement, which mainly affected farmers, probably resulted from inhalation of the conidia.[33,53,64,67,72,83,86,94,120,123,127,135,152] A case was reported in an immunocompetent patient who was working in a thermal bath, being in charge of scrubbing off the sedimented filth at the bottom of the pools after draining the water. *S. apiospermum* was isolated from several samples of the thermal water and the sediment filled

the patient's working place.[138] In one case, the patient suffered a lymphatic and haematogenous dissemination of the fungus via a skin injury while gardening and developed a lymphocutaneous syndrome, similar to sporotrichosis, along with a lung mass.[74] Pulmonary involvement may have been secondary from septic emboli originated from lymphangitis or phlebitis in the left arm. Aspiration of polluted water was reported in 17 patients who developed a CNS infection. It is likely that after an invasive pneumonitis, the fungus can reach the CNS by haematogenous spread facilitated by the immunosuppression.[52] The fungus could also be directly inoculated through a perforated chest wound, or inhaled,[134,145] or transferred from an infected donor to an organ recipient.[143] Patterson et al.,[101] reported a case of nosocomial pseudallescheriasis in a liver transplant patient who was probably not colonized or infected as he was immunocompetent on admission but developed cavitary lung and brain lesions on day 25 post-transplant.

Colonization of bronchial lumen or intracavitary colonization

PSC can grow within poorly draining bronchi, causing an endobronchial saprobic colonization without tissue invasion. The fungus may colonize the respiratory tract of people exposed to a high environmental inoculum in the absence of anatomical or physiological abnormalities of the respiratory tract. This colonization would most likely be transient once the patient is removed from the environmental source. Transient colonization without apparent invasion has been recorded secondary to other diseases or conditions.[67,109,111,126] Rippon and Carmichael[111] reported a case of transient colonization of bronchial lumen in which the patient was on prednisone for 15 years for rheumatoid arthritis, and had coughing, wheezing, and pulmonary congestion. Direct examination of several sputum specimens revealed intertwined hyphal masses and PSC was cultured from all samples. Reddy et al.[109] and Jung et al.[67] described another transient colonization in a farmer's wife with chronic bronchiectasis and chronic obstructive pulmonary disease. Castiglioni et al.[22] reported the case of three solid-organ transplant patients who had airway colonization and received itraconazole (ITZ) prophylaxis, without evidence of disease. Similarly, in an allogenic bone marrow transplant patient with acute lymphocytic leukemia, treated with chemotherapy, cyclosporin and corticosteroids for graft-versus-disease complication, *A. fumigatus* was isolated from sputum culture 5 months following the transplantation. The patient was treated with ITZ and a follow up sputum culture revealed a heavy growth of PSC. Liposomal amphotericin B was added to the treatment and repeated sputum cultures and a bronchoalveolar lavage fluid were negative for PSC.[12] Endobronchial chronic colonization by PSC has been reported in CF patients, often without pathological effects for the host.

Clinical presentations

The role of PSC in producing pulmonary lesions and some of their relevant conditions has already been discussed in earlier reports. However, pseudallescherial lung infections have continued to be reported and consequently their clinical spectrum has been considerably enlarged. The most relevant clinical manifestations of infection are outlined in Table 1. Of those, pneumonitis was the most common clinical manifestation (94/189, 49.7%). Although the chest X-rays were not specific, they were usually helpful in establishing the diagnosis. A dense infiltrate first appears, followed later by cavitation and in some cases by the development of a fungus ball, mostly in the upper lobes. Fulminant spread with invasion through the lung parenchyma and the pleura and development of pleural effusion has commonly been described. Case reports that have based the diagnosis of pulmonary disease on the isolation of PSC from sputum are contradictory.[75] Most patients with this fungus in the sputum do not appear to have invasive infection.[72] Cases of pulmonary pseudallescheriasis appear similar to pulmonary aspergillosis, clinically, radiologically, histologically, and in terms of severity. Macroscopically, pulmonary pseudallescherial infections produce inflammatory cystic or cavitary lesions. Regarding the data obtained from the above-mentioned cases, pulmonary pseudallescheriasis can be subdivided into three categories:

(i) Pulmonary mycetomas and fungus balls (pseudallescheriomas)

Forty-six case reports of non-invasive involvement of intrathoracic cavities, which can be divided into two groups as pulmonary mycetoma (18/46, 39.1%) and pseudallescherioma (28/46, 60.9%), were identified. The terminology used here is based on the specific descriptions made in the different case reports. Pulmonary mycetomas were reported to contain many small, greyish-yellow and white granules, measuring 1–2 mm in diameter, within thick, brownish, semi-fluid, odourless exudate. The granules of pulmonary mycetoma consist of closely intertwined hyphal masses and occasional swollen cyst-like chlamydospores. In rare instances, white or yellow lobulated granules of up to 4 mm in diameter have been observed.[5,8,11,14,21,30,38,53,57,58,81,91,109,141] There has been no evidence of any cementing substance between the hyphae or production of conidia on the periphery of the granules.[10,53,111]

Intercavitary colonization may typically lead to the formation of a mass consisting of loose hyphal strands or conglomeration of intertwined fungal hyphae admixed with mucus and cellular debris within a preexisting pulmonary cavity or ectatic bronchus. A patient with this type of infection may have a chronic pulmonary infiltrate from a previously existing disease, such as sarcoidosis or tuberculosis.[86,111,112] People who have pre-existing lung problems, especially with cavities typically affected by tuberculosis,[92] sarcoidosis etc. are at risk of developing non-invasive amorphous fungal masses, called fungomas, fungus balls or in this case pseudallescheriomas. The fungus settles in a cavity and is able to grow free from interference because the immune system is unable to penetrate the cavity. As the fungus multiplies, it forms a ball which incorporates dead tissue from the surrounding lung, mucus, and other debris.

Pseudallescherioma of the lung is the extreme consequence of intercavitary colonization, where the mass of fungus reaches sufficient size to be visible radiologically.[3,9,14,22,44,69,87,109,111,119,121,123,125,152,154] Radiographs of the pseudallescheriomas show the presence of a solid, round or oval mass with soft tissue opacity within a lung cavity.

Pseudallescherioma may be different in its morphological features; concentric rings of hyphae radiating from a central area were mainly noted.[121] In addition, conidia occur on the surface where the mass is in contact with an air space, generally on the periphery of the pseudallescherioma.[69,72,75,121] Similarly to that which occurs in aspergillosis, pseudallescherioma are found in the upper lobe of patients with pre-existing lung disease and are often associated with a thickening of the cavity wall and adjacent pleura.[140]

In non-invasive type cases, these fungi did not invade the tissues, their presence as a mass within cavities stimulated chronic active inflammation and a markedly vascular granulation tissue response. Based on two case reports,[107,140] Przyjemski[108] hypothesized that fungus balls may begin as "tissue balls" infiltrated by fungus. In the first case,[107] the radiological progression from normal lung through poorly defined infiltrate to fungus ball occurred within two weeks and coincided with recovery from granulocytopenia and derived from infected lung sequestra with inflammatory infiltrate. Since surgically removed fungus balls usually fail to grow on laboratory media,[3,5,69,110,115,140,141] the author concluded that the

Table 1
Overall clinical manifestations of 189 respiratory involvement by *Pseudallescheria*/*Scedosporium* complex.

Clinical manifestations							
Allergic bronchopulmonary pseudallescheriasis		Non-invasive types			Invasive types*		
Number of patients	References	Type	Number of patients	References	Type	Number of patients	References
5	12, 76, 90 (2 p), 111	Pulmonary mycetoma	18	8, 11, 14, 21, 33, 40, 57, 58, 67 (& 109 s), 73, 81, 91, 100, 125 (2 p), 125, 131, 141	Bronchopneumonia	4	34, 44, 144, 151
		Fungus ball	28	3 (&11 s), 5, 9, 10, 22, 25, 30 (&139 s), 32, 39, 44, 60, 67, 69, 87, 92, 109, 111, 119, 120, 123, 125 (3 p), 133, 139, 152 (2 p), 154	Pneumonia	94	1, 4, 5, 7, 12, 15, 16, 17, 18, 22 (3 p), 24, 28, 37 (4 p), 43 (5 p), 45, 53, 56, 65 (3 p), 66, 71, 77, 78, 79, 83, 86 (5 p), 88, 94, 95, 97, 103 (7 p), 104, 106,110, 117 (3 p), 122, 127, 128, 130, 134, 135, 136, 137 (7 p), 138, 143, 146 (3 p), 147 (18 p), 149
					Necrotising pneumonia associated with abscess	18	6, 7, 13, 34, 39, 49, 51, 55, 61, 62, 66, 70, 90, 96, 116,132, 142, 150
					Cavitary necrotizating pneumonia	10	35, 48, 64, 84 (2 p), 98, 99, 114, 118, 149
					Nodular pneumonia	8	9, 17, 22, 43, 54, 72, 101, 124
					Cystic mass formation	3	22, 74, 98
					Intrabronchial polipoid lesions	2	96, 153
					Invasion of pulmonary vessels	2	149, 150

Abbrevations: p: patients; s: the same patient.
* Total of patients is not 189 because some IPP patients had more than one type.

pseudallescherioma formation might be associated with improving host resistance.

Demographic and geographic features. Most cases have been reported from the USA, with occasional cases from the UK, Germany, France, Poland, India, Japan, Canada, Brazil and Australia (female, $n = 24$, male, $n = 20$, gender was not indicated in the other reports, age range = 11–81).

Predisposing factors and underlying conditions. Twenty seven of these 44 patients had associated diseases, which could have contributed to the occurrence and progression of the disease, i.e. tuberculosis and/or tuberculosis cavity (16), sarcoidosis (4), cavitary bronchiectasis (1), chronic bronchitis (1), secular bronch (1), anaplastic cavity in lung (1), lung transplantation (1), systemic lupus erythematosus (1) and alcoholism (1). Four of these 46 patients were otherwise healthy. Pulmonary involvement probably resulted from inhalation of the conidia or ascospores. Seven patients were long time rural residents, or worked closely with soil.

Signs and symptoms. Clinical symptoms varied from none to haemoptysis and general debilitation. Other symptoms included cough, purulent expectoration, malaise, weight loss, respiratory insufficiency, fatigue, and dyspnea. Haemoptysis was the most common, being noted in 16 cases. One patient was asymptomatic.[81] Tuberculin skin test was positive in 5 patients. Precipitating antibodies to PSC were found in 15/56 patients with CF. Complement-fixing antibodies to *A. fumigatus* were present in one case.[3,115]

Radiology. Radiological examination may show a moon-shaped radiolucent sign which caps the fungus ball like the one seen in aspergilloma.[5] In some cases, the mass is separated from the wall of the cavity by an airspace of variable size and shape, resulting in the "air-crescent" sign which is believed to indicate invasive pulmonary aspergillosis.[5,25] Radiographs of one of the cases presented as a solitary round lesion proved to be related to cancer on pathological examination.[33] In three cases, the pseudallescherioma was bilateral, in 13 it was localized in the right upper lobe, and in 3 in the left upper lobe.

Laboratory diagnosis. In most cases, the fungus was isolated from sputum cultures. In 17 cases, it was isolated from surgical specimens. In the case reported by Rosen et al.,[115] PSC was repeatedly isolated from the sputum and intracavitary exudate of a man with cavitary bronchiectasis, *A. fumigatus* also being found in the lungs at autopsy. In a case reported by McCarthy et al.,[87] the diagnosis was made by precipitin test, which gave a strong reaction to the extract of PSC and a weak reaction to *Aspergillus versicolor*. Neither fungus was cultured from the sputum, possibly because of a lack of free communication of the mycetoma with the bronchi. PSC and *A. versicolor* were isolated from cavity contents obtained by thoracotomy. Although repeated sputum cultures and serum immunoprecipitin tests may be helpful,[14,53] surgical excision was often needed to make the diagnosis.

Treatment and outcome. Of the 46 patients, 20 were managed surgically. Lobectomy was performed in three cases and

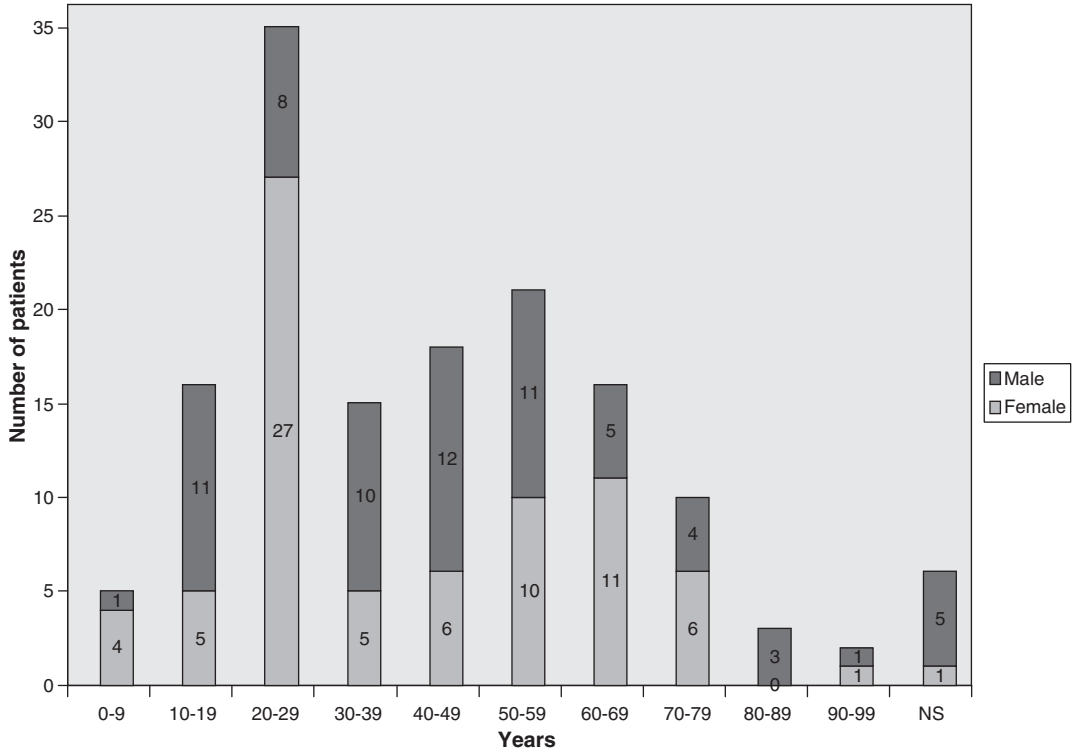

Fig. 1. Age and sex distribution of 138 patients with IPP, 1955–2010.

pneumonectomy in two. Twelve patients were managed medically. Twelve cases were fatal (26.8%), and 22 patients (47.5%) who had undergone surgery (15) or had been treated with miconazole (MCZ),[119] ITZ,[23,32] voriconazole (VRZ)[44,154] or had no therapy,[67,131] survived. In one case, sputum cultures continued to be positive. Following a course of amphotericin B (AMB), the patient remained clinically well without any symptoms.[11] Outcome was not reported in the other cases. Regarding these data, in suitable patients surgery appears a successful treatment choice for a cavitary lesion containing a fungus ball.

(ii) Allergic bronchopulmonary pseudallescheriasis (ABPP)

Although most allergic bronchopulmonary mycoses have been attributed to *Aspergillus* species, this syndrome has been reported in

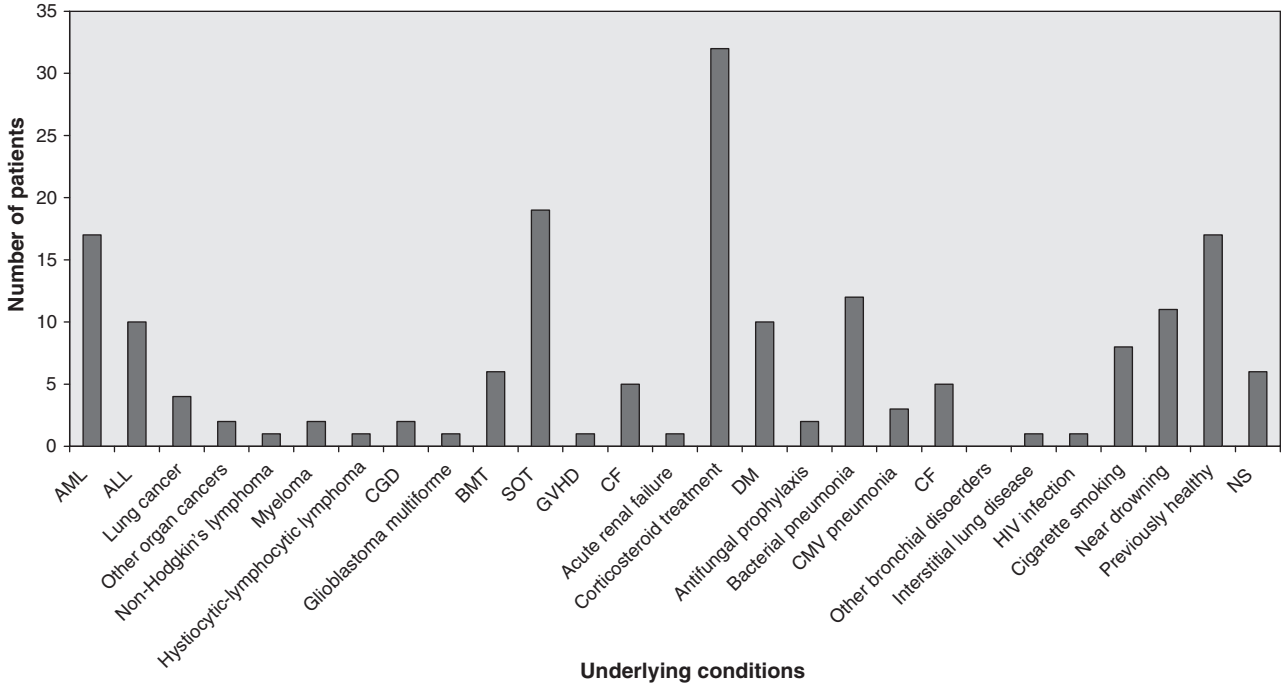

Fig. 2. Frequency of underlying conditions reported in 138 cases of IPP. ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; BMT: bone marrow transplantation; CGD: chronic granulomatous disease; CMV: cytomegalovirus;DM: diabetes mellitus; GVHD: graft versus host disease; NS: non-stated; SOT: solid organ transplantation.

PSC as well.[23,76,90,144] Allergic bronchopulmonary fungal disease is characterized by asthma, peripheral blood eosinophilia, infiltrates on the chest radiograph, raised IgE levels, precipitating antibodies and immediate cutaneous reactivity to the casual fungus.[50]

Lake et al.[76] first suggested allergic bronchopulmonary manifestations induced by PSC. The authors described a case of a 24-year-old woman with asthma and clinical symptoms similar to allergic bronchopulmonary aspergillosis (ABPA) who, on chest roentgenogram, was found to have infiltrates, an elevated serum total IgE, skin prick test reactivity and precipitins against this fungus. Hyphae were seen on direct examination of sputum.

Five ABPP cases were reported from Canada, and Australia.[23,76,131,144] Three of the subjects were female, while gender was not mentioned in the remaining reports; the age of the patients ranged from 18 to 48 years. Five of them had associated diseases such as asthma and CF and two had previously received prednisone therapy for rheumatoid arthritis or previous ABPA.

Little is known about the immunological and allergic features of pulmonary pseudallescheriasis. Precipitating antibodies are frequently present in *Aspergillus* mycetoma, but skin tests are usually negative, in contrast to ABPA, in which typically an intermediate (type I) cutaneous reaction occurs, and a delayed (Arthus type III) reaction frequently follows, giving a dual response.[19,20,50,80,102] Likewise, precipitating antibodies to PSC were reported in several cases in which the fungus proliferated in the airway lumen[21,27,57,69,87,91,111] and failed to continue after surgery in those who underwent resection[69,81] or after antifungal treatment.[91] In most of them, no reaction was detected with extracts of other fungi, including *A. fumigatus*. Eosinophilia was noted in only one patient.[57] Of the three patients reported by Reddy et al.,[109] one was skin tested with an extract of PSC, but had no response. Rippon and Carmichael[111] reported a case of a patient with transient endobronchial colonization with several sputum specimens positive for PSC. Chest radiograph examination showed diffuse interstitial infiltrates; and precipitins against PSC were positive. Although the disease was somewhat similar to ABPP, there was no eosinophilia recorded and skin test sensitivity was not established.

Cimon et al.,[27] reported two cases of ABPP in a prospective study in 128 CF patients, both chronically colonized by PSC and one with previous ABPA treated with a combination of corticosteroids and ITZ, leading to a remission of symptoms. In most cases in this study, colonization with PSC was not associated with allergic disease.

Mixed allergic bronchopulmonary disease due to PSC and *Aspergillus* was also described by Lake et al.[76] in an asthmatic woman without CF, and in two additional cases by Miller et al.,[90] but mixed infections seem uncommon. In the second report, two patients with probable diagnosis of ABPA also presented the fungus in sputum and strongly positive pseudallescheriasis serology, which suggests a contributory role of this fungus in the allergic bronchopulmonary disease.[90]

ABPP was seen in patients with long-standing asthma[76,90] or with CF.[27] On pathological analysis, this form of pulmonary pseudallescheriasis was characterized by the presence of obvious plugs in sputum containing PSC cells and eosinophilia.

(iii) Invasive pulmonary pseudallescheriasis (IPP)

Before the 1980s, PSC was rarely reported as a cause of systemic disease. We have retrospectively examined 138 cases of invasive pulmonary pseudallescheriasis (IPP) including pneumonia, pulmonary abscess, pleuritis and other manifestations. As outlined in Table 1, IPP can vary from nodular pneumonia to necrotizing pneumonias, lung abscess,[6,51,66,89,141] empyema,[16,137] and pleurisy.[16,22,34,35,45,72,74,82,103,136,138,150] Asymptomatic coin lesion,[151] cystic mass[98] and polypoid lesions[96,153] were also occasionally reported. Of these, nodular pneumonia and pleural effusion[15,16,22,34,35,45,54,72,82,103,136] were the most common. One case was also reported of simultaneous pulmonary infection with *Aspergillus terreus* and PSC[64] and a pulmonary infection by *Mycobacterium avium* concomittant with a polypoid bronchial lesion by PSC.[149] Similarly, Morales et al. reported *A. fumigatus* and PSC isolation from sputum of a patient with CF and *Mycobacterium abscessus* infection after lung transplantation.[43]

Table 2
Other sites of involvement in 29 of 138 patients with invasive pulmonary infection.

Body site(s)	Number of patients
Central nervous system	23
Kidney	12
Thyroid	5
Heart	5
Spleen	4
Liver	5
Wall of vessels	1
Blood	4
Bone	1
Gastrointestinal system	3
Eye	3
Subcutaneous tissue	1
Skin	8

Demographic and geographical features. The majority of the 138 invasive pulmonary infections by PSC were reported from the USA, with occasional cases from UK, France, Finland, Germany, Spain, Netherlands, Brazil, Congo, Australia, Japan and Taiwan. Of those, 78 were female and 52 male. The age of the patients ranged from 2 to 90 years, although age was not reported in 8 cases (Fig. 1).

Predisposing factors, underlying conditions. The most frequent underlying conditions reported were corticosteroid treatments, solid organ transplantations (lung 194, heart 5, liver 1, kidney 3) and haematological malignancies. Most patients showed a history of underlying chronic lung disease, cigarette smoking or occupational exposure. Ten patients who suffered near-drowning but who had previously been healthy and two further patients were occupationally exposed to fungal conidia; one patient was immunocompetent with a perforated chest wound; one case occurred in a liver transplant patient following a skull fracture in an accident; and no predisposing conditions or underlying disease were stated in six patients. Fig. 2 shows the frequency of any underlying conditions reported in the reviewed cases, such as cellular immunity and, in particular, neutrophils that might have an important role in the pathogenesis of IPP. Tables 4 and 5 list the underlying conditions and predisposing factors, respectively, found in 44 patients who survived and 75 who died. In the other cases, patient outcome was not reported.

Signs and symptoms. Clinical symptoms are often insidious and nonspecific, such as chronic cough, sputum production, fever,

Table 3
Treatment and outcome of 138 patients with IPP, 1955–2010.

Treatment types	Outcome (Number of patients)			
	Total	Death	Survived	Not stated
Surgery	6	2	3	1
Antifungal	73	40	28	5
Surgery and antifungal	10	4	4	2
None	7	7		
Not stated	42	6	1	22

Table 4
Demographic characteristics, other sites of infection, and therapy given to survivors of IPP ($N = 44$).

Reference	Age/sex	Type of infection	Surgery	Antifungal therapy[a]
Bousley[16]	39/M	Empyema	Thoracentesis	
Jung et al.[67]	60/F		Right upper lobectomy	
	81/M			
Saadah and Dixon[116]	32/F	Necrotizing pneumonia	Antibiotics (5 m), thoracotomy	
Woodard[151]	70/M	Asymptomatic pulmonary coin lesion	Thoracotomy with wedge resection	
Galgiani et al.[43]	50/F	Pulmonary nodule		KTZ (400 mg, 3 m)
	70/F	Progressive diffuse peribronchial thickening		KTZ (200 mg, 4 m)
	50/M	Right upper lobe infiltrate		KTZ (400 mg, 8 m)
	59/F	Right middle lobe cavity	Right middle lobectomy	KTZ (400 mg, 1 m)
	55/F	Right upper lobe infiltrate	Thoracotomy (the lesion had not been excised completely)	KTZ (200 mg, 2 m; 400 mg, 5 m)
Plus and Opal[106]	74/F			Antibacterials (ineffective), KTZ (400 mg/d)
Seale and Hudson[122]	59/M	IPP		MCZ (i.v. 300 mg every 8 h, 30 d)
Travis et al.[142]	39/F	Lung abscess	Surgery	
Dworzack et al.[37]	**2/F**	Lung abscess		AMB (a total of 56 mg), changed to MCZ (a total of 481.8 g i.v. + 2700 mg intrathecally)
Mesnard et al.[89]	17/F			AMB, KTZ (400 mg/d, 8 ws)
Walsh et al.[146]	28/M		Partial lobectomy	AMB (progressively cavitated)
Goldberg et al.[48]	21/M	Simultaneous pulmonary infection with *Aspergillus terreus*	Thoracotomy	AMB (1 mg/kg/d), i.v. MCZ (800 mg t.i.d.) (progression) debridement of necrotic material, ITZ (200 mg po b.i.d., 2 m)
Nomdedéu et al.[99]	39/M			AMB <81 mg/kg/d), stopped after diagnosis, ITZ (600 mg/d)
Stolk-Engelaar and Cox[134]; Verweij et al.[145]	28/M			ITZ (200 mg b.i.d. orally 3 m), relapse (after 20 m therapy, despite adequate serum concentrations) oral TRB (500 mg/d, a total of 9 m) (after 4 m therapy bronchoscopy showed no evidence of fungal infection)
Hung et al.[64]	69/M		Laminectomy	Anti TBC, AMB (0.5 mg/kg/d),
Martino et al.[84]	15/M	An alveolar infiltrate in the ALL	Surgical resection	AMB (1 mg/kg/d, cumulative dose 2 g)

Abbrevations: ALL: acute lymphoblastic leukemia; AMB: amphotericin; b.i.d.: bis in die (twice in day); d: day; F: female; IPP: invasive pulmonary pseudallescheriasis; i.v.: intravenous injection; ITZ: itraconazole; KTZ: ketoconazole; LAMB: lyposomal amphotericin B; M: male; m: month; MCZ: miconazole; t.i.d.: tree times a day; TBC: tuberculosis; TRB: terbinafine.

[a] In parentheses, regimen in mg per day (d) and duration of the treatment in weeks (ws) or months (m) are indicated.

night sweats, chest pain and shortness of breath. Patients often complained of weakness and malaise. Other local and systemic symptoms include pleuritic pain, chills, fever, easy tiredness, anorexia, and weight loss. One patient with a polypoid bronchial lesion had no complaint,[96] and two others were asymptomatic.[142,151]

Radiology. Radiologically, IPP might have manifested itself as consolidation (in 7 patients), nodules (in 13 patients), necrotizing pneumonia (in 9 patients), pulmonary abscess (in 15 patients), and pleural effusions (in 10 patients). Radiological examination might have been less specific, with diffuse infiltration and pneumonia.[5] PSC pneumonia, i.e. lobar pneumonia[56,62,77,84,99,114,136] and bilateral consolidation[22,138] were seen in several cases; two of them[43] occurred in patients with no predisposing conditions. Chest radiographs and CT scan images may show ill-defined nodular opacities.[22,84] The opacity with a peripheral rim of ground glass, known as the "halo sign", was reported in one case.[149] Nodules surrounded by a halo of ground-glass is often considered to be evidence of haemorrhagic infarcts and believed to represent the peripheral rim of haemorrhagic infarction, described in the angioinvasive fungal diseases, aspergillosis, zygomycosis and described as well in PSC infections.[41] Angioinvasive pseudallescheriasis was characterized histologically by the invasion and occlusion of small to medium-sized pulmonary arteries by fungal hyphae.[39,79]

The "air crescent sign"[5,45] can be seen in a pulmonary cavitary process, which is caused by air surrounded by radiopaque material along both its inner and outer margins. The air crescent may transform into a cavity space, filled with necrotic debris, including neutrophils, and fungal elements. However, a similar appearance has been described in a number of infections, including mucorales, *Candida*, herpes simplex or cytomegalovirus, or other conditions such as Wegener granulomatosis, Kaposi sarcoma, and haemorrhagic metastasis. The "air crescent sign" is considered

Table 5
Demographic characteristics, other sites of infection, and therapy given to non survivors of IPP ($N = 79$).

Reference	Age/sex	Type of infection	Other locations	Surgery	Antifungal therapy
Alture-Werber et al.[6]	66/F	Fungal abscess, partly pneumonia	+		Steroids, antibiotics, anti-TBC
Lutwick et al.[82]	66/F	Multiple pulmonary	Renal and brain abscess		AMB
Winston et al.[150]	57/F	Lung abscess			NS
	37/M				Antibiotics, AMB (a total of 576 mg)
Van der Vliet et al.[143]	15/M				NS
Meadow et al.[88]	15/F				Antibiotics, methylprednisolone (1 g/d), then reduced (to 10 mg/d over 10 d), MCZ (i.v. 1200 mg every 8 h)
Gumbart[54]	39/M	Nodular bilateral pneumonia			NS
De Ment et al.[34]	60/F	Necrotizing bronchopneumonia, pleuritis			Empirically antibiotics and MCZ, changed to AMB (0.3 mg/kg/d)
Enggano et al.[39]	16/M	Lung abscess			Antibiotics, empirically AMB (i.v.0.75 mg/kg/d), 5-FC
Shih and Lee[128]	22/M	Lung abscess	Brain, thyroid, kidney, lumen and wall of vessels		None
Smith et al.[130]	41/M	Lung abscess	Brain, skin, liver, thyroid		AMB
Guyotat et al.[55]	26/M		Fungal abscess		AMB (1 mg/kg) (worsened with diffuse infiltrates)
Anaissie et al.[7]	7/F	Lung abscess	Heart, blood, kidney, brain abscess		None
Dworzack et al.[37]	22/F	Lung abscess	Brain, skin	Surgery	MCZ (10 mg every 12 h) (a total of 52 g parenterally and 250 mg intrathecally)
	20/F	Lung abscess	Brain, skin		AMB (a total of 86 mg)
Schawrtz[121]	43/M	Lung abscess	Kidney, skin, cerebral fungus ball		None
Patterson et al.[101]	22/M	Cavitary lesions in both lungs, likely nosocomial infection			AMB + KTZ (400 mg/d, 12 d), MCZ (600 mg every 8 h)
Piens et al.[104]	33/F				AMB (400 mg/kg/d)
Steens et al.[132]	28/F	Atypical pneumonia			Antibiotics (initially erythromycin and then doxycycline, 1 m); broad spectrum antibiotics
Walsh et al.[146]	13/M	Pneumonia			AMB
	41/M	Right upper lobe consolidation	Peritonitis on day 86		AMB (70 mg/d)
Hofman et al.[61]	47/M				NS
Anaissie (1989)	7/F				None
Severo et al.[124]	41/F	Solitary pulmonary nodule			KTZ (400 mg/d), prednisone (20 mg/d) and insulin
Khurshid et al.[70]	61/F	Lung abscess	Liver, spleen, kidney, pancreas, right and left ventricles		AMB
Kusne et al.[74]; Castiglioni et al.[22]	67/M	Lung mass			ITZ (oral, 1 m), VRZ (6 mg/kg every 12 h the first day, 4 mg/kg every 12 h thereafter)
Bonduel et al.[15]	18/F	Pneumonia, pleural effusion			ITZ (200 mg/d, 90 d), L-AMB (2 mg/kg/d, a total dose of 30 mg/kg)
Breton et al.[17]	61/M	Pneumonia		Right pneumonectomy	ITZ (400 mg/d),
Dinesha et al.[35]	36/M		Brain		Anti-tuberculose treatment, frontal craniotomy and excision of the lesion in the left frontal lobe, AMB
Nguyen[98]	78/F				ITZ (oral), AMB (i.v.), L vitrectomy, (after identification) changed to ITZ
Tamm et al.[137]	42/F				ITZ, FLZ
	22/F				ITZ, FLZ
	49/M				ITZ, FLZ
	38/F				ITZ, FLZ
Bartzacet al.[13]	50/M	Lliung abscess	Brain abscess		AMB + FLZ
Castiglioni et al.[22]	30/M	Pneumonia, pleuritis	Pericarditis		ITZ prophylaxis; AMB + MCZ
	37/F				ITZ prophylaxis (beginig 11 m after transplant); broad spectrum antibiotics +MCZ
	36/M	Pneumonia	Brain abscess		ITZ, MCZ
Kleinschmidt-De Masters[71]	41/M	Lung abscess	Cerebritis, multiple small haemorrhagic infarctions, heart, thyroid		NS
Horre et al.[62]	72/F	Pneumonia	A purulent ulceration on her left little toe		ITZ (100 mg/d) (radiologically progression); (200 mg/d)
Klopfenstein et al.[72]	14/F	A 4 cm nodule		Left lung lobectomy	ITZ (200 mg i.v. 3 times daily, AMB empirically, MCZ (600 mg i.v. every 8 h) + 5-FC, VRZ (270 mg i.v. twice a day), (200 mg orally twice a day, 7 m)

Table 5 (*Continued*)

Reference	Age/sex	Type of infection	Other locations	Surgery	Antifungal therapy
Riddell et al.[110]	33/F	Lungs abscess	Thyroid, heart, kidneys, blood infection, brain		NS
Symoens et al.[135]	26/F	Lung	Eye, subcutaneous nodules, CNS		VRZ
Abgrall et al.[1]	68/M	Cavernous lesion and paranchymatous consolidation			VRZ
Cooley et al.[28]	NS/F	Pulmonary abscess	Brain		AMB + ITZ
Morales et al.[94]	NS/NS	Lung			
Sahi et al.[117]	43/M	Recurrent pan-lobar Fungal pneumonia (18 m post-transplant), mediastinitis, pleuritis	Osteomyelitis and a knee abscess		L-AMB (for 8 weeks), after initial clinical improvement, he developed a pulmonary nodule, necrotizing granulomas, ITZ, recurrence
	57/F	Lung abscess	Brain abscess, skin nodules, eye		VRZ high dose + TRB + later PSZ
	19/F	Chest wall cellulitis, mediastinitis, yellow-white endobronchial plaques	Endophthalmitis (4 weeks after T), multiple skin nodules, pansinusitis, vertebral osteomyelitis, and septic arthritis,		VRZ, (eye) CAS + TRB, intravitreal injections of VRZ, oral PSZ (200 mg, 4 times daily with meals to improve absorption) as salvage therapy, granulocyte macrophage colony-stimulating factor as an immunoadjuvant, L-AMB was added, oral PSZ was increased to 1200 mg/d (400 mg 3 times daily with meals)
Caira et al.[18]	NS/NS	Lung abscess			L-AMB (3 mg/kg, 10 d)
	NS/NS	Lung abscess			L-AMB (3 mg/kg, 10 d
	NS/NS	Lung abscess	Blood, skin		L-AMB (3 mg/kg, 10 d
	NS/NS	Lung abscess	Blood		D-AMB (1 mg/kg, 14 d)
Sheu et al.[127]	NS/NS	Lung, pleuritis			
	NS/NS	Lung, pleuritis			
	NS/NS	Lung, pleuritis			
Mario et al.[83]	37/F	Lung	Skin nodules, CNS, blood		VRZ (250 mg, twice a day), CAS (70 mg/kg of body weight/d loading dose, then 50 mg/kg), TRB (250 mg/d)
Maslen and Peel[86]	60/F	Lung			
	45/F	Lung			
	58/M	Lung			
	43M	Lung			
	19/F	Lung			

Abbrevations: AMB: amphotericin B; L-AMB: liposomal amphotericin B; 5-FC: flucytosine; ITZ: itraconazole; FLZ: fluconazole; KTZ: ketoconazole; MCZ: miconazole; VRZ: voriconazole; PSZ: posaconazole; TRB: terbinafine; CAS: caspofungin; NS: not stated, i.v.: intravenous injection; h: hours; d: day; m: month; TBC: tuberculosis; CNS: central nervous system.

characteristic of invasive pulmonary aspergillosis (IPA) when seen in the appropriate clinical setting.[2] Therefore, it is important not to confuse IPP with IPA.

Clinical manifestations. In several cases, the existence of necrotizing pneumonia was detected histologically, characterized by the presence of tissue necrosis and granulomatous inflammation.[22,34,116,138] IPP is characterized by haemorrhagic infarction of lung tissue, secondary to vascular invasion by fungal organisms, causing thrombosis of small arterioles and, sometimes, larger pulmonary vessels, as seen in IPA and invasive fusariosis. Saadah and Dixon[116] described a truly invasive PSC, necrotizing pneumonia in an apparently normal host. The disease was relatively destructive, traversing multiple pulmonary segments, the surrounding pleura, and the recurrent laryngeal nerve. Smears of intrabronchial pus obtained from the surgical specimen had an abundance of septate branching hyphae, while in the tissue sections hyphae were very rare. Based on this finding and a literature review, the authors suggested that actual tissue invasion by PSC is rare and most of the tissue damage in the lung is secondary to the severe inflammatory reaction of the host incited. This hypothesis has been put forward previously to explain the severe tissue reaction present in chronic pulmonary histoplasmosis with the relative absence of the organism in the inflamed tissue. There have been several other cases reported of an absence of fungal elements in lung tissue sections but with positive cultures for PSC.[33,62] Another typical presentation, described in several cases, is pulmonary abscess.[4,17,30,49,66,82,136,140,141]

A coin lesion is a less frequent presentation of the IPP, defined as a single, discrete pulmonary opacity smaller than 3 cm in diameter surrounded by normal lung tissue, and not associated with adenopathy or athelectasis.[93] Although the fungal solitary pulmonary nodules are usually caused by pathogenic dimorphic fungi and usually the result of a self-limiting Woodard[151]reported a case of a solitary pulmonary nodule due to PSC. Histopathological examination of the patient's lesion revealed a fibrosis encapsulated granulomatous nodule with central necrosis and grey granules.[151]

Cystic mass[98] and polypoid lesions[96,153] due to PSC observed in fiberoptic bronchoscopy have been reported in two cases. Yano et al.[153] described a bronchus completely obscured by a dark grey necrotizing lesion after the whitish polypoid lesion by a biopsy forceps. Murayama et al.[96] reported a case in combination with *M. avium* pulmonary disease. Loosely formed grains have also been reported within sinus tracts in lungs in a pediatric patient with disseminated disease.[88] Pleurisy was commonly found in several IPP cases.[16,22,34,45,54,82,86,103,136] Disseminated infection was reported in 29 patients. Table 2 outlines other sites of involvement.

Laboratory diagnosis. Diagnosis was made through histological examination and culture (in 17 cases), or only culture (in 28 cases) of the excised lesion or other respiratory tract samples (sputum, bronchial secretions, endobronchial brushings). Fungi from tissue samples grew in 11 cases, but failed to grow in six. Respiratory

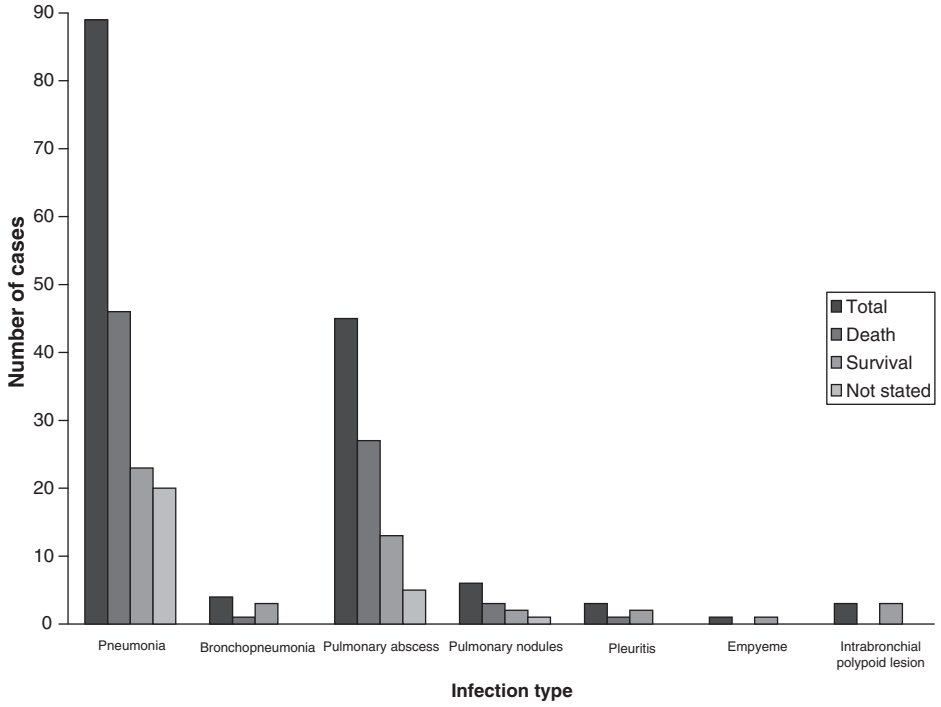

Fig. 3. Mortality differences among 138 patients with IPP by *Pseudallescheria/Scedosporium* complex.

tract samples gave negative results. In one patient a thoracic needle aspiration was performed and the diagnosis was made by examining a stained smear specimen and culture[124]; diagnosis was made postmortem in nine cases. A histopathological study of nodules was made on some patients, and revealed a round pulmonary ischemic infarction due to arterial invasion by the fungus,[42] granuloma with central necrosis,[151] fibrosis mixed with granuloma and microabscess or an abscess.[6,22,39,49,62,64,82,116,136,142] Regarding the questionable significance of isolating PSC, Jung et al.,[67] established criteria for diagnosis as follows: (i) repeated isolation of the fungus, at least four positive cultures per patient being considered to be significant; (ii) growth of the fungus from the excised surgical material; (iii) positive cultures from samples obtained from bronchial washings or selective brushing from the pulmonary lesions through the fiberoptic bronchoscope; and (iv) evidence of tissue invasion in tissue sections.

Treatment and outcome. Table 3 shows the treatment and outcome of those patients analyzed with IPP. Of 138 patients, 5 were managed surgically, and 73 were managed medically with systemic antifungal agents, such as AMB, liposomal AMB, MCZ, ketoconazole (KTZ), ITZ, fluconazole (FLZ), VRZ and terbinafine (TRB). A young immunocompetent patient with previous trauma and having been treated with ITZ suffered a relapse after 20 months of therapy despite adequate serum concentrations.[134] The patient was treated with oral TRB (500 mg/d) and after 4 months bronchoscopy showed no evidence of fungal infection.[145] Seventy nine of the 138 patients with IPP died (57.2%) and 43 (31.1%) survived, while the outcome was not reported in the remaining cases. Tables 4 and 5 summarize the data on survivors and no survivors.

Thirty-two patients had a history of corticosteroid treatment. Murayama et al.[96] diagnosed a bronchial polypoid lesion in a patient with rheumatoid arthritis. In this case, surgical treatment was not undertaken because of extensive *M. avium* pulmonary disease, but methylprednisolone was discontinued soon after establishing the definitive diagnosis and there was no evidence of worsening during a two-year follow up. Similarly, in a report by Rippon and Carmichael,[111] the patient's bronchial lesions disappeared when steroid therapy was discontinued. Horre et al.[62] reported a fatal pneumonia in a patient who had a long history of corticosteroid therapy. Lionakis and Kontoyiannis[79] suggested that the use of steroids, although necessary, could have facilitated opportunistic mould infections in cancer patients. The use of steroids may render the patient susceptible to opportunistic mycoses. Despite having a normal neutrophil count, affected patients have functional neutropenia because the function of the neutrophils is inhibited by the use of high-dose steroids. Based on that data, discontinuation of steroids and immunomodulation of neutrophyl functions, if needed, may be an optional treatment approach.

Tamm et al.[137] analysed risk factors, and the clinical course and outcome of seven lung transplant recipients who had developed IPP infection diagnosed through BAL specimens. The fungus was detected 9–58 months after transplantation. Five patients had been treated for several months with ITZ because of previous detection of *Aspergillus* in BAL. *S. prolificans* was first cultured in three cases and a few months later *S. apiospermum* was found. All seven patients showed airway problems. Combined treatment with ITZ and FLZ was not able to eradicate PSC. Four of the seven patients died 3–35 months after the diagnosis of IPP. The authors concluded that IPP was seen in lung transplant recipients with structurally abnormal airways and under long term therapy with ITZ. Eradication of the fungus proved difficult, but under combined treatment with ITZ and FLZ this infection did not disseminate. Although the role of both drugs in the control of the infections is difficult to understand, ITZ has demonstrated in general poor efficacy against these fungi and FLZ is not usually used for treatment of mycoses caused by filamentous fungi. Differences in mortality rates are outlined in Fig. 3.

Conclusion

In most instances non-invasive forms of pulmonary pseudallescheriasis have been superimposed on some structural

abnormalities such as bronchectasis, tuberculosis or sarcoidosis. Invasive pulmonary infection may result in patients whose immune responses are impaired by underlying disease, chemotherapy, or both. Pulmonary infection with PSC has no pathogenomic manifestations. Chest radiographs may show cavitation and a fungus ball or may resemble tuberculosis. Because other opportunistic agents, particularly *Aspergillus* species, can display similar images, CT findings should be interpreted with caution both in non-invasive and in invasive forms of IPP. Serum precipitating antibodies against PSC have been demonstrated in all forms of pulmonary presence of PSC and is a significant criteron for ABPP. Distinction between pseudallescheriasis and aspergillosis can only be made by culturing the organism. Management of pseudallescheriasis is limited; when it is localized, surgical resection of residual nodules or cavities should be performed. For IPP, conventional antifungal agents and therapy strategies have some effect on the moderately immunocompromised and immunocompetent hosts; the prognosis is very poor for severely immunocompromised hosts. Whenever possible, surgical drainage and debridement of necrotic tissues is essential to the success of therapy, even in immunocompromised hosts.

Conflict on interest

The authors have no conflict of interest to declare

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