A case of adiaspiromycosis causing respiratory failure and a review of human infections due to the fungi Emmonsia and Chrysosporium

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Running title: Adiaspiromycosis causing respiratory failure
We report a case of a 27 year-old male who presented with respiratory distress that required mechanical ventilation. Transbronchial biopsy revealed adiaspores of the fungus *Emmonsia crescens* within granulomata, a condition known as adiaspiromycosis. The patient received amphotericin products and corticosteroids, followed by itraconazole, and made a full recovery. *Emmonsia crescens* is a saprobe with a wide distribution that is primarily a rodent pathogen. The clinical characteristics of the 20 cases of human pulmonary adiaspiromycosis reported since the last comprehensive case review in 1993 are described, as well as other infections recently reported for the genus *Emmonsia*. Pulmonary adiaspiromycosis has been reported primarily in persons without underlying host factors, and has a mild to severe course. It remains uncertain if the optimal management of severe pulmonary adiaspiromycosis is supportive, or consists of antifungal treatment, corticosteroids, or a combination of the latter two. The classification of fungi currently in the genus *Emmonsia* has undergone considerable revision since their original description, including being grouped with the genus *Chrysosporium* at one time. Molecular genetics has clearly differentiated the genus *Emmonsia* from the *Chrysosporium* species. Nevertheless, there has been a persistent confusion in the literature regarding the clinical presentation of infection with fungi of these two genera; to clarify this matter, the reported cases of invasive *Chrysosporium* infections were reviewed. Invasive *Chrysosporium* infections typically occur in impaired hosts, and can have a fatal course. Based on limited in vitro susceptibility data for *C. zonatum*, amphotericin B is the most active drug, itraconazole susceptibility is strain-dependent, and fluconazole and 5-fluorocytosine are not active.
INTRODUCTION

Adiaspiromycosis is primarily a pulmonary infection of rodents, fossorial mammals, and their predators, caused by the soil fungi *Emmonsia crescens* and *E. parva* (5,53). It is a rare human infection. In this infection, inhaled *Emmonsia* conidia enlarge to form non-replicating adiaspores. As in other mammals, the infection in humans usually involves the lungs, with only a few other cases of infection at other sites (36,53).

About seventy cases of human adiaspiromycosis have been described, but much of the literature on this infection has been dispersed in less accessible non-English journals. Furthermore, the inconsistent nomenclature and taxonomy of *Emmonsia* species and their confusion with *Chrysosporium* species has resulted in an overall lack of consistent information on adiaspiromycosis and *Chrysosporium* infections. Herein, we report a case of adiaspiromycosis that resulted in respiratory failure. We also review the true cases of adiaspiromycosis that have reported since the seminal monographs of England and Hochholzer in 1993 (21) and Sigler in 2005 (53) or omitted from those reports. Furthermore, we differentiate the cases of adiaspiromycosis from the true and probable cases of invasive disease due to the genus *Chrysosporium*. In 2011, Pelegrin and coworkers (44) also reviewed cases of adiaspiromycosis, but again the nomenclature adopted by the authors is inaccurate and the genera *Emmonsia* and *Chrysosporium* are not appropriately distinguished.

CASE REPORT

A 27 year-old Hispanic male presented in July 1998 with a 5-day history of nonproductive cough, dyspnea, pleuritic chest pain, and weight loss. Initial vital signs
were temperature 99.2 °F, bp 112/67, pulse 104 per minute, and respiration rate 22 breaths per minute. On exam, there were crackles throughout both lung fields. A chest X-ray showed marked bilateral interstitial infiltrates (Fig. 1). The white blood cell count was 15,800/mm$^3$ (85% pmns, 6% lymphocytes, 4% monocytes, 5% eosinophils). The hematocrit, platelet count, and routine serum chemistry values were within normal limits, except for aspartate and alanine transaminase levels of 45 and 104 U/L, respectively. An arterial blood gas measurement on room air showed pH 7.49, $P_{CO_2}$ 31 mm Hg, and $P_{O_2}$ 50 mm Hg. The impression was miliary tuberculosis or pneumocytosis and the patient received isoniazid, rifampin, pyrazinamide, ethambutol, and trimethoprim/sulfamethoxazole. The patient had emigrated from Mexico two years prior to his presentation and had worked at a construction site near San Antonio (TX). He denied recent travel.

Bronchoscopy with trans-bronchial biopsy was performed on hospital day-3. Acid-fast stain and culture of the biopsy specimen were negative. The Gomori’s methenamine-silver (GMS)-stained and hematoxylin and eosin-stained biopsy specimens showed greater than ten thick-walled, capsulated structures (either empty or with a few internal globules) centrally in non-necrotizing granulomas (Fig. 2). The structures were 35-40 µm in diameter. The initial impression was coccidioidomycosis. The patient received one dose of fluconazole and then amphotericin B 40 mg IV per day. The anti-mycobacterial drugs and trimethoprim/sulfamethoxazole were discontinued.

Serologic studies for coccidioidomycosis, however, were repeatedly negative. Other negative studies included: viral and routine cultures, urine Histoplasma and
Legionella antigens, serum cryptococcal antigen, and serologic tests for the human immunodeficiency virus, *Mycoplasma, Toxocara*, and *Chlamydia*.

Despite treatment with amphotericin B, the patient’s respiratory status deteriorated. On day-13, methylprednisolone 100 mg IV four-times daily was started. Later that day, the patient went into respiratory failure and required mechanical ventilation. On day-16, amphotericin B was changed to amphotericin B lipid complex at 5 mg/kg/d because the patient developed renal tubular acidosis. An open lung biopsy was performed on day-18, which showed only scattered fragments of GMS-positive material.

At this point, the histopathology specimen from the original trans-bronchial biopsy was reviewed again, and a diagnosis of adiaspiromycosis due to *Emmonsia crescens* was made, based on the size of the adiaspores (35-40 µm). The patient’s pulmonary status was gradually improving. He was weaned from mechanical ventilation after 6 days. Amphotericin B lipid complex was discontinued on day-25 and itraconazole 200 mg orally each day was started. A CT scan performed on day-26 showed diffuse bilateral interstitial thickening (Fig. 3). Three days before hospital discharge, pulmonary function tests showed a moderate restrictive defect. The patient was discharged on tapering prednisone and itraconazole 200 mg orally daily for 12 days. At follow-up three months after discharge, the patient was asymptomatic, and he had returned to his previous weight.

With the diagnosis of this unusual mycosis, the patient was interviewed again about exposures. He reported that two weeks prior to the onset of his illness he disposed
of a partially decomposed cat carcass at his construction worksite and some debris showered down upon his face at that time.

Methods

To find previously published cases of infection due to the genera *Emmonsia* and *Chrysosporium* MEDLINE was searched from 1965 to August 2011. Additional cases were found by bibliographic branching. Papers in non-English languages were translated into English by using Yahoo! Babel Fish (http://babelfish.yahoo.com).

RESULTS AND DISCUSSION

Review of Adiaspiromycosis

History of the Description of the Organisms and their Nomenclature and Taxonomy.

The nomenclature and taxonomy of these fungi has been a source of ongoing confusion, which has caused many authors to lump infections due to *Chrysosporium* species together with those caused by *E. crescens* and *E. parva* and so the clinical presentation of disease caused by the two genera has been quite muddled in the literature (40,41,44,63,68,69).

The circuitous history of the taxonomy of these organisms has been recounted by Sigler (53). In 1939, Kirschenblatt described cystic structures in the lungs of rodents from the former Soviet Union and proposed that these were due to a fungus that he named *Rhinosporidium pulmonale* (28). In 1942, Emmons and Ashburn observed spherical non-budding cells up to 14 µm in diameter in the lungs of rodents in Arizona; they thought this fungus was a zygomycete, so they placed it in the genus *Haplosporangium*, and used the species epithet *parvum* because of the small size of its sporangium (19). In 1947, Dowding observed fungal cells, up to 300 µm in diameter, in
the lungs of rodents from Alberta (16). Although this fungus resembled \textit{H. parvum} in its

culture characteristics and microscopic appearance, it formed both larger cells in vivo and

larger chlamydospores when grown at 37°C. In 1951, it was determined that \textit{H. parvum}

was not a zygomycete and was closely allied to the genus \textit{Blastomyces} on the basis of

conidial characteristics (7). Ciferri and Montemartini created the new monotypic genus

\textit{Emmonsia} for \textit{H. parvum} in 1959 (10) and in 1960 Emmons and Jellison (20) added \textit{E.}

\textit{crescens} (the fungus from the Alberta rodents). The two species were differentiated by

the size of their adiaspores and maximum growth temperatures (53).

The confusion commenced in 1962 when Carmichael broadened the genus

\textit{Chrysosporium} to include all fungi that produce aleuroconidia, solitary single-cell

conidia that are released by disintegration of the supporting structure (8), which included

\textit{Emmonsia}. Furthermore, Carmichael treated \textit{E. parvum} and \textit{E. crescens} as varieties of

the same species. Thus, \textit{E. parvum} and \textit{E. crescens} were renamed \textit{C. parvum} var.

\textit{parvum} and \textit{C. parvum} var. \textit{crescens}, respectively (8). Some mycologists embraced the

reclassification (33), but others advocated retaining the genus name \textit{Emmonsia}, but also

designating the two species as varieties, i.e., \textit{E. parvum} var. \textit{parvum} and \textit{E. parvum} var.

\textit{crescens} (66).

Currently, fungi of the genera \textit{Emmonsia} and \textit{Chrysosporium} are classified in the

ascomycete order \textit{Onygenales}, families \textit{Ajellomyctaceae} and \textit{Onygenaceae},

respectively. Other members in the \textit{Ajellomyctaceae} of medical significance include the

genera \textit{Blastomyces} and \textit{Histoplasma}, and \textit{Paracoccidioides brasiliensis}, whereas the

genus \textit{Coccidioides} is placed in the \textit{Onygenaceae} (65). (For a comparison of the genus

\textit{Emmonsia} with these genera, see Sigler (53)).
In 1996, Sigler described the teleomorph (meiotic stage) of *E. crescens*, *Ajellomyces crescens*, which is the same genus in which the teleomorphs of *Blastomyces dermatitidis* and *Histoplasma capsulatum* are contained. Genetic sequencing of these fungi confirmed the relatedness of the genus *Emmonsia* to the genus *Blastomyces* (34,46); in fact, *E. parva* is more closely related to the genus *Blastomyces* than to *E. crescens*. It would be justified, based on genetic analyses, to place the *Emmonsia* in the same genus as *Blastomyces*. However, because of the chaos that would ensue from a genus-level name change of these medically significant fungi, the genera *Blastomyces* and *Histoplasma* have retained their current names (46,53). Also, it is appropriate that *E. parva* and *E. crescens* be considered distinct species (46,53).

In 1998, a cutaneous mycosis was reported in an AIDS patient; histopathologic analysis of the skin revealed small yeast-like budding cells, (2-4 µm in diameter), larger thick-walled cells (8-10 µm in diameter), and pseudohyphae. In culture, the fungus was morphologically compatible with the genus *Emmonsia*, but was genetically distinct from *E. parva* and *E. crescens*, and was described as a new species, *E. pasteuriana* (23).

In the case of a pulmonary infection observed in a rheumatoid arthritis patient, fungi were observed within the macrophages obtained in the bronchoalveolar lavage. The fungus was identified as a possible new *Emmonsia* species based on genetic sequencing, but adiaspores were not observed in the biopsy specimen (74).

Recently, Pelegrin and coworkers (44) reported a case described as disseminated adiaspiromycosis in an HIV-infected liver transplant patient who suffered multiple skin lesions. A skin biopsy revealed multiple GMS-staining organisms; however, these clearly are not adiaspores. The investigators were able to culture the fungus, but the
isolate could not be identified to the species level because its genetic sequence did not closely agree with those of the reference strains. There was 95% similarity with *E. crescens*, 94% with *E. parva*, and 91% with *E. pasteuriana* (23), so the fungus was placed in the genus *Emmonsia*.

Thus, the term adiaspiromycosis is correctly applied only when *Emmonsia* adiaspores are observed in tissue and should not be used in cases where *Emmonsia* isolates produce yeast-like (22) or hyphal forms (44) in tissue or for infections due to fungi of the genus *Chrysosporium* (as in reference 57).

**Clinical Presentation of Human Emmonsia Infection**

The first human case, presenting as a solitary pulmonary nodule, was reported in 1964 (14). Disseminated human pulmonary disease was first observed in 1971 (29). Approximately 67 probable cases of human pulmonary adiaspiromycosis due to *E. crescens* have been described in the literature. England and Hochholzer, in their 1993 case series and review (21), identified 46 cases; there have been 20 other cases reported since that time or omitted from their review (6,11,13,15,31,32,36,37,38,40,50,51,52,56,60,62; see Table 1). Adiaspiromycosis may be discovered incidentally after histopathologic exam of the lung for other conditions. Alternatively, the disease may have an indolent course with fever, weight loss, fatigue, cough, hemoptysis, and dyspnea. In such cases, the chest radiograph usually shows bilateral reticulonodular infiltrates suggestive of miliary tuberculosis. Disseminated pulmonary infection can have a severe or even fatal course (4,6,21,31,36,45,52,56). The patient reported herein suffered moderate restrictive lung disease after the infection, as observed in two prior cases (cases 13 and 14 from Table 1).
In four of the 21 patients with pulmonary adiaspiromycosis due to *E. crescens*, the disease was discovered incidentally during the evaluation of other pulmonary conditions (cases 11, 12, 15, and 16 from Table 1). In the 16 other cases in which a clinical course were described, one case was fatal (case 2, Table 1), and five other patients had severe disease (cases 1, 3, 9, 10, and 17, Table 1), two of these requiring mechanical ventilation (cases 1 and 17 from Table 1). Host factors were not important in the severity of the infection.

There have been two reports of adiaspiromycosis of the appendix that developed after oral ingestion of the fungus (17,30); in one of these cases, peritonitis was observed after appendiceal rupture (17). However, the reported cases of cutaneous adiaspiromycosis (26,57) and adiaspiromycosis of the cornea (68) are due to other fungi (53).

An outbreak of ocular adiaspiromycosis was reported from Brazil in 2006. Local ophthalmologists reported 18 children with conjunctival nodules to health authorities. Subsequently, 5084 children were screened for ocular and visual changes. Active ocular disease was diagnosed in 64 children; 104 had ocular sequelae. Fourteen of the ocular nodules were biopsied; in two specimens, subconjunctival inflammation and adiaspores of *E. crescens* were observed. The investigators hypothesized that exposure to freshwater sponge spicules caused conjunctival irritation; subsequent exposure to airborne conidia of *Emmonsia* caused ocular adiaspiromycosis (35). This is a novel presentation of adiaspiromycosis and may require additional investigation to confirm the identity of the fungus that is involved in these cases.
Two cases of adiaspiromycosis reportedly due to *E. parva* have been described in AIDS patients (cases 1 and 3 in Table 2). In case 1 from Table 2, infection was disseminated to the bone marrow, multiple bony sites, and the lungs. Structures described as adiaspores were observed in the pus obtained during debridement of the bony lesions; hyphae were observed in culture at 20°C and adiaspores at 40°C (18). (However, the dissemination of adiaspores outside the lung would be unprecedented, and thus this is a questionable case of adiaspiromycosis (55)). The second case due to *E. parva* involved a patient with AIDS who presented with cough, dyspnea, and a pulmonary mass (case 3, Table 2). Biopsy of the mass showed “fungai elements”, not otherwise described. A specimen obtained by bronchoalveolar lavage grew a dimorphic fungus, with a mould observed at 25°C and adiaspores (12-15 µm) at 37°C (64).

Pathogenesis and Histopathology

*In vitro*, at 37°C, on brain heart infusion blood agar, the aleurioconidia of *E. crescents* enlarge to become adiaspores 25-400 µm in diameter; *E. parva* requires 40°C to produce adiaspores, which are 10-25 µm in diameter (53). In clinical adiaspiromycosis due to *E. crescents*, the inhaled aleurioconidia, 2-4 µm in diameter, reach the alveoli and enlarge up to a diameter of 500 µm (21), a volume increase of up to more than a million-fold (19). The size of the tissue adiaspores of *E. crescents* is dependent on the duration of illness; for infections of short duration (< 2 months), the average adiaspore diameter is 101 µm, whereas for patients with a longer duration of illness, the average adiaspore diameter is 155 µm (21). The fungus does not propagate in vivo and probably does not disseminate from the lungs (70). This lack of replication in human tissues is unique among pathogenic fungi (9).
The staining characteristics of *E. crescens* are described in detail by Sun et al. (60). With the hematoxylin-eosin stain, the thick walls of the adiaspores appear to be composed of two layers: a narrow eosinophilic outer layer and a chitinous thicker inner hyaline layer (72). With GMS, the wall stains uniformly (72). The adiaspores are usually empty, but may contain small globules (72). The host response to the adiaspores is the formation of large granulomata (0.5-3 mm) composed of epitheloid and giant cells. The granulomata are in a similar stage of evolution, indicating a response to a single exposure (72). Grossly, there may be firm white nodules a few millimeters in diameter in the lung parenchyma (21,45). Necrosis and caseation are typically not observed, but have been reported (9,45).

The extent of pulmonary involvement depends on the quantity of inhaled aleuroconidia (53). If a single conidium is inhaled, a solitary pulmonary nodule results. If numerous conidia are inhaled, disseminated pulmonary disease occurs. Respiratory compromise is due to compression of small airways and displacement of pulmonary tissue by granulomata (70). Dissemination outside the lung has not been reported for *E. crescens* and the case described for *E. parva* (18) is questionable (55). However, extension to the local pulmonary lymph nodes has been reported in humans and animals (2,37).

**Diagnosis of adiaspiromycosis**

*Emmonsia crescens* has been cultured from infected animals and environmental sources, but not from human clinical specimens (46,53). Thus, the diagnosis of human adiaspiromycosis is made by observing its unique histopathologic appearance, typically a single, large thick-walled adiaspore within a granuloma (21,53). Organisms that might
be confused for fungi of the genus *Emmonsia* in histologic specimens are the *Coccidioides* spp. and *Rhinosporidium seeberi* (72). *Coccidioides* spherules typically have distinct endosporulation. However, after necrosis, pulmonary nodules due to fungi of the genus *Coccidioides* may contain empty spherules (43). Nevertheless, these are usually smaller than the adiaspores of *Emmonsia crescens*, with thinner walls. One of the tissue forms of *R. seeberi*, the sporangium, typically measures 100-200 µm, but has thinner walls than *E. crescens* and distinct endosporulation (73). The other tissue form of *R. seeberi* is the trophocyte, which is 10-100 µm in diameter and has a flocculent cytoplasm and a single nucleus. Thus, these tissue forms of *R. seeberi* have internal structure much different from the adiaspores of the *Emmonsia* species (73). Helminths that infect the lungs, such as *Strongyloides* or *Dirofilaria*, may also resemble adiaspores (4,21).

The diagnosis of adiaspiromycosis due to *E. crescens* for the patient described in this case report is based on the size of the adiaspores (35-40 µm) and the absence of endosporulation. Although the adiaspores were smaller than the average size for *E. crescens* reported by England and Hocholzer (21), the patient was ill for a very short period of time (5-days) before seeking medical attention. The adiaspore size observed in the patient in the case report is within the reported size range of 25-400 µm for *E. crescens* adiaspores and larger than those of *E. parva* (53).

**Epidemiology of Human Adiaspiromycosis**

From Table 1, the average age of the patients was 40 years, with a range of 2-74 years old; 90% are male, probably because of greater occupational exposure to dusts. Previous cases of adiaspiromycosis have been reported from: North America (Guatemala,
Honduras, United States (AZ, GA, NC, NY, OK)), South America (Argentina, Brazil, Venezuela), and Europe (the former Czechoslovakia, France, Germany, the former Soviet Union, Spain) (21,53). New countries from which the disease has been reported are Finland and the United Kingdom (13,40); however 62% of the 21 new cases from Table 1 were reported from Brazil (11,31,36,37,38,50,51,56). It is unclear if the E. crescens is more common in Brazil, or if this is simply reporting bias. However, because E. crescens has been observed in more than 100 species of mammals on all continents except Africa and Australia (53), it would be expected that human cases would be observed in many different locales.

The patient described in this case report probably encountered the organism in his occupation as a carpenter at a construction site. In most previous cases of adiaspiromycosis, the persons had occupations with soil or dust exposure (21). The patient specifically remembered inhalation of soil at his worksite two weeks prior to the onset of symptoms. A time frame of several weeks is typical for the granulomatous reaction to occur in the lungs in response to the presence of the fungus or for adiaspiromycosis to develop in experimentally-induced disease (2,53).

Treatment of adiaspiromycosis

The most appropriate treatment for adiaspiromycosis is unknown. Many human cases are self-limited or asymptomatic, but several cases that have resulted in respiratory failure (including death) have been reported (4,6,21,31,36,45,52,56). In the cases of adiaspiromycosis reported in Table 1, 57% of the patients were treated with an antifungal agent.

Recently, the susceptibility of an isolate of E. crescens to various antifungal
agents was determined (5). The MICs (µg/mL) of amphotericin B, itraconazole, voriconazole, caspofungin, fluconazole, and 5-fluorocytosine were 0.06, 0.12-0.25, 0.06, 0.5, 64, and 8, respectively, with no significant difference in susceptibilities between the aleuroconidia and adiaspores. Only amphotericin B was fungicidal (5). The susceptibility to azoles is similar to that of *Histoplasma* and *Blastomyces* (42).

Anecdotally, clinical improvement in patients with adiaspiromycosis has been reported using a number of drugs, including ketoconazole (cases 3, 7, 9, 10, and 14 from Table 1), pimafucin (4,28), levamisole (4), thiabendazole (4), 5-fluorocytosine (47), itraconazole (cases 1, 4, and 20, Table 1), voriconazole (case 19, Table 1), and amphotericin B (cases 1, 2, 8, and 17, Table 1). However, it is uncertain if antifungal treatment accelerated recovery, or if this was merely the natural history of the infection. Patients appeared to benefit from corticosteroids in three previous cases (cases 4 and 21 from Table 1 and reference 29) and in the case described herein as well; this intervention seems reasonable in the immunocompetent patient because the major pathogenic effect of the fungus is due to the host granulomatous response. In severe pulmonary adiaspiromycosis in the immunocompetent host, it is reasonable to give both antifungal treatment to destroy the organism that provokes the inflammation and corticosteroid treatment to modulate that response. The disease is so rare that controlled clinical trial data will never be available; however, an animal model may be able to suggest if antifungal treatment, corticosteroids, both, or none may be beneficial.

### Review of *Chrysosporium* Infection

*Chrysosporium* is a large genus of saprobic soil fungi that includes over sixty species (67). Many of the species are keratinolytic, breaking down shed keratinized
residues, such as hair and feathers (1). *Chrysosporium* species may be encountered in the laboratory as contaminants of cutaneous and respiratory samples, but are occasionally isolated as possible agents of human dermatomycoses (12). The most common *Chrysosporium* species encountered as contaminants or likely to be confused with known pathogens include: *Chrysosporium* anamorph of *Arthroderma curreyi*, *Chrysosporium* anamorph of *Arthroderma cuniculi*, *C. georgiae*, *C. lobatum*, *C. carmichaelii*, *C. evolceanui*, *C. keratinophilum*, *Chrysosporium* anamorph of *Aphanoascus fulvescens*, *C. articulatum*, and *C. tropicum*. The *Chrysosporium* species that have been isolated from human nail and superficial skin infections include *C. keratinophilum*, *C. tropicum*, and *C. queenlandicum* (12). The *Chrysosporium* species have rarely been associated with invasive disease but in the immunocompromised patient, but a few of the species have been shown to be aggressive opportunistic pathogens.

Some of the *Chrysosporium* species share the teleomorph genus *Arthroderma* with species of dermatophytes (27, 61). They can be recovered on selective media used for dermatophytes (61) and on potato dextrose agar (1). The common species of *Chrysosporium* can usually be differentiated by the morphology, location, and size of the conidia (3,27); however, many species share similar features and definitive identification may require genetic sequencing (67). The mycology atlases of de Hoog and coauthors (12) and Kane and coauthors (27) have excellent diagrams to differentiate common species of *Chrysosporium* from those of *Emmonsia*. Unlike *E. crescens* and *E. parva*, specimens from *Chrysosporium* infections reveal hyphae within the tissue (49,59,69). Unfortunately, in several of the cases of reported *Chrysosporium* infection, the fungus
was not identified to the species level and the specimen was not banked to allow a definitive identification (48).

Table 3 shows the eleven reported cases of invasive or localized *Chrysosporium* infection. Species reported include: *C. zonatum* (49,54), *C. tropicum* (24), the *Chrysosporium* anamorph of *Nannizziopsis vriesii* (58), and several unidentified or unclassified species. Thermotolerance may be an important determinant of pathogenicity in the *Chrysosporium* species (1). Unlike adiaspiromycosis, invasive *Chrysosporium* infection occurs in the immunocompromised host and is usually disseminated at the time of diagnosis.

Eleven cases of invasive or localized *Chrysosporium* infection have been described in the medical literature (22,24,25,49,54,57,58,63,68,69; see Table 3). Two of these cases were patients with pulmonary fungal balls (cases 4 and 8 from Table 3) and two had localized disease (cases 6 and 9 from Table 3), leaving seven cases of invasive disease (22,24,49,59,63,69). In six of the invasive cases, there was a specific host factor that promoted the mycosis; five patients were immunosuppressed (cases 3, 5, 7, 10, and 11 from Table 3) and the other had a prosthetic heart valve (case 2 from Table 3). Five of the seven patients (71%) with invasive disease survived, including three of four patients that were highly immunocompromised (22,49,58). In vitro susceptibility data for *Chrysosporium* species are limited; MIC data are available for four strains of *C. zonatum*: amphotericin B (≤ 0.06 to 0.25 µg/mL); itraconazole (0.25 to 2 µg/mL); 5-fluorocytosine (>128 µg/mL); and fluconazole (32 to 128 µg/mL) (49). Thus, for *C. zonatum*, amphotericin B is the most active drug, with itraconazole susceptibility being strain-dependent; fluconazole and 5-fluorocytosine are not active.
CONCLUSIONS

Since the seminal review of England and Hochholzer in 1993 (21), 21 cases of human pulmonary adiaspiromycosis have been reported (including the present one). Brazil has emerged as the country with the most reported cases. The new manifestation of disease of ocular adiaspiromycosis has been described, but requires additional investigation to confirm the identity of the fungus that is involved in these cases. Additional pathogenic species of *Emmonsia* have been described; these do not cause adiaspiromycosis, but have been reported to cause cutaneous and respiratory infections in immunocompromised patients. Molecular genetics has delineated the relationship of the *Emmonsia* species to each other and to the genera *Blastomyces*, *Histoplasma*, and *Paracoccidioides*. The same techniques have also allowed differentiation of *Emmonsia* and *Chrysosporium*, but confusion regarding the two genera persists in the literature. Herein, we have endeavored to clarify the morphologic and clinical characteristics of these two genera. Pulmonary adiaspiromycosis has been reported primarily in persons without underlying host factors, and has a mild to severe course. It remains uncertain if the optimal management of patients with severe pulmonary adiaspiromycosis is supportive care, antifungal treatment, corticosteroids, or a combination of the latter two modalities. Invasive *Chrysosporium* infection typically occurs in impaired hosts, and can have a severe or fatal course. Based on limited in vitro susceptibility data for *C. zonatum*, amphotericin B is the most active drug, itraconazole susceptibility is strain-dependent and fluconazole and 5-fluorocytosine are not active.
References


FIGURE LEGENDS

Figure 1. Chest radiograph on admission of the patient, showing marked bilateral, predominately interstitial, infiltrates and prominent right paratracheal soft tissue, suggesting lymphadenopathy.

Figure 2. Histopathologic section (hematoxylin-eosin) of lung in this patient with adiaspiromycosis, showing an adiaspore with granuloma formation (40-X).

Figure 3. Computerized tomography of the chest of the patient on hospital day-26 showing diffuse bilateral interstitial thickening.
Table 1. Case reports of pulmonary infections due to *Emmonsia crescens* described since the review of England and Hochholzer (20) or omitted from that review.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pub yr (ref)</th>
<th>Patient Location</th>
<th>Host Factor</th>
<th>Species (Author's Nomenclature)</th>
<th>Presentation</th>
<th>Severity</th>
<th>Treatment</th>
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<td>27 y/o M USA (TX)</td>
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<td><em>Emmonsia crescens</em></td>
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<td>Resp failure</td>
<td>Ampho, itra methylpred</td>
<td>Recovered</td>
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<td>2</td>
<td>1989 (36)</td>
<td>31 y/o M Brazil</td>
<td>None</td>
<td><em>Emmonsia parvum var. crescens</em></td>
<td>Fever, cough, myalgias, dyspnea</td>
<td>Diffuse pulmonary/severe</td>
<td>Ampho</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>1989 (52)</td>
<td>37 y/o M Brazil</td>
<td>None</td>
<td>Chrysosporium parvum var. crescens</td>
<td>Fever, cough, dyspnea, anorexia, wt loss</td>
<td>Diffuse pulmonary/severe</td>
<td>Keto</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>1997 (11)</td>
<td>43 y/o M Brazil</td>
<td>None</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Fever, cough, weight loss, dyspnea, thorax pain</td>
<td>Diffuse pulmonary</td>
<td>Itra, thes pred</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>1997 (11)</td>
<td>47 y/o M Brazil</td>
<td>None</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Fever, nonproductive cough, dyspnea, wt loss</td>
<td>Diffuse pulmonary</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>1997 (11)</td>
<td>52 y/o M Brazil</td>
<td>Prior pulm histoplasmosis</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Fever, productive cough, wt loss</td>
<td>Diffuse pulmonary</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>1997 (32)</td>
<td>35 y/o M Brazil</td>
<td>None</td>
<td><em>Emmonsia parvum var. crescens</em></td>
<td>Fever, cough, weight loss over 2 mos</td>
<td>Diffuse pulmonary</td>
<td>Keto</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>1997 (40)</td>
<td>2 y/o F Finland</td>
<td>Asthma</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Fever, dry cough</td>
<td>Mild</td>
<td>Ampho</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>1997 (51)</td>
<td>26 y/o M Brazil</td>
<td>None</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Fever, night sweats, cough, thorax pain</td>
<td>Diffuse pulmonary</td>
<td>Keto</td>
<td>Recovered</td>
</tr>
<tr>
<td>10</td>
<td>1998 (31)</td>
<td>18 y/o M Brazil</td>
<td>None</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Thoracic pain, cough</td>
<td>Severe</td>
<td>Keto</td>
<td>Recovered</td>
</tr>
<tr>
<td>11</td>
<td>1999 (62)</td>
<td>51 y/o M France</td>
<td>Meso-theliotus</td>
<td><em>C. parvum var. crescens</em></td>
<td>Incidental</td>
<td>N/A</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>12</td>
<td>1999 (62)</td>
<td>57 y/o M France</td>
<td>Lung cancer</td>
<td><em>C. parvum var. crescens</em></td>
<td>Incidental</td>
<td>N/A</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>13</td>
<td>2000 (50)</td>
<td>29 y/o M Brazil</td>
<td>Smoker</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Fever, cough, pain, dyspnea, wt loss</td>
<td>Diffuse pulmonary</td>
<td>None</td>
<td>Recovered</td>
</tr>
<tr>
<td>14</td>
<td>2000 (50)</td>
<td>54 y/o M Brazil</td>
<td>Not Specified</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Fever, headache, myalgias, nausea, wt loss</td>
<td>Diffuse pulmonary</td>
<td>Keto</td>
<td>Recovered</td>
</tr>
<tr>
<td>15</td>
<td>2001 (38)</td>
<td>45 y/o M Brazil</td>
<td>None</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Incidental</td>
<td>N/A</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>16</td>
<td>2004 (37)</td>
<td>60 y/o M Brazil</td>
<td>Lung cancer</td>
<td><em>Emmonsia crescens</em></td>
<td>Incidental</td>
<td>Hilar lymph nodes/incidental</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>17</td>
<td>2006 (6)</td>
<td>25 y/o M Argentina</td>
<td>Prior TB</td>
<td><em>Emmonsia parva</em></td>
<td>Cough, dyspnea</td>
<td>Resp failure</td>
<td>Ampho</td>
<td>Recovered</td>
</tr>
<tr>
<td>18</td>
<td>2007 (60)</td>
<td>64 y/o F USA (NY)</td>
<td>Cancer, pulmonary radiation</td>
<td><em>Emmonsia crescens</em></td>
<td>Nonproductive cough, anorexia</td>
<td>Mild</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>19</td>
<td>2009 (15)</td>
<td>30 y/o M France</td>
<td>None</td>
<td><em>Emmonsia crescens</em></td>
<td>Cough, thoracic pain, dyspnea, weakness, wt loss over 2 weeks</td>
<td>Diffuse pulmonary</td>
<td>Itra</td>
<td>Recovered</td>
</tr>
<tr>
<td>20</td>
<td>2010 (56)</td>
<td>40 y/o M Brazil</td>
<td>None</td>
<td><em>Emmonsia parva var. crescens</em></td>
<td>Fever, cough, thorax pain, dyspnea</td>
<td>Diffuse pulmonary/severe</td>
<td>Pred</td>
<td>Recovered</td>
</tr>
</tbody>
</table>
a Year of publication and reference number.
bAmpho = amphotericin B, Itra = itraconazole; Keto = ketoconazole; Vori = voriconazole; Methylpred = methylprednisolone; Pred = prednisone.
c Mis-identified. Should be *E. crescens*.
d Not applicable.
e Not specified, but appears to be *E. crescens*. 
Table 2. Case reports of infections due to other *Emmonsia* species

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pub yr (Ref)</th>
<th>Patient</th>
<th>Location</th>
<th>Host Factor</th>
<th>Species (Author's Nomenclature)</th>
<th>Presentation</th>
<th>Organs affected/ severity</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1993 (18)</td>
<td>32 y/o M</td>
<td>Colombia</td>
<td>HIV infection</td>
<td><em>Chrysosporium parvum var. parvum</em></td>
<td>Wrist pain, swelling</td>
<td>Langs, Bones/widespread</td>
<td>Ampho</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>1998 (23)</td>
<td>40 y/o F</td>
<td>France</td>
<td>AIDS</td>
<td><em>Emmonsia pasteuriana</em></td>
<td>Extensive skin ulcers</td>
<td>Skin/widespread</td>
<td>Ampho</td>
<td>Died, unrelated cause</td>
</tr>
<tr>
<td>3</td>
<td>1999 (64)</td>
<td>40 y/o M</td>
<td>Israel</td>
<td>AIDS, smoker</td>
<td><em>Emmonsia parva var. parvum</em></td>
<td>Cough, dyspnea</td>
<td>Diffuse Pulmonary/severe</td>
<td>Ampho, Flu</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>2003 (74)</td>
<td>64 y/o M</td>
<td>Germany</td>
<td>RA*</td>
<td><em>Emmonsia sp.</em></td>
<td>Dyspnea, fever, fatigue</td>
<td>Diffuse Pulmonary/moderate</td>
<td>Itra</td>
<td>Chronic, relapsing</td>
</tr>
<tr>
<td>5</td>
<td>2011 (44)</td>
<td>46 y/o M</td>
<td>Spain</td>
<td>HIV, liver transplant</td>
<td><em>Emmonsia sp.</em></td>
<td>Multiple skin nodules, asthenia, anorexia</td>
<td>Skin/widespread</td>
<td>L-AB</td>
<td>Died</td>
</tr>
</tbody>
</table>

*a* Year of publication and reference number.

*b* Ampho = amphotericin B, Flu = fluconazole; Itra = itraconazole; L-AB = liposomal amphotericin B.

*c* *Emmonsia parva* based on nomenclature system used herein.

*d* RA = rheumatoid arthritis, on corticosteroids.

*e* Based on genetic analysis, this isolate was placed in the genus *Emmonsia*, but it is not *E. crescens* or *E. parva*.
Table 3. Invasive and localized infections due to *Chrysosporium* species.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pub yr (Ref)</th>
<th>Patient</th>
<th>Place</th>
<th>Host Factor</th>
<th>Species</th>
<th>Organs Affected</th>
<th>Disease</th>
<th>Severity</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1984 (59)</td>
<td>24 y/o M</td>
<td>USA (NY)</td>
<td>None</td>
<td><em>Chrysosporium</em> sp.</td>
<td>Bone</td>
<td>Localized osteomyelitis</td>
<td>Ampho</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1986 (63)</td>
<td>61 y/o M</td>
<td>USA (IL)</td>
<td>Prosthetic aortic valve</td>
<td><em>Chrysosporium</em> sp.</td>
<td>Heart valve</td>
<td>Endocarditis</td>
<td>None</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1991 (69)</td>
<td>18 y/o F</td>
<td>USA (MN)</td>
<td>BMT</td>
<td><em>Chrysosporium</em> sp.</td>
<td>Sinuses, Brain, Lungs</td>
<td>Disseminated</td>
<td>Ampho, 5FC</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1998 (54)</td>
<td>N/a</td>
<td>Japan</td>
<td>Prior TB</td>
<td><em>C. zonatum</em></td>
<td>Allergic Pneumonitis/fungal ball</td>
<td>Colonization</td>
<td>Itra, then Ampho</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1999 (49)</td>
<td>15 y/o M</td>
<td>Greece</td>
<td>CGD</td>
<td><em>C. zonatum</em></td>
<td>Lungs, Pericardium, Bones</td>
<td>Disseminated</td>
<td>Ampho, then Itra, then L-AB</td>
<td>Relapsed, recovered</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1999 (68)</td>
<td>43 y/o</td>
<td>Saudi Arabia</td>
<td>None</td>
<td><em>Chrysosporium parvum</em></td>
<td>Cornea</td>
<td>Localized</td>
<td>Surgery X, Top Mico, Top Ampho, Oral Flu</td>
<td>Relapsing, recovered</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2002 (22)</td>
<td>50 y/o F</td>
<td>Malaysia</td>
<td>Neutropenia</td>
<td><em>Chrysosporium</em> sp.</td>
<td>Lungs, Skin, Brain, Sinus, Blood</td>
<td>Disseminated</td>
<td>Ampho, Itra</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2002 (25)</td>
<td>N/a</td>
<td>Japan</td>
<td>Prior TB</td>
<td><em>C. zonatum</em></td>
<td>Allergic Pneumonitis/fungal ball</td>
<td>Colonization</td>
<td>Pred, Itra, Intracav ampho</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2004 (57)</td>
<td>35 y/o M</td>
<td>USA (NY)</td>
<td>Heart transplant</td>
<td><em>Chrysosporium</em> sp.</td>
<td>Skin</td>
<td>Localized</td>
<td>Topical Ciclopirox, oral Flu</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2005 (58)</td>
<td>38 y/o M</td>
<td>Nigeria</td>
<td>AIDS</td>
<td>CANV</td>
<td>Brain, Sinus, Lungs</td>
<td>Disseminated</td>
<td>Vor, ARV</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2007 (24)</td>
<td>78 y/o M</td>
<td>Spain</td>
<td>Diabetes</td>
<td><em>C. tropicum</em></td>
<td>Sinus, Brain</td>
<td>Severe</td>
<td>Surgery, L-AB, Flu</td>
<td>Recovered</td>
<td></td>
</tr>
</tbody>
</table>

*a* Year of publication and reference number.

*b* BMT = bone marrow transplant; CGD = chronic granulomatous disease; TB = tuberculosis; AIDS = acquired immunodeficiency syndrome.

*c* 5FC = 5-fluorocytosine; Ampho = amphotericin B, ARV = antiretroviral therapy; Flu = fluconazole; Intracav = intracavitary; Itra = itraconazole; Mico = miconazole; Keto = ketoconazole; L-AB = liposomal amphotericin B; Pred = prednisolone; Top = topical.

*d* Based on discussion herein, this is a mis-identification.

*e* CANV = *Chrysosporium* anamorph of *Nannizziopsis vriesii.*