Respiratory Failure Caused by Adiaspiromycosis*

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Adiaspiromycosis is a rare pulmonary disorder caused by the fungus *Emmonsia crescens* (or *Chrysosporium parvum var. crescens*). According to the amount of inhaled conidia, man may develop symptomatic disease. After reaching the alveoli, the adiasconidia do not multiply or disseminate, but will induce a granulomatous inflammatory reaction that may lead to fatal respiratory failure. Up to now, only five cases of disseminated pulmonary infection have been documented. This work describes the occurrence, in Brazil, of two further cases of symptomatic disease with diffuse interstitial infiltrates and severe functional impairment. Possible massive infestation during activities in closed and stuffy environments is suggested. The specific diagnosis was troublesome and could not be made by cultures, skin tests or bronchoalveolar lavage. Both patients were successfully treated, but a spontaneous resolution of the process is seriously considered. (Chest 1990; 97:1171-75)

Adiaspiromycosis is a recently recognized disease, most frequently caused by the fungus *Emmonsia crescens* (now preferably designated *Chrysosporium parvum var. parvum*).1,2 Despite its ubiquitous occurrence in rodents and small wild mammals throughout the world, the disease rarely affects man.

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The first established human case was diagnosed in France, in 1964,7 reported as a localized process. Since then, however, five cases of massive human infestation, leading to a disseminated granulomatous pulmonary process have been reported from Czechoslovakia,4 Union of Soviet Socialist Republics,5,6 Guatemala,7 and France.8

The present work describes two additional cases of disseminated pulmonary adiaspiromycosis occurring in São Paulo, Brazil. In both cases, severe respiratory failure developed a few months after the patients had worked in a stuffy shed and building that had been closed for a long time. The diagnosis of the underlying disorder was distressing. The bronchoalveolar lavage was of no avail and the large size of the fungus in lung sections initially led the pathologists to identify it as helminthic organisms.

**Case Reports**

**Case 1**

A 42-year-old white man was well up to two months before, when he began to suffer from progressive dyspnea, fatigue, fever and night sweats. He was a peasant and had been working at some farms in São Paulo. Four months before entry, he had been cleaning a shed for a whole week. This shed had been closed for over a year, and a great number of rodent remains and bats were found inside it. Besides coughing bouts caused by the large dust clouds kicked up, he had no further complaints then, nor in the subsequent two months. Six weeks before admission, he was treated during a month for a suspected miliary tuberculosis, but his symptoms worsened.

On admission, the patient appeared distressed and toxemic. Temperature was 38°C, pulse was 120 beats per minute, and respirations were 40/min. Blood pressure was 120/90 mm Hg. There was a moderate cough without purulent sputum. Diffuse crackles were heard in both lung fields. No other abnormalities were found.

The hematocrit value was 35 percent, the peripheral blood leukocyte count was 19,800 cell/µm with 13 percent eosinophils, 64 percent neutrophils and 9 percent band forms. Specimens of stool contained no ova or parasites. Arterial blood gas values during room-air breathing showed pH, 7.50; Po2, 55 mm Hg; Pco2, 37 mm Hg. A chest roentgenogram revealed a bilateral interstitial infiltrate with a micronodular pattern (Fig 1). Computerized tomography of the chest (high resolution CT) evinced disseminated pulmonary

**FIGURE 1.** Chest roentgenogram of patient 1. A diffuse interstitial and micronodular infiltrate is evident, especially at the bases.

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nODULES, about 1 to 3 mm in diameter (Fig 2). Pulmonary function studies showed that FVC was 1.76 L (44 percent of predicted), FEV1 was 1.69 L (53 percent), and FEF25-75% was 4.26 L/s (116 percent). Bronchoalveolar lavage showed 38 percent lymphocytes, 9 percent neutrophils, and 14 percent eosinophils. An increased 14C citrate uptake was found in both lungs, markedly at the bases.

Repeated examinations and cultures of the bronchoalveolar lavage or sputum revealed no acid-fast bacilli, fungi, or pathogenic bacteria. Serologic tests for Paracoccidioides brasiliensis, Histoplasma capsulatum, Aspergillus fumigatus and Candida albicans revealed negative immunodiffusion, weakly positive counterimmunoelectrophoresis for A fumigatus, and positive complement-fixing antibodies in titers 1:16 (micromethod), for all the above species. Tuberculin, histoplasmin, paracoccidioidin and haplosporangin (prepared from antigens of Emmonsia paracoccidea) skin tests were negative. Cotrimoxazole, 1600 mg/day was started, with little improvement.

One week later, the patient's status worsened, and he became cyanotic with an arterial PO2 of 45 mm Hg and PCO2 of 35 mm Hg, (room-air breathing). An open chest biopsy was performed. Microscopic examination was initially interpreted as an unidentified helminthic infestation and a therapeutic trial with thiabendazole, 2.5 g/day, and a single dose of levamizole, 150 mg, was started.

Forty-eight hours after the first dose of this "antihelminthic" therapy, fever and signs of toxemia disappeared and the dyspnea progressively improved. Lung sections were carefully reviewed and we then came to the diagnosis of adiaspiromycosis. Thiabendazole therapy was maintained for 40 days. A test of the in vitro antifungal activity of thiabendazole on available strains of E crescens and E paracoccidea was performed. Whereas the crescens variety was resistant (tested concentrations up to 128 μg/ml), the paracoccidea variety was inhibited at concentrations about 1 μg/ml. One month later, despite persistent pulmonary infiltrates and a still altered pulmonary 14C scan, the patient became asymptomatic with normal blood gas analyses. One year later, his chest x-ray film, pulmonary functional tests, and 14C scan results were normal.

Case 2

A 29-year-old white man was well until progressive dyspnea developed. One month before entry, he began to develop corvza, myalgia, anorexia, fever, and headache. Two weeks prior to admission, a nonproductive cough developed. He was a carpenter who had been restoring a factory roof in São Paulo, closed down for several years. A large amount of dust was kicked up while working on the stuffy roof.

On admission, the patient appeared well, with mild dyspnea. Temperature was 38.3°C, pulse was 90 beats per minute, and respirations were 20/min. Blood pressure was 100/70 mm Hg. Inspiratory crackles were heard in both lung bases.

The hematocrit value was 43 percent, the peripheral blood leukocyte count was 16,700 cell/μL with 3 percent eosinophils, 70 percent neutrophils and 6 percent band forms. Specimens of stool contained no ova or parasites. Arterial blood gas values (room-air breathing) showed pH, 7.39; PO2, 76 mm Hg; PCO2, 22 mm Hg. Chest roentgenogram revealed a bilateral interstitial infiltrate with a diffuse micronodular pattern. Pulmonary function studies showed that FVC was 3.47 L (68 percent of predicted). FEV1 was 3.28 L (81 percent), FEF25-75% was 4.83 L/s (103 percent), and DCO was 31.7 ml/min/mm Hg (104 percent).

Repeated examinations and cultures of sputum revealed no acid-fast bacilli or fungi. Tuberculin, histoplasmin, coccidioidin, paracoccidioidin, sporotrichin and haplosporangin skin tests were negative. The DNCB skin test was positive. A transbronchial biopsy was performed, showing a granulomatous process with an unidentified organism in the center of the granulomas. An open chest biopsy was then performed, aimed at a better characterization of the organism. The new histopathologic material was also initially interpreted as a case of helminthic infestation, but the diagnosis of adiaspiromycosis was subsequently confirmed. Forty-eight hours after open lung biopsy, the fever ceased and the patient felt better without any specific therapy. A therapeutic trial with amphoterin...
B was interrupted because of adverse reactions. Inhalations with pimaricin, 2.5 mg tid, were started and maintained for 45 days. A few weeks later, the factory was inspected. There were no traces of rodents in the locality and cultures of the collected dust were negative for Emmonsia crescens. The patient's condition progressively improved. Six months later, he became asymptomatic with normal thorax x-ray film and pulmonary function tests.

**Histopathologic Findings**

The histologic changes were similar in the three performed biopsies—an open lung biopsy of the first patient and an open lung as well as a transbronchial biopsy performed in the second patient. Multiple nodular granulomas were distributed throughout lung tissue resembling miliary tuberculosis. The granulomas had a predominantly interstitial localization, with compression of adjacent blood vessels and small bronchi. Differing from previous descriptions of the disease, a considerable amount of necrosis, caseation, and degenerated inflammatory cells were found (Fig 3, upper). A solitary round adiaconidium occupied the center of some granulomas and multinucleated giant cells of the foreign-body type surrounded the surface of these adiaconidia. A zone of epithelioid cells usually enclosed the giant cells which were surrounded by thick, concentric layers of fibrous connective tissue containing a great number of eosinophils and variable number of lymphocytes, plasma cells, macrophages and fibroblasts. A great variation in size and mural structure of the conidia was found, with an average external diameter of 120 \( \mu \text{m} \) (range of 50 to 200 \( \mu \text{m} \)). The cell walls ranged from 5 to 20 \( \mu \text{m} \) in width. These features were distinctive of the crescens variety of the fungus *Chrysosporium parvum var crescens*. The interior of the conidium was generally empty except for some small and eosinophilic materials with variable dispositions (Fig 3 (upper)). The thick membrane reacted positively to the PAS or Grocott procedures.

Although the majority of granulomas were morphologically uniform, there were some cicatized granulomas with partial or complete resorption of adiaconidia. Some adiaconidia appeared also fragmented, collapsed and folded (Fig 3, lower) or even entirely displaced, probably because of the drag on the microtome knife during sectioning.

**Discussion**

Adiaspiromycosis is a pulmonary disease affecting primarily small wild mammals. By inhaling the elements of the saprophytic stage of the fungus that lives for long periods in soil substrates, man may become an accidental link of the saproparotrophic circulation of the agent. After reaching the human or host alveoli, the infecting cells—or conidia—are converted into the elements of the parasitic stage—adiaconidia—which increase their volume by an estimated factor of 10\(^6\), achieving diameters of 400 to 700 \( \mu \text{m} \). The disease is unique among fungal infections since the conidia apparently do not multiply in host tissues and the disorder seems to remain confined to the lungs. The adiaconidia grow slowly and progressively, being surrounded by granulomatous tissue, a phenomenon that may explain why the fungus cell can not be recovered from sputum or bronchoalveolar lavage, as in our patients. As the fungi probably do not propagate in human tissues, the resulting functional disability must be attributed to a large initial dose of inhaled conidia, leading to massive development of expanding adiaspiromycotic granulomas.

Very few cases of human adiaspiromycosis have been described throughout the world. To our knowledge, only 19 documented cases of human infection have been reported. The disease is generally a self-limited, benign and localized infection with few, if any, symptoms. Such infections have been discovered incidentally in the course of autopsy or histopathologic study of pulmonary tissues due to other causes such as bronchiectasis, pulmonary abscess, aspergillosis, or tuberculosis. The disseminated pulmonary form of the disease with symptomatic presentation was observed on only five previous occasions, two of them with a fatal outcome.

In addition to both cases presented here, two new cases of symptomatic disease were submitted to a regional Congress held in Brazil, one of them evolving to fatal respiratory failure. Unfortunately, beyond histopathologic analysis, very few clinical data were available.

To the best of our knowledge, all cases of human adiaspiromycosis have been ascribed to *Emmonsia crescens* (or *Chrysosporium parvum var crescens*). The other variation of the fungus, *Emmonsia parvum* (or *Chrysosporium parvum var parvum*), was found only among wild animals. In both presented cases, the adiaconidia in lung sections were compatible with the crescens variety, reaching diameters about 200 \( \mu \text{m} \) (Fig 3).

Similar to our patients, the five-year-old French boy described by Quilici and colleagues became sick, presenting a diffuse granulomatous pulmonary process a few weeks after playing several times in a dusty and full hay-loft. Raising and inhaling a great amount of dust, present in warm and closed environments, could be the link between all these cases of massive fungal infestation.

The finding of adiaconidia in the lung of a rodent in São Paulo, Brazil has already been demonstrated. As these small mammals may play the role of reservoir hosts, harboring the fungus in their lungs and disseminating it in human dwellings after their body decomposes, the presence of rodent remains and bats in the surroundings where the first patient worked must be relevant.

To diagnose adiaspiromycosis is still difficult. The increased number of lymphocytes and eosinophils recovered from the bronchoalveolar lavage fluid might not suggest a specific pathologic condition. Further, the presence of adiaconidia could not be proven by direct visualization or by cultures. The negative skin-test of haplosporangin was difficult to interpret: not only was the antigen prepared by Emmons extracted from the parvum variety—and the antigenic relationship with the crescens variety has not been well studied, but also, the sensitivity and specificity of
the test has not been high in animal or human studies. As cross reactions between antigens prepared from *Emmonsia parva*, *Coccidioides immitis*, *Histoplasma capsulatum*, and not so consistently, *P. brasiliensis* have already been demonstrated, the finding of false positive results in serologic tests might be expected, but obviously do not point at a specific disorder. Thus, the diagnosis of both presented cases rested essentially on lung histopathologic examination, either by open lung or by transbronchial route.

The bizarre aspects of adiasconidia found in lung sections may lead the pathologists to classify them as a helminthic or another unidentified organism. Because of their large size, they are sectioned in many different planes showing a wide variation in size and mural structure: those sectioned tangentially usually appear as a solid and small structure, while those sectioned near their equatorial plane often appear as large, empty rings. The internal contents of adiasconidia are usually not seen, but when visible, their appearance is variable and may mimic internal worm organs. Degenerating and apparently dead adiasconidia may appear fragmented, flattened and folded, sometimes resembling a roundworm (Fig 3, lower). In addition to these confusing aspects, the great number of eosinophils in the surrounding granulomas pointed to a parasitic disorder.

The treatment for adiaspiromycosis has not yet been established. Experimental data are scarce and human disease is so rare that up to now, we found only three documented cases of disseminated adiaspiromycosis in which a therapeutic approach with antifungal agents was tried. The combinations of amphotericin B plus 5-flucytosine, pimaricin as aerosol plus systemic corticosteroids, and nystatin plus amphotericin B were respectively used in those three patients, apparently with some success and resolution of the process. However, since information about the natural course of human adiaspiromycosis is still lacking, these seemingly good results must be carefully evaluated. In the Brazilian Congress, we were informed that one of the patients with disseminated adiaspiromycosis achieved spontaneous remission without any specific therapy. The evolution of our second patient also suggested a spontaneous resolution, since the patient was feverless and began to improve a few days before the nebulizations with pimaricin. Therefore, it is possible that all the above reported improvements are not related to any specific therapy.

Nevertheless, adiaspiromycosis is not always a benign disorder. The mortality can be high in disseminated forms of the disease—three fatal cases in nine of those reported. We consider that, although experimental, these therapeutic alternatives reported should be considered in severe disseminated adiaspiromycosis. Since amphotericin B and pimaricin were effective in experimental models of disease, they should remain as the agents of choice. The efficacy of thiabendazol, whose antifungal properties have been demonstrated in other human diseases, was suggested in the present work by the evolution of the first patient. However, as its efficacy against the crescents variety could not be demonstrated "in vitro," its therapeutic indication remains doubtful as well as the use of 5-flucytosine, nystatin or corticosteroids for the same purpose. Beneficial immunoregulatory effects of levamizole administered to this patient are not to be excluded but require further studies.

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REFERENCES

2. Otcenasek M, Frokopic J, Hamácek F. Adiaspiromycoses—one of the less well-known tropical diseases. Z Erkranck Am Tmr 1982; 150:131-45

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