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Micrograndulomatous Aspergillosis After Shoveling Wood Chips: Report of a Fatal Outcome in a Patient With Chronic Granulomatous Disease

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Chronic granulomatous disease is characterized by recurrent infections that result from an inability of phagocytes to kill organisms effectively. We describe a patient with this disease who developed aspergillus pneumonia after shoveling moldy cedar wood chips. Despite aggressive therapy, the patient's condition deteriorated and he died. At autopsy, the lungs revealed diffuse granulomas, all of the same age, with aspergillus organisms confined to the granulomas. We propose the term "micrograndulomatous aspergillosis" for this response, which does not conform to the commonly described aspergillus syndromes. We conclude that susceptible immunosuppressed patients should be advised to avoid occupational situations where high spore concentrations are generated.

Key words: aspergillus, occupational exposure, mold hazards, granulomatous disease

INTRODUCTION

Chronic granulomatous disease is an inherited disorder of phagocytes characterized by recurrent infections of the skin, lungs, lymph nodes, liver, and gastrointestinal tract [Mouy et al., 1989; Tauber et al., 1983]. Bacteria, especially catalase-positive species, are the major pathogens causing infection in these patients, but fungal infections, especially those caused by aspergillus species, are a common cause of infection as well. We present a patient with chronic granulomatous disease who developed pneumonia associated with occupational exposure to an identifiable point source of aspergillus contamination. Here, we describe an unusual pulmonary response to aspergillus and discuss the implications for prevention and therapy.

CASE REPORT

A 32-year-old white man with chronic granulomatous disease was admitted for fever and cough. The day prior to admission, he spent six hours shoveling cedar chips

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for a landscaping project. He described the wood chips as "moldy" and specifically remembered inhaling the dust created by shoveling. No respiratory protection was used. Six hours after finishing, he noted the abrupt onset of fevers, rigors, nonproductive cough, bilateral pleuritic chest pain, and dyspnea. He also complained of headache and mild anorexia. He reported no wheezing, sputum production, angina, nocturnal dyspnea, orthopnea, or specific gastrointestinal or urinary symptoms.

As a child, the diagnosis of chronic granulomatous disease was made on the basis of absent nitroblue tetrazolium (NBT) reduction and deficient intracellular bactericidal function of his neutrophils. His brother had a similar clinical syndrome and pattern of neutrophil dysfunction. His mother and two sisters exhibited a carrier phenotype. There was a past history of multiple superficial skin infections and a perirectal abscess. Four years prior to admission, he was hospitalized for a pneumonia of uncertain etiology that responded to broad spectrum antibiotics. He was in good health prior to this acute illness and was in excellent athletic condition. There were no HIV risk factors and he was taking no medications. There was no history of cigarette smoking or marijuana use.

On admission, his blood pressure was 104/60 mm Hg, pulse 92/min, temperature 38°C, and respiratory rate 24/min. He was alert, in mild respiratory distress, and coughed with deep inspiration. The only positive findings on physical examination were acrocyanosis and basilar rales in the left chest.

The white blood cell count was 18.7 K/μl, with 96% neutrophils, 1% eosinophils, 2% lymphocytes, and 1% monocytes. The hemoglobin was 16.5 gm/dl and the platelet count was 89 K/μl. Serum electrolytes, BUN, glucose, liver function tests, and amylase were normal. A specimen of arterial blood, drawn while the patient was breathing room air, disclosed that the partial pressure of oxygen (pO_2) was 61 mm Hg, the partial pressure of carbon dioxide (pCO_2) was 34 mm Hg, and the pH 7.48. A urine sample had a specific gravity of 1.020, a pH of 7.0, and trace proteinuria. The microscopic examination showed no hematuria, pyuria, or bacteriuria. His chest radiograph (Fig. 1) was remarkable for a diffuse reticular pattern most prominent at the bases especially on the left. There was no evidence of consolidation, lymphadenopathy, or volume loss.

After blood, urine, and sputum cultures were obtained, he was given supplemental oxygen and started on intravenous nafcillin, tobramycin, and ceftazidime. On the second hospital day, his temperature rose to 38.7°C, but his exam was otherwise unchanged. His chest radiograph was similar, except for a small right pleural effusion. The white cell count rose to 19.8 K/μl, but the remainder of his laboratory data remained essentially unchanged. A bronchoscopic examination revealed erythematous airways. A right middle lobe lavage and right lower lobe transbronchial biopsies were obtained. The KOH preparation of the lavage specimen and an AFB smear of the lavage and biopsy were negative. The cell differential from the right middle lobe lavage revealed 69% neutrophils, 6% neutrophilic band forms, 5% eosinophils, 13% macrophages, and 7% lymphocytes. The transbronchial biopsies were nondiagnostic. Intravenous erythromycin and amphotericin B were added to his antibiotic regimen. Progressive respiratory distress was noted on the third hospital day. An arterial blood gas while using a 50% face tent revealed a pH of 7.50, a pCO_2 of 39 mm Hg, and a pO_2 of 55 mm Hg. A chest radiograph showed worsening diffuse infiltrates.

The patient was transferred to the intensive care unit on the fourth hospital day for progressive respiratory distress and hypoxemia. Oral rifampin and trimethoprim/

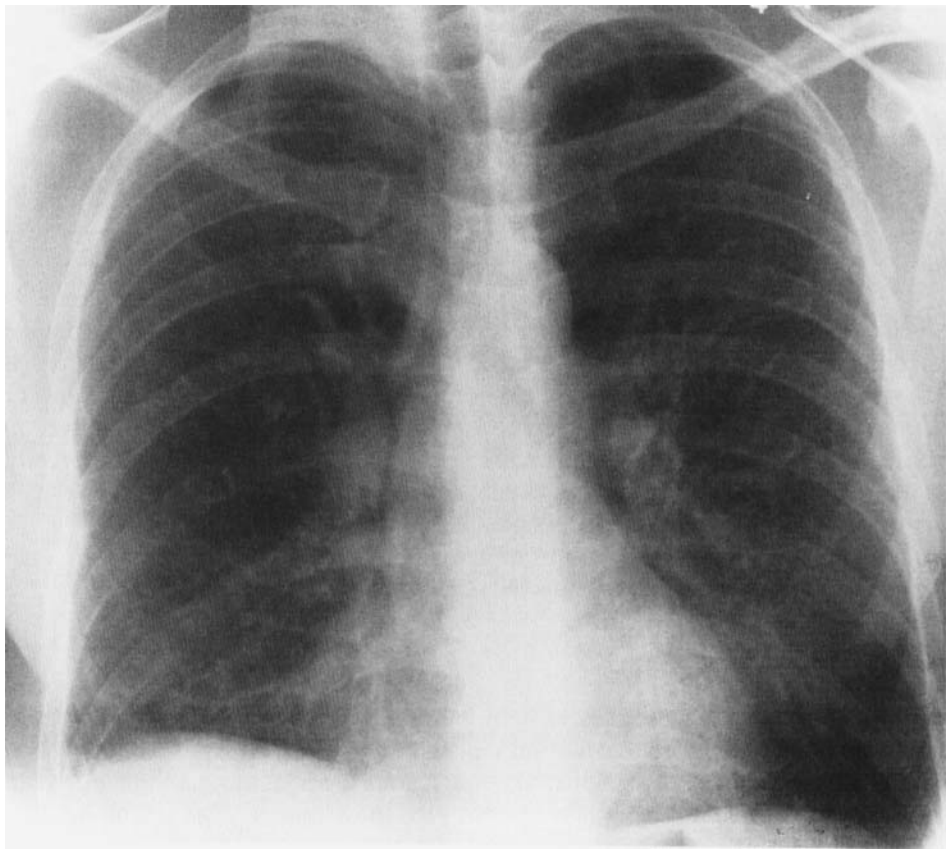

Fig. 1. Chest radiograph obtained on admission of the patient with CGD, showing a fine reticular infiltrate most prominent at the base.

sulfamethoxazole were added to the antibiotic regimen. Further invasive diagnostic procedures were deferred after extensive discussions with the patient and his family. His clinical status declined and he was intubated on hospital day seven. Ganciclovir and cytomegalovirus (CMV) immune globulin were given after culture of the bronchoalveolar lavage fluid yielded CMV. In addition, daily transfusions of irradiated granulocytes were initiated. The following day a few colonies of *Aspergillus fumigatus* were identified in the cultures of the bronchoalveolar lavage fluid obtained five days earlier. Several sputum cultures yielded *A. fumigatus*. Starting on hospital day eleven, gamma interferon (0.1 mg/m^2 every other day) was given subcutaneously. His clinical status declined despite full aggressive therapy; he died on the seventeenth hospital day.

Cultures of the landscaping wood chips to which the patient had been exposed were obtained during this hospitalization and yielded *A. fumigatus* colonies morphologically identical to those isolated from the sputum and bronchoalveolar lavage. Serologic studies for mycoplasma, legionella, and aspergillus were negative.

At autopsy, the pleural space was partially obliterated by fibrous adhesions. The heart showed mild left ventricular hypertrophy and generalized chamber dilation. The

lungs (right 2,260 g, left 2,450 g) were diffusely consolidated. The hyperemic cut surfaces were studded with coalescing tan nodules, 0.1 to 0.2 cm in diameter in all lobes. The liver, spleen, and kidneys were congested and edematous.

Histologically, the lungs showed randomly scattered, discrete, and confluent cellular granulomas with central purulent exudate. The granulomas consisted of epithelioid cells and numerous multinucleated giant cells, mostly of the foreign body type. The granulomas had rims of chronic inflammatory cells. There was little fibrosis. All granulomas were of similar size and morphology indicating that they were all of the same age (Fig. 2a). Gomori methenamine silver stains showed branching septate hyphae of aspergillus (Fig. 2b). Most granulomas had ony a few hyphae in the exudate, and no hyphae were found outside the granulomas. Most of the intervening parenchyma showed organizing alveolar damage consistent with oxygen toxicity. No cytomegalovirus inclusion bodies were seen. A non-specific, erosive purulent tracheitis and a fibrinous pleuritis were also present. Hilar lymph nodes contained no granulomas, and there was no evidence of aspergillus infection elsewhere in the body. Reaction to the acute infection was manifested elsewhere as splenitis and as myeloid hyperplasia of bone marrow. Histiocytes in the liver, spleen, and intestinal lamina propria contained yellow-brown lipochrome pigment, characteristic of chronic granulomatous disease. The kidneys showed acute tubular necrosis.

COMMENTS

This case report describes an unusual adult patient with CGD who inhaled aspergillus from a point source and subsequently developed a diffuse granulomatous pneumonia that we classify as microgranulomatous aspergillosis. Although the biochemical variant in our patient is not known, the most common variant, an X-linked disorder, is characterized by a deficiency of cytochrome b_{558} [Clark et al., 1989]. Infections of lungs, lymph nodes, and skin are commonly associated with CGD; however, any organ may be involved. Catalase-positive bacteria, such as *Staphylococcus aureus* and Gram negative rods, are the major causes of the bacterial infections. *Pneumocystis carinii* and mycobacteria have also been reported to cause disease in CGD [Mouy et al., 1989; Tauber et al., 1983].

In a review of 245 cases of CGD, fungal infections occurred in 20.4% of the cases, with aspergillus accounting for 78% of the fungal infections. *Candida albicans* and *Torulopsis glabrata* comprised the remaining fungal infections [Cohen et al., 1981]. In a more recent series, 40% of the patients had an aspergillus infection which accounted for 16% of all infections [Mouy et al., 1989]. The overall mortality of patients with CGD and pulmonary or disseminated fungal infections has been reported to be from 26% to 44% [Mouy et al., 1989; Cohen et al., 1981].

Our patient gave a remarkable history of an acute respiratory illness beginning six hours after occupational exposure to wood chip dust. Fungal and thermophilic bacterial organisms that have been isolated from wood chips include aspergillus, mucor, penicillium, talaromyces, and thermoactinomyces [Lacey and Crook, 1988; Jappinen et al., 1987]. Although aspergillus was not the only organism isolated from the wood chips handled by our patient, it was the only fungal pathogen cultured from the patient's sputum and lavage and the only organism apparent on histologic examination.

Although the airborne concentration inhaled by our patient was not measured,

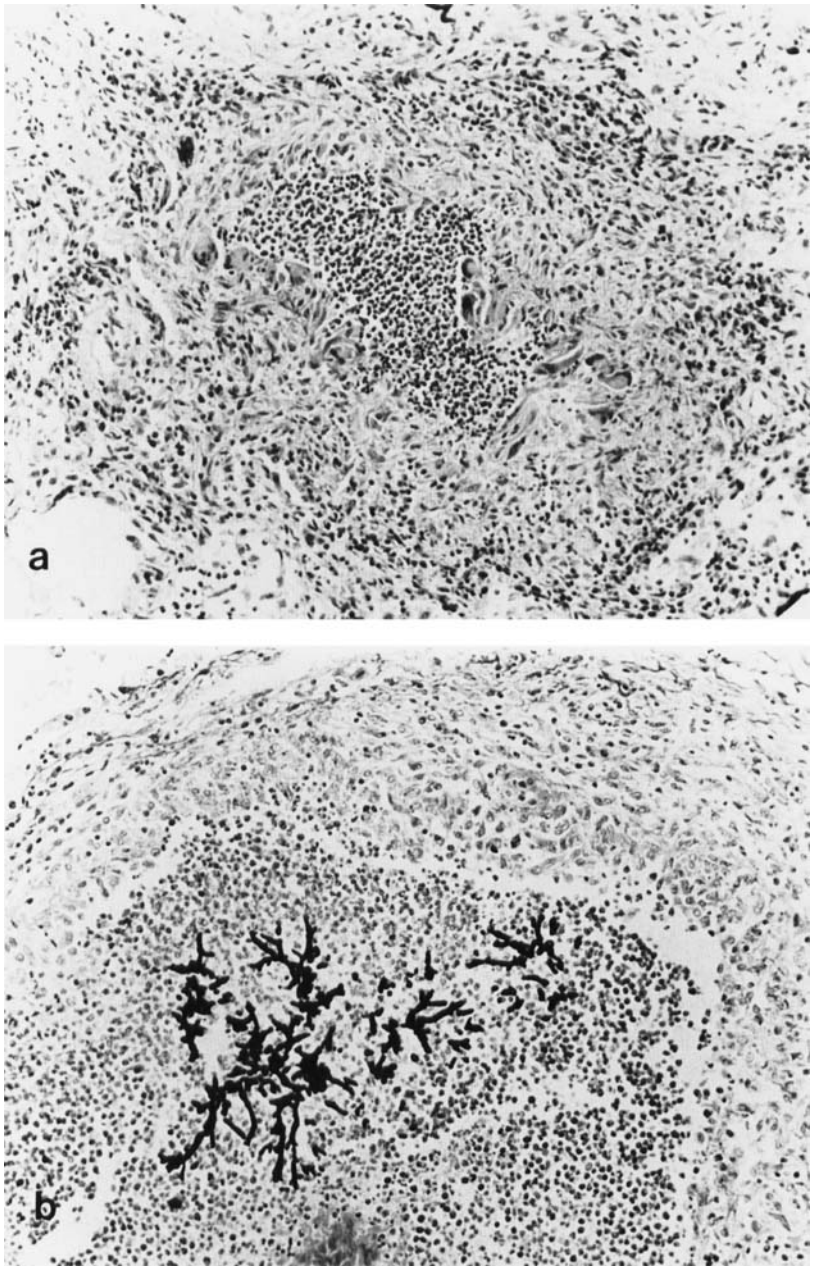

Fig. 2. **a.** Cellular granuloma with giant cells and central purulent exudate from a post mortem specimen of lung tissue in a patient with CGD. H & E stain. × 120. **b.** Gomori methenamine silver stain showing branching, septate hyphal forms of aspergillus confined to the central exudate of the granuloma. × 120.

other studies have documented spore levels in certain work settings 30–40 times that in noncontaminated environments. Recent data on airborne contamination by aspergillus in dairy barns demonstrated levels in excess of 1,000 ng/m^3, compared with

levels of only 25 ng/m^3 in a moldy house [Campbell et al., 1989]. The airborne spore level reported in a bulldozer cabin during work with wood chips was 195,000 colony-forming units (cfu)/m^3. In that study, 47–58% of the spores were in the respirable range (< 5 μ). Although species specific levels were not reported in that study, *A. fumigatus* was described as the most prevalent spore type [Jappinen et al., 1987]. In another study of air contamination, the mean level of aspergillus in grain elevators was 25,000 cfu/m^3, compared with only 800 cfu/m^3 in control noncontaminated environments [Smalley et al., 1977]. Even lower levels of baseline environmental aspergillus (< 100 cfu/m^3) have been reported near a sewage sludge composting site [Jones and Cookson, 1983].

Aspergillus species are implicated as the cause of a variety of pathophysiologic pulmonary syndromes, including mycetoma, allergic bronchopulmonary aspergillosis (ABPA), invasive pneumonia, hypersensitivity pneumonia, and organic dust toxic syndrome (ODTS). Only the last three were clinically relevant to this case. Our patient had findings suggesting features of all three of these conditions but wholly consistent with none.

Invasive or disseminated aspergillosis, characterized histologically by hemorrhage and necrosis, is usually seen in immunosuppressed individuals. Predisposing factors include antineoplastic or corticosteroid therapy and neutropenia. The progressive downhill course of our patient, despite aggressive intervention, supported a clinical impression of invasive fungal infection in an immuno-compromised host. However, the early onset of symptoms after the occupational exposure to wood chip dust suggested either ODTS or hypersensitivity pneumonitis. Hypersensitivity pneumonia is a T-lymphocyte-mediated inflammatory reaction that causes fever, chills, nonproductive cough, dyspnea, and malaise. It typically occurs in a host with normal cell mechanisms for killing organisms. A restrictive ventilatory defect with an associated reduction in lung volumes develops, and the diffusing capacity for carbon monoxide falls. Serum precipitating antibodies to the causal antigen are present. Organic dust toxic syndrome (ODTS) characteristically causes fever, chills, and cough beginning several hours after exposure and may occur after working with wood chips or other plant material highly contaminated with bacteria and molds [MMWR, 1986]. This syndrome differs from hypersensitivity pneumonitis in that prior sensitization is not necessary, specific antibodies do not develop, and radiographic changes are not typically seen. The diffuse radiographic abnormalities and hypoxemia were atypical for ODTS, but were consistent with severe hypersensitivity pneumonitis or overwhelming aspergillus pneumonia. The neutrophilia of the BAL fluid was more characteristic of ODTS [Lecours et al., 1986; Emmanuel et al., 1975] than hypersensitivity pneumonitis where lymphocytosis is more typical.

In view of the clinical course, which could not be specifically differentiated in terms of these three diagnostic alternatives, the autopsy findings were enlightening. The histologic findings in our patient reflected a diffuse spread of spores via the airways and subsequent encapsulation of their hyphae by granulomas. No hyphae were found beyond the granulomas. The distribution throughout the lung probably depended, in part, on deep inhalation during occupational exertion. This form of aspergillosis, which we term "micrograniulomatous aspergillosis," has not been previously differentiated from other pathological responses to aspergillus. Several reports describe clinical-pathological features relevant in part to our patient, although no point source was found. Casale and later Chusid described four children with

aspergillus infections associated with a diffuse nodular pattern on x-ray and a granulomatous inflammatory response [Casale et al., 1984; Chusid et al., 1988]. A histologic pattern much like that in our case occurred in a patient with CGD who died following a huge fungal inoculum from shoveling moldy barley [Kelly et al., 1986]. The authors of that report astutely emphasized the importance of an impaired host response in the face of a heavy exposure to aspergillus, but retained the nosology of "invasive pulmonary aspergillosis" to classify their case. In contrast, the fungal invasion, hemorrhage, and necrosis of invasive aspergillosis were absent in our patient. Furthermore, the numerous well-formed granulomas with purulent centers and lack of prominent lymphocytic peribronchiolar inflammation distinguish this entity histologically from hypersensitivity pneumonitis. The absence of clinical or radiographic improvement over time after exposure ceased, and lack of serum precipitins for aspergillus do not support the diagnosis of hypersensitivity pneumonitis.

In summary, we present a patient with chronic granulomatous disease who developed an overwhelming *A. fumigatus* pneumonia after inhaling dust from an occupational exposure to moldy wood chips. The diagnosis of aspergillus-related disease must always be considered in patients with chronic granulomatous disease with pneumonia. The reverse has also been suggested, namely that CGD should be suspected in patients with an aggressive aspergillus pneumonic process that is characterized by granuloma formation. A diagnostic approach including bronchoscopy and open lung biopsy should be used to make an early diagnosis and initiate appropriate therapy. Therapy may include antifungal agents such as amphotericin B and itraconazole [Casale et al., 1984; Chusid et al., 1988; van't Wout et al., 1990] as well as experimental interventions such as γ interferon [Newberger and Eskowitz, 1988; Bernhisel-Broadbent, 1991]. However, the efficacy of these therapeutic interventions may be limited, if, as this case suggests, the host response rather than the agent pathogenicity dictates the clinical course. At the present time, prevention of occupational exposure may offer a more practical approach to reducing morbidity, particularly when recognizing the importance of point source aspergillus contamination rather than viewing fungal spore inhalation as a ubiquitous and therefore irremediable problem. Moldy wood chips and decomposing timber harbor organisms that are pathogenic for susceptible immunosuppressed individuals. Such individuals should receive counseling prior to potential occupational or environmental exposures.

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