Fulminant Mulch Pneumonitis: An Emergency Presentation of Chronic Granulomatous Disease


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Background. Chronic granulomatous disease (CGD) is associated with multiple and recurrent infections. In patients with CGD, invasive pulmonary infection with Aspergillus species remains the greatest cause of mortality and is typically insidious in onset. Acute fulminant presentations of fungal pneumonia are catastrophic.

Methods. Case records, radiograph findings, and microbiologic examination findings of patients with CGD who had acute presentations of dyspnea and diffuse pulmonary infiltrates caused by invasive fungal infection were reviewed and excerpted onto a standard format.

Results. From 1991 through 2004, 9 patients who either were known to have CGD or who received a subsequent diagnosis of CGD presented with fever and new onset dyspnea. Eight patients were hypoxic at presentation; bilateral pulmonary infiltrates were noted at presentation in 6 patients and developed within 2 days after initial symptoms in 2 patients. All patients received diagnoses of invasive filamentous fungi; 4 patients had specimens that also grew Streptomyces species on culture. All patients had been exposed to aerosolized mulch or organic material 1–10 days prior to the onset of symptoms. Cases did not occur in the winter. Five patients died. Two patients, 14 years of age and 23 years of age, who had no antecedent history of recognized immunodeficiency, were found to have p47phox-deficient CGD.

Conclusions. Acute fulminant invasive fungal pneumonia in the absence of exogenous immunosuppression is a medical emergency that is highly associated with CGD. Correct diagnosis has important implications for immediate therapy, genetic counseling, and subsequent prophylaxis.

Chronic granulomatous disease (CGD) of childhood, first described in 1959 [1], is caused by defects in 1 of 4 structural components of the reduced nicotinamide adenine dinucleotide phosphate oxidase enzyme. Mutations in the X-linked gp91phox account for ~70% of cases, and the remainder are autosomal recessive in p22phox, p47phox, and p67phox [2]. Patients with CGD are prone to develop characteristic bacterial and fungal infections due to pathogens such as Staphylococcus aureus, Serratia marcescens, Burkholderia cepacia, Nocardia species, and Aspergillus species [2, 3]. In addition, these patients develop steroid-responsive granulomatous complications, including inflammatory bowel disease, urinary tract obstruction, and wound dehiscence, presumably because of abnormal degradation of inflammatory mediators [2, 4, 5].

Unique to CGD among genetic immunodeficiencies is susceptibility to invasive infection with filamentous fungi, especially Aspergillus species, which typically occurs in the pulmonary system, is difficult to treat, and is the single greatest cause of mortality associated with CGD [3, 6]. In general, fungal infection in patients with CGD is more indolent than infection due to bacteria [3, 7], and patients rarely experience pulmonary cavitition or hemoptysis because of Aspergillus infection. High-level exposure to aerosolized fungi, such as that which can occur during mulching, may lead to an acute fulminant presentation, with fever, dyspnea, and pulmonary infiltrates, and to death. Two such cases of the
initial presentation of CGD in adolescents and young adults led us to review cases to better characterize this clinical entity.

MATERIALS AND METHODS

The case records of 156 patients with CGD who were followed up according to approved protocols at the National Institutes of Health (NIH; Bethesda, MD) since 1986 were reviewed for acute presentations of fever, dyspnea, diffuse pulmonary infiltrates, and filamentous fungal infection. We also solicited cases from outside the NIH.

Patient 1. A previously healthy 14-year-old boy presented to his local hospital in the fall of 2004 with a 3-day history of fever, sore throat, and shortness of breath. A chest radiograph revealed bilateral infiltrates (figure 1A). One week previously, the boy had cleaned gutters containing dead leaves. Despite cefuroxime and azithromycin therapy for community-acquired pneumonia, his hypoxia worsened, leading to intubation and mechanical ventilation on hospital day 4. Meropenem, metronidazole, clarithromycin, and fluconazole were added to his treatment regimen, but respiratory failure progressed; high-dose methylprednisolone therapy was started for possible vasculitis. On hospital day 11, a lung biopsy specimen showed necrotic lung tissue with fungal hyphae and grew *Aspergillus fumigatus*. The dihydrorhodamine test result was consistent with CGD. Voriconazole, caspofungin, and IFN-γ therapy, as well as neutrophil transfusions, were initiated. High-level oxygenation requirements and deterioration of hepatic and renal function led to death 1 month after presentation. Autopsy revealed disseminated fungal infection, granulomatous foci in the lungs and brain with *A. fumigatus*, and extensive vascular invasion and infarction (in the lungs, kidneys, liver, and spleen) due to *Absidia corymbifera*. The patient was subsequently confirmed to have had p47phox deficiency.

Patient 2. A previously healthy 23-year-old female athlete presented to an emergency department in the summer of 2003 with acute onset of dyspnea 1 day after having performed heavy mulching. The initial chest radiograph was read as normal, and the patient was discharged from the hospital (figure 1B). Twenty-four hours later, her dyspnea worsened and was accompanied with fever and bilateral infiltrates (figure 2A). Antibiotic therapy for community-acquired pneumonia was initiated. The findings of bronchoscopic examination were not diagnostic. Fever and dyspnea progressed to hypoxia, and the patient required intubation and mechanical ventilation. A visually assisted thoracoscopic biopsy was performed on hospital day 8; observation of the specimen revealed intense pyogranulomatous inflammation, with invasive hyphae, and the specimen grew *A. fumigatus* and *Rhizopus* species (figure 3A–C). The dihydrorhodamine test result was consistent with p47phox-deficient CGD. When the patient was transferred to the NIH (figure 4A and B), treatment with voriconazole, caspofungin, meropenem, and methylprednisolone led to gradual improvement. Her course was complicated by recurrent bilateral pneumothoraces and exacerbation of pulmonary inflammation upon reduction of prednisone therapy. A second biopsy was performed, and degenerating hyphal elements were seen but did not grow from the biopsy specimens. The patient recovered, with return to normal lung function (figure 4C and D). She had had several respiratory infections during infancy and an episode of “cat scratch disease,” all of which had resolved with
oral antibiotic treatment. She and her 25-year-old brother, who had had 2 episodes of “cat scratch disease” and 1 episode of cellulitis, were subsequently confirmed to have p47<sup>phox</sup> deficiency.

**Patient 3.** A 20-year-old man with known gp91<sup>phox</sup> deficiency who was receiving prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) therapy presented in the summer of 2001 with a 3-day history of fever, cough, and progressive dyspnea. For 3 weeks prior to hospital admission, he had been working in the forest, chipping wood. At hospital admission, he was hypoxic, with bilateral crackles. Despite treatment with amphotericin B, rifampin, and fluoxacin, the patient required intubation 24 h after hospital admission because of respiratory failure. Sputum and tracheal aspirates grew *A. fumigatus*. Respiratory worsening, with bilateral recurrent pneumothoraces, led to death 10 days after hospital admission. No autopsy was performed.

**Patient 4.** A 23-year-old man with known gp91<sup>phox</sup> deficiency who was receiving prophylactic TMP-SMX and itraconazole, as well as prednisone (5 mg every other day), for granulomatous bowel disease, presented to the NIH in the fall of 2001 with a 1-week history of fever, progressive cough, and flu-like symptoms after working in a lawn mower repair shop. His temperature was 39.8°C, and he had tachypnea and bilateral interstitial infiltrates (figure 1C). A treatment regimen of levofloxacin, ceftriaxone, TMP-SMX, liposomal amphotericin B, and solumedrol (1 mg/kg daily) was initiated. Percutaneous lung biopsy was performed, and the specimen grew *A. fumigatus*, *Aspergillus niger*, *Rhizopus* species, *Penicillium* species, and *Streptomyces thermoviolaceus*. Respiratory failure led to intubation, mechanical ventilation, and bilateral pneumothoraces. The patient died 1 month after presentation. Autopsy revealed extensive abscess formation in the lungs, with abundant hyphal forms consistent with *Aspergillus* species.

**Patient 5.** A 64-year-old man with known p47<sup>phox</sup>-deficient CGD, insulin-dependent diabetes mellitus, and atherosclerotic coronary artery disease was receiving prophylactic TMP-SMX, itraconazole, and IFN-γ therapy. His initial diagnosis was reported elsewhere [8]. He presented in the fall of 2001 with a 1-day history of dyspnea and cough, oxygen saturation of 91% on room air, with bilateral pulmonary infiltrates (figure 2B). One week previously, the man had been mulching trees in his yard. A treatment regimen of intravenous ceftriaxone, TMP-SMX, amphotericin B deoxycholate, and solumedrol (60 mg every 12 h) was initiated. Bronchoscopic examination revealed branching septate hyphae, and specimens grew *A. fumigatus*, *A. niger*, and *Penicillium* species. Dyspnea and hypoxia led to intubation and mechanical ventilation on hospital day 5. The patient was extubated on day 14, and steroid therapy was gradually tapered. Although his fungal infection resolved, the patient’s course was complicated by diabetes, congestive cardiac failure, and recurrent respiratory failure. He died of respiratory failure 1 year after admission to the hospital. No autopsy was performed.

**Patient 6.** A 16-year-old boy with known gp91<sup>phox</sup> deficiency who was receiving prophylactic TMP-SMX and IFN-γ therapy presented in the fall of 1999 with fever, cough, dyspnea, and bilateral patchy infiltrates 1 week after riding a tractor while harvesting a field of peppermint (figure 1D). On admission to the NIH, a treatment regimen of ceftriaxone, TMP-SMX, amphotericin B deoxycholate, and methylprednisolone (60 mg every 12 h) was initiated. Culture of bronchoalveolar lavage specimens grew *Aspergillus nidulans*. The patient’s health gradually improved while receiving therapy, and he was discharged from the NIH after 1 month, with return to normal lung function while receiving itraconazole therapy (200 mg/day).

**Patient 7.** An 8-year-old boy with known X-linked CGD who was receiving prophylactic TMP-SMX and IFN-γ therapy presented in the fall of 1999 with fever, cough, rhinorrea, headache, fatigue, and normal chest radiograph findings 1 week after playing in a moldy garden shed. Therapy with ceftriaxone and gentamicin led to some improvement, but on hospital day 3, the patient became tachypneic and hypoxic, with bilateral infiltrates. Treatment with amphotericin B deoxycholate, vancomycin, TMP-SMX, and azithromycin was initiated. On transfer to the NIH (20 days after presentation), the boy had a temperature of 38.6°C and was tachypneic and hypoxic (figure 1E). Therapy was changed to levofloxacin, imipenem, amphotericin B deoxycholate, and prednisone (1 mg/kg daily). An open lung biopsy was performed, and the specimen revealed...
hyphae consistent with Aspergillus species; however, culture of the specimen showed no growth. The patient’s health improved gradually, and steroid therapy was tapered. The patient was discharged from the hospital 22 days after NIH admission, with return to normal lung function while receiving amphotericin B deoxycholate therapy.

**Patient 8.** An 18-year-old man with known p47^phox^-deficient CGD who was receiving TMP-SMX and IFN-γ therapy presented in the summer of 1995 with a 4-day history of fever, cough, dyspnea, nausea, malaise, and fatigue. Six days before hospital admission, he had swept a trailer that was used for hauling mulch. On admission to the NIH, he had a temperature of 38.4°C and was hypoxic, with diffuse bilateral infiltrates. Treatment with ceftriaxone, TMP-SMX, ciprofloxacin, amphotericin B deoxycholate, and methylprednisolone (60 mg daily) was initiated. Culture of bronchoalveolar lavage specimens grew A. niger, Rhizopus species, and Streptomyces species. Dyspnea and hypoxia led to intubation and mechanical ventilation. Treatment with ceftazidime, oxacillin, gentamicin, TMP-SMX, amphotericin B deoxycholate, and solumedrol (100 mg every 8 h) was initiated. Culture of bronchoalveolar lavage specimens grew A. fumigatus, Rhizopus species, and Streptomyces species. A decrease in respiratory function, bilateral pneumothoraces, and shock led to death 1 week after admission to the NIH. Autopsy revealed severe diffuse necrotizing Aspergillus pneumonia.

**RESULTS**

**Clinical presentations.** The above cases illustrate a temporal relationship between exposure to mold, especially mulch, and presentation with clinical pneumonia in patients with CGD. All patients presented within 10 days after an identifiable ex-
A. niger patients, with who had been extensively pretreated; however, examination of positive from at least 1 source in all patients, except patient 7, veolar lavage or lung biopsy specimens. Culture results were monia was made on the basis of examination of bronchoal-

diagnosis. The diagnosis of fungal pneumonia was made on the basis of examination of bronchoal-
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Figure 4. Chest radiographs and CT of patient 2 at transfer to the National Institutes of Health (day 10 of hospitalization; A and B, respectively) and 2 months after transfer (C and D, respectively). Note the remarkable resolution of infiltrates and the absence of pneumatoceles, despite the occurrence of pneumothoraces.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Genotype</th>
<th>Season</th>
<th>Infiltrates</th>
<th>Hypoxia</th>
<th>Exposure</th>
<th>Time from exposure to presentation, days</th>
<th>Duration of hospital stay, days</th>
<th>BAL result</th>
<th>Lung biopsy result</th>
<th>Organisms on culture</th>
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<tr>
<td>1</td>
<td>14</td>
<td>M</td>
<td>p47&lt;sup&gt;phox&lt;/sup&gt;</td>
<td>Fall</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Leaves</td>
<td>7</td>
<td>30</td>
<td>NP</td>
<td>Fungal elements</td>
<td>Aspergillus fumigatus, Absidia corymbifera</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23</td>
<td>F</td>
<td>p47&lt;sup&gt;phox&lt;/sup&gt;</td>
<td>Summer</td>
<td>No</td>
<td>Yes</td>
<td>Mulch</td>
<td>1</td>
<td>30</td>
<td>Not diagnostic</td>
<td>Fungal elements</td>
<td>A. fumigatus, Rhizopus species</td>
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<td>3</td>
<td>20</td>
<td>M</td>
<td>gp91&lt;sup&gt;phox&lt;/sup&gt;</td>
<td>Summer</td>
<td>NP</td>
<td>Yes</td>
<td>Wood chips</td>
<td>&lt;21</td>
<td>3</td>
<td>NP</td>
<td>NP</td>
<td>A. fumigatus</td>
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<td>23</td>
<td>M</td>
<td>gp91&lt;sup&gt;phox&lt;/sup&gt;</td>
<td>Fall</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Mulch</td>
<td>7</td>
<td>10</td>
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<td>M</td>
<td>p47&lt;sup&gt;phox&lt;/sup&gt;</td>
<td>Fall</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Mulch</td>
<td>10</td>
<td>354</td>
<td>Branching septate hyphae</td>
<td>NP</td>
<td>A. fumigatus, Aspergillus niger</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>M</td>
<td>gp91&lt;sup&gt;phox&lt;/sup&gt;</td>
<td>Fall</td>
<td>Bilateral</td>
<td>No</td>
<td>Hay</td>
<td>7</td>
<td>35</td>
<td>Negative</td>
<td>NP</td>
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<tr>
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<td>8</td>
<td>M</td>
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<td>Fall</td>
<td>No</td>
<td>Yes</td>
<td>Garden shed</td>
<td>7</td>
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<td>M</td>
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<td>Summer</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Mulch</td>
<td>6</td>
<td>30</td>
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<td>Negative</td>
<td>A. fumigatus, A. niger, Rhizopus species, Streptomyces species</td>
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<tr>
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<td>10</td>
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<td>Fall</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Mulch</td>
<td>Unknown</td>
<td>6</td>
<td>Branching septate hyphae</td>
<td>NP</td>
<td>A. fumigatus, Streptomyces species</td>
</tr>
</tbody>
</table>

**NOTE.** At the time of severe clinical illness, all patients had abnormal chest radiograph findings. BAL, bronchoalveolar lavage; NP, not performed.

<sup>a</sup> The findings of the initial chest radiographs of patients 2 and 7 appeared to be normal.
invasive aspergillosis and the similarity of those cases to the cases presented here, we suspect that they might represent undiagnosed CGD.

Environmental exposure to mold is ubiquitous. Conidia develop invasive hyphae, with an incubation period ranging from 2 days to 3 months [15]. The infectious inoculum for Aspergillus species is undefined, but in CGD mouse models, it was lower in the gp91<sup>phox</sup>-deficient animals than it was in the p47<sup>phox</sup>-deficient ones [16, 17]. Interestingly, patients 2 and 5, who were both p47<sup>phox</sup>-deficient, had spread mulch several times previously without ill effects.

The initial symptoms of this acute fungal pneumonitis overlap with viral syndromes, community-acquired pneumonia, and hypersensitivity pneumonitides. Failure of adequate therapy directed at common pathogens should lead to consideration of other etiologies, especially when the patient has a history of an immune defect, such as CGD.

All of our patients had large exposures and relatively short incubation periods, emphasizing the importance of obtaining a careful history of the type and degree of recent exposures when confronted with a compatible clinical scenario. Similar clinical characteristics in older individuals should not preclude consideration of the diagnosis, because CGD can present later in life [18].

Radiograph findings obtained early in the course of infection may have been negative, but all of the patients developed a similar diffuse radiographic result 2–10 days after the initial complaint. In contrast, most immunocompromised individuals, especially those with neutropenia, develop nodular or focal Aspergillus lesions [17], which are also seen in patients with the typical fungal pneumonia associated with CGD, confirming that this diffuse interstitial presentation after exposure to mulch is clinically and pathophysiologically distinct [3].

The clinical and radiographic pattern seen in association with this syndrome is reminiscent of that seen in association with other syndromes in which there are significant host response components, such as hypersensitivity pneumonitis, which may occur as a consequence of exposure to various environmental pathogens, including bacteria, mycobacteria, fungi, proteins, metals, or chemicals [19]. Farmer’s lung and “hot tub lung” are caused by exposure to thermophilic actinomycetes and exposure to Mycobacterium avium complex, respectively [20]. They represent inflammation with or without infection, and patients with these syndromes can present with hypoxia, cough, fever, bilateral interstitial infiltrates with necrotizing or non-necrotizing granulomas, and patchy interstitial pneumonitis [19]. Important to understanding the use of steroid therapy, gp91<sup>phox</sup>-deficient mice who were made to inhale heat-killed aspergillus hyphae developed extensive granulomatous lung disease, whereas normal mice did not [21]. Therefore, at least part of this clinical picture is likely to be caused by the host immune response, even in the absence of invasive fungal infection.

Allergic bronchopulmonary aspergillosis is characterized by elevated anti-Aspergillus IgE, eosinophilia, fleeting pulmonary infiltrates, and reactive airways. It has been reported in individuals with CGD [22] and is a differential in this syndrome, but the diagnosis is complex. Antibodies and immediate cutaneous reactivity to Aspergillus species are typically demonstrated [19]. Histologic examination may reveal loosely organized granulomas, with prominent interstitial infiltrates and bronchiolitis. Acute presentations or exacerbations may include nodular pulmonary infiltrates, and CT may reveal bronchiectasis. However, allergic bronchopulmonary aspergillosis is not typically associated with invasive disease, and until recently, treatment of the infectious cause was not attempted. Successful use of high-dose steroids for the treatment of allergic bronchopulmonary aspergillosis is a strong argument for the resilience of the normal host defense against Aspergillus species, because steroid treatment for prolonged periods is rarely associated with invasive disease.

Invasive aspergillosis is usually diagnosed when clinical suspicion is raised in the appropriate clinical context and appropriate microbiologic data is collected. One of the surrogate markers of fungal infection, galactomannan, is less reliable in patients with CGD than in others [23]. Patients with CGD often receive treatment empirically, and such treatment should incorporate agents effective against relevant pathogens, especially if a specific exposure is known.

Survival for patients with invasive aspergillosis who do not have CGD remains dismal, at 34%–42% [24]. In contrast, overall survival for patients with CGD who are infected with Aspergillus species other than A. nidulans is considerably higher [3, 6, 11]. Therapy for invasive aspergillosis has changed markedly over the past 10 years, from amphotericin derivatives to the azole derivatives (i.e., itraconazole, voriconazole, and posaconazole) [25, 26] and echinocandins [27–30]. Although the morbidity and mortality among patients with fungal infections who have CGD will likely continue to decrease, overwhelming exposure, such as through mulching, will continue to be problematic. Patients should be cautioned regarding such exposures.

Although CGD is a primary immunodeficiency, steroid therapy successfully controls inflammation [5, 6], particularly in the gastrointestinal and genitourinary tracts. Steroid use has also been reported in individuals with CGD and invasive aspergillosis [31–33]. The defect in inflammatory control is likely to be caused by inadequate degradation of inflammatory mediators, such as LTB4, C5a, and IL-18 [4]. Impaired metabolism of inflammatory mediators may play a role in the acute morbidity and mortality associated with invasive aspergillosis disease and requires further evaluation in mouse models. Our current practice is to use high-dose steroid treatment (1 mg/kg per day...
for 1 week, followed by gradual taper) early in the course of treatment to dampen the acute pulmonary inflammation in patients with CGD who present with pneumonitis after high-level symptomatic mulch exposure.

Acute invasive pulmonary aspergillosis in the absence of known iatrogenic deficiency or AIDS should prompt consideration of CGD, regardless of patient age, in the appropriate clinical context. Early and aggressive therapy, including therapy with antifungals and steroids, is crucial. Acute invasive Aspergillus pneumonia following mulch exposure may be pathognomonic for CGD.

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