Bowel Infarction as the Initial Manifestation of Disseminated Aspergillosis

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Disseminated aspergillosis in the immunocompromised patient most commonly presents with clinically apparent pulmonary involvement and roentgenographic infiltrates. We report a patient with acute myelogenous leukemia who developed bowel infarction due to gastrointestinal infiltrates of Aspergillus fumigatus as the initial manifestation of widespread fungal disease. (Chest 1992; 101:877-79)

Disseminated aspergillosis is a rapidly progressive and highly lethal infection in patients with altered host defenses resulting from such conditions as hematologic malignancies and immunosuppressive therapy. Although Aspergillus species can invade the gastrointestinal tract, patients with bowel involvement in the setting of disseminated disease have been reported to invariably present with coexisting, clinically predominant lesions in other organs, which almost always include the lung. We report a patient with acute myelogenous leukemia and drug-induced granulocytopenia who developed intestinal infarction as the initial organ manifestation of disseminated aspergillosis before the onset of pulmonary symptoms or chest roentgenographic abnormalities.

Case Report

A 33-year-old man with acute myelogenous leukemia underwent induction therapy with cytosine arabinoside and daunomycin. Ten days later, the patient developed a fever with a temperature of 39.8°C and pancytopenia with a granulocyte count of 200 cells/µl. The physical examination was unremarkable and a chest roentgenogram was normal. Blood and sputum cultures were negative. Therapy was initiated with amikacin and ceftazidime, and when fevers persisted three days later, therapy with amphotericin B and vancomycin was started. Three days later, the patient became afebrile but developed a generalized maculopapular rash that prompted the discontinuation of all antibiotics. Treatment with fluconazole was started in consideration of the patient's apparent response to amphotericin B.

The patient remained well until one week later when fever (39.7°C) recurred during a second course of therapy with cytosine arabinoside and daunomycin. A chest roentgenogram remained normal and blood and sputum cultures were negative. Amikacin and vancomycin were started with resolution of febrile episodes two days later. During a third course of chemotherapy while still receiving antibiotics, however, the patient developed a fever with a temperature of 40°C associated with watery diarrhea (2,000 mL/day) and mild abdominal discomfort. The abdominal physical examination revealed mild tenderness without signs of peritonitis, and chest roentgenograms disclosed no abnormalities. Stool fungal and bacterial cultures and Clostridium difficile toxin assays were negative. Two days later, the patient developed more severe abdominal pain with signs of peritonitis and underwent an exploratory laparotomy that demonstrated a 10-cm length of necrotic distal ileum and a...
normal-appearing liver.

After resection of the necrotic bowel, the patient appeared to have improved with a clear postoperative chest roentgenogram. Twenty-four hours after surgery, however, a repeat chest roentgenogram revealed a new right upper lobe 3-cm nodular infiltrate. Pathologic examination of the resected bowel revealed transmural necrosis with branching hyphae invading arterioles (Fig 1). The patient rapidly deteriorated during the following 72 h with recurrent signs of peritonitis, fever, and hypotension despite extended antibiotic coverage with fluconazole, amphotericin B, vancomycin, amikacin, and metronidazole. The right upper lobe pulmonary infiltrate progressed with dense consolidation. At repeat laparotomy, extensive necrosis of large and small bowel was noted along with multiple liver nodules. The abdomen was closed, and the patient died the next day. Tissue cultures from the initial bowel resection subsequently grew *Aspergillus fumigatus*. The family refused an autopsy.

**Discussion**

The extraordinarily invasive nature of Aspergillus species in patients with hematologic malignancies promotes rapid spread of infection from localized sites to widespread disease that can involve any combination of organ systems. Fungal invasion of the gastrointestinal tract develops relatively frequently with a reported incidence as high as 47 percent in patients with disseminated aspergillosis. Antemortem detection of bowel involvement rarely is achieved, however, because the typical symptoms of abdominal pain, gastrointestinal hemorrhage, and polymicrobial bacteremia are nonspecific and overshadowed by other manifestations of disseminated disease. Only rarely does extensive fungal invasion of the bowel wall with associated perforation or infarction occasion a specific diagnosis of gastrointestinal aspergillosis during surgical evaluation of an acutely affected abdomen.

In most patients with gastrointestinal aspergillosis, a systemic mycosis is suspected because of the prominent pulmonary roentgenographic manifestations of fungal infection that almost invariably accompany disseminated disease. Because the airway is the commonest portal of entry for Aspergillus conidia, more than 94 percent of patients with localized invasive or systemic aspergillosis display features of lung involvement, most commonly in the form of necrotizing bronchopneumonia or hemorrhagic infarctions.

The isolated occurrence of gastrointestinal infection in the absence of pulmonary disease appears to be distinctly unusual in disseminated aspergillosis. Meyer and colleagues reported 23 patients with disseminated disease, 22 of whom had pulmonary infection and none of whom presented primarily with gastrointestinal manifestations. Similarly, Young and co-workers observed in 34 patients with disseminated aspergillosis at the National Institutes of Health that 32 patients had prominent lesions in the lung. Although one instance of fungal intestinal ulcerations in the absence of lung involvement was reported in this series, the patient had brain abscesses as an additional sign of a disseminated fungal disease. A single case report describes a patient with leukemia who presented with fever, abdominal pain, and diarrhea consequent to invasion of Aspergillus hyphae into the bowel wall. Results of preoperative and postoperative chest roentgenograms, however, are not described in the report.

The present patient represents a clear instance of gastrointestinal aspergillosis as the initial presentation of disseminated disease in the absence of roentgenographic manifestations of pulmonary involvement. The severe extent of intestinal infarction that preceded evidence of dissemination suggests that the bowel may have been the primary site of infection. A preexisting necrotizing enterocolitis may have disrupted mucosal barriers, providing a portal of entry for germinating Aspergillus spores. Subsequent free spread of hyphae through tissue barriers with invasion of mesenteric arteries, intravascular thrombosis and tissue infarction are characteristic features of Aspergillus infections. The patient's copious diarrhea may have been an expression of progressive enterocolitis or the initial manifestations of the bowel infarction.

The extreme mortality of disseminated aspergillosis, which approaches 90 percent in some series, mandates the rapid and often empiric initiation of amphotericin B to improve outcome in patients with presumed infection. Diagnosis and management have been enhanced during the last decade by the recognition of the typical patient profile of disseminated aspergillosis, which comprises a nonresolving febrile course with pulmonary infiltrates in an immunocompromised host after several days of broad-spectrum antibiotic therapy.

This patient with clinical manifesta-

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**Figure 1.** Top. Photomicrograph of the surgical specimen from the ileal resection showing A. fumigatus hyphal elements obstructing and invading through the wall of a submucosal muscular artery (hematoxylin-eosin, original magnification ×100). Bottom, The adjacent ileal submucosa demonstrates tissue infarction and hyphal invasion through the mucosal wall (hematoxylin-eosin, ×400).
tions of a preexisting enterocolitis indicates that invasive gastrointestinal aspergillosis may precede the usual pattern of presentation with pulmonary densities.

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REFERENCES

Atelectatic Lung Escaping Radiation Pneumonitis*
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An 80-year-old man was admitted to our division because of hemoptoem, cough, and chest pain for three months. A chest roentgenogram, chest CT scanning, and bronchoscopic examinations revealed adenocarcinoma of the lung with atelectasis of the right upper lobe. The patient developed radiation pneumonitis after receiving radiation therapy (5,100 cGy) for lung cancer. At the same time, the right upper lobe atelectasis improved and movement of infiltrates consistent with radiation pneumonitis to the middle lung fields occurred. A chest roentgenogram taken when the atelectasis had improved revealed the absence of pneumonitis shadows in the right upper lobe, suggesting that the atelectatic lung escaped radiation pneumonitis. (Chest 1992; 101:579-90)

CT = computed tomography

Severe radiation pneumonitis is an uncommon complication in patients receiving radiation therapy for intrathoracic malignancies in whom a localized disease is sometimes seen. The clinical syndrome that results consists of two phases: radiation pneumonitis, which occurs 6 to 12 weeks after radiation therapy, and radiation fibrosis, which occurs subsequently.1 Symptomatic radiation pneumonitis is a sporadic illness, which varies in severity from a troublesome cough to severe respiratory distress and even death.1,5 The changes in radiation pneumonitis generally are confined to only that part of the lung included in the radiation fields, but a previous report demonstrated bilateral reaction after unilateral irradiation.4 We recently encountered a rare case useful to a better understanding of the mechanisms by which radiation pneumonitis develops. The case history presents a very interesting patient who escaped radiation pneumonitis in atelectatic lung fields, although these were within the radiation therapy fields.

CASE REPORT
In March 1990, an 80-year-old man was diagnosed as having adenocarcinoma of the right upper lung with atelectasis and hilar-paratracheal adenopathy (T2N2M0, clinical stage 3), based on a chest roentgenogram (Fig 1, A), chest CT scanning and a transbronchial lung biopsy. The patient received radiation therapy (Fig 1, A, area within rectangle) for the intractable disease from March 19, 1990. When a total dose of 5,100 cGy in 25 fractions was delivered to the right upper lung fields and hilar disease by 10-mV linear accelerator x-ray, the patient complained of cough and mild dyspnea on exertion. Physical examination revealed a temperature of 37.9°C and a few fine crackles over the right upper lung fields. A chest roentgenogram taken on May 14, 1990, showed paramediastinal fluffy infiltrates which approximated the radiation therapy fields (Fig 1, B). These infiltrates were not present on earlier chest roentgenograms, including one performed on March 12 (Fig 1, A). Arterial blood gas levels on room air showed a PaO₂ of 71 mm Hg; PaCO₂, 41 mm Hg; and pH, 7.43. At this time, no clinical symptoms consistent with respiratory tract infections appeared. Extensive infectious evaluation was nondiagnostic. An empiric trial of antibiotic therapy was without clinical improvement. Radiation therapy was discontinued. A chest roentgenogram taken on May 23 revealed disappearance of the right upper lobe atelectasis and movement of infiltrates consistent with radiation pneumonitis to the right middle lung fields (Fig 1, C). A lateral view chest roentgenogram taken at the same time also showed infiltrates consistent with radiation pneumonitis in the right middle lobe (data not shown). Seventy days later, however, a chest roentgenogram taken on August 2 showed recurrence of the right upper lobe atelectasis due to tumor regrowth and movement of fluffy shadows to the right paramediastinal site (Fig 1, D). After two weeks there was resolution of all symptoms consistent with radiation pneumonitis and then the patient was discharged. However, the patient died of carcinomatous pleuritis and bacterial pneumonia on January 19, 1991.

COMMENT
Our results suggest that an atelectatic lung, despite being within radiation therapy fields, may escape radiation pneumonitis. During radiation therapy for intrathoracic malignancies x- or γ-rays excite electrons by collision with them.5 The accelerated electrons generate ion pairs and thence free radicals. In predominantly aqueous solution at neutral pH, similar to the cytoplasm of pulmonary parenchyma, the most abundant products are, in order, OH-, e⁻, H2O2, H2O, H⁺, and H2. Free radicals such as OH⁻ are very energetic and can produce breakage of covalent bonds in all molecules, small and large. Some of these changes are reversible but if oxygen is present, peroxidation of the molecular lesion may occur, leading to pulmonary damage. In our case, paramediastinal fluffy infiltrates should be distinguished from bacterial pneumonia. However, no clinical symptoms consistent with respiratory tract infections appeared through the patient's clinical course. Furthermore, extensive infectious evaluation was nondiagnostic and an empiric trial of antibiotic therapy was without clinical improvement.

There is considerable speculation concerning the effect

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CHEST / 101 / 3 / MARCH, 1992 879