0002-9270/87/8206-0563
THE AMERICAN JOURNAL OF GASTROENTEROLOGY

Vol. 82, No. 6, 1987
Printed in U.S.A.

Invasive Aspergillosis: An Unusual Cause of Hemorrhagic Pancreatitis

Karen S. Guice, M.D., Martin Lynch, M.D., and Lee Weatherbee, M.D.

Departments of Surgery and Pathology, Ann Arbor Veterans Administration Hospital, The University of Michigan, Ann Arbor, Michigan

Advances in chemotherapy have improved survival in patients with hematological malignancies, solid tumors, and have allowed for rapid progress in the field of organ transplantation. However, the frequency of opportunistic, specifically mycotic, infections has risen and provides a new challenge in the treatment of these patients. The following case report illustrates the need for early diagnosis and treatment and is the first known case reported of fatal hemorrhagic pancreatitis secondary to disseminated aspergillosis.

INTRODUCTION

Multidisciplinary care has significantly improved survival in patients with lymphomas, leukemias, and other hematological malignancies. Because these patients currently survive longer while immunosuppressed from chemotherapy, opportunistic infections are seen with increasing frequency (1, 2). Immunosuppressed transplant recipients and patients receiving chemotherapy for solid tumors also constitute populations at risk from opportunistic infections (12, 15, 16). Mycotic infections are the most frequent and the most difficult of the opportunistic infections to manage. Aspergillus is second only to *Candida albicans* as a pathogen in these immunosuppressed patients. In a recent review Meyer *et al.* (2) noted that the incidence of aspergillus infection has quadrupled since 1964–65. Previous reports have described aspergillus infections involving lung, brain, gastrointestinal tract, thyroid, heart, kidney, and skin (5, 8–10, 14). We recently cared for a patient who developed hemorrhagic pancreatitis as a consequence of disseminated aspergillosis.

CASE REPORT

A 63-y-old Caucasian man presented initially with fatigue and bilateral inguinal lymphadenopathy. Excisional biopsy of one inguinal lymph node revealed a diffuse histiocytic lymphoma. He was referred to the Ann Arbor Veterans Administration Hospital for diagnostic work-up and treatment. His physical examination was remarkable only for a single 2 cm right axillary lymph node. His only medications at that time were hydrochlorothiazide and potassium chloride supplementation. Evaluation included an abdominal CT scan, bone biopsy and marrow examination, and a thoracic CT scan. All of these were normal. The patient was therefore classified as having stage I_EA according to the Ann Arbor Staging Classification and was enrolled in the Southwest Oncology Group protocol 8503 (Table 1). He was begun on outpatient chemotherapy 2 wk after diagnosis. He developed insulin-dependent diabetes mellitus after 3 wk of chemotherapy. Ten wk after beginning chemotherapy he complained of increased fatigue and dizziness. A chest x-ray at that time was normal. The next week he was admitted to the hospital with dyspnea and fever. A repeat chest x-ray demonstrated bilateral apical infiltrates (Fig. 1).

His admission temperature was 100.2°C and room air blood gases revealed a pAO_2 of 44 torr, pCO_2 of 31 torr, and pH of 7.50. Multiple cultures of blood, urine, and sputum were taken after which broad spectrum antibiotics (mezlocillin, tobramycin, erythromycin, and trimethoprim) were begun. He required endotracheal intubation and mechanical ventilation the next day for progressive hypoxemia and hypercarbia. Bronchoscopy was performed but the findings of mild erythema and mucosal edema were nonspecific. No endobronchial or anatomic abnormalities were identified. Brochioalveolar lavage showed a preponderence of abnormal but nonspecific large lymphocytes, consistent with inflammation. Because of concern regarding pulmonary hypersensitivity to bleomycin, high dose steroids (methylprednisolone, 480 mg/day) were begun 2 days after admission. On the 8th hospital day the antibiotics were changed to cefataxime, erythromycin, and trimethoprim. He developed a pneumothorax that same day requiring tube thoracostomy. The suspected diagnosis at this time was a hypersensitivity reaction to chemotherapeutic agents, specifically bleomycin. Because of continued deterioration and concern of ongoing sepsis, a 12-day course of amphotericin B was initiated on the 10th hospital day. The following day Acyclovir was started because of the development of herpetic lesions around the mouth. All antibiotics were stopped on the 23rd hospital day, but vancomycin, mezlocillin, and

Received Dec. 2, 1986; accepted Jan. 12, 1987.

TABLE 1
Protocol 8503: Southwest Oncology Group

Cytoxan, 650 mg/M^2	Day 1
Adriamycin, 25 mg/M^2	Day 1
Etopiside, 120 mg/M^2	Day 1
Prednisone, 60 mg/M^2	Days 1–14
Aramycin-C, 300 mg/M^2	Day 8
Bleomycin, 5 mg/M^2	Day 8
Vincristine, 1.4 mg/M^2	Day 8
Methotrexate, 120 mg/M^2	Day 8
Leukovorin, 25 mg/M^2	Days 9–12

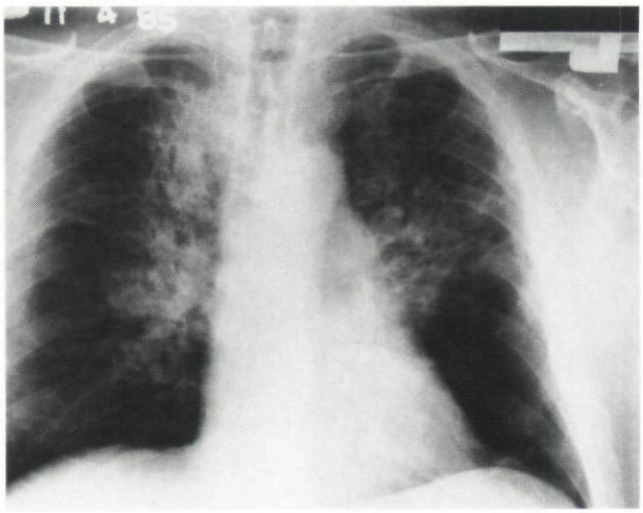

FIG. 1. Admission chest x-ray showing bilateral apical infiltrates.

tobramycin were started 4 days later for a worsening pneumonia. All cultures remained negative until the 6th wk of hospitalization when a sputum culture grew *Pseudomonas aeruginosa*. On the 38th hospital day thienamycin was begun. On the 25th hospital day the patient developed an upper gastrointestinal hemorrhage. Esophagogastroduodenoscopy demonstrated two small ulcers in the mid-body of the stomach. Two months after admission his hematocrit fell precipitously and he simultaneously developed a palpable mass in his right upper abdomen. Shortly thereafter he developed a fever of 103°C, hypotension, a tender right lower quadrant, and a distended abdomen. An abdominal CT scan showed peripancreatic edema and pancreatic enlargement in addition to ascites. Abdominal paracentesis was performed; the ascitic fluid contained 5,800 white blood cells per cm^3, 390,000 red blood cells per cm^3, and had an amylase of 2730 IU. An exploratory laparotomy was performed on the 70th hospital day because of the clinical coexistence of sepsis and hemorrhagic pancreatic ascites.

At exploration both old and fresh blood clot surrounding the pancreas were found. The clot extended into the right retroperitoneum from the pancreas to the iliac crest and had ruptured through the right mesocolon into the peritoneal cavity. The right colic artery and vein were thrombosed and the colon infarcted. The

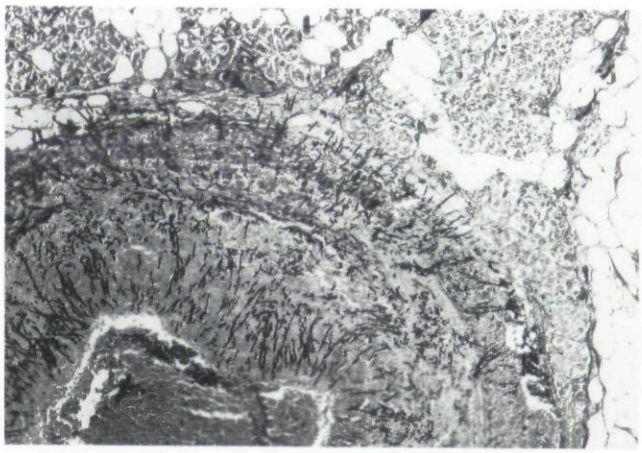

FIG. 2. Low power view of pancreatic artery with relatively recent thrombus. The silver methenamine stain demonstrates hyphae of aspergillus extending through the entire wall into adjacent adipose tissue and pancreas.

pancreas was hemorrhagic with extensive necrosis of the pancreas itself and saponification of the peripancreatic adipose tissue. The nonviable areas of pancreas and retroperitoneal tissue were debrided and a right colectomy with ileostomy and mucous fistula was performed. Multiple large drains were placed into the pancreatic bed and right retroperitoneum.

Postoperatively he was kept on clindamycin, thienamycin, and tobramycin. Despite fluid resuscitation and dopamine support he remained hypotensive. Forty-eight h after exploration the patient developed atrial-ventricular dissociation and required placement of a temporary transvenous pacemaker. Phentolamine and norepinephrine were added for persistent hypotension. He developed seizures, ventricular tachycardia, and progressive hypotension refractory to inotropic agents. He died on the 73rd day of hospitalization.

Autopsy demonstrated invasive pulmonary and disseminated systemic fungal infection. Microscopic identification of the fungus was consistent with aspergillus. Arterial thromboemboli containing fungal hyphae (Fig. 2) were present in the remaining pancreas. There was evidence of fungal atrial endocarditis, ventricular myocarditis, and pericarditis with fungal hyphae present in necrotic and viable myocardium. Thromboemboli were also present in the kidneys with evidence of fungal invasion into the parenchyma. Throughout the gastrointestinal tract submucosal vessels containing thromboemboli with fungal hyphae were identified.

COMMENTS

Aspergillus is second only to *Candida albicans* in frequency of mycotic infections among immunosuppressed patients (5, 7). Most of these infections occur in patients with hematopoietic malignancy but renal (12) and cardiac transplant patients and patients with collagen vascular disease and sarcoidosis are also at risk (6, 16).

The lungs are the most common site of infection and presenting symptoms usually include dyspnea, fever, tachypnea, and a nonproductive cough (6, 7). The pulmonary infection may present as an aspergilloma, necrotizing patchy bronchopneumonia, hemorrhagic pulmonary infarction, intraparenchymal abscess, or allergic bronchopulmonary pneumonia (6). Aspergillus is rarely cultured from sputum specimens whereas bronchial biopsies are more frequently positive (5)

Disseminated aspergillosis is classically defined as involving two or more noncontiguous visceral organs (6) as was present in our patient. Predisposing factors include a primary diagnosis of hematological or lymphoreticular neoplasia (3), neutropenia, corticosteroid therapy, or antecedent broad-spectrum antibiotic treatment (2). The association of aspergillus after a documented pseudomonas infection has been previously noted (2, 7). Patients may also have concomitant infections with candida, herpes, or cytomegalovirus (2, 7).

Of these predisposing factors, our patient had the diagnosis of lymphoma, had been on intermittent steroids as part of his chemotherapy protocol, and had been placed on broad-spectrum antibiotic regimen and high dose steroids at the time of his hospital admission and at multiple times during the course of his hospitalization. He additionally had both pseudomonas pneumonia and perioral herpetic lesions.

The gastrointestinal tract is often involved when aspergillus is disseminated but can also be the only site of fungal infection. The esophagus is most frequently involved, with ulcerative esophagitis being the most common lesion (6, 16). Cecal and small bowel ulcers have also been reported (6). Stomach ulcers may occur and, as in our patient, may be the source of significant blood loss.

Other reported sites of involvement, usually in the disseminated disease, include the central nervous system, thyroid, kidneys, liver, and skin (1, 2, 5). The characteristic histological finding is vascular invasion with thromboemboli containing typical fungal hyphae (2, 3).

Antemortem diagnosis of aspergillus infection is difficult (3). Rarely are sputum specimens positive. Bronchoscopy with bronchial biopsy has yielded a higher percentage of positive cultures. Blood cultures are seldom, if ever, positive (2). Demonstration of the characteristic branching hyphae on hematoxylin and eosin or methenamine silver stained tissue sections of biopsy material may be the only method of definitive diagnosis (7, 11).

Pancreatic involvement with disseminated aspergillosis is previously unreported. Furthermore, this patient developed clinically important disease, hemorrhagic pancreatitis with pancreatic ascites, as a result of his pancreatic aspergillosis.

Early aggressive treatment is mandatory for patients with invasive aspergillosis. Reduction of immunosuppression to the minimum is also important. Amphotericin B remains the drug of choice in invasive aspergillosis but is not highly effective (5). Recommended dosage for serious fungal infections is 0.5–1.0 mg/kg per day until a maximal total dose of 2.5–3.0 g is reached (7).

The most common clinical pattern is unremitting fever and persistence or worsening pulmonary infiltrates despite antibiotic treatment (11). If routine cultures are negative, bronchial or lung parenchymal biopsies may be necessary (13).

We have presented a case of disseminated aspergillosis in an immunocompromised patient. His illness includes pancreatic aspergillosis with hemorrhagic pancreatitis ascites. This unique clinical course is the first such case in the English literature.

Reprint requests: Karen S. Guice, M.D., Department of Surgery, Taubman Health Care Center, The University of Michigan, Ann Arbor, MI 48109.

REFERENCES

1. Fisher BD, Armstrong D, Yu B, et al. Invasive aspergillosis. Progress in early diagnosis and treatment. Am J. Med 1981; 71:571–7.
2. Meyer RD, Young LS, Armstrong D, et al. Clinical studies. Aspergillosis complicating neoplastic disease. Am J Med 1973; 54:6–15.
3. Hutter RVP, Lieberman PH, Collins HS. Aspergillosis in a cancer hospital. Cancer 1964;17:747–56.
4. Khoo TK, Sugai K, Leong TK. Disseminated aspergillosis. Case report and review of the world literature. Am J Clin Pathol 1965;45:697–703.
5. Prystowsky SD, Vogelstein B, Ettinger DS, et al. Invasive aspergillosis. N Engl J Med 1976;295:655–8.
6. Young RC, Bennett JE, Vogel CL, et al. Aspergillosis. The spectrum of the disease in 98 patients. Medicine 1970;49:147–73.
7. Salit I, Hand R. Invasive fungal infection in the immunosuppressed host. Int J Clin Pharmacol 1975;11:267–76.
8. Winzelberg GG, Gore J, Yu D, et al. Aspergillus flavus as a cause of thyroiditis in an immunosuppressed host. Johns Hopkins Med J 1979;144:90–3.
9. Henze G, Aldenhoff P, Stephani U, et al. Successful treatment of pulmonary and cerebral aspergillosis in an immunosuppressed child. Eur J Pediatr 1982;138:263–5.
10. McCormick WF, Schochet SS Jr, Weaver PR, et al. Disseminated aspergillosis. Aspergillus endophthalmitis, optic nerve infarction, and carotid artery thrombosis. Arch Pathol 1975;99:353–9.
11. Lynch JP III. Approach to the immunosuppressed patient with pulmonary infiltrates. Int J Dermatol 1980;19:577–84.
12. Gallis HA, Berman RA, Cate TR, et al. Fungal infection following renal transplantation. Arch Intern Med 1975;135:1163–72.
13. Mills SA, Wolfe WG. Opportunistic infections of the lung. Surg Clin North Am 1980;60:913–30.
14. Hamilton P, Darbyshire PJ, McKeever P, et al. Disseminated aspergillosis following radiation therapy for medulloblastoma. Postgrad Med J 1985;61:345–7.
15. Codish SD, Tobias JS. Trends in therapy. Managing systemic mycoses in the compromised host. JAMA 1976;235:2132–4.
16. Warren RE, Warnock DW. Clinical manifestations and management of aspergillosis in the compromised patient. In: Warnock DW, Richardson MD, eds. Fungal infection in the compromised patient. John Willey and Sons Ltd, 1982:119–53.