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PATHOLOGIC MANIFESTATIONS OF INVASIVE PULMONARY ASPERGILLOSIS IN CANCER PATIENTS: THE MANY FACES OF ASPERGILLUS

Brian A. Babbin, MD, John N. Greene, MD, Russell Vega, MD, Shohreh Iravani, MD, Ni Ni K. Ku, MD, and Ramon L. Sandin, MD, MS

From Emory University School of Medicine, Atlanta, Ga (BAB), Department of Infectious and Tropical Diseases (JNG) and the Pathology Service (NNKK, RLS) at the H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida, Tampa, Fla, Hillsborough County Medical Examiner’s Office, Tampa, Fla (RV), and the James A. Haley Veterans’ Hospital, Tampa, Fla (SI).

Introduction

Invasive pulmonary aspergillosis (IPA) is a fulminant and highly lethal infection of severely immunocompromised patients with a reported mortality rate of approximately 60%. Patients who are at considerable risk include those who are granulocytopenic due to bone marrow transplantation, those who are undergoing intensive cytotoxic chemotherapy for the treatment of neoplasia, and those with a history of corticosteroid use. Four decades ago, aspergillosis was a rare infection, even among immunosuppressed patients. Reports of fungal infection complicating malignant disease began appearing in the late 1950s and early 1960s. Since that time, the incidence of IPA has dramatically increased due to several possible reasons: an increase in the number of immunosuppressed patients, more intensive chemotherapies that result in prolonged neutropenia, and better control of bacterial infections. IPA is a major problem clinically because accurate diagnosis is difficult, the therapy is toxic, and the high mortality rate associated with this infection is high.

The pulmonary manifestations of IPA are variable. These range from solitary or multiple nodular infarctions with discrete spherical appearances to necrotizing/abscess-like lesions in which the lung parenchymal tissue drops out, leaving a cavitary deficit. A myriad of other manifestations exist between these two extremes. The following two cases exemplify these two extremes in the continuum of pulmonary manifestations of aspergillosis.

Case 1

A 39-year-old woman with a history of poorly differentiated infiltrating ductal carcinoma of the left breast initially presented with bronchitis, rib pain, fatigue, and cough. A subsequent biopsy revealed multiple bone lesions diagnosed as metastatic adenocarcinoma. She underwent a trial of ifosfamide, carboplatin, and etoposide (mini-ICE) chemotherapy, and she subsequently underwent ICE chemotherapy and autologous bone marrow transplantation. Following her transplant, she had partial marrow engraftment with increasing white blood cell counts, but she developed pneumonia and respiratory insufficiency. Chest radiographs revealed bilateral pleural effusions, and sputum studies were positive for Aspergillus. In addition, oral secretions were positive for herpes simplex virus. There was no evidence of metastatic carcinoma in the lungs. Despite aggressive treatment, she had a progressively downhill course, eventually developing hepatic failure and veno-
occlusive disease. Her clinical status continued to worsen, and she subsequently died.

At autopsy, the patient was found to have multiple subpleural nodular infarcts (2.0-3.5 cm) in the right lung, two in the right upper lobe, and one in the posterolateral middle lobe (Figs 1-5). A single nodular infarct in the left posterior upper lobe also was identified. Bilateral effusions were present, with the right-sided effusion more prominent and exudative. Fibrinopurulent adhesions along the posterior and basal surfaces of the right lung were evident as well as subpleural fibrosis and minimal interstitial fibrosis. The tracheobronchial tree contained a moderate amount of thick, gray-brown tenacious mucus. Microscopic examination of the lungs revealed bilateral patchy pneumonia with occasional multinucleated giant cells but no intranuclear or cytoplasmic inclusions suggestive of a viral process. The right pulmonary nodules consisted of necrotic lung with dense infiltration of fungal ele-
ments (Fig 6). Numerous septated hyphal elements were identified in the infarcted tissue, some invading the vasculature and demonstrating oriented, dichotomous branching at a 45° angle. Figs 7–9 show clear evidence of fungal transgression of the vessel wall from the lung parenchyma into the vessel lumen. This phenomenon is associated with intraluminal thrombi, tissue ischemia, and infarction. Postmortem pulmonary cultures were negative for viruses, acid-free bacilli, and Nocardia and were positive for A. terreus. A solitary fungal abscess was identified in the myocardium of the interventricular septum. The heart otherwise showed no other changes suggestive of infarction, congestive heart failure, a more diffuse myocarditis, or endocarditis/pericarditis. However, a mild lymphocytic infiltrate of the myocardium of unclear etiology was seen. The liver was markedly enlarged (2,700 g) and bile was stained with prominent, diffuse centrilobular necrosis. There was also congestion of the hepatic sinusoids. Although a mild inflammatory infiltrate was present, no other findings of acute or chronic active hepatitis were detected, and there was no evidence of hepatic vascular thrombosis by the fungus. These findings were consistent with early fulminant veno-occlusive disease. In conclusion, the patient died of disseminated aspergillosis infection with severe pneumonia, remarkable pulmonary nodular infarcts due to A. terreus, and fulminant veno-occlusive disease following autologous bone marrow transplantation.

Case 2

A 43-year-old man with a history of tobacco use, alcohol/drug dependence, and hepatitis B and C was found to have bony destruction of the SI–S2 vertebrae after complaining of persistent back pain. Fine-needle aspiration biopsy performed at our institute showed a poorly differentiated adenocarcinoma of unknown primary. The tumor cells were subsequently found to be positive for low-molecular-weight cytokeratin and epithelial membrane antigen and focally positive for vimentin and carci-noembryonic antigen. The tumor cells were also negative for S-100, alkaline phosphatase antigen, prostate-specific antigen, prostatic-specific acid phosphatase, and mucin. This suggested the thyroid as a source of the neoplasia. A computed tomography (CT) scan of the chest revealed multiple bilateral pulmonary nodules, the largest posterior to the left hilum (2.1 ×
2.0 cm), and mediastinal adenopathy. An abdominal CT scan revealed a right adrenal mass, and a pelvic CT scan showed the aforementioned sclerotic lesions of the sacral and iliac bones. Ultrasound examination of the kidneys showed areas of low attenuation bilaterally.

The patient was treated with localized irradiation of the pelvic area for 2 weeks before presenting at our center with a 1-week history of shortness of breath, anorexia, hemoptysis, weakness, increasing confusion, and lower extremity edema. The patient was in severe respiratory distress upon presentation. Fiber-optic bronchoscopy revealed edematous, friable airways, and a polypoid lesion of the superior segment of the left lower lobe. Bronchial washings and sputum were positive for \textit{A. fumigatus}. Subsequent chest radiographs disclosed a large right pleural-based nodule measuring up to 5 cm and a small right hilar mass that appeared to have significantly increased in size compared with prior studies. The pulmonary nodules were believed to represent metastatic disease or pulmonary aspergillosis with associated post-obstructive pneumonia or both. Treatment with amphotericin B was initiated.

Mild macrocytic anemia with severe thrombocytopenia and severe lymphopenia was observed. The patient exhibited mental status changes, and he became progressively lethargic. He continued to exhibit shortness of breath with hypoxic episodes and low-grade fevers. The patient died with a preliminary clinical diagnosis of respiratory distress secondary to pulmonary aspergillosis.

At autopsy, the most significant findings were severe bilateral, necrotizing, cavitary, and hemorrhagic pulmonary aspergillosis with microabscess formation, systemic aspergillosis with microabscesses in multiple organs including thyroid gland, left ventricle and septum of the heart and right and left kidneys, and bilateral basal ganglia. Grossly, the lung parenchyma showed diffuse areas of consolidation and multiple cystic areas of degeneration. There were bilateral cavitary/necrotizing areas of abscess formation with tissue liquefaction and a rim of fibrosis significantly replacing lung parenchyma. Some of the discrete abscess cavities measured 4-5 cm (Figs 10 and 11). Microscopically, the lungs demonstrated extensive coagulative necrosis, necrotic inflammatory debris, intraalveolar hemorrhage with hemosiderin-laden macrophages, and numerous septated fungal hyphae exhibiting 45° branching. Infiltration of large-caliber vessels with fungal elements was observed. Reactive epithelial cell atypia and focal pneumocyte hyperplasia, as well as moderate to severe emphysematous changes, were present.

The patient also had a 1.5-cm oval encapsulated nodule on the superior aspect of the left lobe of the thyroid in addition to the \textit{Aspergillus} microabscess. Microscopically, sections through the nodule revealed the presence of papillary thyroid carcinoma with focal anaplasia. This was the source of the carcinoma destroying the S1-S2 vertebrae, and it had also metastasized to the right and left kidneys as well as to mediastinal lymph nodes.

**Discussion**

The variability in the gross pathologic pulmonary manifesta-
tions of IPA can be attributed to several factors. One is the site of initial infection. Aspergillus can invade any tissue in the body. Depending on where the invasion begins, this infection can have disease processes that appear different. IPA has been classified into distinct clinicopathologic forms that include acute bronchopneumonia, acute tracheobronchitis, and pleural aspergillosis. These disease processes overlap, and ultimately the manifestations represent a continuum, which is another factor accounting for variability in gross findings. This continuum is explained by the general pathogenesis of this infection in the immunocompromised host. As the infection progresses, many different gross manifestations can occur. After conidia normally present in the atmosphere are inhaled, spores germinate and hyphal elements invade the surrounding tissue, whether it be in the tracheobronchial tree or in the alveolar space. This generally produces an acute necrotizing pyogenic pneumonitis. It is important to note, however, that severely neutropenic immunocompromised hosts may not produce a marked pyogenic pneumonic response. The vasculature is then invaded, which can result in hemorrhage, thrombomycotic occlusion with resultant ischemic infarction, or hemorrhagic infarction.

If angioinvasion induces ischemia, the result is the formation of the nodular pulmonary infarct as exemplified in Case 1. These infarcts are more often multiple than solitary. They are composed of a discrete spherical zone of ischemic necrosis that is often centered on an occluded blood vessel and may be surrounded by a peripheral rim of hemorrhage. This tissue is densely infiltrated with hyphae and undergoes separation from adjacent tissue resulting in an intracavitary sequestrum of necrotic tissue (pseudomyxoma). The necrotic material can then undergo liquefaction and drain into the involved airway, leaving a cavitary deficit. Mediators of infarcted tissue degradation include autolysis, proteolysis from neutrophil enzymes, elastolysis by Aspergillus elastase, and phagocytosis by macrophages and giant cells. Nodular infarcts that have cavitated may then be infiltrated with hyphae resulting in mycetoma formation. Pulmonary vascular invasion resulting in hemorrhagic infarctions usually produces a large, wedge-shaped lesion that is pleural based with visible thrombosed vessels. Hemorrhage can result in consolidation of a lobe or portion of a lobe, and along with fungal elements and an inflammatory infiltrate, the gross appearance of a lobar pneumonia may result. Another consequence of angioinvasion is hematogenous dissemination (which occurred in both cases presented) that can produce lesions anywhere in the body including cartilage and bone. However, lesions are typically produced in the central nervous system, myocardium, kidneys, liver, spleen, and gastrointestinal tract.

A landmark experimental and pathologic study by Shibuya et al emphasized the key role of the neutrophil in determining the type of pathology that is produced in different patients by pulmonary aspergillosis. In neutropenic patients, the most frequent finding is that of the large, round nodule with numerous hyphae and abundant coagulative necrosis but without an inflammatory cell response. On the contrary, patients showing a neutrophilic response most frequently manifested lesions with central liquefactive necrosis, tissue drop-out, cavity formation, proliferating hyphae around the lesion, and prominent neutrophilic infiltrate. Both cases reported in this paper were unusual for IPA in several aspects: both had solid rather than hematologic tumors, neither had received corticosteroid therapy, and neither had remarkable prior bacterial infections. The first patient, however, had undergone bone marrow transplantation and was neutropenic. The second case had no apparent predisposing factor other than the extent of dissemination of a solid neoplasia.

Conclusions

Given the nature of IPA in the immunocompromised patient, a myriad of gross pulmonary pathologic manifestations may ensue. The major problem to successful management of IPA arises from the difficulty in establishing the diagnosis. In the immunocompromised host, fever and a pulmonary infiltrate can be induced by many infectious complications. Moreover, many patients suspected of having IPA cannot withstand inva-
sive procedures to obtain a tissue specimen. Empiric therapy has been unwarranted in the past because of drug toxicity. However, liposomal formulations of amphotericin B have become drugs of choice for empirical and preemptive treatment of suspected invasive aspergillosis. Attempts have also been made to reach a diagnosis serologically, and many centers worldwide now use Aspergillus antigen testing in serum and polymerase chain reaction as a screening test and as a means to confirm other parameters. At the microscopic level in a histopathologic specimen, a fungus with the usual septated, bifurcating hyphae could be one of several Aspergillus look-alikes, such as Penicillium, Fusarium, Paecilomyces, Pseudallescheria, and Scedosporium, and experimental use of specific immunohistochemical stains could be an improvement. The diagnosis of IPA is best made with identification of species of fungi recovered in culture that are histologically compatible with the organism observed in a tissue specimen. This has become even more important, with the increasing frequency of molds that look like Aspergillus in tissue but are resistant to amphotericin B, such as isolates of the genera Pseudallescheria and Scedosporium.

References