Case of the Month: April’s Diagnosis

Invasive Aspergillosis

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This patient had a satisfactory course for the first 3 years after orthotopic hepatic transplantation for cirrhosis secondary to chronic infection by hepatitis C virus (HCV), the disease for which hepatic transplantation is most commonly performed. He presented with a 1-week history of fever, chills, malaise, productive cough, and a Pseudomonas urinary tract infection that was treated appropriately with antibiotics. In addition, he had hyperbilirubinemia and evidence of acute and chronic rejection on hepatic biopsy at the time of admission. (We have not been told about the antirejection medications he was taking at the time.) After treatment with steroids, he developed progressive acute on chronic renal failure and coagulopathy. Methicillin-resistant Staphylococcus aureus (MRSA) bacteremia followed. Shortly thereafter, he developed pericardial effusion requiring treatment. Cardiac arrhythmias, hypoxemia, and pancytopenia also developed, and mental status declined. Chest radiography demonstrated alveolar infiltrates in both upper lobes, focally ill-defined alveolar infiltrates in the right lower lung, and atelectasis in the left lower lobe. A magnetic resonance imaging (MRI) scan of the brain showed multiple nonenhancing acute infarctions. His medical history revealed diabetes and nephrolithiasis; interestingly, biopsy of sigmoid colon polyps revealed histoplasmosis.

This immunosuppressed patient developed a documented urinary tract infection, concurrent infection of the hepatic graft, rejection, and failure, followed by progressive multisystem organ failure and death.

Three general categories of diseases causing multisystem organ failure must be considered as potential explanations for the patient’s clinical course: (1) unusual neoplastic syndromes, (2) inflammation/rejection, and (3) infection.

Patients who have undergone solid-organ transplantation are at increased risk for certain neoplasms, especially lymphoproliferative diseases. Epstein-Barr virus (EBV) infects B-lymphocytes in up to 90% of the population. EBV-infected B-lymphocytes undergo many rounds of proliferation within the T-cell population. If the immune system has successfully eliminated the initial EBV infection, reactivation does not occur, except in transplant patients and others with severely suppressed immune systems. At least 50% of solid-organ transplant patients harbor the virus in the oropharynx, and are at risk for EBV-associated lymphoproliferative disorder, with at least 5% of all patients developing the disease. Additional neoplasms with widespread system involvement, as seen in this patient, include other lymphomas, Kaposi’s sarcoma, metastatic solid tumor, and leukemia. Some features of the patient’s current presentation — bilateral pulmonary infiltrates and multiorgan involvement — could be caused by this disease, but the predominant apical nature and the computed tomography (CT) scan of the head are not typical. EBV-associated disease can occur after transplantation and can be rapidly progressive; typically, the onset would be soon after transplantation. This diagnosis was therefore excluded.

Causes of fever, pulmonary infiltrates, and organ failure that are neither infectious nor neoplastic could include pancreatitis, chronic thromboembolism, collagen vascular disease, and amyloidosis, among others. Organ rejection, necrosis, and superinfection could explain the patient’s general course. No elevations in serum amylase were reported, nor was abdominal tenderness or radiological evaluation of his abdomen. The head CT findings would then have to result from a separate process. Chronic thromboembolism, collagen vascular disease, and amyloidosis are systemic diseases that could mimic some of the findings in this patient, but none of them is likely to be the cause of his multisystem failure in light of his known diagnoses.

The remaining discussion focuses on infectious processes that could explain this patient’s clinical picture. The risk of infection in transplant patients can generally be thought of as having 2 components: the intensity of exposure to a potential pathogen, and the net state of immunosuppression. Even minimal environmental exposure to a pathogen of low virus load can cause invasive infection in a patient with a maximal level of immunosuppression; exposure occurs both in the community and in the hospital. Community exposure includes current and remote exposure to geographically restricted systemic mycoses (such as Blastomyces dermatitidis, Coccidioides immitis, and Histoplasma capsulatum); Mycobacterium tuberculosis; and Strongyloides stercoralis. Short-term community exposure may involve respiratory viruses and food-borne pathogens. Excessive environmental exposure can occur through contamination of air or potable water with pathogens such as Aspergillus, Legionella, or gram-negative bacteria such as Pseudomonas aeruginosa. Outbreaks of van-
comycin resistant enterococcus (VRE), MRSA, and Clostridium difficile are well described.

The net state of immunosuppression is related to the dose, duration, and temporal sequence of individual agents, the presence or absence of infection with human immunodeficiency virus (HIV) and other immunomodulating viruses (cytomegalovirus [CMV], EBV, hepatitis B [HBV]), as well as to the residua of any technical complications of the transplant. Prescribed posttransplant medications, HCV, and recent steroid boluses contributed to the net state of immunosuppression in this patient.

The span of time between transplant surgery and onset of infection is generally helpful for categorizing the pathogens that are likely to be involved. Certain infections occur within 1 month of transplantation, others within 2 to 6 months, and others 6 months after surgery. Viral infections can be transmitted from the donor to the recipient early after transplantation, as was the case with the unusual, recent transmission of the West Nile virus. More typically, however, we are concerned about transmission of bacteria and fungi from the donor to the recipient. If the donor organ is infected, vascular infection, mycotic aneurysms, and catastrophic rupture can occur. Even when the recipient’s immune system is not compromised, more than 90% of infections during the first month after transplant surgery are secondary to bacterial or fungal infections of the surgical wound, of the lungs and urinary tract, or are due to the catheters.

During the 2 to 6 months following transplantation, additional infectious etiologies must be considered. The immunomodulating viruses CMV, EBV, HBV, and HCV begin to exert clinically significant effects. The combination of sustained immunosuppression and viral infection makes possible opportunistic infections such as Pneumocystis carinii, Aspergillus, and Listeria monocytogenes even in the absence of an excessive environmental hazard.

More than 6 months have passed since this patient underwent transplantation. In a patient who is doing well, immunosuppressive therapy is minimized and infections, most commonly respiratory, are those of the general community. Opportunistic infection is unusual unless environmental exposure is intense. At least 10% of patients have chronic or progressive infection with HBV, HCV, CMV, or EBV, or papillomavirus. In another 5% to 10% of transplant recipients, recurrent or chronic rejection develops. The consequent exposure to steroids renders patients vulnerable to chronic viral infections. Such patients are at greatest risk of opportunistic infections, including invasion by P carinii, L monocytogenes, Nocardia asteroides, Cryptococcus neoformans, and Aspergillus. This patient’s immunomodulating virus (HCV) and recent steroid boluses placed him at special risk for opportunistic infections as well as for common bacterial infections.

**Disease Course**

The course of this patient’s disease can be approached by examining specific organ dysfunction, time course, and possible pathogens.

This patient entered Johns Hopkins Hospital with a urinary tract infection and developed progressive renal failure, pericarditis, and sepsis. Given his history of renal calculi early in the course of his hospitalization, the physician would have obtained a renal ultrasound to rule out an obstructed infected kidney as a cause of both infection and renal failure. Certainly, pericarditis and rhythm disturbances could be related to the progression of renal failure. In addition, the calcineurin inhibitors can be associated with renal insufficiency and at the same time have many cytochrome P450 drug interactions. Thus while drug toxicity may have had a role in the patient’s chronic renal insufficiency, these agents were not likely the cause of his acute renal failure. His chronic renal failure could also have been related to his diabetes. His acute renal failure was most probably associated with progressive hepatic failure and sepsis.

His progressive hepatic insufficiency was secondary to both recurrent HCV infections and mild-to-moderate rejection. Recurrence of HCV occurs with 10- to 20-fold levels of viremia in virtually all patients after liver transplantation. The natural history of this hepatitis is characterized by progression to cirrhosis in 6% to 23% of patients at a median of 3 to 4 years after transplantation. The development of cirrhosis is associated with reduced graft and patient survival rates. Several studies have demonstrated that the degree of immunosuppression — defined as the number of methylprednisolone boluses administered, use of antilymphocyte globulin, and total cumulative dose of corticosteroids — is strongly associated with both a greater incidence of recurrent hepatitis C and a more aggressive course. Many centers have chosen to implement immunosuppressive regimens with rapid steroid withdrawal. However, this recent change in therapy has not proven effective. Recent studies suggest that despite rapid steroid withdrawal, the progression from hepatitis C to cirrhosis has occurred at a more rapid pace in recent years. In this patient, HCV recurred and the transplant was rejected, necessitating that he be treated repeatedly with high-dose steroid therapy. Therefore, we must consider whether his subsequent prolonged hospital course is related to a different acquired infection, reactivation of a known infection, or simply progression of his underlying hepatic and, consequently, renal diseases.

While in the intensive care unit, the patient developed S aureus bacteremia. We are not told whether it was associated with a vascular catheter. S aureus is a common nosocomial pathogen and frequently is associated with vascular catheters and endovascular and pneumonic processes. We are told that he had a single blood culture that was positive for this pathogen. While S aureus has a propensity for metastatic infection and could easily have been involved in a myocardial or valvular infection with subsequent embolism to the brain, this explanation is unlikely with a single positive blood culture. Furthermore, the character of the brain lesions is not typical. For an embolic infectious source, we would expect a lesion to have some aspect of rim enhancement. In addition,
the echocardiography study does not tell us about a valvular lesion. A transesophageal study would have provided a more definitive answer to this question than the transthoracic study that was most probably performed. S aureus could cause focally ill-defined, bilateral alveolar infiltrates to be present in the upper lobes. However, S aureus grows easily in culture and the pattern of infection is more typically lobar, and only rarely miliary in origin. A negative bronchoalveolar lavage makes it unlikely that the cause was S aureus pulmonary infection with septic shock and progressive end-organ failure with metastatic lesions to the brain.

Possible Diagnoses

We must now consider the remaining symptoms, signs, and laboratory and radiological information. This patient had bilateral alveolar infiltrates concentrated in the upper lobes, which had progressed rapidly since admission. We must remember, however, that at his original presentation he had a cough, fever, and malaise, and that he arrived with a mild headache but without visual disturbance. He also had declining mental status, with multiple infarcts not restricted to a specific intracranial distribution, likely indications for a hematogenous source of emboli or necrotizing infection. Therefore, we will want to consider diseases that are characterized by both of these processes. Although his pericardial disease could be explained by progressive renal failure and uremia, we will want to additionally consider diseases that also involve the pericardium and possibly the myocardium. We will want to review diseases that are associated with bone marrow suppression or involvement, and those that are more likely to occur and rapidly progress in patients with immunosuppression and bone marrow suppression.

Apparent trivial complaints such as a persistent dry cough may prove to be an early sign of impending pneumonia from Aspergillus, respiratory syncytial virus, or influenza virus. Thoracic CT scans are more sensitive for detecting pulmonary infiltrates compatible with aspergillosis than are chest radiographs. We will come back to this diagnosis.

Bronchoalveolar lavage (BAL) specimens from patients with pulmonary infiltrates should be subject to a battery of tests: smears for P carinii, the acid-fast bacilli and Nocardia spp, bacteria, and molds; and cultures for fungi and bacteria, including Legionella spp, Mycobacterium spp, Nocardia spp, and for respiratory viruses (influenza and parainfluenza viruses, adenovirus, respiratory syncytial virus [RSV], and CMV). Rapid assays by enzyme-linked immunosorbent assay, direct fluorescent antibody, or dot blot are also available for some of these viruses. Nasopharyngeal swabs can detect RSV and can be tested using one of the rapid assays. While RSV could explain the pulmonary infiltrates, there is no report of any coryza, or nasal congestion. In addition, outbreaks of RSV typically occur in the Baltimore area from November to April, not in May, as in this case. Parvovirus can explain the patient’s bone marrow suppression but is not likely to explain the complex of remaining symptoms. CMV, either primary or reactivation disease, is common in transplant patients but tends to occur in the 2- to 6-month period following transplantation. However, reactivation can occur with episodes of immunosuppression. Pneumonitis, bone marrow suppression, retinitis, esophagitis, hepatitis, myopericarditis, meningitis, and encephalitis can all be present with CMV disease. While most of this patient’s clinical picture could be explained by CMV reactivation, and he was at risk, the timing of the disease is unusual, and the CT findings are not typical. We are not told of a positive antigen or other confirmatory invasive biopsy.

Many organisms are transmitted through the air from the physical environment, particularly fungi such as Aspergillus, Coccidioides, Histoplasma, and Cryptococcus. Aspergillus, cryptococcal, and nocardial infections are seen in all geographic regions, but posttransplantation coccidioidomycosis is usually a problem of certain endemic regions. Baltimore is not among them; coccidioidomycosis will not be considered further.

The major presenting symptoms of P carinii pneumonia in the compromised host are shortness of breath, fever, and a nonproductive cough. On physical examination, tachypnea and tachycardia are found in acutely ill patients. The chest radiograph classically exhibits bilateral diffuse infiltrates extending from the perihilar region. Atypical manifestations have ranged from normal films to unilateral infiltrates, nodules, cavities, pneumatoceles, lymphadenopathy, and effusion. Extrapulmonary P carinii has been occasionally reported, especially in HIV patients. Among the focal manifestations of extrapulmonary pneumocystosis are a rapidly enlarging thymic mass, pancytopenia from bone marrow necrosis, retinal cotton-wool spots, polyloid lesions in the external auditory canal, pleural effusion, numerous hypodense lesions in the spleen on computed tomography, and punctate calcifications in the spleen, liver, adrenals, or kidney. Because lesions outside the lung are unusual, this diagnosis will be excluded from further consideration.

Nocardiosis always should be considered — along with other actinomycetes (eg, M ycobacterium, Actinomyces spp.) and eumycetes (eg, C neoformans, Aspergillus spp) — in the differential diagnosis of indolent pulmonary disease, particularly in the setting of cellular immune compromise. Pulmonary disease is the predominant clinical finding of nocardia (more than 40% of reported cases) with almost 90% of such cases caused by members of the N asteroides complex. Clinical manifestations of established infection include endobronchial inflammatory masses, pneumonia, lung abscess, and cavitary disease with contiguous extension to surface and deep structures, including effusion and empyema. Radiological manifestations include irregular nodules (usually cavitating when large), reticulonodular or diffuse pneumatic infiltrates, and pleural effusions. In immunosuppressed patients, pulmonary nocardiosis may occur as alveolar infiltrates rather than cavitary disease. Clues to a nocardial etiology include spread to contiguous structures, especially with soft tissue swelling or external fistulas, and to the central nervous system (CNS). This disease frequently progresses over
months to years. Disseminated infection is characterized by widespread abscess formation. The most commonly reported sites include the CNS and eyes (particularly the retina), skin and subcutaneous tissues, kidneys, joints, bone, and heart. Typically the CT study will show a mass lesion often confused with a neoplasm. The absence of skin lesions, the lack of information about the eye examination, and the lack of a typical CT scan will remove this cause from additional consideration.

The course of toxoplasmosis in almost all immunocompetent individuals is relatively benign, but it is a serious and often life-threatening disease in immunodeficient patients. Toxoplasmosis in these patients may be due either to newly acquired or to reactivated latent infection. In immunosuppressed patients with toxoplasmosis, 76% have CNS involvement, 58% have myocardial involvement, and 23% pulmonary involvement. Toxoplasmosis with multiorgan involvement, manifesting with acute respiratory failure and hemodynamic abnormalities similar to septic shock, has been reported. The characteristic presentation usually has a subacute onset with focal neurologic abnormalities in 58% to 89% of patients. However, in 15% to 25% of cases, the clinical presentation may be more abrupt, with seizures or cerebral hemorrhage. The diagnosis may be made by demonstration of the parasite in BAL fluid. Illness may be clinically indistinguishable from Pneumocystis carinii pneumonia (PCP). Extrapulmonary disease may be present in about 50% of patients with toxoplastic pneumonitis. Though a CT scan may be normal, a classic ring-enhancing lesion is typically seen. The BAL in this case did not reveal this pathogen, making it unlikely. Moreover, exposure to a source of this parasite (e.g., a cat) is not described, so this diagnosis will be set aside as well.

The onset of CNS cryptococcosis may be acute or insidious. Acute manifestations are more common in persons receiving corticosteroids. Symptoms may be referable to the CNS, although they may be mild, nonspecific, and include headache, irritability, clumsiness, and obtundation. Most patients have minimal or no nuchal rigidity. Papilledema is noted in up to one third of cases, and cranial nerve palsies in about one fifth. Visual loss may be total. Pulmonary cryptococcosis may be asymptomatic or may cause the production of only scant, sometimes blood-streaked, sputum. Patients may present with cough and dyspnea. Single or multiple skin lesions may be found in 5% to 10% of patients. There have been no reports of skin lesions and no reports of a potential exposure to bats or to pigeons.

CT or MRI findings may be normal or reveal diffuse atrophy, cerebral edema, hydrocephalus, or focal mass lesions. Multiple nonenhancing lesions may be present, most often in the basal ganglia and thalamus, but sometimes at other sites, including infratentorial areas. On T2-weighted MRI, nonenhancing parenchymal cryptococcomas may also be associated with nonenhancing, hyperintense, dilated perivascular Virchow-Robin spaces. Even in asymptomatic patients, CT or MRI studies may find diffuse atrophy or cerebral edema, as revealed by focal homogeneous or doughnut-shaped, contrast-enhanced areas; these areas may be present with or without surrounding circumferential areas of decreased density. Cryptococcal masses must be distinguished from other causes of such intracranial mass lesions, including pyogenic, necocardial, or Aspergillus-associated abscesses; tuberculosis; toxoplasmosis; hemorrhage; and lymphoma or other neoplasms. To make these determinations, MRI, particularly with gadopentetate dimeglumine enhancement, is more sensitive than CT scanning. Multiple small enhancing subarachnoid or parenchymal nodules may be present. Various other patterns are seen less often, including segmental pneumonia, thick-walled single cavities, lymphadenopathy, pleural effusion, and generalized miliary disease. The clinical findings in such patients are often indistinguishable from those of patients with acute pneumonia caused by P carinii, M tuberculosis, H capsulatum, or other organisms. Bronchoscopy with washings and brushings is usually diagnostic but, since we are not told of this on the BAL report, this diagnosis will be excluded as well.

With an appropriate remote history or with environmental exposure, development of primary (or reactivation of Mycobacterium) tuberculosis could explain this patient's diffuse systemic involvement and bone marrow suppression. Tuberculous pericarditis is most often caused by extension from a contiguous focus of infection, usually mediastinal or hilar nodes, but also the lung, spine, or sternum. Less commonly, it occurs during miliary tuberculosis. Tuberculous pericardial fluid demonstrates many of the characteristics of tuberculous pleural fluid, with acid-fast smears rarely being positive, and cultures being positive in approximately 50% of cases. Postprimary pulmonary tuberculosis in adults is usually asymmetric and characterized by caseation, cavity formation, and fibrosis. It begins as a patch of pneumonitis in the subapical posterior aspect of an upper lobe, usually just below the clavicle or first rib. Bronchogenic spread may establish foci of infection in the lower lobe and anterior portions of the upper lobe, producing a polymorphous motting on chest roentgenogram. CNS involvement from Mycobacterium is usually a meningeal rather than a necrotizing lesion as seen in this case. Thus on the basis of no previous history, no known exposure, and an apparent negative BAL, this diagnosis will also be excluded.

Listeria may arise from contaminated food sources, but a source is rarely identified in the sporadic cases of meningitis that are seen in patients who have undergone transplantation. Many patients with listerial bacteremia or CNS infection give a history of antecedent gastrointestinal symptoms, including diarrhea, nausea, and vomiting, often accompanied by fever. Listerial endocarditis accounts for about 7.5% of adult listerial infections and can produce both native valve and prosthetic valve disease. It has a high rate of septic complications and a mortality of 48%. Although pleuropulmonary infection can occur, it is not a hallmark of the disease. In addition, the typical CNS presentation of meningitis involves seizures,
CASE OF THE MONTH

Histoplasmosis

Patient was known to have had meningitis but are often present independently. Although this trast medium. Histoplasmomas may be associated with exhibits ring enhancement with the administration of contrast material. Therefore, we need to consider whether either acute or subacute histoplasmosis could account for this clinical picture. In acute progressive disseminated histoplasmosis (PDH), the onset usually is abrupt. Fever and malaise are the two most common manifestations, followed by weight loss, cough, and diarrhea. Physical findings include hepatosplenicomegaly in nearly all patients, lymphadenopathy—especially of the cervical chain—in about 30%, and rales. Jaundice is observed in a minority of cases, and oropharyngeal ulcers may be seen. Anemia, leukopenia, and thrombocytopenia are frequently seen. Serum levels of the liver enzymes alanine aminotransferase and alkaline phosphatase may be elevated in a high percentage of cases. Chest roentgenograms most often reveal a patchy pneumonia with mediastinal and hilar node enlargement. Up to 20% of patients with PDH have CNS involvement. The more aggressive forms of acute PDH include encephalitis, acute meningitis, and encephalopathy. Histoplasmoma of the CNS and chronic meningitis are manifestations of a more indolent form of PDH. Chest radiographs typically demonstrate widely scattered nodular opacities or those having a diffuse reticular pattern.

Infrequently, patients exhibit a sepsis-like syndrome characterized by disseminated intravascular coagulation, encephalopathy, acute respiratory distress syndrome, vascular collapse and, subsequently, multiorgan failure. Subacute PDH is distinguished from the acute form primarily by the more prolonged nature of the symptoms. Physical findings include hepatosplenicomegaly and oropharyngeal ulcers. One of the notable features of subacute PDH is the presence of focal lesions in various organ systems, including the gastrointestinal tract, endovascular structures, CNS, and adrenal glands. Aside from liver and spleen, the gastrointestinal tract is one of the organs most commonly affected in subacute PDH. Endocarditis and infection of other vascular structures also may be manifestations of subacute PDH. On echocardiography, the lesions tend to be extensive, and large-vessel embolization can be the presenting symptom. CNS infection may be present in all age groups and causes chronic meningitis, mass lesion, and cerebritis. Among these, chronic meningitis is the most frequent. Symptoms include headache, altered sensorium, and cranial nerve deficits. Associated physical findings consist of hepatosplenicomegaly in approximately one third of patients, lymphadenopathy, and mucocutaneous lesions.

Histoplasmosis causes a mass effect and on CT may initially be mistaken for a malignancy or abscess because it exhibits ring enhancement with the administration of contrast medium. Histoplasmomas may be associated with meningitis but are often present independently. Although this patient was known to have had histoplasmosis infection earlier, and he currently has pulmonary infiltrates, lack of hepatosplenicomegaly, and lack of mass enhancement make this diagnosis unlikely.

FINAL DIAGNOSTIC CLUE

The final clue to solving this case lies in the analysis of the CT and MRI scans of the brain. Following the injection of contrast material, the characteristic CT appearance of a brain abscess is a hypodense center with peripheral uniform ring enhancement; this is surrounded by a variable hypodense area of brain edema. Other CT findings include nodular enhancement and areas of low attenuation without enhancement, the latter being observed during the early cerebritis stage before abscess formation; as the abscess progresses, contrast enhancement is observed. Once the abscess becomes encapsulated in the later stages, contrast material no longer differentiates the lucent center, and the CT appearance is similar to that of the early cerebritis stage. MRI is more sensitive than CT and therefore offers significant advantages in the early detection of cerebritis, cerebral edema, with greater contrast between edema and adjacent brain, more conspicuous spread of inflammation into the ventricles and subarachnoid space, and earlier detection of satellite lesions. On T1-weighted images, the abscess capsule often appears as a discrete rim that is isointense to mildly hyperintense. Contrast enhancement with the paramagnetic agent gadolinium diethylenetriaminepentaacetic acid provides the added advantage of clearly differentiating the central abscess, surrounding enhancing rim, and cerebral edema surrounding the abscess. On T1-weighted images, enhancement of the abscess capsule occurs. On T2-weighted images, the zone of edema that surrounds the abscess is one of marked high-signal intensity; the capsule now appears as a well-defined hypointense rim at the margin of the abscess. It is important to note that therapy with corticosteroids can decrease enhancement with both CT and MRI. Therefore, many of the diagnoses were excluded due to the lack of rim enhancement on the CT study. However, rim enhancement may have been present on CT and MRI but could have been modulated by steroids.

One diagnosis remains that fits well with this patient's course. Although fungi are infrequently recognized as a cause of pericarditis, Candida, Aspergillus, C. neoformans, and other fungi can cause disseminated infection in severely debilitated and immunocompromised patients, especially those with prolonged neutropenia who are receiving multiple courses of antibiotics. Overt myocarditis is common in disseminated toxoplasmosis. Conversely, systemic aspergillosis and candidiasis may also involve the heart.

Because the patient was managed with fluconazole, we must consider fungal pathogens that are not treated with this agent. We previously considered both Cryptococcus and Toxoplasmosis, and now we will further consider Aspergillus.

Most patients with invasive aspergillosis have pulmonary disease (80% to 90%). Invasive pulmonary aspergillosis (IPA) is manifested differently in various patient groups. Patients who are most fully immunocompromised have few symptoms...
Initially but the progression rate is rapid (acute IPA). The earliest symptoms are a dry cough and low-grade fever. Hypoxemia is usual in patients with bilateral diffuse IPA or in those with extensive consolidation. The appearance of invasive aspergillosis on chest radiographs is heterogeneous. Consolidation is common. Cavitation and pleural-based wedge-shaped lesions are the most distinctive features of invasive aspergillosis. Nodular shadows with and without cavitation are also seen, along with thick- or thin-walled cavities and “alveolar” consolidation that coalesces over time to form small nodules and larger areas of consolidation. Diffuse fine shadowing, usually in the lower lobes, is also seen. Pleural effusion is uncommon.

High-quality CT scans of the chest can play a major role in early diagnosis. The most distinctive early lesions are 1 or more small nodules and small pleural-based lesions with straight edges and surrounding low attenuation (the “halo” sign), particularly in neutropenic patients. As IPA progresses, the nodules may cavitate (typically with neutrophil recovery) and reveal an “air-crescent” sign. Both the “halo” and “air-crescent” signs are highly distinctive for invasive fungal disease of the lung. They are usually caused by Aspergillus, occasionally by other molds, and rarely by P aeruginosa. These lesions represent infarcted lung tissue full of hyphae that extend beyond the area of infarction. Bronchoscopy is essential if airway disease is possible, but rarely yields Aspergillus on culture, especially if the patient has peripheral, focal disease of the lungs. Although we are not told of a classic finding on the chest CT, the chest radiograph and the negative BAL, along with the patient’s risk factor profile, invite us to consider this diagnosis further.

Cerebral aspergillosis occurs in about 10% to 20% of cases of invasive aspergillosis and is usually the worst manifestation.
of disseminated disease. Patients with Aspergillus brain abscess most commonly manifest signs of a stroke syndrome (secondary to ischemia or intracerebral hemorrhage, or both) referable to the involved area of brain. Thus, disseminated Aspergillus infection is the most likely diagnosis of the patient's disease and cause of his death. This conclusion is based on his CT and MRI findings, pulmonary disease, bone marrow involvement, and risk factor profile. In the absence of microbiological or pathological material, other highly unusual emerging pathogenic fungi (Fusarium, Scedosporium, Scopulariopsis, etc) also would be possible causes.

PAMELA A. LIPSETT'S DIAGNOSIS:
1. Recurrent hepatitis C infection posttransplantation with cirrhosis
2. Acute on chronic renal failure secondary to acute tubular necrosis, chronic drug exposure, and diabetes
3. Pericarditis, myocarditis, pulmonary, cerebral, and bone marrow involvement with disseminated Aspergillus infection.

AUTOPSY FINDINGS
An autopsy excluding examination of the head was requested and performed, as requested by the patient's family. Internal examination revealed numerous lesions, most smaller than 1 cm, varying from tan nodules with hyperemic rims to hemorrhagic ulcers with necrotic centers. These lesions were present on numerous organs, including the heart, lung, gastrointestinal tract, kidneys, and thyroid. Histologic examination of these lesions revealed collections of septate fungal hyphae with acute dichotomous branching. The presence of fungi was highlighted with silver (GMS) and PAS stains. Examples of lesions involving the heart (Figures 1A, 1B), lungs (Figures 2A, 2B) and thyroid (Figure 3) are provided below. These morphologic features, in addition to the angioinvasion in some of the sections, are strongly suggestive of disseminated infection with Aspergillus species. However, in the absence of confirmation by culture, with demonstration of characteristic fruiting bodies, one cannot speciate this fungus. Other fungal pathogens with similar morphologies must be considered, including Fusarium and Pseudallescheria boydii. Clinical features favor the diagnosis of Aspergillosis. First, these other fungi are far less common human pathogens than are Aspergillus species. Second, the patient lacked a history of water exposure to suggest P. boydii. Thus, the presumptive diagnosis in this case is invasive Aspergillosis.

ADDITIONAL READINGS