Successful management of sequential pulmonary infections in a cardiac transplant recipient

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ABSTRACT: A case of a cardiac allograft recipient who had an initial combined pulmonary infection with cytomegalovirus, Aspergillus fumigatus and Nocardia asteroides, successfully treated with liposomal amphotericin B and sulfisoxazole and followed by an episode of respiratory syncytial virus pneumonitis, is presented. This case illustrates the role of computed tomographic imaging in the recognition, diagnosis and monitoring of complex opportunistic pulmonary infections and the benefits of liposomal amphotericin B in the treatment of aspergillosis. Can J Infect Dis 1990;1(3):85-91

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INFECTIONS ARE A COMMON CAUSE OF MORBIDITY AND mortality after cardiac transplantation (1,2). Since the introduction of cyclosporine as an immunosuppressive agent, the overall incidence of infectious complications and death after cardiac transplantation has declined (1). Improved recognition and treatment of infectious diseases in the post transplant setting may also have contributed to this decline (2). A patient who had an initial combined pulmonary infection with cytomegalovirus, Aspergillus fumigatus and Nocardia asteroides followed by respiratory syncytial virus pneumonitis is reported. This case illustrates the role of computed tomographic imaging in the recognition, diagnosis and monitoring of complex pulmonary opportunistic infections and the potential benefits of liposomal amphotericin B in the treatment of aspergillosis.

CASE PRESENTATION

A 61-year-old, asymptomatic, afebrile male, who five months previously had an orthotopic cardiac transplant for end-stage atherosclerotic heart disease, was admitted to the University of Alberta Hospitals because of radiographic evidence of enlarging pulmonary nodules. These were discovered incidentally on routine follow-up chest x-ray.

In his assessment two months prior to transplant, the patient was noted to have a positive Mantoux test in the absence of clinical or radiographic evidence of tuberculosis, and had been started on prophylactic isoniazid. The patient’s postoperative course had been complicated by steroid-induced hyperglycemia. He had experienced three mild to moderate rejection
Representative sections of computed tomography scans of the chest done on admission demonstrate multiple pulmonary nodules in the right upper lobe (left) and a portion of a nodule within the lingula, adjacent to the cardiac apex (right). Biopsy of one of the nodules revealed Aspergillus fumigatus.

Episodes. These occurred at two, four and eight weeks postoperatively, and were treated with pulse methylprednisolone, and on two occasions with antithymocyte globulin. The patient was cytomegalovirus antibody positive prior to transplant and received a heart from a cytomegalovirus seropositive donor. Four weeks after transplant, the patient began to excrete cytomegalovirus in the urine and saliva and developed a cytomegalovirus-specific IgM response. He remained asymptomatic. At the time of his admission with pulmonary nodules, his medications included oral cyclosporine 125 mg bid, oral azathioprine 150 mg once daily, and oral prednisone 10 mg bid. His physical exam was unremarkable except for Cushingoid features and minimal bilateral basilar lung crepitations. Computed tomography scan of the chest confirmed the presence of multiple nodules suspected on the initial chest x-ray (Figure 1). Liver function studies were normal. Serum creatinine was 104 μmol/L.

Since the pulmonary nodules were not accessible to transbronchial biopsy, the patient underwent a computed tomography-guided percutaneous fine needle aspiration biopsy. Cytomegalovirus was grown from the aspirated material; culture and direct examination of the specimen were negative for bacteria and fungi. Because of a persistent clinical suspicion of fungal infection, the patient had a computed tomography-guided biopsy of a second nodule which revealed dichotomously branching hyphae confirmed by culture to be A. fumigatus. The second biopsy samples were culture positive for cytomegalovirus. Further investigations, including a computed tomography scan of the head and a gallium scan, failed to reveal any evidence of extrapulmonary infection.

Immunosuppressive therapy was reduced and the patient started on systemic amphotericin B. Doses varied from 6 to 50 mg/day (0.8 mg/kg). This therapy was followed by a progressive rise in serum creatinine (Figure 2). A repeat chest computed tomography scan 18 days later showed regression of the previously noted nodules. However, a new nodule was detected in the right middle lobe (Figure 3). A needle biopsy of this new lesion was performed and culture and direct examination of the biopsy was negative except for the isolation of cytomegalovirus. Intravenous ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl] guanine) 175 mg every 24 h was then added to the therapeutic regimen. Because of the continuing rise in serum creatinine, a liposomal preparation of amphotericin B was substituted for the standard preparation. The patient had received a total of 1.02 g of conventional amphotericin B at the time of this substitution. The introduction of liposomal amphotericin B was closely followed by a drop in serum creatinine (Figure 2).

Despite ganciclovir therapy for more than a week, the right middle lobe lesion continued to enlarge and a fourth biopsy under computed tomographic guidance was performed. Direct smear of the aspirated material revealed delicate branching Gram-positive bacilli that were partially acid-fast; these were subsequently proven to be N. asteroides. Thirty-one days after initiation of therapy with amphotericin B for aspergillosis, the
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Figure 2) Summary of patient's course. The times of the computed tomography-guided needle biopsies (Bx) and bronchoscopy are noted at the top of the figure along with the respective microbial isolates. A bar graph illustrates the daily amphotericin B dose (Shaded bars Conventional amphotericin B: Clear bars Liposomal amphotericin B). The lower graph compares the serum creatinine with the cumulative dose of amphotericin B.

The patient was started on oral sulfisoxazole 2 g every 6 h. A chest computed tomography scan 12 days later showed resolution of all nodules (Figure 4). The serum creatinine continued to decline (Figure 2) and the patient was discharged a week later.

As an outpatient, the patient was continued on liposomal amphotericin B and oral sulfisoxazole 1.5 g qid. Daily liposomal amphotericin B varied from 0.6 to 1.3 mg/kg towards a total dose of 3.69 g of amphotericin B, 2.57 g of which were given in the liposomal form. Just prior to completing this course of medication the patient's serum creatinine rose transiently (Figure 2), concurrent with the highest daily dose of liposomal amphotericin B administered.

One month later the patient remained asymptomatic but was found to be mildly anemic with a normal bone marrow examination. Stools for occult blood were positive and on gastroscopic examination antral erosions were seen. Inclusions characteristic of cytomegalovirus infection were identified in mucosal biopsies from these areas. The patient was treated supportively with clinical improvement.

However, two weeks later the patient was readmitted to hospital with a two day history of cough...
productive of scant amounts of clear sputum accompanied by fever and malaise. Chest x-ray revealed a new infiltrate in the right lower lobe. Arterial blood gases on room air were $P_{O_2}$ 50 mmHg, $P_{CO_2}$ 33 mmHg, pH 7.44, and $S_aO_2$ 88%. Leukocyte count was $8.1 \times 10^9$/L with 89% polymorphonuclear leukocytes, 5% lymphocytes and 6% monocytes. Radiographs of paranasal sinuses demonstrated evidence of acute sinusitis. The patient underwent bronchoscopy which revealed copious white secretions. Gram stain of these secretions demonstrated many polymorphonuclear cells but no bacteria. Cultures failed to grow any bacteria or fungi; however, a direct fluorescent antibody test for respiratory syncytial virus was positive. Respiratory syncytial virus antibody titres rose from less than 1:8 to 1:256. Cytomegalovirus was also isolated from the bronchoscopic washings.

The patient had been started on empiric broad

Figure 3] Computed tomography scans of the chest at approximately the same level as seen in Figure 1 following two weeks of treatment with amphotericin B, showing considerable regression in the size of all previously seen nodules (left). An additional nodule, not seen on the initial scans, is seen in the right middle lobe (right). A biopsy of this new nodule revealed Nocardia asteroides

Figure 4] Computed tomography scan of the chest after 13 weeks of treatment with amphotericin B and nine weeks of treatment with sulfisoxazole shows resolution of all right upper lobe nodules (left). A parenchymal scar is seen in the middle lobe at the site of the 'new' nodule (right)
spectrum antibiotic treatment at the time of admission. Within 48 h he had dramatically improved. The antibiotic therapy was discontinued and the patient discharged one week later.

The patient has remained asymptomatic and has completed a one year course of sulfisoxazole. He has no evidence of recurrent disease 12 months after stopping amphotericin B therapy. His serum creatinine remains stable at 167 μmol/L.

**PREPARATION AND ADMINISTRATION**

The liposomal amphotericin B was prepared according to protocols used for early clinical trials described by Lopez-Berestein et al (3). Briefly, 600 mg of deoxycholate-free amphotericin B (provided by Squibb Pharmaceuticals, New Jersey) dissolved in 1460 mL of methanol was added to 4.2 g of dimyristoylphosphatidylcholine (DMPC) and 1.8 g of dimyristoylphosphatidylglycerol (DMPG) (Avanti Polar Lipids, Birmingham, Alabama) dissolved in 240 mL of chloroform. The solvents were evaporated under sterile conditions and 90 mL of pyrogen-free sterile saline was added for the liposomes with continuous shaking. The resultant liposomes were centrifuged to remove very large particles, and the total volume, amphotericin B and lipid compositions were determined. Sterility of the liposome preparations was determined by direct inoculation onto blood and chocolate agar plates. All cultures were incubated for three days before being considered negative for growth and before the liposomes were released for use. The final solutions delivered to the hospital pharmacy contained 90 mL of saline with 3.2 g lipid (total) and 205 mg of amphotericin B. The liposomes were stored for up to five days at 4°C.

The preparation and administration of this drug was authorized by the ethics committee of the University of Alberta Hospitals and the Bureau of Prescription Drugs, Health and Welfare Canada, and informed consent was obtained from the patient prior to drug administration. The prescribed daily liposomal amphotericin B dose was added to 50 mL of saline and infused over 20 mins through a blood filter (170 μm). The tubing was then flushed with 50 to 100 mL of saline. The patient initially received a test dose of 1 mg of liposomal amphotericin B and the dose was increased to a maximum of 1.2 mg/kg. The daily doses of liposomal amphotericin B varied according to the availability of the customized product.

**DISCUSSION**

This case illustrates several interesting aspects in the diagnosis and treatment of opportunistic pulmonary infections in cardiac allograft recipients. Not only are such patients particularly susceptible to opportunistic pulmonary infections, but they also may have residual changes from thoracotomy on plain chest radiographs which cloud the interpretation of suspicious lesions. On retrospective review of the patient’s early biweekly chest radiographs, a new and enlarging pulmonary nodule in the left lower lobe at the site of an old chest tube could be seen six weeks prior to the recognition of these nodules. At this time the computed tomography scan definitively demonstrated the extent of the pulmonary nodules and localized them for subsequent biopsy. In addition, in this patient, serial computed tomography scans documented a new and enlarging nodule in the face of other shrinking lesions. This led to persistent and aggressive attempts which were fruitful in identifying a second pathogen.

Earlier detection and diagnosis of pulmonary opportunistic infections is associated with improved outcome (4). Seemingly subtle changes on chest radiographs are often diagnostically discernible on computed tomography scan (5,6), and hence it seems prudent to use this mode of diagnostic imaging for recognition and monitoring response to therapy in patients similar to the present one. This case also illustrates the safety of percutaneous fine needle aspiration biopsy and the sampling error which may result, recently reviewed by deVivo et al (7).

Cytomegalovirus was isolated repetitively from lung aspirates more than four months after the patient was known to be shedding the virus. Cytomegalovirus is often found in conjunction with other pathogens, and in this patient it is not certain whether the treatment of cytomegalovirus had any impact on clinical outcome. There is evidence to suggest that many asymptomatic patients shedding cytomegalovirus may have sub-clinical pulmonary involvement (8). Culture of cytomegalovirus may be too sensitive a technique for the diagnosis of clinically significant cytomegalovirus pneumonitis (9).

Cytomegalovirus itself is immunosuppressive. Cardiac allografts with cytomegalovirus infection have been demonstrated to be at significantly higher risk of superinfection with opportunistic pathogens such as Gram-negative bacteria, fungi and *Pneumocystis carinii* compared to patients who do not develop cytomegalovirus infection following transplant (10). The possible effects of antiviral therapy on this immunosuppressive effect are uncertain.

Invasive aspergillosis is a common and serious infection in immunocompromised patients (1,2, 11,12). It has been most commonly described in patients with hematologic malignancies and in...
bone marrow transplant recipients (13-16). Untreated, it is uniformly fatal. Even with therapy, reports have described mortality rates varying from 67 to 100% (13). However, a recent report described a mortality rate of only 13% in leukemic patients with invasive aspergillosis (16). The improved survival was attributed to early, even empiric, therapy.

There is some evidence to suggest that the prognosis for solid organ transplant recipients treated for invasive aspergillosis may be better. It has been postulated that this may relate to the more free adjustment of immunosuppressive drug regimens in organ transplantation compared to leukemia (15). Gentry and Zeluff (2) describe a series of seven cardiac allograft recipients with invasive aspergillosis; six died despite treatment with conventional amphotericin B. The one surviving patient was treated with liposomal amphotericin B.

The drug of choice for treatment of invasive aspergillosis is amphotericin B. Unfortunately, its effectiveness in the conventional form is limited by serious adverse effects including fever, chills, nausea, vomiting, generalized pain, phlebitis, cardiovascular toxicity, arrhythmias, hypotension, renal toxicity, hypokalemia, hypomagnesemia, anemia and hepatotoxicity (14,17). This narrow therapeutic index problem appears to have been overcome by a liposome-encapsulated form of amphotericin B, recently reviewed by Wiebe and DeGregorio (17). In animal experiments and in humans liposomal amphotericin B appears to have increased antifungal activity, perhaps the result of the increased dose which can be given. Although the mechanism by which this increased activity is achieved remains speculative, it likely involves enhanced uptake by the liver, spleen and lungs (17). In addition to enhanced antifungal activity, clinical trials so far have revealed a marked reduction in systemic toxicity. Specifically, no chronic hepatic, renal or hematoxicity has been demonstrated in immunocompromised patients receiving liposomal amphotericin B despite dosages as high as 5 mg/kg/day (17-19). This is of particular concern in allograft recipients who may already have cyclosporine-induced renal dysfunction and in whom renal impairment due to conventional amphotericin B makes cyclosporine dosing difficult. In the present case the authors observed a dramatic fall in serum creatinine after initiation of liposomal amphotericin B therapy (Figure 2). Other advantages of liposomal amphotericin B include a shorter period of infusion – 10 to 15 mins versus 3 to 4 h – and a lower fluid volume – 50 mL versus 500 for the conventional infusion.

Infections due to N. asteroides are relatively common after solid organ transplantation (1,7,20,21). The reported incidence of nocardia infections in allograft recipients varies from 0 to 10.2% in renal allograft recipients and from 0 to 15.3% in cardiac and liver transplant recipients (20). Hoffman et al (1) has noted an apparent decline in the frequency of nocardia infections in cardiac allograft recipients since the introduction of cyclosporine. However, in some centres nocardia remains a frequent cause of opportunistic pulmonary infections in cardiac transplant patients (7). Sulfonamides with or without trimethoprim are the mainstay of therapy for nocardiosis (20). The use of cotrimoxazole prophylaxis in allograft recipients for the prevention of P carinii pneumonia and urinary tract infections may be having a significant impact on the incidence of nocardia infections in some centres. Mortality due to nocardia infection in allograft recipients varies from 0 to 42% (20,21). Survival depends on underlying disease, site of infection and rapidity of diagnosis (20).

In a review article reporting the incidence of nocardia infections during early experience with cardiac transplantation at Stanford University, Krick et al (21) found that two of seven patients with N. asteroides infection also had concurrent infection with aspergillus. The possibility of dual opportunistic infections should be considered in this patient population.

The present patient's clinical course was further complicated by the development of respiratory syncytial virus pneumonitis. Although respiratory syncytial virus is known to cause upper respiratory tract disease in adults, it has recently been reported to be a cause of lower respiratory tract infection in allograft recipients (22). Although the efficacy of ribavirin as a therapeutic agent has been confirmed in infants with severe respiratory syncytial virus infection, the present patient demonstrated spontaneous improvement with supportive care alone. Respiratory syncytial virus should be included in the growing list of potential opportunistic pulmonary pathogens in cardiac transplant recipients.

Pulmonary infections with pathogens known to produce severe life threatening infections can occur with relatively few symptoms in the immunocompromised host. A high index of clinical suspicion must be maintained along with an aggressive diagnostic approach. However, newer diagnostic imaging and therapeutic modalities can enhance the likelihood of a positive clinical outcome.
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