Acute aortic occlusion from aspergillosis in a healthy patient with survival

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Valvular endocarditis caused by Aspergillus is a lethal disease. Only two survivors, both with infections of prosthetic valves, have been reported in the world literature. This report describes a patient with an Aspergillus valvular endocarditis on a native valve with embolization to the right axillary, left iliac, and left popliteal arteries and the distal aorta. Diagnosis was made from a thromboembolectomy specimen. Treatment consisted of removal of the peripheral arterial emboli, mitral valve replacement, and prolonged intravenous infusion of high-dose amphotericin B. The patient presently has the longest survival period of any patient with an Aspergillus infection on a native heart valve. The importance of early diagnosis and aggressive operative management by the vascular surgeon needed to properly treat these patients is emphasized. (J VASC SURG 1986; 4: 187-91.)

Acute arterial insufficiency is commonly due to emboli, but only rarely is it a mycotic embolus. Vo, Russell, and Becker1 reviewed 44 cases of mycotic emboli to peripheral vessels, and although Aspergillus endocarditis is much less common than that caused by Candida species, almost 50% of these cases of embolism were from Aspergillus. In a complete literature review of Aspergillus endocarditis, reported in 1974, Krammer and Utz2 found that major arterial embolism occurred at a rate of 83% in 40 cases. Unfortunately, only two survivors have been reported after documented aspergillosis infection of prosthetic valves,3 4 and no survivors have been reported of patients with Aspergillus on native heart valves.5 Herein is reported a previously healthy patient with Aspergillus endocarditis in whom embolization to the right axillary artery, aortic bifurcation, left iliac artery, and left popliteal artery occurred at separate times; she was treated aggressively and has survived 6 months without evidence of recurrence.

CASE REPORT

A 36-year-old woman first noted night sweats, fever, weight loss, diffuse rash, and splinter hemorrhages about 4 months before admission. She had previously been a healthy woman, gravida 2, para 2, abortus 0, except for a history of “asthma” since childhood. Her pulmonary problem had not required hospitalization, but she did have intermittent thick sputum for the past 15 years. The patient had been told as a child she had a heart murmur, but no further information regarding this was available, and she had been asymptomatic. She smoked one pack of cigarettes a day for 20 years, denied drug use, and was not taking medications. When a child her father had coccidioidomycosis acquired from the family chickens. An older sister had previously undergone an aortoiliac endarterectomy at 36 years of age for distal aortic occlusion caused by atherosclerosis.

Five weeks before admission, the patient had an episode of disorientation that lasted several hours (possibly a transient ischemic attack). Four weeks before admission, she had sudden onset of right arm pain, which slowly...
improved over a few days. Three weeks before admission, she had sudden onset of left leg pain, coolness, and numbness and was admitted to another hospital. A diagnosis of bacterial endocarditis was made; she was given penicillin and streptomycin, although several blood cultures were negative. One day before admission she had sudden onset of more pain in the left leg and new right leg pain. At this point she was transferred to St. Louis University Hospitals.

During evaluation at admission she had ischemic lower extremities with absent femoral pulses and ankle-arm indices of 0.27 and 0.25 in the right and left legs, respectively. There were no pulses in the right arm, but there was no evidence of severe ischemia, and the left upper extremity had normal pulses.

Laboratory results showed white blood cell count, 17,000/μl; hemoglobin, 11.2 gm/dl; creatinine, 0.8 mg/dl; erythrocyte sedimentation rate, 85 mm/hr; urinalysis was normal. Chest x-ray film was normal, as was the electrocardiogram. A two-dimensional (2-D) echocardiogram was read as "suggestive of mitral valve prolapse" with no evidence of vegetations on any valve. Aortography revealed distal aortic occlusion with reconstitution of the external iliac vessels (Fig. 1), as well as left popliteal occlusion with reconstitution of the anterior tibial and posterior tibial arteries distally.

At celiotomy, the aortic wall was inflamed and the aortic bifurcation was blocked by a smooth, round, firm, white embolus with clot propagating down the common iliac arteries bilaterally (Fig. 2). Pathologic examination of the specimen showed Aspergillus species; no cultures had been taken.

Immediately after operation, the patient had large amounts of thick mucus, which required repeated bronchoscopies and intubation to keep the left lung expanded. The sputum culture never grew Aspergillus, which is frequently the case with Aspergillus-caused pneumonia. Amphotericin B (1.0 mg/kg/day) was started postoperatively. The serum concentration of IgE was 259 mg/100 ml, with normal values to 85 mg/100 ml. Skin testing for Candida and mumps indicated an active immune system. The tuberculin skin test was negative. Five days after operation, a repeated 2-D echocardiogram was reported as negative for vegetations.

Because of the lack of vegetation seen on 2-D echocardiography and the significant pulmonary problems the patient had suffered after the aortic surgery, we elected to treat her with amphotericin B and to repeat 2-D echocardiograms every 3 weeks to document which valve was involved. However, 23 days after aortoiliac thromboembolectomy she had an embolus to the left iliac artery. A 2-D echocardiogram performed at that time showed large vegetations on the anterior leaflet of the mitral valve. She subsequently underwent a left iliobifemoral embolectomy and concomitant mitral valve replacement. The tricuspid and aortic valves were also examined and were free of disease. The anterior leaflet of the mitral valve was almost completely destroyed by Aspergillus (Fig. 3), but the anulus and myocardium appeared normal. The patient tolerated the mitral valve replacement well and continued to receive 50 mg (1.0 mg/kg) of amphotericin B via a Hickman catheter daily at home; a visiting nurse administered the drug. Blood work was done twice a week. A brief readmission was required to correct a decreased serum potassium level, but the patient otherwise did well. The right arm remained without pulses, and the dorsalis pedis pulse did not return after the second embolectomy. Therefore, she was readmitted for arteriography of the right upper extremity and
left lower extremity. The aorta and left iliac artery were studied for any evidence of a mycotic aneurysm. The arteriogram showed occlusion of the right axillary artery and the left popliteal artery (Fig. 4). A 2-D echocardiogram done 47 days after valve replacement while the patient was still taking amphotericin B did not show valve vegetation and the prosthetic mitral valve was functioning normally. Thrombectomy of the right axillary artery and proximal portion of the popliteal occlusion was performed; results of pathologic examination were normal, and cultures of the specimens were negative. The patient received altogether 3.3 gm of amphotericin B during an 80-day period.

**DISCUSSION**

*Aspergillus* vegetative endocarditis is a highly lethal disease. There are several reviews of this illness, but only two survivors with documented infections have been reported and both had prosthetic valve infections. This patient represents the first of 12 reported cases of infection on a native valve to have survived. Several reasons account for this high mortality rate and an understanding of these is necessary if other patients with this condition are to survive.

Zimmerman in 1950 described three basic factors that predispose patients to fungal infections—debilitating disease (e.g., leukemia), a break in the skin or mucus membranes providing portal of entry, and disturbances in the saprophyte-host relationship produced by drugs (e.g., antibiotics, steroids, or chemotherapy). Patients with *Aspergillus* endocarditis occurring after cardiac surgery and valve replacement fit these criteria. Six of the 13 patients with native valve infection fit the criteria for being at risk; data are insufficient for two patients. However, five patients did not have debilitating illness, although three had a poorly defined chronic lung condition. None of these five patients had undergone surgery or had been taking long-term antibiotics when first diagnosed. Because not all patients with *Aspergillus* endocarditis fit into this long-held stereotype of a patient at risk for fungal infection, there is often a delay of weeks to months before the correct diagnosis is made. Eight of the 13 cases were diagnosed at autopsy. When diagnosis was made before death, in all cases it was made from removed emboli. Two patients had peripheral artery emboli that were not examined pathologically and the diagnosis from these was made at autopsy. The delay in diagnosis allows for more
Fig. 4. Arteriogram demonstration of occlusions by aspergilloma (A). Occluded brachial artery with large collateral to ulnar artery (B). Occluded left mid popliteal artery.

embolization with dissemination, valvular destruction, and progressive invasion of tissues by Aspergillus. This had led to the destruction of the heart bundle,10 myocardial abscesses, and emboli to almost every organ in the body.2 Therefore, the most effective therapy begins with early detection. New murmurs, fever, and negative blood cultures in patients who have had valve replacement are well-known hallmarks of fungal infection of the prosthetic valve. In patients with native valve involvement, symptoms at admission suggest subacute bacterial endocarditis; but all blood cultures are negative, the vegetations are usually very large (up to 2.5 cm), and major vessel emboli occur. The diagnosis should then be suspected in these patients when 2-D echocardiography shows large vegetations518 and will be confirmed by pathologic examination of the emboli. Unfortunately, 2-D echocardiography is not infallible and two cases in addition to the current one had, at certain times in their course, images that did not reveal any vegetations.10 20 This may have happened because the large vegetations had already embolized; and, until new mycelia grow, the valve would not show large vegetations.

Fungal endocarditis has a major vessel embolus rate between 30% to 83% with Aspergillus at the higher end of the spectrum.12,21 Any patient in whom the diagnosis of endocarditis is suspected who has an embolus to a major vessel should have the embolus removed irrespective of the degree of ischemia, so that the embolus can undergo thorough pathologic examination and culture. If the embolus is of an Aspergillus species, the patient should have prompt valve replacement of the involved valve.54 9 19 Direct examination of the mitral and aortic valve during valve replacement should be considered, as there are reports of both valves being involved.3 Valve replacement should be performed very soon after the diagnosis is made, since there are several documented cases of emboli, some fatal, while the patient is taking full-dose amphotericin B.11,14,19 Fifty percent of deaths in patients with native valve infections were from central nervous system emboli. In the present case, on the twentieth day of treatment with amphotericin B at 50 mg/day, 15 days after a “normal” 2-D echocardiogram, recurrent embolization to the left iliac artery occurred. There is no safe time period between episodes of emboli, and amphotericin B provides no protection. Only valve replacement will prevent recurrent embolization.

 Cultures from the mitral valve in the present case grew Aspergillus flavus with a minimal inhibitory concentration (MIC) and minimal bactericidal concentration of 3.9 ng/ml to amphotericin B. Often Aspergillus organisms have MICs of 5 to 15 ng/ml, which may increase to 500 ng/ml while on treatment.22 Serum concentrations of 2 ng/ml are possible with 0.6 mg/kg doses of amphotericin B.23 This patient’s Aspergillus had an MIC of 500 ng/ml to rifampin and 1000 ng/ml to 5-fluorocytosine. Whether there is a synergistic effect in vivo between amphotericin B and fluocytosine or rifampin is unknown. Amphotericin B with daily dosages increased up to 1.0 to 1.2 mg/kg/day should be started as soon as the diagnosis is made. It is the best drug available and long-term use against some Aspergillus species probably allows the body to sterilize small numbers of the fungus. This is probably what happened in our patient who had a relatively competent immune system. The total dose of amphotericin B required for effective treatment of Aspergillus vegetative endocarditis is not well known, but 2 to 3.5 grams may be appropriate. The only two survivors who had Aspergillus emboli, one from a prosthetic valve4 and our patient, received 2.1 and 3.3 gm, respectively, of amphotericin B as well as valve replacement. The other survivor reported, also a prosthetic valve case, had no emboli and no evidence of dissemination and was cured with valve replacement alone.3 Because all sur-
vivors have had valve replacement and large peripheral emboli either removed or not occur, we believe surgical removal of the Aspergillus infection is the cornerstone of treatment.

SUMMARY

Aspergillus infection of the native valve demands aggressive diagnostic and therapeutic methods to ensure survival. Left untreated or treated only with amphotericin B, this entity will lead uniformly to myocardial abscess, recurrent emboli, and death. It occurs most often in patients with preexisting valvular disease with either a depressed immune system or a chronic low-grade Aspergillus infection of the lungs. Anyone with a clinical picture of subacute bacterial endocarditis and negative blood cultures should be suspected of having fungal endocarditis. If embolization to a major vessel occurs, the diagnosis should be made from the embolus through pathologic examinations and culture. If Aspergillus is documented, the patient should have prompt valve replacement and removal of all fungal emboli. Rapid valve replacement is critical to prevent further emboli, risk of major stroke, and extension of the Aspergillus into the myocardium, which to date has been an incurable condition. The patient should be kept on a regimen of high-dose amphotericin B for a total dose of 2 to 3.5 gm to help rid the body of microemboli and possibly sterilize the pulmonary tract, which may be colonized or infected with Aspergillus. The vascular surgeon is in a prime position to make the diagnosis in these patients through embolus removal and should also play an active role in therapy by removing all major emboli and assuring that timely removal of the involved valve occurs. Hopefully, with this course of action, there will be more survivors of this rare but real disease.

REFERENCES