Aspergillus Endocarditis Superimposed on Aortic Valve Prosthesis

Case report

The patient was a forty-six-year-old white female housewife who had had rheumatic fever at age nineteen. She remained asymptomatic, with one uneventful pregnancy. In 1960 she noted myalgias, increasing exertional chest tightness, edema, and easy fatigability.

She was first admitted to Montefiore Hospital in December, 1963, for chest pain and was found to have aortic stenosis without evidence of myocardial infarction. The patient was readmitted in April, 1965, for progressive congestive heart failure. Cardiac catheterization revealed a systolic aortic valve gradient of 100 mm. Hg and an elevated left ventricular end diastolic pressure. An electrocardiogram was compatible with marked left ventricular hypertrophy.

On June 4, 1965, the patient underwent cardiac surgery, with total cardiopulmonary bypass and right and left coronary artery perfusion with normothermia. Her severely stenosed and highly calcified aortic valve was replaced with a number 8 Starr-Edwards valve. Total perfusion time was one hour and thirty-five minutes, with transient episodes of preperfusion hypotension and postperfusion right ventricular failure. Heparin, protamine, and antibiotics (penicillin, methicillin sodium, and sodium oxacillin (Prostaphlin) were administered. The postoperative course was characterized by good prosthesis functioning. Left bundle-branch block was present on the electrocardiogram. Forty-eight hours postoperatively, facial paralysis developed which gradually improved. Maintenance antibiotics and anticoagulants were administered. On June 30, 1965, the patient had a syncopal episode followed by severe headache and nuchal rigidity. She was afebrile, and she had Hoffmann's sign and upper extremity hyperreflexia on the left side, mild optic disk congestion, and
slight deviation of the tongue to the left.

Two days later, on July 3, 1965, the headache and nuchal rigidity increased in severity, concomitant with a sudden spike in temperature to 103°F. with chills and the development of Brudzinski's and Kernig's signs.

Physical examination on July 4, 1965, revealed evidence of meningeal irritation and abnormalities of the ninth and tenth cranial nerves. There were residual central and upper-extremity pareses and increased deep-tendon reflexes in the upper extremity on the left side. A basal holosystolic murmur was present, but there was no diastolic murmur. Three lumbar punctures all produced grossly xanthochromic fluid at elevated pressures (over 250). Transient relief of the headache followed each lumbar puncture. Fever spikes to 102°F. continued for five days despite a twenty-four-hour trial of 20 million units of penicillin. There were transient episodes of expressive aphasia, fluctuating states of consciousness, and a persistent tachycardia. There was one episode of pleuritic chest pain without cough, hemoptysis, or x-ray or electrocardiographic changes.

Following discharge the patient continued to have diffuse myalgias with malaise, pleuritic chest pain, easy fatigability, low-grade fever (100°F.), intermittent headaches, nausea, anorexia, low-back pain, and frequent palpitations. A painful nodule was noted on one toe which subsided within twenty-four hours. Her hematocrit remained at 32 with a persistently elevated sedimentation rate.

On the day of the last admission, September 8, 1965, and three months postoperatively, the patient developed acute abdominal pain with nausea, vomiting, diaphoresis, lightheadedness, and palpitations.

Physical examination revealed markedly decreased bowel sounds and left upper quadrant and epigastric tenderness, without rebound. A diastolic murmur was heard at the left sternal border.

**Laboratory Data.** Six blood cultures, 4 spinal fluid cultures, and 2 urine cultures were all negative for bacteria and fungi. An India ink stain of the spinal fluid for Torula gave negative results. The white blood cell count was persistently elevated (12,000 to 19,000 per cubic millimeter), rising to 34,000 on the day of demise. There was an increase in polymorphonuclear leukocytes with a shift to the left. Eosinophilia was variable (1 to 970), with toxic granulation and Döhle's inclusion bodies in the peripheral blood smear. Hematocrits varied from 28 to 39, with hypochromia, basophilic stippled red cells, polychromatophilia, and burr cells. Platelets were 150,000 to 250,000 per cubic millimeter. Urinalysis revealed a range of specific gravities from 1.007 to 1.025 with trace to 2 plus albumin, 0 to 20 white blood cells, and rare red blood cells until the day of death when many red blood cells were present. There were occasional casts including granular, epithelial, waxy, and hyaline; ureteral and pelvic epithelial cells were noted. The fasting blood sugar was 121 mg. per 100 ml. with a uric acid of 6.4; blood urea nitrogen did not exceed 29 mg. per 100 ml. Sodium was 135 mEq. and potassium 2.9 to 5.4 mEq. per liter. Prothrombin times varied between 13 to 22 seconds with a control of 11 seconds. There was a reversed albumin-globulin ratio (albumin 2.7 to 2.8 Gm. and globulin 3.2 to 2.7 Gm. per 100 ml.).

**Cerebrospinal fluid.** White blood cells varied from 160 to 3,100 per cubic millimeter with a predominance of polymorphonuclear leukocytes. Red cells varied from 380 to 4,300 per cubic millimeter. Sugar varied from 31 to 79 mg. per 100 ml. Protein varied from 52 to 870 mg. per 100 ml. India ink stain for Torula showed negative findings.

**X-ray films.** On admission an emergency abdominal x-ray film revealed distended loops of ascending transverse and descending colon without any free air or evidence of obstruction. The chest x-ray film revealed no signs of congestive heart failure, infiltrates, or cardiomegaly.

**Hospital course.** The hospital course was characterized by increasing left upper quadrant tenderness, bilateral flank pain, persistent increasing lethargy, and fluctuating states of consciousness. On the third hospital day, the patient developed nuchal rigidity of gradually increasing severity followed by recent memory impairment, twitchings, focal seizures, and finally grand mal convulsions and coma. Neurologic examinations revealed a right retinal hemorrhage, exudates in both fundi, bi...
lateral ankle clonus, bilateral Hoffmann's signs, decreased abdominal reflexes, generalized hyperreflexia, crossed extensor reflexes, and Kernig's and Brudzinski's signs. She received massive doses of antibiotics (penicillin, streptomycin sulfate, chloramphenicol (Chloromycetin), sodium cephalothin (Keflin), sodium methicillin (Staphcillin), and sulfisoxazole diolamine (Gantrisin)). In addition, she received anticonvulsant, analgesic, hypothermic, antiallergic, and steroid therapy, to no avail.

^terminally, the pupillary light reactions diminished, and the pupils remained fixed and dilated for the last forty hours. Bilateral Babinski's signs, fresh retinal hemorrhages and exudates, and a right retinal infarction developed before the demise. The blood pressure fell without signs of peripheral vascular collapse; it could not be maintained with vasopressors, and the patient died.

**Pathologic Findings.** Pertinent autopsy findings were as follows: The heart weighed 490 Gm., with cardiomegaly due predominantly to left and right ventricular hypertrophy. There was dilatation of all chambers. The pericardial cavity was completely obliterated as a consequence of fibrous and organizing fibrinous adhesions, secondary to previous cardiac surgery. A well-healed ventriculotomy scar was present. Organizing mural thrombi were noted in both ventricular cavities. A Starr-Edwards aortic valve prosthesis was sutured in place; the remaining natural valves were entirely unremarkable. The cage of the valve prosthesis was layered superiorly by an organizing thrombus; the interior of the cage was filled by an adherent, grayish-white, friable, soft mass (Fig. 1). The latter enveloped the ball of the prosthesis, extending to the inferior surface of the prosthetic ring. At the root of the aorta, in the region of the origin of the right coronary artery, a small abscess measuring 1 cm. in diameter was present. On evacuation of its greenish purulent contents, the prosthetic anchoring sutures were seen in the wall of the abscess. The cut surface of the myocardium was red-brown in color and diffusely spotted by minute, round, firm, grayish-white lesions measuring approximately 1 to 2 mm. in diameter.

Microscopic sections of the prosthetic vegetations revealed masses of fibrin, polymorphonuclear leukocytes, cellular debris, and mycelia consisting of dichotomously branching septate hyphae, morphologically compatible with Aspergillus species. Postmortem heart blood had been submitted for bacteriologic investigation and was reported as showing a “common fungal contaminant” and hence discarded without any attempt at further identification of the organism. Sections of the myocardium revealed the previously described minute lesions to be mycotic microabscesses consisting of hyphae, amorphous cellular debris, and polymorphonuclear leukocytes surrounded by necrotic and degenerating myocardial fibers. Sections of the wall of the abscess at the root of the aorta revealed a dense fibrous connective tissue wall contiguous with degenerating myocardial fibers and containing enmeshed hyphae of the fungus, with cellular debris and polymorphonuclear leukocytes.

Mycotic microabscesses were also noted in the liver, kidneys, ovaries, and cerebrum.
Organizing mycotic emboli were found in the superior mesenteric and cerebral arteries. They were associated with infarcts of the small bowel and cerebrum respectively. A healed mycotic aneurysm of a branch of the left middle cerebral artery was also noted. Except for the presence of right lower lobe atelectasis and a diffuse necrotizing tracheobronchitis, the lungs were microscopically unremarkable.

Comment

Aspergillus is a ubiquitous fungus with a world-wide distribution, commonly found in soil, and resulting in airborne infection. Since it is a frequent contaminant, it must be consistently isolated in large numbers from pathologic specimens, in the absence of a known pathogen, to be considered an etiologic agent. Pathologically, Aspergillus produces chronic suppuration, granulomatous changes, arteritis, necrosis, and abscesses. Morphologically, the Aspergillus hyphae are large and wide (3 to 4 microns), with unilateral branching (Fig. 2B). Spore forms are rarely seen in tissue sections.

Aspergillosis is most commonly seen clinically as a pulmonary disease. Involvement of the ear, orbit, eyes, paranasal sinuses, skin, bones, nails, and vagina have been reported. Central nervous system and endocardial involvement, usually of a secondary nature, have also been reported. The disease is of varying severity and occurs most frequently in adults. It may be localized or disseminated, spreading either by direct invasion or hematogenously. Primary and secondary forms occur. The primary form is usually associated with no antecedent disorder, whereas the secondary form is preceded by debilitation, prior disease, antibiotics, and/or steroid therapy. Disseminated primary aspergillosis is rare.

Aspergillus endocarditis is classified among the secondary disseminated forms of the disease. Predisposing factors in the reported cases included debilitation, prior antibiotic and/or steroid therapy, a portal of entry, and some form of trauma or stress. Following cardiac surgery, denuded endothelium provides a nidus for fungal implantation. Possible portals of entry would then include cardiac catheterization, the pump oxygenator, instruments used during surgery, prosthetic intracardiac materials, air in ventilating systems, talc or starch in surgical gloves, and indwelling intravenous catheters.

The only case reported of Aspergillus endocarditis following cardiac surgery was that of a twenty-one-year-old white male who developed the Aspergillus infection on a Starr-Edwards mitral valve. Despite the possibility of bacterial endocarditis with a febrile postoperative course and two...
embolic episodes, the patient was given anticoagulant therapy for presumed bland thrombosis on the valve with embolization. Postmortem cultures of thrombi from the prosthesis, containing Aspergillus hyphae, were sterile for bacteria and fungi. However, antemortem blood cultures were later reported as positive for Aspergillus fumigatus.

Two recent articles dealing with prostheses infection mentioned 3 cases of infection with positive cultures for Aspergillus which were associated with concomitant bacterial organisms. The infection was on Teflon patches in 2 of the cases and on an aortic ball valve in the third.

Fever was a constant manifestation in the 7 cases. Fever is characteristic of all fungal endocarditis, often being the first clinical manifestation. The high incidence of major arterial embolization has been attributed to the extremely large size of the vegetations. Classical signs of endocarditis were notably absent in the Aspergillus cases, although they are commonly present in other types of fungal endocarditis. No case was diagnosed ante mortem, and therefore in none was antifungal therapy instituted. There were no recoveries.

The case reported here is the first such instance involving a Starr-Edwards valve. The patient sustained at least three complications of open-heart surgery and prosthetic valve replacement, the development of left bundle-branch block, calcium embolization, and fatal infection. The infection probably first developed one month postoperatively with fever and syncope secondary to a ruptured mycotic aneurysm. During the two and a half-month duration of illness, she developed most of the classical signs of bacterial endocarditis, including the development of a diastolic murmur, fever, and major arterial embolizations. There were numerous possibilities for portals of entry including cardiac catheterization, surgery, and indwelling catheters.

The clinical diagnosis ante mortem was bacterial endocarditis, with serious consideration being given to a fungal cause. However, diligent search for fungal organisms proved unrewarding. As in the 7 previous cases, massive antibiotic therapy was administered, and this may have accelerated the pace of the already established fungal infection.

Antifungal therapy could not be administered since the organism was not isolated. Surgical intervention, with removal of the infected valve, was planned after a trial of antibiotics, but the patient's rapid deterioration precluded this. Some authors have alluded to the difficulty in sterilizing prostheses infected with bacteria, and it would seem that this would be even more difficult in the presence of large fungal vegetations.

Blood cultures and vegetations failed to grow Aspergillus, although postmortem heart blood grew out a "mold" which was discarded as a contaminant. The final diagnosis, therefore, was based on morphologic identification of the fungus. The vegetations and emboli contained "numerous, filamentous, branching, septe mycelium, all oriented in the same direction," which as Littman has pointed out, "is characteristic of Aspergillus." Fungal endocarditis should be suspected in any patient with clinical manifestations of endocarditis or with negative blood cultures and a poor response to antibiotics, especially following cardiac surgery and in the presence of intracardiac foreign material. The only available agent, amphotericin B, has been uniformly unsuccessful in the treatment of fungal endocarditis without surgical intervention. The difficulty in achieving fungal cure is probably caused by the large size of the fungal vegetations and the availability of only a static agent. Surgical intervention may effect a cure by removing the nidus of infection.

A new agent, X-5097C, purported to be effective in aspergillosis but ineffective in disseminated candidiasis, has not fulfilled its original expectations. Most recently, the use of long-term antibiotic prophylaxis, preoperatively and postoperatively, has apparently been effective in decreasing the incidence of bacterial endocarditis, without any reported increased incidence of fungal superinfection. For the present, such prophylaxis would seem justified, in view of the severity of prosthesis infections with bacteria. There is presently no adequate prophylactic agent against fungal infections on prostheses.

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Summary

The case history and pathologic findings of a patient who developed a clinical course compatible with that of bacterial endocarditis following Starr-Edwards valve replacement is presented. Postmortem examination revealed massive vegetations on the prosthesis with multiple septic emboli due to Aspergillus.

The incidence of bacterial endocarditis following prosthetic replacement is 1 to 4 per cent. Fungal endocarditis is less frequent. Prior to this, there have been 19 cases of fungal endocarditis following cardiac surgery, all but 2 due to Candida species. The second postoperative case due to Aspergillus is presented here. The clinical features of Aspergillus endocarditis are not unique from those of any other fungal endocarditis. Prominent manifestations include fever and major arterial embolization. Pathologically, there are large vegetations.

The prior cases have been briefly reviewed. Medical therapy has been uniformly unsuccessful, largely because of failure to identify the causative agent.

A fungal cause should be suspected in postoperative cases with clinical manifestations of endocarditis, fever, negative blood cultures, and poor response to adequate antibiotic therapy. Special cultural techniques may be required for diagnosis. Surgical intervention may be necessary to achieve cure with fungal infections on prosthetic valves.

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