Aspergillus Species Endocarditis

The New Face of a Not So Rare Disease

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Aspergillus flavus endocarditis developed in a 13 year old girl after mitral valve replacement. Thirty-nine other cases of Aspergillus species endocarditis were found in the medical literature. Twenty-nine of these infections occurred in postcardiac surgery patients. Fever was the most common presenting manifestation (35 patients). Cardiac murmurs were present in 25. Lesions were in the left side of the heart in 38 (95 per cent), and there were major arterial emboli in 33 (83 per cent).

The diagnosis was made antemortem in only nine patients. The diagnostic specimen in eight of these was an embolus. Aspergillus sp. were cultured from the blood of only three (8 per cent). Two (5 per cent) patients survived; in both infected prostheses were replaced, and one received antifungal chemotherapy. Aspergillus sp. endocarditis should be suspected in any postcardiac surgery patient presenting with endocarditis and emboli whose blood yields no organisms in culture.

Careful surveillance and control of fungal contamination of the surgical environment is urged. Cultures of arterial blood should be obtained, and both solid and liquid microbiological media utilized. Early valve replacement and chemotherapy with both amphotericin B and flucytosine are recommended.

In 1958, Merchant et al. [1] reviewed the medical literature on endocarditis caused by fungi. Aspergillus species were the etiologic agents in only four [2–5] of the 34 cases reported to that date. Fourteen years later, reported cases of Aspergillus sp. endocarditis alone number 39 [2–34].

This marked increase in prevalence parallels the rise of cardiac surgery. The first report of a case occurring after cardiac surgery was that of Hadorn [7] in 1960. Newman and Cordell [11] published the first case involving an intracardiac prosthesis. In 29 of the 39 reported cases, Aspergillus sp. endocarditis occurred within the 1st year of cardiovascular surgery. Twenty-four patients received prosthetic valves or homografts.

The correct antemortem diagnosis was made only nine times. Furthermore, only two patients survived, despite therapy. Means of prevention, accurate diagnosis and effective treatment remain unsolved problems.

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CASE REPORT

When patient L. F. (9-38-62-84), a black girl born on August 18, 1958, was first seen at the Medical College of Virginia Hospital in 1964, she had severe pulmonary edema. Marked cardiomegaly was present, and grade 3/6 apical murmurs were audible in systole and diastole. Acute rheumatic fever with myocarditis and mitral valvulitis was diagnosed, and therapy with digoxin, mercurial diuretics, oxygen and corticoids was begun. Her condition improved slowly, but murmurs and cardiomegaly persisted. After a 3 month hospitalization, she was discharged on a regimen of benzathine penicillin, 1.2 million units every 28 days, digoxin and sodium restriction. She did well until June 1970 when exertional dyspnea and ankle edema prompted a brief readmission for cardiac catheterization. Severe mitral regurgitation was demonstrated. Diuretics were added to the therapeutic regimen. Atrial fibrillation led to intractable heart failure in January 1971.

On February 1, 1971, the deformed mitral valve was replaced by a Starr-Edwards prosthesis. Surgery was uncomplicated, but fever developed 8 hours later. Nafcillin, benzyl penicillin and streptomycin were administered pre- and postoperatively. The patient remained febrile to 38.9°C (102°F). Polymorphonuclear leukocytosis was noted. No bacteria or fungi were cultured from blood and urine specimens. Antibiotic therapy was discontinued on February 8, and her temperature returned to normal over the next week. Her temperature rose again on February 19, she was treated with phenoxymethyl penicillin, and defervesced. No cause for the pyrexia and leukocytosis was found. On February 28, following electrical cardioversion, she was discharged on a regimen of benzathine penicillin every 28 days, quinidine, warfarin sodium and digitoxin.

Atrial fibrillation recurred, and the patient was briefly admitted in April 1971 for cardioversion. She was afebrile and otherwise doing well. No murmurs were heard.

On June 24, she was readmitted after the sudden onset of severe pain in the right lower extremity. Her oral temperature was 37.4°C (99.4°F). Pulse rate was 68/min and regular. A grade 2/6 apical systolic murmur was present. Absence of the right femoral, popliteal and dorsalis pedia pulses was noted. Hemoglobin level was 9.8 g/100 ml, and the leukocyte count was 25,200/mm^3 with 99 per cent polymorphonuclear cells. The prothrombin time was 21 seconds, the control was 12 seconds. Urine had 1+ protein, many leukocytes and 15 erythrocytes/hpf.

A large embolus was removed from the right common iliac artery 6 hours after admission. On the following day, June 25, re-exploration was performed because of poor blood flow, and 3 more emboli were removed from the right iliac and femoral arteries.

Benzyl penicillin, nafcillin and streptomycin were administered postoperatively. Temperature spikes to 38.9°C (102°F) and 40.6°C (105°F) occurred on June 26 and 27, respectively. A right hemiparesis and aphasia were noted on June 27 as well as subconjunctival hemorrhages. The systolic murmur disappeared. Again no organisms could be cultured from 10 blood specimens. On June 28 fungal hyphae resembling Aspergillus sp. were seen in sections of the emboli, and amphotericin B therapy was begun with a dose of 10 mg intravenously. The Starr-Edwards mitral prosthesis was replaced 12 hours later on June 28. The excised valve was coated with friable clots from which Aspergillus flavus was subsequently cultured. Fever and leukocytosis persisted, and azotemia developed, which forced reduction of the amphotericin B dose from 20 to 5 mg on July 1. The hemiparesis diminished, and the patient began to speak. A brain scan on July 6 demonstrated a focal area of increased uptake in the left posterior temporal area. The apical systolic murmur was heard again that day. She was given 20 mg of amphotericin B on July 7, bringing the total to 115 mg. A few hours later she suddenly became tachypneic, ventricular fibrillation developed, and she died. No autopsy was permitted.

This case is typical and illustrates the more common features of Aspergillus sp. endocarditis: (1) organic heart disease with valve prosthesis; (2) previous antibacterial therapy; (3) unexplained fever; (4) polymorphonuclear leukocytosis; (5) anemia; (6) pyuria and microscopic hematuria; (7) emboli to major vessels, especially to central nervous system and extremities; (8) sterile blood cultures; (9) diagnosis made by histology and culture of embolus; and (10) death.

REVIEW AND ANALYSIS OF THE LITERATURE

The clinical and pathologic features of 40 cases of Aspergillus sp. endocarditis are presented in Tables I and II. An analysis of these data follows.

Fungus Isolated. From 30 patients, a species of Aspergillus was cultured from valves, vegetations or emboli. Of these, 14 were A. fumigatus, 6 A. flavus and 5 not speciated. There was one isolate each of A. niger, A. ustus, A. terreus, A. glaucus and A. sydowi. There were no clinically distinctive features related to species.

Age and Sex. Aspergillus sp. endocarditis occurs most frequently in young men. The average age at onset was 31 years, the range was 51 days to 63 years, and 78 per cent of the subjects affected were male.

Presenting Manifestations and Physical Findings. The protean clinical presentations of Aspergillus sp. endocarditis are catalogued in Table I. Frequency data for the more commonly encountered findings are listed in Table III. These signs and symptoms suggest the diagnosis of endocarditis. However, the great frequency of emboli to major vessels of the central nervous system and extremities distinguishes Aspergillus sp. and Candida sp. endocarditis from that due to aerobic bacteria [35].

The clinical diagnosis was bacterial endocarditis in 19 cases. In five patients, primary disease of the central nervous system, i.e., brain abscess or meningitis, was suspected. Specific reference to fungal etiology was conspicuously absent in every case.

TABLE I Aspergillus sp. Endocarditis: Clinical Aspects

Case No.	Source	Fungus	Age (yr) and Sex	Presenting Manifestations	Physical Findings				
					Heart Murmur	Fever	Petechiae	Splenomegaly	Hepatomegaly
1	Cawley [2]	A. fumigatus	8, M	Central nervous system abnormalities	...	...	...	...	...
2	Zimmerman [3]	Aspergillus sp.	25, M	Emboli, fever	+	+	...	+	...
3	Welsh, Buchness [4]	A. flavus	18, M	Fever	...	+	...	−	...
4	Kirschstein, Sidransky, [5]	A. flavus	50, M	Fever	...	+	...	+	+
5	Grcevic, Mathews, [6] Case 3	Aspergillus sp.	22, M	Fever, arthritis, coma	−	+	+	−	+
6	Hadorn [7]	A. fumigatus	33, M	Fever	+	+	...	−	−
7	Luke et al. [8]	A. fumigatus	51 days, M	Fever	+	+	−	+	+
8	Vogel, Heinitz [9]	Aspergillus sp.	48, M	Headache	+	+	−	−	−
9	Paradis, Roberts [10]	A. fumigatus	2 mo, F	Dyspnea, coma	...	−	+	+	+
10	Newman, Cordell [11]	A. fumigatus	24, M	Fever, petechiae	+	+	+	...	...
11	Khoo et al. [12]	A. flavus	2 mo, F	Diahrrhea, fever	−	+	−	−	+
12	Darrell [13]	A. fumigatus	40, F	Eye pain, blurred vision	−	+	+	...	...
13	Leffert, Hackett [14]	Aspergillus sp.	26, M	Fever	+	+	−	−	−
14	Satoyoshi et al. [15]	Aspergillus sp.	62, M	Orbital pain	+	+	−	−	+
15	Doughten, Pearson [16]	Aspergillus sp.	5, M	Fever	+	+	+	+	+

Evidence of Major Emboli to	Other	Associated Disease	Drug Therapy Before Onset	Total Duration From Probable Onset (mo)	Clinical Diagnosis
...	Pneumonia	None	Sulfonamides	6	Disseminated aspergillosis
Leg	...	Septic amputation	Penicillin	1/2	Bacterial endocarditis
...	...	Neutropenia, interstitial pneumonia	ACTH, antibiotics	1	Connective tissue disease
...	...	Chronic lymphocytic leukemia	ACTH, antibiotics	1	Leukemia
Brain	Pneumonia	None	Penicillin, tetracycline, streptomycin, sulfonamide	1/10	Brain abscess
Femoral arteries, brain	...	Subaortic stenosis, postoperative	Erythromycin, chloramphenicol, corticoids	3/4	Endocarditis
Brain	...	Erythroblastosis	Penicillin, chloramphenicol, tetracycline, prednisone	1/2	Meningitis
Brain, eyes	...	...	...	2	Meningitis
Brain	...	Prematurity, cytomegalovirus infection	...	1/2	Acute lymphocytic leukemia
Brain, leg, hand	...	Rheumatic heart disease, Starr-Edwards mitral valve	Penicillin, streptomycin, chloramphenicol	1 3/4	Endocarditis
Brain	...	...	...	1/2	...
Brain	Uveitis	Rheumatic heart disease, mitral valve prosthesis	Penicillin, streptomycin	1	Uveitis, bacterial endocarditis
...	...	Congenital heart disease, Starr-Edwards aortic prosthesis	Penicillin, streptomycin	1 1/2	Bacterial endocarditis
Brain	Arthritis, adenopathy	...	...	3	Bacterial endocarditis
Meninges	...	Congenital heart disease, atrial septal defect repair, mitral repair	...	2/3	Bacterial endocarditis, disseminated intravascular coagulation

Continued

TABLE I (Cont'd) Aspergillus sp. Endocarditis: Clinical Aspects

Case No.	Source	Fungus	Age (yr) and Sex	Presenting Manifestations	Physical Findings				
					Heart Murmur	Fever	Petechiae	Splenomegaly	Hepatomegaly
16	Caplan et al. [17]	A. fumigatus	39, M	Anorexia, malaise, weight loss	+	+	−	+	+
17	Khan et al. [18]	A. fumigatus, C. albicans	41, M	Tachycardia	+	+	+	+	+
18	Mahvi et al. [19]	A. niger	9, M	Leg pain, fever	+	+	+	+	−
19	Mershon et al. [20]	A. terreus	15, M	Low back pain	+	+	+	−	−
20	Hairston, Lee [21] Case 2	A. fumigatus	26, M	Fever	+	+	...	...	...
21	Hairston, Lee [21] Case 4	A. fumigatus	13, M	Fever	+	+	...	...	...
22	Hairston, Lee [21] Case 5	A. fumigatus	63, M	Fever, central nervous system symptoms	+	+	+	...	...
23	Hairston, Lee [21] Case 6	A. flavus	31, M	Fever	+	+	...	...	...
24	Jones et al. [22]	Aspergillus sp.	46, F	Fever, abdominal pain	+	+	+	...	...
25	Br Med J [23]	A. sydowi	31, F	Numbness right leg, Osler's nodes, fever	+	+	+	...	...
26	Aslam et al. [24]	Aspergillus sp.	51, M	Fever	+	+	−	−	−
27	Hairston, Lee [25] Case 6	Aspergillus sp.	14, F	Valve dysfunction	+	...	...	...	...

Evidence of Major Emboli to	Other	Associated Disease	Drug Therapy Before Onset	Total Duration From Probable Onset (mo)	Clinical Diagnosis
Aortic bifurcation, brain	...	Alcoholism, post-gastrectomy	Penicillin, chloramphenicol	1 1/2	Endocarditis
...	...	Rheumatic heart disease, Hufnagel mitral prosthesis	Penicillin, methicillin, streptomycin	1/4	Bacterial endocarditis
Brain, distal aorta	Calf tenderness	Congenital aortic stenosis, post-operative valvuloplasty	Penicillin	3	Bacterial endocarditis
Brain	...	Fibrous body aneurysm, post-operative repair	Oxacillin, streptomycin, ampicillin	2	Bacterial endocarditis
...	...	Rheumatic heart disease, Starr-Edwards aortic prosthesis	Penicillin, streptomycin	1/2	...
Left leg	...	Congenital heart disease, Starr-Edwards aortic prosthesis	Penicillin, streptomycin	4	...
Brain, left heel	...	Aortic insufficiency, Starr-Edwards prosthesis	Cephalothin, corticoids	3/4	...
None	...	Mitral prosthesis, tricuspid repair	Cephalothin preoperatively, "multiple" antibiotics postoperatively	7 1/2	...
Brain	...	Rheumatic heart disease, Starr-Edwards aortic prosthesis	Penicillin, oxacillin, methicillin	3	Bacterial endocarditis
Right femoral artery, right axillary artery	...	Aortic insufficiency, fascia lata repair	...	7	Bacterial endocarditis
Brain, left leg	...	Myxomatous degeneration, Starr-Edwards aortic prosthesis	Erythromycin, streptomycin, cephalothin	1	...
...	...	Mitral and tricuspid insufficiency, mitral prosthesis	Methicillin, penicillin, streptomycin, corticoids	...	Mitral insufficiency

Continued

TABLE I (Cont'd) Aspergillus sp. Endocarditis: Clinical Aspects

Case No.	Source	Fungus	Age (yr) and Sex	Presenting Manifestations	Physical Findings				
					Heart Murmur	Fever	Petechiae	Spleno-megaly	Hepato-megaly
28	Chaudhuri [26] Case 1	A. fumigatus	28, M	Fever, renal failure	...	+	...	...	...
29	Chaudhuri [26] Case 4	Aspergillus sp.	33, M	Fever	...	...	+	...	...
30	Gage et al. [27] Case 2	A. fumigatus	36, M	Fever	...	+	−	−	−
31	Gage et al. [27] Case 3	A. fumigatus	43, M	Fever, convulsions	...	...	+	−	−
32	Br Med J [28]	A. fumigatus	58, M	...	...	+	...	...	...
33	Doshi [29]	A. fumigatus	40, M	Fever, hemiparesis	...	...	+	...	...
34	Ostermiller et al. [30] Case 4	Aspergillus sp.	57, F	Dyspnea	−	+	−	−	−
35	Lawrence et al. [31] Case 1	A. ustus	41, M	...	+	−	−	−	−
36	Lawrence et al. [31] Case 2	Aspergillus sp.	48, M	Leukocytosis	−	+	+	−	−
37	Chelloul et al. [32]	Aspergillus sp.	50, M	Fever, aphasia	...	+	...	...	+
38	Malcolm et al. [33]	A. flavus	34, M	Foot and calf pain	+	+	+	−	−
39	Schelbert, Muller [34]	A. glaucus	31, F	Pain in right leg, fever	+	+	+	+	−
40	Kammer	A. flavus	13, F	Leg pain	+	+	+	−	+

	Evidence of Major Emboli to	Other	Associated Disease	Drug Therapy Before Onset	Total Duration From Probable Onset (mo)	Clinical Diagnosis
	...	Pneumonia	Rheumatic heart disease, Starr-Edwards aortic prosthesis	Penicillin	1/2	Endocarditis
	Brain, eyes, femoral and brachial arteries	Jaundice	Rheumatic heart disease, Starr-Edwards mitral prosthesis	Penicillin	2	Bacterial endocarditis
	...	Weakness	Rheumatic heart disease, Starr-Edwards aortic prosthesis	Penicillin, methicillin, streptomycin, oxacillin	1/2	Bacterial endocarditis
	Brain	Hypotension	Aortic stenosis, Starr-Edwards prosthesis	Penicillin, cephalothin	1/10	...
	...	...	Aortic repair (homograft)	...	...	...
	Brain	...	Rheumatic heart disease, aortic homograft repair	...	3	Bacterial endocarditis
	...	...	Aortic stenosis, Starr-Edwards prosthesis	Methicillin	...	...
	Femoral artery	Valve click disappeared	Aortic stenosis, Starr-Edwards prosthesis	Cephalothin	5	Valve dysfunction
	Femoral artery	...	Aortic stenosis, Starr-Edwards prosthesis	Penicillin, methicillin, chloramphenicol, streptomycin	1/2	...
	Brain	Jaundice, calf tenderness	Mitral stenosis, Starr-Edwards prosthesis	Antibiotics, corticoids	4	...
	Brain, leg	Arthritis	Bicuspid aortic valve postvalvotomy	Penicillin	5	Embolic phenomena
	Left femoral artery	...	Rheumatic heart disease, Starr-Edwards mitral prosthesis	None	1	Bacterial endocarditis
	Brain, leg	...	Rheumatic heart disease, Starr-Edwards mitral prosthesis	Penicillin, nafcillin, streptomycin	1/2	Endocarditis

TABLE II Aspergillus sp. Endocarditis: Laboratory and Anatomic Pathology

Case No.	Source	Urine	Hemogram: Total Leukocyte Count (per mm³)	Hemogram: Anemia	Blood Culture	Location of Vegetation (Endocardial or Endothelial Lesions)	Fungus Identified Microscopically in Vegetation or Embolus	Culture of Vegetation or Embolus (for Aspergillus sp.)	Previous Valvular Damage	Major Emboli to
1	Cawley [2]	...	...	...	...	Left ventricle	V+	V+	—	Spleen, kidneys, brain
2	Zimmerman [3]	...	...	...	—	Aortic and tricuspid valves	V+	...	—	Kidneys
3	Welsh, Buchness [4]	...	1,100 to 3,500	...	—	Right ventricle	V+	V+	...	...
4	Kirschstein, Sidransky [5]	Normal	850	+	...	Tricuspid valve	V+	V+	—	Lungs
5	Grcevic, Mathews [6]	Albumin, pyuria hematuria	35,200	+	—	"Endocardium"	V+	Aspergillus sp. grown from pulmonary lesions	—	Brain, thyroid, kidneys, lungs
6	Hadorn [7]	...	...	+	—	Supravalvular aorta	V+ E+	V+ E+	Subaortic stenosis, postoperative	Legs, brain
7	Luke et al. [8]	Proteinuria, pyuria	...	+	One culture "overgrown by mold"	Right and left ventricles	V+	V+	—	Brain, kidneys
8	Vogel, Heinitz [9]	Occasional erythrocyte	6,200	—	—	Mitral valve	V+	...	—	Meninges, eyes
9	Paradis, Roberts [10]	...	37,000	+	—	Left ventricle	V+	Fungus cultured from pleura	—	Eyes, brain, kidneys, thyroid, jejunum
10	Newman, Cordell [11]	Granular casts	Normal	—	Postmortem +	Starr-Edwards mitral prosthesis (Teflon® sewing ring)	V+	...	Mitral prosthesis	All major vicera, legs
11	Khoo et al. [12]	...	17,600	—	...	Right atrium, right ventricle, left ventricle	V+	V+	—	Brain, kidneys, spleen, thyroid
12	Darrell [13]	Many erythrocytes, albumin	20,000	+	—	Prosthetic Starr-Edwards mitral valve	V+	V+	Mitral prosthesis	Brain, eyes

13	Leffert, Hackett [14]	—	...	...	—	Valve ring, supravalvular aorta	V+	—	Aortic prosthesis	Kidney
14	Satoyoshi et al. [15]	...	4,100	+	—	Mitral and aortic valves	V+	...	—	Brain, kidneys, spleen, liver
15	Doughten, Pearson [16]	...	11,000 to 143,750	+	—	Atrial septum	V+	...	Atrial septal defect repair, mitral repair	Meninges
16	Caplan et al. [17]	Normal	Normal	+	—	Aortic valve, mitral valve, mycotic aneurysm	V+ E+	V+ E+	Rheumatic valvulitis	Brain, kidneys, spleen, liver, aortic bifurcation
17	Kahn et al. [18]	...	13,300	+	—	Mitral prosthesis	V+ E+	E+	Mitral prosthesis	Spleen
18	Mahvi et al. [19]	...	24,000	...	—	Mitral valve, thrombus in aortic root	V+ E+	E+	Aortic valvuloplasty	Brain, spleen, aortic bifurcation
19	Mershon et al. [20]	Many erythrocytes, protein 1+	13,000	—	—	Left atrium, posterior leaflet mitral valve, over homograft	V+	V+	Fascia lata graft repair of mitral leaflet	"Every organ"
20	Hairston, Lee [21] Case 2	...	...	...	—	Aortic prosthetic valve	V+	V+	Aortic prosthetic valve	None
21	Hairston, Lee [21] Case 4	...	...	...	—	Aortic prosthesis	V+ E+	V+	Aortic prosthetic valve	Renal artery, leg
22	Hairston, Lee [21] Case 5	...	...	...	—	Aortic prosthesis	V+	V+	Aortic prosthetic valve	...
23	Hairston, Lee [21] Case 6	...	...	...	+	Mitral prosthesis	V+	?	Mitral prosthesis, tricuspid repair	...
24	Jones et al. [22]	Protein 2+ leukocytes, erythrocytes	12,000 to 34,000	+	—	Starr-Edwards valve ring, cage, and ball	V+	...	Aortic prosthesis	...

Continued

TABLE II (Cont'd) Aspergillus sp. Endocarditis: Laboratory and Anatomic Pathology

Case No.	Source	Urine	Hemogram: Total Leukocyte Count (per mm³)	Hemogram: Anemia	Blood Culture	Location of Vegetation (Endocardial or Endothelial Lesions)	Fungus Identified Microscopically in Vegetation or Embolus	Culture of Vegetation or Embolus (for Aspergillus sp.)	Previous Valvular Damage	Major Emboli to
25	Br Med J [23]	..:	Leukocyte count 20,000	...	—	Aortic valve cusp	V+ E+	V+	Aortic repair (homograft)	Axillary artery, right
26	Aslam et al. [24]	...	...	...	—	Prosthetic valve ring, supraval-vular aorta	V+	...	Aortic prosthe-sis	Kidneys, spleen
27	Hairston, Lee [25] Case 6	...	...	...	—	Annulus of pros-thetic mitral valve	...	V+	Mitral prothe-sis, tricuspid repair	...
28	Chaudhuri [26] Case 1	...	...	...	—	Prosthetic valve, aorta, left ven-tricle	V+	V+	Prosthetic aortic valve	Kidneys
29	Chaudhuri [26] Case 4	...	...	+	—	Prosthetic mitral valve, atrial and ventricular surfaces	V+	...	Prosthetic mitral valve	Brain, kidneys, spleen
30	Gage et al. [27] Case 2	...	Leukocytosis	+	—	Prosthetic aortic valve, mycotic aneurysm of aorta	V+	...	Prosthetic aortic valve	...
31	Gage et al. [27] Case 3	...	Leukocytosis	+	—	Prosthetic aortic valve	V+	...	Prosthetic aortic valve	...
32	Br Med J [28]	...	...	...	+ × 2	Aortic valve	V+	V+	Aortic homo-graft repair	...
33	Doshi [29]	Leukocytes, erythrocytes (many)	...	...	—	Cusps of aortic homograft, as-cending aorta	V+	V+	Aortic repair homograft	Kidneys, spleen
34	Ostermiller et al. [30] Case 4	...	...	...	—	Annulus of aortic prosthesis	V+	V+	Aortic prosthe-sis	"Systemic circu-lation"

35	Lawrence et al. [31] Case 1	...	...	+	−	Aortic valve ring, anterior mitral leaflet	E+	E+	Aortic prosthesis	Leg
36	Lawrence et al. [31] Case 2	No erythrocytes	...	+	−	Below aortic prosthesis, obstructing ventricular outflow tract	...	V+ E+	Aortic prosthesis	Femoral artery
37	Chelloul et al. [32]	...	Leukocytosis	...	−	Mycotic aortic aneurysm, innominate artery	V+	...	Mitral prosthesis	...
38	Malcolm et al. [33]	...	8,200	−	−	Supravalvular aorta	V+	V+	Valvotomy	Brain, kidneys, spleen, leg
39	Schelbert, Muller [34]	...	...	...	−	Mitral prosthesis	V+ E+	E+	Mitral prosthesis	Lungs, liver, spleen, kidneys
40	Kammer	Many leukocytes, 10–15 erythrocytes	25,200 to 38,400	+	−	Prosthetic mitral valve	V+ E+	V+ E+	Prosthetic mitral valve	Brain, leg

TABLE III Aspergillus sp. Endocarditis: Presenting Manifestations and Physical Findings

	Patients (no.)
Presenting manifestation	
Fever	24
Central nervous system abnormalities	8
Symptoms relating to emboli (excluding central nervous system)	8
Physical findings	
Fever	35
Signs relating to emboli	28
Cardiac murmurs	25
Petechiae	15
Hepatomegaly	11
Splenomegaly	9

Associated Disease. Organic heart disease was present in 30 (75 per cent) cases. Twenty-nine patients had prior cardiovascular surgery. Cardiac disease was defined in 20 cases; rheumatic in 11, congenital in 9. Prosthetic valves were implanted in 20 patients (12 aortic, 8 mitral). Four patients received homografts for aortic valve repair. Only five patients had no apparent underlying disease.

Drug Therapy Before Onset. Determining the onset of illness was difficult in many instances. However, of the 40 patients, 30 received antibacterial therapy prior to clinically detected fungal infection. Of the 29 postoperative patients, 23 received prior antibacterial therapy. Twenty-one were given antibiotics at the time of the surgical procedure. Benzyl penicillin was administered to 19 patients, a semisynthetic penicillin to 9, and a cephalosporin to 5. Twelve patients also received streptomycin. Of the remaining 10 patients, 4 received no prior antibacterials, and in the last 6 data were not provided. Corticoids were administered to seven patients.

Hemogram and Urinalysis. Of the routine blood studies, anemia was the most frequent abnormality, being present in 17 (77 per cent) of the 22 cases in which values were given. Leukocytosis, primarily polymorphonuclear, was present in 15 (71 per cent) of 21.

The urine was described in only 13 case reports. In nine some abnormality was present. Pyuria, hematuria and proteinuria were encountered with equal frequency.

Blood Cultures. Blood was cultured in 37 (93 per cent) of 40 patients, but Aspergillus sp. were grown in only 3. A. fumigatus was cultured from blood obtained antemortem in two patients (Cases 10 and 32). In one (Case 10) fungal growth was first noted after 2 weeks' incubation, and after the patient had

TABLE IV Aspergillus sp. Endocarditis: Site of Vegetations

Site	Patients (no.)
Left side of the heart	38
Aortic prosthetic valve	13
Mitral prosthetic valve	8
Ventricle	7
Aorta	7
Mitral valve	5
Aortic valve	4
Aorta only	3
Right side of the heart	5
Ventricle	3
Tricuspid valve	2
Atrium	1
Biventricular	3
Other	
Atrial septum	1
Mycotic aneurysm	4

NOTE: Involvement of multiple sites in several cases results in apparent numerical discrepancies.

died. A. flavus was cultured from blood in one patient (Case 23), but only after 20 days' incubation.

Location of Endocardial or Endothelial Lesions. Precise localization of endocardial or endothelial lesions was possible in every instance either at surgery or autopsy. Endocardial lesions were identified histologically in 37 hearts, and endothelial lesions involving the supravalvular aorta in the remaining 3 (Cases 3, 37 and 38). We have chosen to include the latter because their illness was clinically indistinguishable from endocardial disease. The pathology was left-sided in 38 (95 per cent) cases, biventricular in 3, and confined to the right side of the heart in only 2. These data are summarized in Table IV.

TABLE V Aspergillus sp. Endocarditis: Embolic Phenomena

Organ Involved	Patients (no.)
Brain	18
Kidneys	18
Spleen	13
Extremities	11
Liver	6
Thyroid	2
Eyes	2
Meninges	2
Lungs	2
Ovaries	1
Jejunum	1

Histologic and Cultural Data. Dichotomously branching, septate hyphae were found in endocardial or aortic lesions in 36 patients, and from surgically removed emboli in 9. From 22 of these endocardial lesions and from 7 emboli, Aspergillus sp. were cultured. In two patients with endocardial lesions, Aspergillus sp. were cultured only from another hyphae-containing site, pulmonary abscess in one (Case 5) and pleura in the other (Case 9).

Anatomic Pathology—Major Emboli. Evidence of embolic disease was found in 33 (83 per cent) cases. Brain (55 per cent) and kidneys (55 per cent) were most frequently involved (Table V).

Diagnosis, Therapy and Outcome. The diagnosis, therapeutic regimen and outcome in nine cases diagnosed antemortem appear in Table VI. In eight of these, Aspergillus sp. were found in surgically removed emboli. In the remaining case, Aspergillus sp. were cultured from an infected valve.

Only in one patient (Case 35) was a prolonged

TABLE VI Aspergillus sp. Endocarditis: Diagnosis, Therapy and Outcome

Case No.	Diagnostic Specimen	Microscopic	Culture	Therapy	Outcome
6	Embolus	+	+	Griseofulvin 2 days	Death
16	Embolus	+	+	Amphotericin B 10 days-? dose	Death
18	Embolus	+	+	Amphotericin B 10 days-? dose	Death
21	Embolus	+	+	Amphotericin B,* debridement of vegetations	Death
25	Embolus	+	+	Amphotericin B, unknown dose or duration; valve replacement	Death
27	Valve	?	+	Valve replacement only	Well (1 year)
35	Embolus	+	+	Valve replacement and removal of vegetations, amphotericin B 30–50 mg/day for 60 days, and flucytosine 8 g/day for 4 mo	Well
39	Embolus	+	+	Amphotericin B 3 days	Death
40	Embolus	+	+	Valve replacement, amphotericin B 10 days total dose 115 mg	Death

* No dosage or duration of therapy was stated, but the patient was discharged from the hospital which suggests a completed course of therapy.

course of antifungal therapy administered. The infected valve was replaced also. Another patient (Case 21) may have completed a course of amphotericin B therapy, but his sudden death 3 months afterwards may have represented continuing or recurrent disease.

Seven patients died during therapy. The two who survived had had their valve prostheses replaced. One of these also received long-term antifungal chemotherapy with amphotericin B and flucytosine.

COMMENTS

Predisposing Factors. It seems clear to us from the review of the literature that Aspergillus sp. endocarditis is an opportunistic infection. All but five patients had another disease with potential for adversely altering host defense. As early as 1950, Zimmerman [3] anticipated the current opportunistic epidemic, and in 1955 [36] enumerated the major factors. The detailed discussion of host factor alterations, relating specifically to the opportunistic mycoses, by Hart et al. [37] is recommended in lieu of a multifactorial review here. We will confine our discussion to those host factors having particular relevance to Aspergillus sp. endocarditis.

The average age of the 40 patients was 31 years. This probably reflects selection of young patients for valvular cardiac surgery.

There is a striking male preponderance in this disease. Several investigators have noted similar male to female ratios in other forms of aspergillosis [37–40]. In vitro growth of A. fumigatus was inhibited by physiologic concentrations of estradiol in studies by Mohr et al. [41]. Thus the female milieu, with all its estrogens, may be physiologically hostile to these fungi.

Probably the most important alteration of host defenses in the postoperative cases is the surgical procedure itself. Airborne inoculation of the ubiquitous spores during the prolonged operative exposure remains the most likely source of infection. In the report of Gage et al. [27], Aspergillus sp. were cultured repeatedly from operating room surfaces and occasionally from the air. These fungi were also cultured from areas near the intake port of the operating suite's air conditioning system. Extracorporeal perfusion devices, prosthetic valves or suture material are all potential infective vehicles. Suture lines were frequently the site of attachment for vegetations. Careful surveillance of the surgical environment for pathogenic fungi, and their removal, are reasonable preventive measures.

Potential nonsurgical sources of infection include the multiple violations of the vascular system before, during and after surgery, i.e., intravenous catheters, central venous pressure monitors, cardiac catheters and multiple venipunctures. Although Candida sp. fungemia and endocarditis have been reported in heroin addicts [42], and in patients receiving total parenteral nutrition (hyperalimentation) [43,44], endocarditis due to Aspergillus sp. has not been encountered in these circumstances. However, in one of our patients (Case 7), infection may have resulted from a nonsterile exchange transfusion performed shortly after birth.

The presence of an avascular foreign body, such as a prosthetic valve or suture, probably is a factor in perpetuating infection once inoculation has occurred. However, this is not a requisite as illustrated in this review by 10 cases in which no surgery had been performed. Valvular infections due to relatively avirulent organisms such as Staphylococcus epidermidis are clearly more common in patients with intracardic prostheses [45]. This phenomenon is also seen in neurosurgical patients with intracranial shunts.

Thirty (75 per cent) patients received antibacterial therapy before Aspergillus sp. endocarditis developed. Those with known rheumatic heart disease had received prophylactic penicillin for years. In none of those known to have rheumatic disease did Aspergillus sp. endocarditis occur before valvular surgery. Caplan's patient (Case 16) had rheumatic valvulitis at autopsy but gave no history of rheumatic fever and received no prophylactic penicillin.

Diagnostic Problems. The correct antemortem diagnosis is rarely made. Failure to recognize the clinical milieu in which Aspergillus sp. endocarditis occurs is one reason. Fungal endocarditis was not suspected in any patient. Of 29 case reports listing a clinical diagnosis, it was bacterial endocarditis in 19. Emboli to the central nervous system were misinterpreted as primary neurologic disease in five patients. Embolization was incorrectly attributed to inadequate anticoagulation in several cases.

Blood obtained antemortem grew Aspergillus sp. on only three occasions, yet infected emboli were found in almost every organ. Bulky, friable vegetations were located in areas of turbulent blood flow. Fungemia must occur. Perhaps we are sampling the wrong blood. Left-sided cardiac lesions occurred in 38 (95 per cent) patients. Is the infective hyphal particle too large to traverse the systemic capillary bed and never, or rarely, enters the venous system? Arterial blood cultures were obtained in only two patients, and these were negative. Intermittent fungemia may be the reason why blood specimens rarely yield Aspergillus sp. in culture.

Aspergillus sp. grow in most blood culture media. In 1971 these fungi were isolated 18 times in blood culture bottles at our hospital. Growth may occur too late to be helpful or to be detected by the laboratory. Our blood cultures are discarded after 14 days. In

one of our patients (Case 10), growth was noted after 2 weeks, but the patient was already dead. In another (Case 23), growth occurred after 20 days of incubation. Many laboratories, including ours, would have discarded these latter cultures 6 days earlier.

It is not entirely clear why growth is delayed. On glucose peptone agar, growth of Aspergillus sp. is usually apparent in 48 to 72 hours. However, molds growing in liquid media may not cloud the bottles, as bacterial growth frequently does. Inoculating blood or subculturing onto solid media may permit earlier detection. Examining smears from negative-appearing blood cultures may increase the percentage of positive findings.

Cultural results may be misinterpreted. Aspergillus sp. are often considered as contaminants in the laboratory. In one of our patients (Case 7), the blood culture report read "overgrown by mold," and the culture was thus discarded and disregarded.

Serologic technics may prove to be useful. They are currently being studied in this disease [46]. Base line serum would ideally be obtained before cardiac surgery. A titer of precipitins to Aspergillus sp. would be a helpful diagnostic tool, if it could be correlated with the presence of disease.

Perhaps detection of circulating Aspergillus sp. endotoxin would facilitate earlier diagnosis. Several species, including A. fumigatus and A. flavus, are known to produce endotoxins. Latex particle agglutination using preformed antibody is one possible approach. Presence of endotoxin might precede antibody production or dissemination.

Therapeutic Considerations. Optimal therapy for Aspergillus sp. endocarditis cannot be defined at this time from this sample. Only nine patients were treated. Four received antifungal chemotherapy only. One patient was treated with valve replacement only. The remaining four patients were treated with chemotherapy and surgery.

All four patients treated with chemotherapy alone died. One (Case 6), received a 2-day course of griseofulvin, a drug without expected efficacy. The other three (Cases 16, 18 and 39) were treated with amphotericin B. None received an adequate course of amphotericin B, if death is the ultimate standard of treatment failure.

One patient (Case 27) was treated with valve replacement alone. She survived. In this case, the diagnosis was made by culturing Aspergillus sp. from the infected valve. Thus, this represents the only case recognized prior to dissemination. In all other cases diagnosed, treatment followed embolectomy, de facto evidence of dissemination. It is unlikely that such localized disease will be encountered often. Even if arterial blood or other body fluid yields the fungus in culture, widespread dissemination will have already occurred, and antifungal chemotherapy will be essential.

Four patients (Cases 21, 25, 35 and 40) were treated with surgery and antifungal therapy. One survived (Case 35). In three, the infected valves were replaced (Cases 25, 35 and 40). In one (Case 21) the vegetations were debrided, but the valve was not replaced. Valve replacement plus chemotherapy with both amphotericin B and flucytosine was the successful regimen in Case 35.

No patient has yet survived without valve replacement. Therefore, chemotherapy alone cannot be recommended. Valve replacement alone seems unwise also, since most patients had disseminated disease at the time of diagnosis. Should combined chemotherapy with both amphotericin B and flucytosine be given? We believe so for the following reasons. No available chemotherapeutic agent is ideal. Many Aspergillus sp. are resistant to amphotericin B, and 75 per cent studied by Shadomy [47] were resistant to 12.5 μg/ml of flucytosine. However, amphotericin B and flucytosine have different sites of action on the fungal cell. Polyene antibiotics, such as amphotericin B, bind to sterols in the fungal cell membrane and induce alterations in permeability [48]. Flucytosine, a fluoro pyrimidine, competes with essential pyrimidines and blocks the biosynthesis of nucleic acids [49,50]. Medoff et al. [51] recently demonstrated in vitro synergism using combinations of amphotericin B and flucytosine against Candida sp. and C. neoformans. These investigators postulated that amphotericin B altered cell membrane permeability allowing flucytosine to enter the fungal cells in greater quantities. Initiating chemotherapy using both drugs seems reasonable pending in vitro sensitivity data.

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