CASE REPORTS

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Bacterial Endocarditis Due to Actinobacillus Actinomycetemcomitans In a Patient with a Prosthetic Aortic Valve

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A 42-YEAR-OLD MAN WHO HAD had a Starr-Edwards prosthetic aortic valve inserted five years previously was admitted for evaluation of fever, chills, nocturnal diaphoresis, and weight loss. Splenomegaly, anemia and microscopic hematuria were found on admission and a diagnosis of bacterial endocarditis was made. Seven of nine initial blood cultures yielded Actinobacillus actinomycetemcomitans. The patient was treated with penicillin and streptomycin over a six-week period, cure apparently resulting. This represents the first report of Actinobacillus actinomycetemcomitans endocarditis in a patient with a prosthetic heart valve. The clinical experience of infection due to Actinobacillus actinomycetemcomitans is reviewed.

Actinobacillus actinomycetemcomitans (A.a.) is a rare cause of bacterial endocarditis. Twenty-three cases of A.a. endocarditis are cited by Page and King in an extensive review of human infection due to this organism and Hemophilus aphrophilus.[1] However, only eight cases of endocarditis in which A.a. was the sole infecting microorganism have been previously described in detail.[2-9] Five of these eight patients had underlying rheumatic valvular heart disease; one had a bicuspid aortic valve and coarctation of the aorta, and one had no underlying heart disease. In one case, sufficient information to determine the presence or absence of previous heart disease was lacking. Actinobacillus actinomycetemcomitans endocarditis has not been previously described as a complication of a prosthetic valve operation.

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Case Report

The patient, a 42-year-old white man, had rheumatic fever at age 21 with subsequent aortic insufficiency, complicated by congestive heart failure, chest pain and dizziness. He was said to have had mycardial infarction at age 28. He was admitted to the San Francisco Veterans Administration Hospital for the first time on May 31, 1961, with a history of fever to 104° F, chills, diaphoresis, and anorexia for the preceding ten days. No physical findings of bacterial endocarditis were present and five blood cultures, urine cultures and throat culture were negative. It was felt that he had a viral illness, and he improved without specific treatment.

On May 15, 1962, and again on May 27, 1965, he underwent right and transeptal left heart catheterization which confirmed the presence of moderately severe aortic insufficiency. On February 22, 1966, he was readmitted because of progressive angina and dyspnea on exertion. Early in the hospital course, he had a non-specific febrile illness attributed to "flu," and all of 20 blood cultures were negative. He improved without specific therapy. On March 9, 1966, a Starr-Edwards prosthetic aortic valve was inserted. At operation the aortic valve cusps were found to be thin and delicate without fibrosis, but because of redundancy they failed to coapt and thus produced aortic insufficiency. It was

felt that the valve defect was due to rheumatic valvulitis. The postoperative course was complicated by intermittent fever, lymphocytosis and splenomegaly, which were attributed to postperfusion syndrome. No embolic manifestations or changing murmurs were present to suggest bacterial endocarditis and 48 out of 50 blood cultures were negative. The other two yielded an anaerobic diphtheroid and Pseudomonas, both presumably contaminants. The patient was treated with corticosteroids, with gradual improvement. When discharged on May 28, 1966, the patient had a grade II/VI diastolic murmur along the left sternal border. Hemoglobin was 12.1 grams per 100 ml of blood and the hematocrit was 36 percent.

Subsequently the patient did well until April 1969, when he had an episode of infectious hepatitis. During that admission, a new grade III/VI pansystolic ejection murmur was heard over the entire precordium. The diastolic murmur was unchanged; the spleen was not palpable, and no other signs of bacterial endocarditis were present. One blood culture was negative.

The patient was readmitted on December 21, 1970, at the age of 42. Seven weeks previously he had been struck on the leg by a falling desk, which caused a skin abrasion. The next day he began to experience chills, fever, nocturnal diaphoresis, anorexia, weakness and malaise, and over the next week he lost 14 pounds. On November 19, 1970, he consulted a private physician, and physical examination was unrevealing except for aortic systolic and diastolic murmurs described above. A complete blood count and urinalysis were normal. The sedimentation rate was 75 mm in one hour. Two blood cultures were negative. Erythromycin was given, 250 mg orally four times a day for five days, with considerable symptomatic relief. Two weeks later he again experienced malaise and fever and was treated with erythromycin by mouth for ten days, with improvement. No further blood cultures were obtained. However, nocturnal diaphoresis and fever to 38.9 C (102° F) recurred and on December 16, 1970, the tip of the spleen was felt. He was then referred to the San Francisco Veterans Administration Hospital. The patient denied recent dental or urological manipulations and had had no known recent urinary or respiratory infections.

On physical examination he appeared acutely ill. Blood pressure was 115/70 mm of mercury, pulse 90, temperature 37.1° C (98.8° F). The skin was pale; no splinter hemorrhages, Osler's nodes, Janeway lesions, or mucosal lesions were present. No Roth spots were seen in the fundi. The lungs were clear. A grade III/VI harsh systolic ejection murmur was heard over the aortic area radiating to the neck, and a grade II/VI diastolic descrescendo murmur was heard along the left sternal border; both murmurs were unchanged from April 1969. The prosthetic valve sounds were judged to be within normal limits. The liver was felt 3 cm below the right costal margin. The spleen tip was felt and tenderness on pressure was noted. Neurological examination was unremarkable except for mild generalized weakness.

Admission laboratory data included hemoglobin of 12.3 grams per 100 ml of blood, hematocrit of 39 percent and leukocytes 9,400 per cu mm with 79 percent neutrophiles, 17 percent lymphocytes, 3 percent monocytes, and 1 percent band forms. The corrected Wintrobe erythrocyte sedimentation rate was 30 mm in one hour (normal 0-10 mm). The platelet count was 220,000. Urinalysis showed 100 to 200 red blood cells per high power field. Blood urea nitrogen, creatinine, fasting blood glucose, total protein, albumin, alkaline phosphatase, SGOT, uric acid, and electrolytes were within normal limits. A cardiac x-ray series showed clear lung fields, normal heart size and prominence of the aortic arch; the prosthetic valve was in appropriate position. An abdominal x-ray confirmed the presence of slight splenomegaly. Electrocardiogram showed left ventricular hypertrophy, with no significant change since September 17, 1968. No evidence of aortic ball variance was seen on a phonocardiogram.

The admitting diagnosis was bacterial endocarditis. Nine blood cultures were obtained in the two-day period before the initiation of antibiotics. On the second hospital day the patient had fever of 38.8 C (101.9° F). Therapy with penicillin G, five million units intravenously every six hours, and streptomycin, 500 mg intramuscularly every 12 hours, was begun. On this regimen he became afebrile by the eleventh day. Streptomycin was discontinued after 19 days because of signs of eighth nerve toxicity, which subsequently disappeared. After three weeks of antibiotic therapy, serum was bacteriostatic and

bactericidal against the organism described below at a dilution of 1:8 immediately after penicillin administration and at a dilution of 1:1 one hour and 45 minutes afterward. The penicillin dose was therefore increased to 30 million units per day (five million units intravenously every four hours) and probenecid was added. On this regimen, which was maintained for an additional three weeks, serum was bacteriostatic and bactericidal at a dilution of 1:128 immediately after and at a dilution of 1:16 one hour and 15 minutes after penicillin administration. During the six weeks of penicillin therapy the microscopic hematuria and splenomegaly gradually cleared. There was no change in the heart murmurs heard on admission. The patient remained afebrile except for transient fever during the fifth week of therapy, which was attributed to a "flu" syndrome.

The first of the nine blood cultures yielded two strains of diphtheroids, thought to represent contaminants. Of the remaining eight, one was negative and seven grew, after five days of incubation, a fastidious, Gram-negative coccobacillary organism which was later identified by the National Center for Disease Control in Atlanta, Georgia, as Actinobacillus actinomycetemcomitans (N.C.D.C. number 51-B7359-71). The biological and biochemical properties of this organism, which allowed for its initial recognition at the N.C.D.C. are shown in Table 1. Antibiotic sensitivities, as determined by the disc method, were difficult to determine and inconsistent because of the low yield of organisms. Eight blood cultures were obtained over a five and a half week period after the initiation of antibiotics. All were negative. After conclusion of antibiotic therapy the patient was observed for four days and in that time had no fever or other evidence of recurrence of illness. On February 8, 1971, he was discharged to the care of his private physician. Results of cardiac examination showed no change, the spleen was not palpable, and there was no hematuria. He was doing well on follow-up outpatient visits at three weeks and again at four months after discharge.

TABLE 1.—*Biological and Biochemical Properties of Actinobacillus Actinomycetemcomitans Isolated in Case Here Reported

1. Fermentation Characteristics

Medium	*Result*
glucose	+(A)†
mannitol	+(A)
maltose	+(A)
xylose	–
lactose	–
sucrose	–

†(A) = acid production

2. Growth on Selected Media

Medium	*Result*
MacConkey	–
S.S. plate	–
Citrate slant	–
Urea	–
Nitrate broth	+
Indol broth	–
Gelatin stab	–
H_2S paper	1+

3. Miscellaneous Characteristics
   - CO_2 required for growth
   - 37° C temperature required for growth
   - Catalase production positive
   - Oxidase production negative
   - Motility absent

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Discussion

Actinobacillus actinomycetemcomitans is a bacterial species first described in 1912 by Klinger, who isolated it from the pus of patients with actinomycosis.[10] Numerous subsequent reports describe the close association between this organism and Actinomyces.[11-14] In 1951, Thjøtta and Syndes reported a case of infection of the jaw of a young woman after tooth extraction, but the fermentation characteristics of the organism isolated were not those of A.a.[15] In 1953, Vallee and Gaillard mentioned (in a footnote) isolation of A.a. in blood cultures of patients with endocarditis, but no details were given.[16] Because the organism they described fermented arabinose, it is doubtful that it was in fact A.a. King and Tatum were the first to describe unequivocal cases in which A.a. was the sole infecting agent in man.[17] They reported 32 cases of documented A.a. infection unassociated with actinomycosis and compared the biochemical and serological characteristics of 33 strains of A.a. and 34 strains of Hemophilus aphrophilus, an organism closely related to A.a. These data have more recently been reviewed by Page and King, who noted that of the 32 cases in which A.a. was isolated, 23 were cases of endocarditis, which seems to be the most common type of infection due to this organism.[1]

Rarely, however, is A.a. isolated as a pathogen

TABLE 2.—*Data on Reported Cases of Actinobacillus Actinomycetemcomitans Endocarditis*

Source	*Age*	*Sex*	*Heart Disease*	*Cultures Positive*	*Antibiotic Treatment*	*Outcome*
1. Thomas[2]	49	M	Bicuspid aortic valve and coarctation of aorta	4/?	Penicillin, streptomycin, erythromycin, chloramphenicol	Died
2. Serra and Tonato[3]	41	M	Rheumatic	12/12	Ampicillin, streptomycin	Cured
3. Vogelzang[4]	27	M	Rheumatic aortic stenosis	Initial cultures negative; all positive at 8 days	Penicillin, tetracycline, streptomycin	Died
4. Goss, et al[5]	39	M	No underlying disease	10/?	Penicillin, streptomycin	Died
5. Overholt[6]	57	M	Rheumatic mitral insufficiency	6/6	Penicillin, chloramphenicol, streptomycin	Died
6. Kayser[7]	52	M	Rheumatic mitral valvulitis	4/?	Cephalothin, penicillin, streptomycin	Cured
7. Underhill[8]	68	M	Mitral valve disease (? rheumatic)	More than 9 cultures positive	Ampicillin, streptomycin	Cured
8. Mitchell and Gillespie[9]	50	M	Rheumatic	Four initial cultures negative; three subsequent cultures positive	Penicillin, streptomycin	Cured
9. Present Case	42	M	Prosthetic aortic valve	7/9	Penicillin, streptomycin	Cured

in human infection, possibly due to its fastidious growth characteristics and difficulty in identification. These factors presumably account for failure of two blood cultures obtained in the first week of our patient's illness to yield A.a. Page and King reported seven patients with soft-tissue lesions from which A.a. was recovered, and in four of them the clinical diagnosis was actinomycosis. Of the remaining three, one had an abscess of the jaw and another had a facial abscess. A.a. has also been recovered as a pathogen in at least one case of urinary tract infection.[18] A.a. has been found in the normal flora of the mouth.[19-20] A.a. endarteritis has been described in a patient with a congenital fistula of the right coronary artery to the right ventricle.[21]

Numerous articles reviewing experience with endocarditis make no mention of A.a.[22-27] Only eight cases of well-documented A.a. endocarditis have been found in the literature; four were fatal (Table 2.) It is of interest that the patient described by Vogelzang and our patient were from the same county (Stanislaus) in California. Five of the nine patients had illnesses of varying types for which they were treated with antibiotics, usually penicillin, shortly before the onset of clinically recognizable endocarditis.

The portal of entry of the organism in our case is not clear. Entry through the skin abrasion acquired seven weeks before admission is speculative. In the case reported by Underhill, it was presumed that a dental abscess was the portal of entry, and the patient of Mitchell and Gillespie had a dental extraction covered with penicillin six months before the onset of symptoms. In view of the findings of A.a. in the normal mouth flora, these reported cases suggest that oral lesions may be a significant mode of entry. Major embolic complications, common in previous cases, were absent in our patient. In each of the fatal cases cited, autopsy confirmed endocarditis involving an abnormal heart valve.

Postcardiotomy endocarditis is most often caused by Staphylococci,[28-29] but a wide variety of other microorganisms have been implicated. The bacterial group is diverse and includes Streptococcus, Escherichia coli, diphtheroids, Alcaligenes faecalis, Pseudomonas, Achromobacter species, Aerobacter, Proteus, Paracolobactrum aerogenes, Herrellea, Paracolon hafnia, Serratia marcescens, and Neisseria perflava.[28-32] The fungal group includes several species of both Candida and Aspergillus.[29,33,34,35] Although postcardiotomy endocarditis usually appears within the first two to four weeks after operation,[28] cases have been reported as long as six years after a surgical procedure.[36-37] In our case, 56 months elapsed between operation and onset of symptoms of endocarditis. The occurrence of prosthetic valve endocarditis long after operation raises questions about the origin of the infection.[32] Sources such as tooth extractions, urinary tract manipulations, respiratory infections, pyelonephritis, and pyoderma have been cited.

Prosthetic valve endocarditis is associated with high morbidity and mortality.[38] In 97 cases recently reviewed by Shafer and Hall, the mortality rate was 72 percent.[32] Nevertheless, cure of prosthetic valve endocarditis has been accomplished with antibiotic therapy alone or in conjunction with surgical operation. Conservative management with antibiotics alone has generally been unsuccessful, although in three of ten cases cited by Killen the patient survived without resort to surgical operation.[39] There is uniform agreement that replacement of the infected prosthetic device is indicated for infections unresponsive to antibiotics alone and for hemodynamic imbalance due to valvular insufficiency or obstruction by vegetations or thrombi. The case herein described represents another report of apparent cure by antibiotic therapy. The high mortality of prosthetic valve endocarditis emphasizes the need for early recognition of this complication and treatment with appropriate antibiotic therapy.

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Severe Obstructive Nephropathy

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URINARY TRACT OBSTRUCTION has a profound effect on renal physiology and may be indistinguishable from severe primary renal disease. The standard textbooks[1,2,3] provide excellent reviews of historic and current physiologic thinking, yet beyond these there are few quantitative reports of high grade obstructive nephropathy.

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