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Fatal *Vibrio fetus* Endocarditis: Report of One Case and Review of the Literature

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Summary. Clinical, bacteriologic, and autopsy findings in a case of a 67-year-old man confirmed the diagnosis of *Vibrio fetus* endocarditis of the aortic, mitral, and tricuspid valve. To our knowledge, this is the first case to involve three valves. The bacterial endocarditis was superimposed on an old, probably rheumatic, endocarditis of the aortic valve, with minimal involvement of the mitral and tricuspid valves. A review of the literature indicates that the aortic valve is the most frequent site of *V. fetus* endocarditis.

Whereas, *Vibrio fetus* is known to cause infectious abortion in cattle and sheep, it is a rare cause of human infections. In human *V. fetus* infection, an important manifestation is endocarditis. We know of five previous publications (Auquier *et al.*, 1956; King, 1957; Lawrence *et al.*, 1967; Loeb *et al.*, 1966; Thibault *et al.*, 1955) describing eight cases of *V. fetus* endocarditis. In only one of the eight cases has the endocarditis been confirmed at postmortem examination (Loeb *et al.*, 1966). Recently, we have observed another case of *V. fetus* infection in which we confirmed the presence of the endocarditis at autopsy.

Report of Case

A 67-year-old white farmer was seen on Apr. 29, 1968. He had had a heart murmur for 20 years, but there was no history of rheumatic fever. In August and November 1965, diagnoses of prostatic carcinoma (needle biopsy) and aortic stenosis were made at the Mayo Clinic. An orchiectomy was performed, and the patient was given diethylstilbestrol. Reexaminations in July 1966 and January 1968 revealed no evidence of metastasis from the prostatic malignancy.

Early in March 1968, 2 months prior to admission, the patient had a temperature of 102 F, chills, sweats, diarrhea that lasted for about 1 week, anorexia, nausea, a 10-lb loss of weight, fatigability, malaise, and an accentuation of recurring epigastric distress that had been noted for several years. One month prior to admission, a 10-minute episode of double vision occurred. The patient had been hospitalized on Mar. 8 and had been given antibiotics both orally and parenterally for 1 week; no diagnosis was made, but the symtoms were controlled. On Mar. 22, 1 week after dismissal, chills and fever recurred. An antibiotic was given orally for an additional week; the last dose was taken on Apr. 15. After this, fever and sweats, increasing fatigability, weakness, and anorexia recurred, and the patient returned to the Mayo Clinic on Apr. 29, 1968.

Additional medical history revealed only some effort dyspnea, and an increasing frequency and severity of epigastric and right upper quadrant dull aching pain mentioned previously, which had been present intermittently but was now constant during the present illness. This pain was associated with fatty-food ingestion, when it became sharper and more severe. There was associated nausea with the pain but no vomiting or extension of the pain from the areas mentioned.

Physical examination revealed a thin, sickly man. The pertinent physical findings were a temperature of 101 F, a slightly enlarged heart, and a grade 4 to 5 (on the basis of grade 1 to 6) aortic systolic murmur, which was transmitted to the apex and to the carotid arteries (an apparent change from earlier examination). There was a thrill associated with the murmur. The carotid pulses revealed thrills over the arteries. Rectal examination revealed an irregular enlarged prostate with areas of stony hardness. The testes were absent. Minimal-to-moderate ankle edema up to the middle of the calf was present. One questionable petechial lesion was noted on the left big toe, but no other evidence of embolization was found.

The pertinent laboratory findings were: blood hemoglobin value of 11 g/100 ml initially and 7.9 g 2 weeks later, leukocyte counts of 7,400 to 12,200/cu mm, serum iron value of 24 mg/100 ml, and reticulocyte counts of 2.3 to 4.2%. Blood smears showed fragmented red cells and were interpreted as representing a microangiopathic and hemolytic disorder. A sulfobromophthalein test revealed 8% retention. Serum protein electrophoresis revealed a reduced value for total proteins of 5.71 g/100 ml, with a reversal of the ratio of albumin (1.85 g) to globulin (3.86 g).

No abnormalities were indicated by numerous blood chemistry and blood enzyme determinations, two peripheral blood lupus erythematosus clot tests, blood febrile agglutination tests, stool studies, thick blood smears for malaria, and immunologic studies for histoplasmosis. The tuberculin skin test with the single-strength tuberculin PPD was positive. Roentgenograms of the kidneys, gallbladder, and stomach, and electrocardiograms were normal. A roentgenogram of the chest was normal initially, but 1 week later, another showed questionable increase in the transverse diameter of the heart. Urinalyses revealed occasional hyaline, granular, red blood cell, epithelial, waxy, and leukocytic casts and a moderate number of red blood cells and pus cells per high-power field, as well as minimal proteinuria. On two occasions, urine cultures revealed 5 to 10,000 colonies of enterococci per milliliter. The creatine clearance was 74 ml/min/1.73 sq m and the serum creatinine was 1.05 mg/100 ml initially and 3.15 mg terminally.

Eighteen blood cultures were obtained from Apr. 30 through May 10, and all were negative after 2 days of incubation.

The clinical course was one of progressive deterioration during the observation period. The patient was febrile daily, with the temperature as high as 102.6 F. On May 7, the day after admission, pain and tenderness were present in the left calf; a diagnosis of left sural thrombophlebitis was made. On May 9, anticoagulant treatment was started because of progressive phlebitis and the negative blood cultures and because it was thought that the clinical findings were not consistent with bacterial endocarditis but were more consistent with metastatic carcinoma and associated peripheral phlebitis. On May 12, the condition of the left calf showed improvement, and anticoagulant therapy was stopped. By May 15, the 18 blood cultures were still negative. However, because of the continued deterioration of the patient and because of the potential likelihood of endocarditis, therapy was started with 40 million units of penicillin-G and 1 g of streptomycin per day. The next day, ileus and abdominal distention developed. On May 17, the patient's course appeared terminal, even though his temperature had gradually decreased to normal, and a preliminary report on the blood cultures revealed the presence of a gram-negative rod; eventually 10 of the 18 blood cultures grew organisms identified as *V. fetus*. Because of this, tetracycline given intravenously was added to the program. The next day, acute pulmonary edema developed and the patient died.

Postmortem examination revealed that the heart and lungs were the sites of the main pathologic findings. The heart weighed 400 g (normal 285 g). There was left and minimal right ventricular hypertrophy. The tricuspid, pulmonary, and mitral valves were competent. There was minimal thickening of the tricuspid valve, with tiny vegetations at the atrial surface, particularly of the septal leaflet (Fig. 1). The pulmonary valve showed no gross

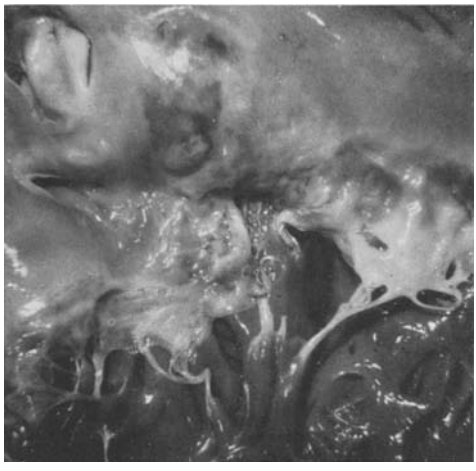

Fig. 1. Tricuspid valve. Posterior and septal leaflets are somewhat thickened, with tiny vegetations on atrial surface. Base of penetrating ulcer of aortic valve can be seen through the somewhat puckered atrial endocardium, just above posterior leaflet and anterior to foramen ovale

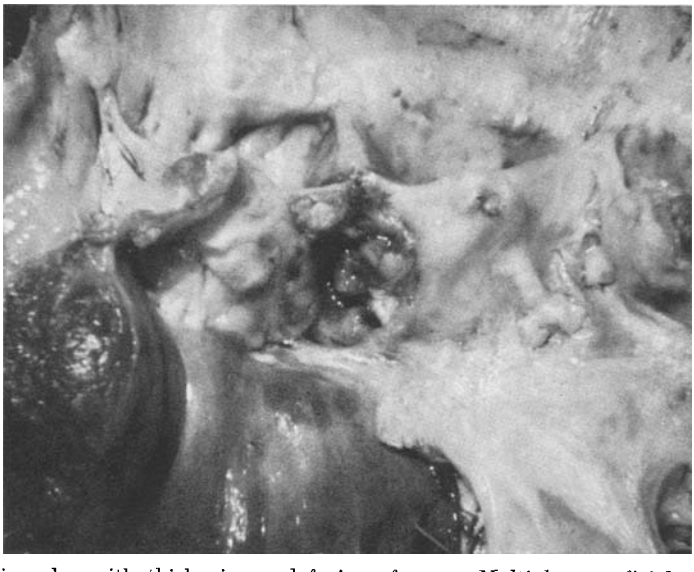

Fig. 2. Aortic valve with thickening and fusion of cusps. Multiple superficial vegetations. Ulcer at commissure between right coronary and noncoronary cusps

abnormalities. The mitral leaflets also showed minimal thickening, with tiny vegetations at the atrial surface. The aortic valve was most severely affected: all three cusps were thickened, scarred, retracted, and fused at the commissures, rendering the valve insufficient and stenotic. Multiple, yellowish gray, and friable vegetations, as much as 5 mm in diameter, were found at the aortic and ventricular surface of all three cusps. An ulcer of about 1.5 cm in diameter was found between the right coronary and noncoronary aortic cusps (Fig. 2), penetrating into the wall of the right atrium. The base of this ulcer appeared under the right atrial endocardium (Fig. 1). There were no other sites of endocarditis. Severe coronary atherosclerosis and a recent myocardial infraction in the posterior wall of the left ventricle were also present.

Microscopic examination of the heart revealed vascularization, fibrosis, and calcification of the cusps of the aortic valve, with granulation tissue (Fig. 3 A). The superficial vegatations and the walls of the ulcer consisted of granulation tissue, numerous polymorphonuclear leukocytes, fibrin, cellular debris, and necrosis. The mitral valve (Fig. 3 B) and the tricuspid

valve (Fig. 3C) showed minimal fibrosis, with superficial foci of acute endocarditis, characterized by small areas of fibrinoid necrosis, and cellular debris intermingled with inflammatory cells, predominantly polymorphonuclear leukocytes. Numerous gram stains were prepared of all valvular lesions; no microorganisms were found.

Examination of the lungs showed bronchopneumonia and congestion with hemorrhagic edema. Neither the gross nor the microscopic examination revealed septic metastases.

Additional significant findings were: bilateral hydrothorax; passive congestion of the liver, spleen, and kidneys; petechial hemorrhages of the skin and intestinal mucosa; microscopic adenocarcinoma of the prostate without metastases; gynecomastia secondary to diethylstilbestrol therapy, and an old (3 years) bilateral orchiectomy. The sural veins were not studied.

Ten blood cultures taken between May 6 and May 15, 1968, became positive 7 to 15 days later, growing a small, slender gram-negative bacillus, which after repeated subcultures became curved in appearance. The bacillus grew poorly on subculture on trypticase soy and heart-infusion agar, and growth was enhanced by blood enrichment and incubation in an environment with 10% carbon dioxide. Even under these conditions, however, growth was very scanty at 48 hours and became heavier only after 3 to 4 days of incubation.

Biochemically, the organism was oxidase- and catalase-positive, and it reduced nitrates to nitrites. Citrate was not utilized, urea was not hydrolyzed, indole was not produced, and results of methyl red and Voges-Proskauer tests were negative. Further study by Dr. Robert Weaver of the National Communicable Disease Center in Atlanta demonstrated the following: no fermentation of glucose, xylose, mannitol, lactose, sucrose, or maltose; no growth in either open or closed tubes of oxidative-fermentative (O-F) medium; negative gelatin liquefaction, motility, esculin hydrolysis, or growth on cetrimide agar; a small amount of H_2S production, as detected by lead acetate paper; and growth at 25 and 37° C but not at 42° C. Because the organism was rough, Dr. Weaver was unable to complete agglutination studies.

Postmortem bacteriologic cultures, as well as myobacterial, fungal, and viral cultures, of heart blood, right pleural fluid, and vegetation on the aortic valve were negative.

Discussion

Vincent and associates reported the first case of human *V. fetus* infection in 1947. In 1965, Kilo and associates reviewed 30 cases, including a series of 15 cases of King (1957), with detailed clinical data. During the last 3 years, 11 additional cases of human vibriosis came to our attention (Darrell *et al.*, 1967; Eden, 1962; Killiam *et al.*, 1966; Lawrence *et al.*, 1967; Loeb *et al.*, 1966; White, 1967; Willis and Austin, 1966). The ages ranged from infancy to 74 years. The infection was far more common in males than in females. Only seven women were affected, four of whom were pregnant.

The cardiac and vascular endothelium seemed to be the predominant site of *V. fetus* infection (Auquier *et al.*, 1956; Kahler and Sheldon, 1960; Loeb *et al.*, 1966). Some evidence of cardiovascular involvement was noted in 15 of 42 cases. Bacterial endocarditis was diagnosed in eight (Auquier *et al.*, 1956; King, 1957; Lawrence *et al.*, 1967; Loeb *et al.*, 1966; Thibault *et al.*, 1955) of these cases; our own case makes a total of nine. Symptoms of thrombophlebitis were observed in five cases (Auquier *et al.*, 1956; Kahler and Sheldon, 1960; Kilo, 1965; King,

Fig. 3. A Aortic cusps. Fibrosis and calcification. Superficial layer of granulation tissue. Vegetation mainly consisting of fibrin and infiltrates of polymorphonuclear leukocytes. (Hematoxylin and eosin; ×60.) B Mitral valve with superficial focus of endocarditis. Polymorphonuclear leukocytes, fibrinoid necrosis, and cellular debris are present. Note swelling of endothelial cells. (Hematoxylin and eosin; ×170.) C Tricuspid endocarditis. Similar changes as in mitral valve. (Hematoxylin and eosin; ×160; Figure reduced to $^{19}/_{20}$)

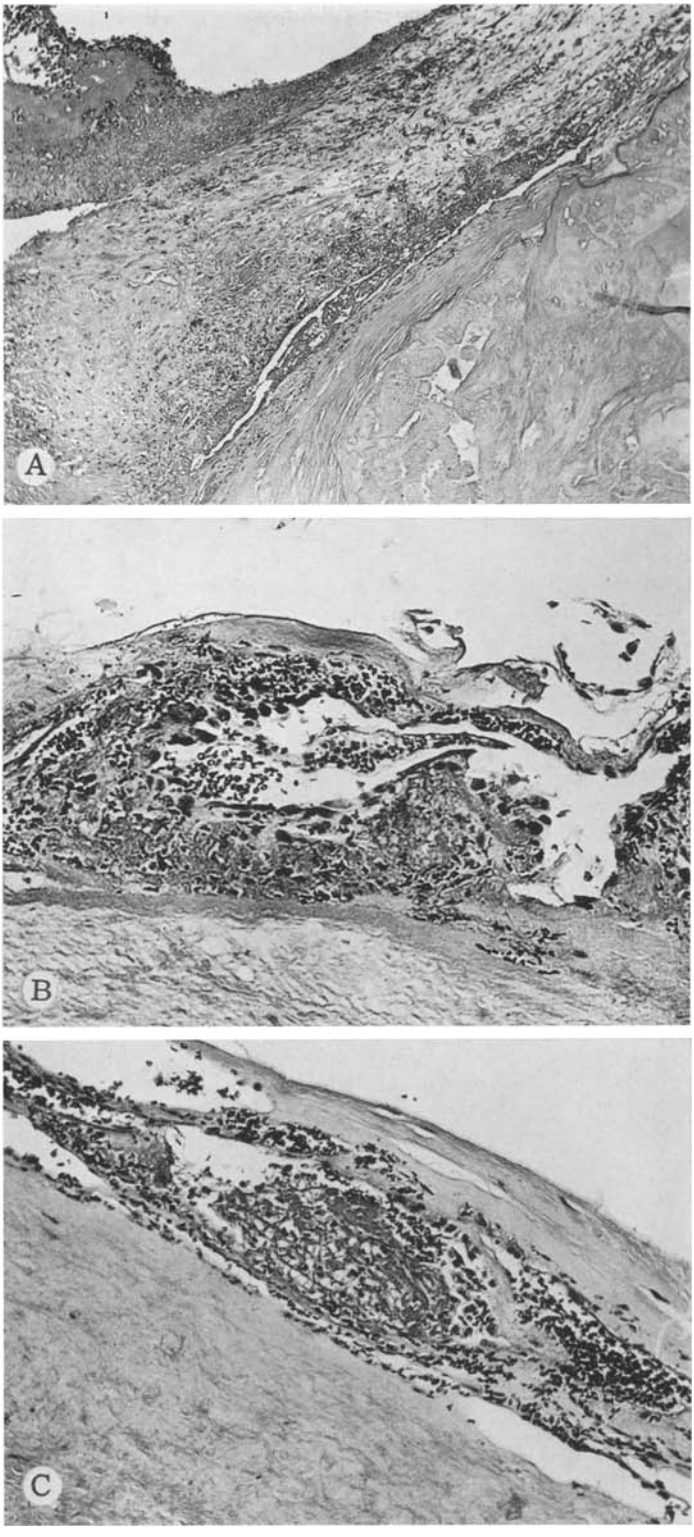

Abb. 3 A—C

Table. *Summary of nine cases of Vibrio fetus endocarditis*

Sex and age, yr	Occupation	Previous condition	Main symptoms	Cardiac findings	Treatment	Outcome
♂, 51 (Thibault *et al.*, 1955)	Lathe operator	Rheumatic fever with mitral valve disease; cardiac decompensation	Fever and chills	Not described	Aureomycin	Cured; cerebral embolism resulting in paresis
♂, (?) (Thibault *et al.*, 1955)	Unknown	6 teeth extracted 8 days prior to onset of endocarditis	Fever and chills	Diastolic murmur (location not described)	Penicillin, steptomycin, and oxytetracycline, no effect; chloramphenicol, temperature to normal, blood culture became negative	Cured; heart murmur persisted
♂, 44 (Auquier *et al.*, 1956)	Stockman in warehouse	Maxillary sinusitis; 6 teeth extracted (for root abscess) 8 days prior to onset of endocarditis	Fever, chills, and headache	Murmur of aortic insufficiency; apical systolic murmur	Penicillin, oxytetracycline, and erythromycin, no effect; chloramphenicol, temperature to normal, blood culture became negative	Cured; aortic insufficiency and cardiac decompensation persisted
♂, 50 (King, 1957)	Painter	Athletic heart; "bad teeth" extracted	Fever and chills	Subacute bacterial endocarditis (no further description)	No treatment	Unknown
♂, 47 (King, 1957)	Janitor	Cirrhosis of liver	Fever	Subacute bacterial endocarditis	No treatment	Died, gastrointestinal hemorrhage; endocarditis possibly due to *E. coli*

♂, 67 (Loeb *et al.*, 1966)	Construction laborer	Old pulmonary tuberculosis; chronic alcoholism; debility	Fever, chills, and mental confusion	Normal on admission	Cortisone, isoniazid, streptomycin, and penicillin, no effect	Died, 8th hospital day; autopsy confirmed aortic and mitral endocarditis
♂, 49 (Loeb *et al.*, 1966)	Cab driver	Informed of "heart condition" at age 12 yr; no symptoms	Fever, chills, and pain and tenderness of left thigh	Murmur of aortic insufficiency and stenosis; aneurysm of left femoral artery	Penicillin and streptomycin, no effect; responsed to tetracycline	Died, 1 mo later; acute pulmonary edema; no autopsy
♀, 49 (Lawrence *et al.*, 1967)	Housewife	Chorea at age 5 yr, congestive heart failure and atrial fibrillation 2 mo prior to onset of endocarditis	Fever and chills	Murmur of mitral stenosis and insufficiency and aortic insufficiency	Ampicillin and streptomycin, no effect; responded to tetracycline	Cured; well until 1 yr later, congestive heart failure secondary to mitral and aortic insufficiency (by catheterization); blood and cervix cultures were negative
♂, 67 (present case)	Farmer	Aortic valve disease; murmur known for 20 yr	Fever and chills; left sural thrombophlebitis	Moderately loud systolic aortic murmur	Penicillin and streptomycin	Died, 12th hospital day, bacterial endocarditis; aortic, mitral, and tricuspid valves affected

1957), and evidence of both endocarditis and phlebitis in one case (Auquier *et al.*, 1956). *V. fetus* pericarditis (Killiam *et al.*, 1966) and a myotic femoral artery aneurysm complicating *V. fetus* endocarditis (Loeb *et al.*, 1966) also have been described.

Nine cases of *V. fetus* endocarditis are summarized in the Table; four of the patients died. Postmortem examination confirmed the diagnosis of endocarditis in one case of Loeb and associates (1966) and in our case. In King's series (1957), endocarditis was also diagnosed at autopsy in one case, but infection was believed to be due to *Escherichia coli* rather than *V. fetus* (Finegold, personal communication to the authors). The aortic valve was most often involved. Evidence of an old aortic endocarditis of probable rheumatic origin was found in five cases, with mitral involvement in two, and minimal mitral and tricuspid involvement in our own case. There were three cases reported (Auquier *et al.*, 1956; King, 1957; Thibault *et al.*, 1955) in which teeth had been extracted prior to the onset of *V. fetus* endocarditis; thus it

appears reasonable to assume that just as in other types of bacterial endocarditis, the microorganism may enter the bloodstream from infected teeth.

Our patient did not have the classic clinical features of bacterial endocarditis. The diagnostic problem was complicated by a history of cancer of the prostrate and clinical findings consistent with metastatic disease, such as physical deterioration, fever, upper abdominal pain, and peripheral thrombophlebitis, in addition to the early absence of positive blood cultures. Despite blood cultures incubated under a cover of carbon dioxide, the blood cultures did not become positive until 7 to 15 days of incubation. In retrospect, antibiotic therapy on an empiric basis perhaps should have been given earlier, and this probably would have been done if the acute sural thrombophlebitis had not occurred.

Diagnosis of *V. fetus* infection can be made only by isolation and identification of the organism, as described by King (1962) The appearance of short-curved gram-negative bacilli may be helpful in the diagnosis, but these were absent in our case until after repeated subcultures. The fastidious and microaerophilic nature of the organism complicated identification, particularly when the organism was first isolated. Unfortunately, agglutination studies were not satisfactory because of roughness of the antigen.

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