Infective endocarditis due to *Actinobacillus actinomycetemcomitans* in a patient with a porcine prosthetic mitral valve

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Increased sophistication in bacteriologic diagnosis has resulted in the identification of many unusual organisms as causes of infective endocarditis. Even experienced specialists in infectious diseases may have limited acquaintance with endocarditis caused by esoteric bacteria that are part of the oral and intestinal flora. Proper management rests not on previous experience with the causative organism, but rather on careful use of selected microbiologic tests combined with clinical judgement.

Endocarditis caused by *Actinobacillus actinomycetemcomitans* represents such a situation. The organism, normally part of the oral flora, is a rare cause of disease. Its fastidious growth requirements make identification slow and difficult. In addition, it is often resistant to commonly used antibiotics when tested by conventional methods involving the use of drug-impregnated discs.

In this paper we describe a patient with infective endocarditis caused by *A. actinomycetemcomitans*. We believe this to be the first report of infective endocarditis due to this organism in a porcine xenograft, a valve prosthesis thought to be more resistant to infection than mechanical prostheses. Management was complicated by penicillin allergy and by the delayed results of the microbiologic tests caused by the slow growth of the organism.

Case report

Clinical course

A 33-year-old woman was admitted to hospital because of fever and chills of 5 months' duration.

She had undergone mitral valve replacement with a Hancock porcine xenograft at age 31 for the treatment of rheumatic heart disease with congestive failure. Two years later she began to experience episodes of fever, chills and rigors. These increased in frequency during the week preceding admission. She also gave a history of progressive fatigue and malaise in the 2 months before admission. An urticarial rash had developed following the administration of penicillin 10 years previously.

At the time of admission to hospital her temperature was 40.2°C, her blood pressure 120/80 mm Hg and her pulse rate 140 beats/min. The pertinent physical findings included a grade 2/6 pansystolic murmur, best heard in the fifth intercostal space at the left sternal border, that radiated to the base and apex, and a grade 1/6 apical, nonradiating diastolic murmur that had not been heard before. There were no signs of embolic phenomena, and the spleen was not palpable. The rest of the physical examination, including a dental examination, yielded normal results. The hemoglobin level was 11.2 g/dl, the leukocyte count 9.6 × 10^9/l with a normal differential count, and the erythrocyte sedimentation rate 42 mm/h. The results of urinalysis were normal except that microscopic hematuria was detected; it was later shown to be caused by menometrorrhagia. Routine biochemical tests and electrocardiography yielded normal results. A chest roentgenogram confirmed the presence of a prosthesis at the location of the mitral valve but was otherwise unremarkable. All cultures, except those of the blood to be described, were negative or showed normal flora.

Intravenous therapy was started with erythromycin, 2 g and gentamicin, 5 mg/kg daily for septicemia of undetermined cause. Over the next 4 days febrile episodes occurred daily and tender, erythematous macules 5 × 5 mm developed over the lateral aspect of the left foot. An area of redness, edema and tenderness 2 × 3 cm also developed over the dorsum of the right hand near the extensor tendons of the thumb.

The combination of erythromycin and gentamicin had not brought her fever under control after 5 days of therapy. At this point all the cultures still were negative or showed normal flora. We therefore decided to attempt desensitization to penicillin, since the diagnosis of culture-negative endocarditis was becoming more likely. The intradermal injection of 0.1 ml of 1 × 10^{-6} M penicilloyl polylysine resulted in a wheal 10 mm in diameter. Because of the positive skin test with this purified major determinant, we made no attempt to skin test the patient with penicillin mixtures containing minor determinants. The patient showed no allergic reactions during the desensitization, and erythromycin was replaced with penicillin G, 18 million U/d given intravenously in six divided doses. The administration of penicillin was without incident.

Seven days after the patient's admission to hospital the cultures of blood drawn on her first day in hospital revealed growth of a small gram-negative coccobacillus that was identified several days later as *A. actinomycetemcomitans* (the identification was subsequently confirmed by the Laboratory Centre for Disease Control, Ottawa). All five sets of cultures of blood drawn prior to the start of antibiotic therapy were positive, as was the first of four sets of cultures of blood drawn while the patient was receiving erythromycin. Cultures of blood drawn while the patient was receiving penicillin were negative.

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The patient's clinical condition improved in the days following the institution of penicillin therapy, and by day 12, 7 days following the start of penicillin therapy, she had become afebrile. On day 17 the daily dose was increased to 40 million U when it was learned that a blood sample drawn immediately before penicillin administration on day 8 was bactericidal in a serum dilution of only 1:2. The higher dose resulted in a serum bactericidal titre of 1:8. But in view of the high mortality associated with infective endocarditis due to this organism, the high minimum bactericidal concentration of penicillin and the absence of evidence that the serum bactericidal titre of 1:8 was adequate to combat this organism, we decided on day 25 to add rifampin, 600 mg/d given orally, to the antibiotic regimen. This resulted in serum bactericidal titres of 1:16 immediately before penicillin was administered and 1:256 1 hour later.

Table I—Biologic and biochemical properties of the isolated *Actinobacillus actinomycetemcomitans*

Test	Result*
Production of	
Catalase	+
Oxidase	–
Urease	–
Indole	–
Hydrogen sulfide	–
Hydrolysis of	
Esculin	–
Gelatin	–
Growth on	
MacConkey agar	–
Methyl red/Voges-Proskauer broth	–
Triple sugar–iron agar	A/A
Growth improved by carbon dioxide	+
Reduction of nitrate	+
X factor (hematin) required	–
Fermentation of	
Lactose	–
Sucrose	–
Xylose	A
Mannitol	A
Fructose	A
Glucose	A
Maltose	A
Raffinose	–
Trehalose	–
Sorbitol	–
Salicin	–
Arabinose	–

*+ = positive; – = negative; A = acid produced; A/A = acid produced in both slope and butt.

The remainder of the clinical course was uncomplicated and the patient was discharged from hospital after 6 weeks of treatment. At her most recent clinic visit, 8 months after discharge, she was well.

Bacteriologic findings

A small, nonmotile, nonencapsulated coccobacillus grew anaerobically from Columbia broth in the first six blood cultures. On blood agar plates the organism formed smooth, opaque, adherent colonies 0.5 to 1.0 mm in diameter after 2 to 3 days of incubation in an anaerobic or a carbon dioxide-enriched atmosphere.

In broth the bacteria formed small granules adherent to the walls of the tube; the broth remained clear. The results of the identification tests performed in our laboratory are shown in Table I. All conform with those described in previous studies of *A. actinomycetemcomitans*[1,2] and clearly differentiate the organism from the closely related *Hemophilus aphrophilus*. The differentiation is important since *H. aphrophilus* is more sensitive to penicillin than *A. actinomycetemcomitans*.[3]

Antibiotic sensitivity testing by the Kirby–Bauer disc method showed that the organism was resistant to penicillin and its derivatives (Table II). The discs contained 10 U (6 μg) of penicillin. Aside from aminoglycoside antibiotics, the organism was sensitive to drugs that were judged unsuitable for long-term intravenous therapy. Tube dilution studies showed that the organism was sensitive to achievable serum levels of penicillin and gentamicin, and very sensitive to rifampin.

The slow growth of the organism in broth and on agar plates delayed the results of diagnostic and therapeutic tests throughout the patient's illness.

Discussion

A. actinomycetemcomitans was first isolated by Klinger[4] from lesions in patients with actinomycosis,[4] but was thereafter shown to cause infection in humans without necessarily being associated with *Actinomyces*.[1] It is part of the normal mouth flora.[5] We were able to find in the literature 54 additional cases of infection in humans caused by *A. actinomycetemcomitans* alone.[3,6-28] In 45 cases the diagnosis was endocarditis;[3,6-25] 19 of these cases have been reported in detail.[7-24] Abscesses of the brain,[26] face,[3] jaw[3] and thyroid,[27] a pleural sinus,[3] pneumonia[17] and urinary tract infection[28] were present in seven of the remaining nine cases, and two patients had septicemia from an unknown primary focus.[3]

The usual presentation of *A. actinomycetemcomitans* endocarditis is subacute, with fever, fatigue, weight loss, nocturnal diaphoresis, splenomegaly, hematuria, anemia and a high erythrocyte sedimenta-

Table II—Results of antibiotic sensitivity testing of the isolate

Antibiotic	Result*		
		Tube dilution method	
	Kirby–Bauer disc method	MIC (μg/ml)	MBC (μg/ml)
Penicillin	R	3.1	6.2
Erythromycin	M	–	–
Clindamycin	R	–	–
Tetracycline	S	–	–
Chloramphenicol	S	–	–
Cephalothin	R	–	–
Amoxicillin	R	–	–
Gentamicin	S	3.1	3.1
Sulfonamides	R	–	–
Carbenicillin	R	–	–
Kanamycin	S	–	–
Vancomycin	–	50	50
Rifampin	–	0.04	0.08

*R = resistant; M = moderately resistant; S = sensitive; – = not tested; MIC = minimum inhibitory concentration; MBC = minimum bactericidal concentration.

tion rate.[22] Manifestations of microembolism to the skin and mucous membranes have rarely been seen. The organism has usually been reported to be sensitive to chloramphenicol, gentamicin, kanamycin, streptomycin and tetracycline; susceptibility to ampicillin, cephalothin and erythromycin has been variable, and resistance to penicillin and its derivatives has been frequent. In our case the organism was reported as resistant to all penicillins by the Kirby–Bauer method. Only after the tube dilution tests were done was the organism found to be sufficiently sensitive to penicillin to warrant treatment with this drug. In four other cases in which penicillin sensitivity was tested by tube dilution studies the minimum bactericidal concentrations varied from 0.31 to 12.5 μg/ml.[9,15,22,24] In one of these, initial studies with antibiotic-impregnated discs showed penicillin resistance; the patient was successfully treated with penicillin when tube dilution studies showed a minimum bactericidal concentration of 4 μg/ml of penicillin.[9] Roughly 35% of isolates of *A. actinomycetemcomitans* are susceptible to 3.1 μg/ml of penicillin.[3] Most of the patients described in the literature have been treated with a combination of penicillin and aminoglycosides. Rifampin was used as a third drug in our case. The organism was very sensitive to this antibiotic, and its use in combination with penicillin and gentamicin resulted in better serum killing power. Rifampin is a bactericidal antibiotic with little toxicity; its usefulness is limited by the ready emergence of resistant bacteria. However, in combination with other antibiotics it may be very effective, as in our case.

Of the 45 patients with endocarditis due to *A. actinomycetemcomitans* described in the literature 13 (29%) died. Six of them have been described in detail: three died of valve destruction attributed to endocarditis,[13,19,23] two others died of congestive heart failure within 16 days of the diagnosis of infective endocarditis,[11,12] and one died of cerebral embolism 29 days after the diagnosis of infective endocarditis.[8] The high mortality may be attributed to at least two factors: the difficulty in isolating and identifying the organism, with the consequent delay in the institution of antibiotic therapy; and the moderate resistance of the organism to penicillin and its derivatives, which may result in the use of penicillin in inadequate doses or of antibiotics that are ineffective.

Our patient gave a history of penicillin allergy that was confirmed by skin test reactivity to purified penicilloyl polylysine. The administration of penicillin to this patient was undertaken with caution: an initial dose of 0.1 U was administered when an intravenous line was in place, and medication for the treatment of anaphylaxis was at the bedside and ready for immediate administration. However, increasing the dose 10-fold at 20-minute intervals until a therapeutic dose was reached resulted in no untoward reaction. We felt that the risk of reaction was outweighed by the usefulness of penicillin in the treatment of what at first seemed to be a case of culture-negative endocarditis. When the organism was later identified and its sensitivity to penicillin measured, the penicillin was indispensable for obtaining adequate serum bactericidal levels.

Prosthetic valve endocarditis due to resistant organisms is particularly difficult to treat since the foreign body may require surgical removal for cure. Three of the previously reported cases of *A. actinomycetemcomitans* endocarditis have involved prosthetic aortic valves. All were cured by antibiotic treatment.[18,22,24] In our case the presumptive site of infection was a porcine mitral valve prosthesis. In two large series of patients there was a very low frequency of endocarditis following porcine valve insertion, with one case of endocarditis in 120 patients in one series,[29] and two cases of bacteremia treated as endocarditis in 111 patients in the other.[30] This led to the suggestion that these valves might be more resistant to infection than mechanical prostheses.[30] However, in a more recent series of 373 patients 11 cases of endocarditis and 6 cases of early bacteremia were found.[31] In 10 of the 11 patients with endocarditis antibiotic treatment without valve replacement was successful in curing the infection. Thus, the frequency of endocarditis following xenograft insertion is probably similar to that following insertion of a mechanical prosthesis. On the other hand, there is a suggestion from these data that infected xenograft valves may be easier to sterilize by antibiotic treatment than mechanical prostheses.

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BOOKS

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continued on page 330