Subacute bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*

Report of a case with a review of the literature

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SUMMARY A case of subacute bacterial endocarditis due to *Actinobacillus actinomycetemcomitans* is reported. The patient was successfully treated first by a combination of gentamicin and ampicillin and then, because of severe allergic reactions, ampicillin was replaced by co-trimoxazole; symptoms did not recur and blood cultures remained sterile. A synoptic table is presented of 19 reported cases of infection caused by *A. actinomycetemcomitans* not connected with actinomycosis, with particular regard to their clinical features, treatment, and outcome.

Actinobacillus actinomycetemcomitans is rarely recognised as an aetiological agent in subacute bacterial endocarditis, possibly owing to its slow growth and requirement of CO₂ for primary isolation. The potential of this organism for aggressive invasion has been recognised in the past. Early isolation and recognition of this unfamiliar pathogen and appropriate antibacterial treatment are mandatory.

A recently observed case of subacute bacterial endocarditis due to this microorganism is presented. The literature has been reviewed with regard to other infections caused by *A. actinomycetemcomitans* in man excluding those associated with actinomycosis.

Case report

A 47-year-old Caucasian man with mitral valve insufficiency, but without a history of rheumatic fever, started to complain, in July 1974, of dyspnoea on exertion. Physical examination revealed a grade IV-V holosystolic murmur at the cardiac apex, radiating to the axilla and to the base of the heart. A chest x-ray revealed marked cardiac enlargement, left atrial hypertrophy, and accentuation of the pulmonary vessels. An electrocardiogram showed left ventricular hypertrophy. The patient was subsequently treated with digitalis and a sodium-free diet. He did well until the end of June 1975, when he experienced fatigue, weakness, night sweating, an irritating cough, and fever ranging between 38° and 38.5°C, but without chills. A weight loss of

several kilograms occurred. A few days before admission the patient discovered an Osler's node on the fifth finger of the left hand. Because of a diffuse reddening of the pharynx, his physician had prescribed oral penicillin. After five days the patient's condition deteriorated further and penicillin was stopped. After 11 blood cultures had been made over a period of four days, oral treatment was begun with ampicillin (2 g/day) and cloxacillin (2 g/day). Under this treatment the patient's condition rapidly improved and he became afebrile. Ten days later Gram-negative bacilli were grown from all 11 blood samples and were identified as *A. actinomycetemcomitans*. On July 25 the patient was admitted to hospital for further treatment. On admission he had no special complaints and was afebrile. Dental examination revealed severe caries. The neck veins were not distended and the lungs were clear. Physical examination of the heart revealed marked cardiomegaly; the auscultatory findings were unchanged. There was slight hepatomegaly but no splenomegaly. Laboratory findings: ESR 40 mm/h; haematocrit 39.5%; white cell count $7.3 \times 10^9/l$ with 75% polymorphonuclear leucocytes, 2% band forms, 18% lymphocytes, and 5% monocytes; urine-protein and glucose negative; 1-2 erythrocytes and 1-2 leucocytes per high-power field; urea 4.6 mmol/l; creatinine 123.7 $\mu\text{mol/l}$; serum albumin 31.1 g/l; gamma globulin 15.6 g/l. The chest radiograph revealed generalised cardiomegaly and enlargement of the pulmonary arteries.

Antibiotic therapy with ampicillin, 3 g every six hours intravenously, and gentamicin, 80 mg every eight hours intramuscularly, was started. This choice

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was made on the basis of the *in vitro* sensitivity tests and in view of the synergism shown by this association in the treatment of streptococcal endocarditis. On the second day the patient developed an erythematous macular rash. Ampicillin was reduced to 1 g every six hours and subsequently the rash disappeared. Thereafter ampicillin, 1 g six times a day intravenously, and gentamicin, 60 mg twice a day, were administered. On day 16 gentamicin was stopped. A severe rash with a temperature rise to 37.8°C reappeared on the 21st day. Ampicillin was discontinued. Over a period of three days five blood cultures were performed, which remained sterile.

Ampicillin was replaced by co-trimoxazole. On day 30 the patient was discharged from hospital but oral administration of two daily doses of 480 mg co-trimoxazole was continued for a period of two months. The patient was re-examined in November 1975. He was free of symptoms and remained afebrile. Three blood cultures over a period of one week remained sterile. In September 1976, 14 months after antimicrobial therapy had been stopped, the patient was feeling perfectly well.

BACTERIOLOGICAL FINDINGS

Eleven consecutive blood specimens, examined over a period of four days, after stopping the oral penicillin and just before starting the combined ampicillin-cloxacillin treatment, all grew the same Gram-negative, non-motile, rod-shaped microorganism. All subsequent blood cultures, five taken after ampicillin had been stopped and three after the termination of antibiotic treatment, remained sterile. Every blood specimen consisted of 10 ml venous blood divided equally between two culture bottles, one containing 50 ml Brain-Heart Infusion Broth with PAB and agar (Difco) and the other containing 50 ml Schaedler Broth with 0.05% sodium polyanetholsulphonate (Liquoid, Roche-Diagnostica) and 1 g per litre agar.

Visible growth on these media was detected in all cases in the form of delicate granules in the depth of the sedimented blood. A Gram stain of the growth showed dense aggregates of short somewhat coccobacillary rods. In a few cases growth was visible as early as the third day. It was always apparent before the tenth day when the cultures were discarded.

After the growth had been plated into horse blood agar and incubation in a candle extinction jar, minute colonies developed after one night, reaching a diameter of 0.5 mm after two nights. The colonies were convex, opaque, and greyish with a rough surface. They were firmly adherent to the surface of the medium and difficult to suspend. Primary growth was very poor or absent in an atmosphere not enriched in CO₂. Growth was also apparent, but slower to appear, on Trypticase Soy Agar (BBL)

and in Trypticase Soy Broth. There was rather luxuriant granular growth over the full length of a tube of thioglycollate broth. Oxidase production was absent but colonies were strongly catalase positive. No growth enhancement was observed in the vicinity of a streak of staphylococcal growth or around commercial V, X, and VX strips (BBL). There was no growth on Simmons citrate agar or on MacConkey agar. Nitrate was reduced to nitrite, but indole and urease were not produced. There was slow and sparse growth with slight acidification of the slope and the butt of a tube of Kligler Iron Agar without production of gas or blackening of the medium. In Cystine Trypticase Agar (BBL) and in Andrade peptone water containing 10% human serum there was acidification after two to three days of glucose and mannitol. Carbohydrates which were not attacked after an observation period of 30 days were lactose, sucrose, arabinose, raffinose, salicin, sorbitol, trehalose, and xylose.

All the growth characteristics and biochemical reactions are in agreement with the description of *A. actinomycetemcomitans*, a species which is listed in the eighth edition of *Bergey's Manual of Determinative Bacteriology* (1974, p. 375) as *species incertae sedis* under the name of *Bacterium actinomycetemcomitans*. In spite of its allocation to a different genus, *A. actinomycetemcomitans* closely resembles and must be differentiated from *Haemophilus aphrophilus*, another Gram-negative coccobacillus, growth of which is improved by CO₂. *H. aphrophilus* has also been incriminated as a cause of endocarditis (Sutter and Finegold, 1970). The positive catalase test of *A. actinomycetemcomitans*, and the absence of fermentation of lactose and sucrose, are the most useful differentiating features (Page and King, 1966; Sutter and Finegold, 1970). The identity of our isolate was independently confirmed by Dr R. Weaver at the Special Bacteriology Unit, CDC, Atlanta, Georgia, USA.

Antibiotic sensitivity tests were carried out according to the standardised technique of Bauer, *et al.* (1966) and using Mueller-Hinton Medium enriched with 10% horse blood. Our isolate was resistant to penicillin G, oxacillin, lincomycin, and clindamycin but sensitive to ampicillin, cephalothin, streptomycin, kanamycin, gentamicin, tetracycline, chloramphenicol, colistin, erythromycin, carbenicillin, sulphonamide, and co-trimoxazole.

Discussion

A. actinomycetemcomitans was first isolated by Klinger (1912) from the pus of patients with actinomycosis. In 1951, Thjøtta and Sydnæs reported its isolation in pure culture from a long-standing

abscess which had developed after tooth extraction, but the fermentation characteristics of the organism, as reported by these authors, were not those of *A. actinomycetemcomitans*. In 1953 Vallée and Gaillard reported very briefly on the isolation of *A. actinomycetemcomitans* from the blood of two patients with endocarditis. In 1962, King and Tatum presented data on 32 unequivocal isolations of *A. actinomycetemcomitans* not associated with actinomycosis. In 23 instances the organism was isolated from the blood of patients presenting clinical signs of endocarditis. In 18 patients, endocarditis was associated with either rheumatic heart disease (14 cases) or a congenital heart defect (4 cases).

The Table summarises the clinical features, anti-

biotic treatment, and outcome of 19 well documented cases of human infection due to *A. actinomycetemcomitans* not related to actinomycosis. Only six of these cases, including the present one, were reported from Europe. Fourteen (73%) of these patients had endocarditis: 10 had suffered previously from either rheumatic or congenital heart disease; one patient had a prosthetic aortic valve; in three cases there was no underlying disease. In the remaining five patients, the infection presented respectively as coronary artery endarteritis, brain abscess, urinary tract infection, pneumonia, and a thyroid abscess. The preponderance of males (18 of 19 cases) has been stressed previously (Page and King, 1966). As the bacterium can be isolated from the normal

Table Analysis of fully reported infections due to *A. actinomycetemcomitans* not associated with actinomycosis

Reference	Country	Age	Sex	Possible precipitating factor	Duration of illness prior to isolation of A.a.	Diagnosis	Associated or underlying condition	Complications	Treatment ¹	Outcome
Mitchell and Gillespie (1964)	UK	50	M	Tooth extraction	6 mth	Endocarditis	RHD	None	P-S	Recovered
Overholt (1966)	USA	57	M	—	4 mth	Endocarditis	None	CHF; emboli to kidneys	P-S-C	Died
Kayser and Bircher (1967)	Switzerland	52	M	—	4 wk	Endocarditis	None	None	Cf-P-S	Recovered
Symbas <i>et al.</i> (1967)	USA	20	M	Dental caries	Short	Coronary artery endarteritis	Congenital anomaly coronary artery	None	P-S	Recovered
Vogelzang (1967)	USA	27	M	—	—	Endocarditis	RHD	CHF; coronary embolus	P-S-T	Died
Thomas (1967)	USA	49	M	Thoracotomy	3 mth	Endocarditis	Bicuspid aortic valve, coarctation	CHF	E-C-P-S	Died
Martin <i>et al.</i> (1967)	USA	62	M	Otitis	—	Brain abscess	Carcinoma of ear	CHF, diffuse bleeding	P-C-Co	Died
Goss <i>et al.</i> (1967)	USA	39	M	—	10 mth	Endocarditis	None	Cerebral, pulmonary, renal emboli	P-S	Died
Underhill (1968)	Canada	68	M	Oral abscess	—	Endocarditis	—	None	P-S	Recovered
Townsend and Gillenwater (1969)	USA	55	M	Prostatic hypertrophy	—	Cystitis, urethritis	Renal tuberculosis	None	K	Recovered
Serra and Tonato (1969)	Italy	41	M	Head trauma	10 mth	Endocarditis	RHD	Cerebral, renal, peripheral emboli	A-S	Recovered
Vandepitte <i>et al.</i> (1970)	Belgium	54	M	—	3 mth	Endocarditis	VSD	None	P-S	Recovered
Meyers <i>et al.</i> (1971)	USA	56	M	—	4 wk	Pneumonia	Multiple myeloma	None	A	Recovered
		57	F	Dental manipulation	4 mth	Endocarditis	None	Cerebral embolus	K	Recovered
Stauffer and Goldman (1972)	USA	42	M	Skin abrasion	7 wk	Endocarditis	Prosthetic aortic valve	None	P-S	Recovered
Burgher <i>et al.</i> (1973)	USA	31	M	—	1 mth	Thyroid abscess	None	Brain abscess, cutaneous abscess	A-S	Recovered
Block <i>et al.</i> (1973)	USA	29	M	Swollen jaw; dental caries	4 wk	Endocarditis	Aneurysm of sinus of Valsalva	CHF; renal and splenic emboli	A-S	Died
Macklon <i>et al.</i> (1975)	UK	55	M	—	3 mth	Endocarditis	Mitral insufficiency	CHF	A-S	Recovered
Present study	Belgium	47	M	Dental caries	4 wk	Endocarditis	Mitral insufficiency	None	A-G-CT	Recovered

CHF = congestive heart failure; RHD = rheumatic heart disease; VSD = ventricular septal defect; — not specified.

¹A = ampicillin; C = chloramphenicol; Cf = cephalothin; CT = co-trimoxazole; Co = colistin; G = gentamicin; K = kanamycin; P = penicillin; S = streptomycin; T = tetracycline.

mouth flora (Heinrich and Pulverer, 1959) it has been suggested that oral lesions (dental caries, dental abscess) or respiratory tract infections may serve as a portal of entry. Some other possible sources, such as skin abrasions, thoracotomy, and urinary tract manipulations, have been suspected, but in most cases the origin of the infection is not clear.

The clinical course of endocarditis due to *A. actinomycetemcomitans* is frequently complicated by multiple emboli (7 of 14 cases) and congestive heart failure (6 of 14 cases). In five cases there was a fatal outcome (34%); four patients died from congestive heart failure and one from pulmonary and cerebral embolisms.

The most frequently used antibiotic regimen consisted of the association of penicillin G and streptomycin. Three cases of *A. actinomycetemcomitans* endocarditis were cured by the combination of ampicillin and streptomycin.

The present case was treated with a combination of gentamicin for two weeks and ampicillin for four weeks. Because of a severe skin rash the ampicillin had to be stopped, but blood cultures no longer showed a growth of *A. actinomycetemcomitans*. It is impossible to deduce from our observations to what extent the treatment with co-trimoxazole contributed to the ultimate cure of the patient. A definitive conclusion as to the relative value of the various antibiotic combinations in *A. actinomycetemcomitans* endocarditis cannot yet be drawn.

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References

- Bauer, A. W., Kirby, W. M., Sherris, J. C., and Tenckhoff, M. (1966). Antibiotic susceptibility testing by a simple disc method. *American Journal of Clinical Pathology*, **45**, 493-496.
- Block, P. J., Fox, A. C., Yoran, C., and Kaltman, A. J. (1973). *Actinobacillus actinomycetemcomitans* endocarditis: report of a case and review of the literature. *American Journal of the Medical Sciences*, **266**, 387-392.
- Burgher, L. W., Loomis, G. W., and Ware, F. (1973). Systemic infection due to *Actinobacillus actinomycetemcomitans*. *American Journal of Clinical Pathology*, **60**, 412-415.
- Goss, J. E., Gutin, R. S., and Dickhaus, D. W. (1967). Bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. *American Journal of Medicine*, **43**, 636-638.
- Heinrich, S., and Pulverer, G. (1959). Zur Ätiologie und Mikrobiologie der Aktinomykose. III. Die pathogene Bedeutung des *Actinobacillus actinomycetemcomitans* unter den 'Begleitbakterien' des *Actinomyces israeli*. *Zentralblatt für Bakteriologie*, **176**, 91-101.
- Kayser, F. H., and Bircher, J. (1967). Bakterielle Endocarditis durch einen *Actinobacillus*. *Deutsche Medizinische Wochenschrift*, **92**, 21-23.
- King, E. O., and Tatum, H. W. (1962). *Actinobacillus actinomycetemcomitans* and *Hemophilus aphrophilus*. *Journal of Infectious Diseases*, **111**, 85-94.
- Klinger, R. (1912). Untersuchungen über menschliche Aktinomykose. *Zentralblatt für Bakteriologie*, **62**, 191-200.
- Macklon, A. F., Ingham, H. R., Selkon, J. B., and Evans, G. J. (1975). Endocarditis due to *Actinobacillus actinomycetemcomitans*. *British Medical Journal*, **1**, 609-610.
- Martin, B. F., Derby, B. M., Budzilovich, G. N., and Ransohoff, J. (1967). Brain abscess due to *Actinobacillus actinomycetemcomitans*. *Neurology*, **17**, 833-837.
- Meyers, B. R., Bottone, E., Hirschman, S. Z., Schneerson, S. S., and Gershengorn, K. (1971). Infection due to *Actinobacillus actinomycetemcomitans*. *American Journal of Clinical Pathology*, **56**, 204-211.
- Mitchell, R. G., and Gillespie, W. A. (1964). Bacterial endocarditis due to an actinobacillus. *Journal of Clinical Pathology*, **17**, 511-512.
- Overholt, B. F., (1966). *Actinobacillus actinomycetemcomitans* endocarditis. *Archives of Internal Medicine*, **117**, 99-102.
- Page, M. I., and King, E. O. (1966). Infection due to *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus*. *New England Journal of Medicine*, **275**, 181-188.
- Serra, P., and Tonato, M. (1969). Subacute bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. *American Journal of Medicine*, **47**, 809-812.
- Stauffer, J. L., and Goldman, M. J. (1972). Bacterial endocarditis due to *Actinobacillus actinomycetemcomitans* in a patient with a prosthetic aortic valve. *California Medicine*, **117**, 59-63.
- Sutter, V. L., and Finegold, S. M. (1970). *Haemophilus aphrophilus* infections: clinical and bacteriologic studies. *Annals of the New York Academy of Sciences*, **174**, 468-487.
- Symbas, P. N., Schlant, R. C., Hatcher, C. R. Jr., and Lindsay, J. (1967). Congenital fistula of right coronary artery to right ventricle complicated by *Actinobacillus actinomycetemcomitans* endarteritis. *Journal of Thoracic and Cardiovascular Surgery*, **53**, 379-384.
- Thjøtta, T., and Sydnes, S. (1951). *Actinobacillus actinomycetemcomitans* as the sole infecting agent in a human being. *Acta Pathologica et Microbiologica Scandinavica*, **28**, 27-35.
- Thomas, J. R. (1967). *Actinobacillus actinomycetemcomitans* endocarditis in a patient with bicuspid aortic valve and coarctation of the aorta. *Southern Medical Journal*, **30**, 783-784.
- Townsend, T. R., and Gillenwater, J. Y. (1969). Urinary tract infection due to *Actinobacillus actinomycetemcomitans* (Letter). *Journal of the American Medical Association*, **210**, 558.
- Underhill, E. (1968). Endocarditis due to *Actinobacillus*

- actinomycetemcomitans*. *Canadian Journal of Medical Technology*, **30**, 125-127.
- Vallée, A., and Gaillard, J. A. (1953). Infection pyogène contagieuse de la souris déterminée par *Bacillus actinomycetem comitans*. *Annales de l'Institut Pasteur*, **84**, 647-649.
- Vandepitte, J., Decraene, P., Kesteloot, H., Maris, J., and Eyckmans, L. (1970). Bacterial endocarditis caused by *Actinobacillus actinomycetemcomitans*. *Acta Clinica Belgica*, **25**, 109-115.
- Vogelzang, R. M. (1967). Bacterial endocarditis due to *Actinobacillus actinomycetemcomitans*. *Archives of Internal Medicine*, **120**, 99-101.