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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 aetioloigical 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 μmol/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 cocccobacillus, 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, carbencillin, sulphonamide, and co-trimoxazole.

Discussion

A. actinomycetemcomitans was first isolated by Kligler (1912) from the pus of patients with actinomycosis. In 1951, Thjetta and Sydnes 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 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, antibiotic 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                  | Treatment¹ Outcome |
|----------------------------|---------|-----|-----|-------------------------------|---------------------------------------------|--------------------------------------|-----------------------------------|----------------------------------|----------------------|-------------------|
| Mitchell and Gillespie (1964) Overholt (1966) | USA     | 50  | M   | Tooth extraction              |                                            | Endocarditis                        | RHD                               | None                             | P-S                  | Died               |
|                            | USA     | 57  | M   |                               | 6 mth                                      | Endocarditis                        | None                              | CHF, emboli to kidneys           | P-S-C                | Died               |
| Kayser and Bircher (1967)   | Switzerland | 52  | M   |                               |                                            | Endocarditis                        | None                              | None                             | Cf-P-S               | Recovered          |
| Symbas et al. (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 et al. (1967)        | USA     | 62  | M   | Otitis                         |                                            | Brain abscess                       | Carcinoma of ear                   | CHF, diffuse bleeding            | P-C-Co               | Died               |
| Goss et al. (1967)          | USA     | 39  | M   |                               |                                            | Endocarditis                        | None                              | Cerebral, pulmonary, renal emboli| P-S                  | Recovered          |
|                            | Canada  | 68  | M   | Prostatic hypertrophy          |                                            | Endocarditis                        |                                   | Cerebral, renal, peripheral emboli| P-S                  | Recovered          |
|                            | USA     | 55  | M   | Head trauma                    | 10 mth                                     | Endocarditis                        |                                   | None                             | A-S                  | Recovered          |
| Vandeputte et al. (1970) Meyers et al. (1971) | Belgium | 54  | M   |                               |                                            | Endocarditis                        | VSD                               | None                             | P-S                  | Recovered          |
|                            | USA     | 56  | M   |                               |                                            | Pneumonia                           | Multiple myeloma                   | None                             | A                   | Recovered          |
|                            | USA     | 57  | F   | Dental manipulation            |                                            | Endocarditis                        | None                              | Cerebral embolus                 | K                   | Recovered          |
|                            | USA     | 42  | M   | Skin abrasion                  |                                            | Endocarditis                        | Prosthetic aortic valve            | None                             | P-S                  | Recovered          |
|                            | USA     | 31  | M   |                               |                                            | Thyroid abscess                     | Brain abscess, cutaneous abscess   | None                             | A-S                  | Died               |
|                            | USA     | 29  | M   | Swollen jaw; dental caries     |                                            | Endocarditis                        | Aneurysm of sinus of Valsalva      | CHF                              | A-S                  | Recovered          |
| Block et al. (1973)         | USA     | 55  | M   |                               |                                            | Endocarditis                        | Mitral insufficiency               | 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.
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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 *Actinobacillus 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 *Actinobacillus 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 *Actinobacillus 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 *Actinobacillus actinomycetemcomitans* endocarditis cannot yet be drawn.

We thank Dr R. Weaver, of the Special Bacteriology Unit, Communicable Disease Center, Atlanta (Ga), USA, who has confirmed the identity of our isolate.

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