Corynebacterium group D2 urinary tract infection

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Abstract **An unusual multiply resistant corynebacterium was isolated from the urine of a comatose patient. This organism was resistant to sulphafurazole, trimethoprim, nalidixic acid, cefazolin, nitrofurantoin, clindamycin, erythromycin, oxacillin, penicillin, gentamicin, amikacin, cinoxacin, ceftazidime and cefotaxime, but was susceptible to ciprofloxacin, ofloxacin, norfloxacin, vancomycin and fucidin. It was identified as the first reported isolate in South Africa of corynebacterium group D2, an organism recently implicated in alkaline-encrusted cystitis and urinary tract infection. We discuss the case history of the patient and review the literature.**

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In September 1990, our attention was drawn to an unusual isolate from the urine of a patient in a coma. The organism appeared to be a coryneform on Gram staining and was susceptible only to vancomycin and ciprofloxacin. Corynebacterium group D2 (CGD2) has been incriminated as a cause of urinary tract infection (UTI) and a condition known as alkaline-encrusted cystitis.[1,2] This is a chronic inflammatory condition of the bladder, the occurrence of which is usually preceded by the presence of an existing lesion, bladder trauma or catheterisation. Infection with a urea-splitting organism leads to an alkaline pH in the urine and the deposition of crystalline crusts of triple phosphates in the bladder.[3] This organism was first reported in 1985 from Spain and subsequently from other European countries and the USA.[1,4,5] We believe this to be the first reported isolation of this organism in Africa.

Materials and methods

Qualitative biochemical analysis of the urine was performed with the Ames Multistix 10SG (Miles Laboratories, Slough, UK).

The organism was cultured by standard techniques on blood agar base (Columbia Agar, Oxoid, Basingstoke, England) under 10% CO_2 at 35°C for 48 hours. Minimum inhibitory concentrations were measured using National Committee for Clinical Laboratory Standards (NCCLS) criteria.[6] Speciation of the corynebacterium was confirmed using the Analytical Profile Index (API) system, Coryne (Bio Merieux, Lyons, France).[7]

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Case history and results

In February 1985 a 56-year-old woman with a history of epilepsy, who had suffered a cerebrovascular accident, was investigated at Coronation Hospital, Johannesburg. A computed tomography (CT) scan revealed a large arteriovenous malformation in the left parietal area. Her condition improved and she was discharged. In August 1990 the patient's condition deteriorated and she was readmitted in a coma. She was catheterised and remained comatose or semi-comatose until her death.

Her white cell count (WCC) was 23,2 × 10^9/l. The white cells exhibited left shift and toxic granulation. A urine investigation revealed a pH of 8,5, protein +++, blood +++, white blood cells 125 000/ml and red blood cells > 750 000/ml. Culture yielded a pure growth (> 100 000/ml) of CGD2. Blood cultures were negative. Six days later the WCC was still elevated at 26,7 × 10^9/l. No specific antimicrobial therapy was given. Ten days after the initial isolate was discovered, CGD2 was again isolated in pure growth (> 100 000/ml).

The patient remained catheterised. Eighteen days later *Klebsiella pneumoniae* and *Escherichia coli* (> 100 000/ml) were isolated from her urine; during the remainder of her stay in hospital these organisms were isolated in heavy growth from her urine. Her WCC remained elevated and she died 15 days later.

Discussion

The biochemical features of the CGD2 organism isolated are compared with previously reported data[8] (Table I). The API Coryne profile of 2001004 identified the organism as belonging to CGD2,[7] which is a factor in cases of asymptomatic bacteraemia, uncomplicated cystitis, encrusted cystitis, pyelonephritis, bacteraemia and endocarditis.[2] It can be isolated from the healthy skin, especially that of the groin, of hospitalised patients, most of whom (63%) will have received antimicrobial treatment in the previous week.[9] Aguado *et al.*[2] found that 90% of a group of 43 patients from whom CGD2 was isolated had received antibiotics before isolation. It is recognised that the use of broad-spectrum antibiotics may affect the normal skin flora by selecting those organisms with a greater inherent

TABLE I.
Biochemical analysis of corynebacterium group D2

Test	Coyle and Lipsky's strain[8]	Our strain
Catalase	+	+
Beta-haemolysis	–	–
Nitrate reduction	–	–
Urease	+	+
Gelatin hydrolysis	–	–
Motility	–	–
Esculin hydrolysis	–	–
Glucose	–	–
Maltose	–	–
Sucrose	–	–
Mannitol	–	–
Xylose	–	–
Pigment	none	none
Response to serum	+	+

resistance.[10] Larson *et al.*,[11] who investigated corynebacterium group JK skin colonisation patterns, found that it is also an organism found predominantly on the perineum and have suggested that resistance may originate in the gastro-intestinal tract, with subsequent spread to the skin. The same may be true for CGD2.[9,11]

The factors associated with CGD2 infections are as follows:[2] (*i*) underlying disease/immunosuppression; (*ii*) urological procedures; (*iii*) previous use of antibiotics; (*iv*) age > 65 years; (*v*) previous UTI; (*vi*) bladder lesions; and (*vii*) general urinary tract symptoms. Renal patients were found to be at particularly high risk in a later study.[12]

The ability of the organism to produce struvite stones in the urinary tract has been demonstrated in studies of normal human urine and rats inoculated with CGD2.[13] Normal urine inoculated with CGD2 and incubated for 24 hours became alkaline with the formation of triple phosphate crystals. As previously stated, this is a symptom of alkaline-encrusted cystitis.[3]

Fernandez-Rablas *et al.*[14] looked at the *in vitro* activities of nine antimicrobial agents against CGD2. It was found that ciprofloxacin, ofloxacin, norfloxacin, vancomycin and teicoplanin were very active against both clinical and skin isolates. These drugs were active against the South African isolate. High pH affects the activity of most antimicrobial agents, but the quinolones and vancomycin are still active against CGD2 at an elevated pH. Resistance to the quinolones does exist and is on the increase against ciprofloxacin and norfloxacin.[15]

Aquado *et al.*[2] described the characteristics of the urine of the 43 patients from whom they isolated CGD2. These features include pH > 7,1, triple phosphate crystals, haematuria and pyuria, and an absence of bacterial growth after 24 hours' incubation.

Pyuria was present in 76% of those patients with urological symptoms. CGD2 was cultured in pure growth from 82% of patients with urinary symptoms, accounting for 0,2% of all urine samples submitted to their laboratories. Only patients with 2 or more isolates of CGD2 were included.[2] The Spanish authors[2,12,13] claim that up to 60% of CGD2 isolates have clinical significance. In addition, their animal studies satisfy most of Koch's postulates for determining the pathogenic role of CGD2.[13] We suggest that each patient be individually assessed to decide the role of this organism when isolated.

In the case history presented here, the pathogenic role of CGD2 was not confirmed. The patient was not treated with specific antimicrobial agents and her comatose state precluded information on urinary symptoms. CGD2 was, however, isolated in pure culture from pyogenic urine on two occasions over a period of 10 days. She also had an elevated WCC with no other apparent source of infection. It should be noted that Aguado *et al.*[2] dealt with 5 catheterised patients in their series, some of whom had had strokes. In 2 of these patients, removal of the catheter resulted in the eradication of CGD2. In another study involving 82 patients, 60 patients (73%) had indwelling catheters when the organism was isolated.[12]

We conclude that CGD2 is an organism of pathogenic potential. Because of its resistant nature and the possibility of acute complications such as alkaline-encrusted cystitis and pyelonephritis, we recommend that it be sought in hospitalised patients at risk for urinary tract infections. Prompt specific antimicrobial treatment and removal of indwelling urinary catheters (where possible) are indicated for this condition.

REFERENCES

1. Soriano F, Ponte C, Santamaria M, *et al.* Corynebacterium group D2 as a cause of alkaline-encrusted cystitis: report of four cases and characterisation of the organisms. *J Clin Microbiol* 1985; **21:** 788-792.
2. Aguado J, Ponte C, Soriano F. Bacteriuria with multiply resistant species of corynebacterium (corynebacterium group D2): an unnoticed cause of urinary tract infection. *J. Infect Dis* 1987; **156:** 144-150.
3. Hager BH, Magath TB. the etiology of encrusted cystitis with alkaline urine. *JAMA* 1925; **85:** 1352-1355.
4. Sofras F, Yiannopoulou K, Kostakopoulos A, Dimopoulos C. Corynebacterium-induced cystitis with mucosal encrustations. *J Urol* 1988; **139:** 810.
5. Marshall R, Routh K, MacGowan A. Corynebacterium CDC group D2 bacteraemia. *J Clin Pathol* 1987; **40:** 813-814.
6. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically: Approved Standard* (NCCLS Publication M7-A). Villanova, Pa: NCCLS, 1990.
7. API Coryne. *Catalogue Bio Merieux SA.* Lyon: API system, 1990.
8. Coyle MB, Lipsky BA. Coryneform bacteria in infectious diseases: clinical and laboratory aspects. *Clin Microbiol Rev* 1990; **3:** 237-246.
9. Soriano S, Rodriquez-Tudela J, Fernandez-Roblas R, Aguado J, Santamaria M. Skin colonisation by corynebacterium groups D2 and JK in hospitalised patients. *J Clin Microbiol* 1988; **26:** 1878-1880.
10. Pearson TA, Braine HG, Rathburn HK. Corynebacterium sepsis in oncology patients: predisposing factors, diagnosis and treatment. *JAMA* 1977; **238:** 1737-1740.
11. Larson E, McGinley K, Leyden J, Cooley M, Talbot G. Skin colonisations with antibiotic-resistant (JK group) and antibiotic-sensitive lipophilic diphtheroids in hospitalised and normal adults. *J Infect Dis* 1986; **153:** 701-706.
12. Soriano F, Aguado J, Ponte C, Fernandez-Roblas R, Rodriquez-Tudela J. Urinary tract infection caused by corynebacterium group D2: report of 82 cases and review. *Rev Infect Dis* 1990; **12:** 1019-1034.
13. Soriano F, Ponte C, Santamaria M, Castilla C, Fernandez-Roblas R. *In vitro* and *in vivo* study of stone formation by corynebacterium group D2 (*Corynebacterium urealyticum*). *J Clin Microbiol* 1986; **23:** 691-694.
14. Fernandez-Roblas R, Priesto S, Santamaria M, Ponte C, Soriano F. Activity of nine antimicrobial agents against Corynebacterium Group D2 strains: isolates from clinical specimens and skin. *antimicrob Agents Chemothr* 1987; **31:** 821-822.
15. Soriano F, Fernandez-Roblas R, Zapardiel J, Rodriquez-Tudela J, Aviles P, Romero M. Increasing incidence of corynebacterium group D2 strains resistant to norfloxacin and ciprofloxacin. *Eur J Clin Microbiol Infect Dis* 1989; **8:** 1117-1118.