

Donovanosis – hope after years of despair



Ivan Bastian

Clinical Microbiology Consultant
Institute of Medical &
Veterinary Science
PO Box 14, Rundle Mall,
Adelaide SA 5000
Tel: (08) 8222 3291
Fax: (08) 8222 3543
Email:
ivan.bastian@imvs.sa.gov.au

Donovanosis (granuloma inguinale) is an indolent genital ulcerative disease (GUD). After years of neglect and despair, the recent introduction of a molecular diagnostic test and an effective convenient therapy (azithromycin) have helped to control this disease in Indigenous Australian communities.

Donovanosis is a disease of poverty that is prevalent in the populations of developing countries, for example in India, southern Africa, South America and Papua New Guinea^{1,2}. The disease also occurs in Indigenous Australian communities where similar impoverished conditions exist because of dispossession, unemployment and the resulting sequelae.

The disease is presumably sexually transmitted and has an estimated incubation period of about fifty days^{1,2}. The initial lesion may be a firm papule or subcutaneous nodule that then ulcerates. The resulting ulcer is not painful and usually bleeds easily on contact (Figure 1). Chronic infections can lead to significant physical and social complications. The ulcers may extend into the groin, anus and pubic regions, and can result in genital deformity and even destruction^{1,2}. The lesions are typically malodorous so that the affected individual becomes reclusive, depressed and too embarrassed to seek medical attention. Extragenital lesions (eg lips, gums) account for 6% of cases¹. Other complications include disseminated disease, osteomyelitis and the development of squamous carcinomas in the chronic genital ulcers. Like other GUDs, donovanosis may

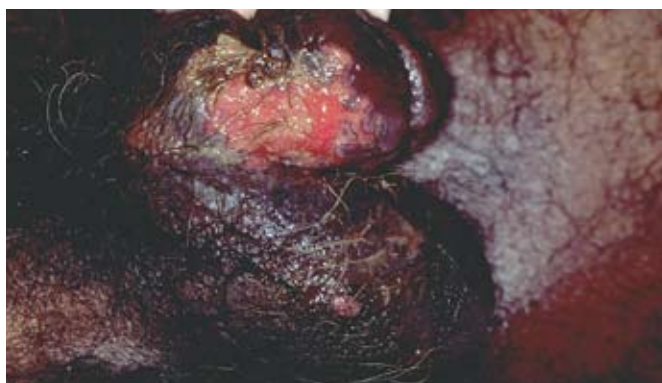


Figure 1. Large ulcerative penile lesion typical of donovanosis (non-identifying picture published with patient consent).

also potentiate transmission of the human immunodeficiency virus (HIV)¹.

The association with HIV transmission has sparked renewed interest in this neglected disease, over the last decade in Australia and South Africa¹. Studies at the AIDS/STD Unit and the Menzies School in Darwin attempted to improve the diagnosis and treatment of donovanosis.

Improved detection

The causative organism, known until recently as *Calymmatobacterium granulomatis*, cannot be cultured using routine microbiological techniques. Until recent isolations in cell cultures¹, only fourteen successful cultivations in chick embryo yolk sacs had been documented; the last in 1962^{1,2}. Therefore, examination of a biopsy specimen by an expert histopathologist remained the definitive diagnostic test for most of the last century with a sensitivity of 95% – 100% and the ability to exclude malignancy, which must be considered in the differential diagnosis of a non-healing genital ulcer (Figure 2)³. However, biopsies are not acceptable to patients and expert histopathologists are not available in many donovanosis-endemic regions. Examination of Giemsa-stained impression smears are more agreeable for the patient but have variable sensitivity (as low as 38.3%) and specificity, depending on the skill and experience of the microscopist³.

Calymmatobacterium granulomatis had been linked with the *Klebsiella* species on the basis of common morphological characteristics, serological cross-reactivity and similar pathogenicity (ie *K. rhinoscleromatis* causes rhinoscleroma, a chronic destructive ulceration of the nasopharynx). The advent of PCR, which could detect non-cultivable organisms using conserved primers, allowed this association to be investigated at the molecular level. Initially, a *Klebsiella*-like sequence was amplified from the genital lesions of three donovanosis patients using conserved primers targeting the *pboE* gene, which encodes a porin protein and is conserved among the family *Enterobacteriaceae*⁴. Further studies repeatedly detected this PCR product in specimens from other donovanosis patients but not among patients with unrelated genital conditions (confirming that the molecular identification was specific)⁵. The amplification of the same PCR product from the causative organism when isolated using a modified chlamydia culture method from

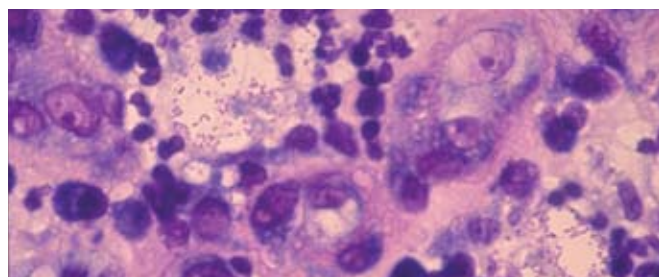


Figure 2. Giemsa stain demonstrating the causative organism within histiocytic vacuoles (100x magnification).

three donovanosis patients, provided more convincing evidence. These accumulated findings argue for the reclassification of the donovanosis organism as *K. granulomatis*⁵.

Most importantly, these molecular investigations allowed the development of a convenient PCR-based diagnostic test for donovanosis that could be performed on biopsy or swab specimens⁶. Evaluation of the performance characteristics of this PCR assay has been confounded by low numbers of positive samples, the use of different specimen types (including formalin-fixed tissue blocks) and test formats, and the choice of a 'gold standard' (ie clinical diagnosis or histological confirmation). Large formal evaluations of the donovanosis PCR are required. In the interim, a pooled estimate of the sensitivity of the PCR assay based on several small studies is 80.5% (95% CI 65.1 – 91.2%) and the specificity is likely to be very high³.

Better treatment

Many antibiotics (eg erythromycin, tetracycline, co-trimoxazole, chloramphenicol, ceftriaxone, ciprofloxacin, gentamicin) had proved effective in treating donovanosis if taken daily (or more frequently) for several weeks^{1,2,7}. However, treatment failures and relapses were common because of poor adherence with the prolonged regimens. Azithromycin, a long-acting azalide antibiotic, offered several promising features as a donovanosis treatment: better Gram-negative activity than erythromycin; good penetration into genital tissue; and the ability to concentrate within and be released slowly from macrophages (ie the intracellular niche of the causative organism).

A pilot study conducted in 1994-1995 in the Northern Territory confirmed that azithromycin was an ideal antibiotic for treating donovanosis⁷. Eleven patients with histologically-confirmed donovanosis received either 1.0 g once weekly for four weeks (regimen A) or 500 mg daily for seven days (regimen B). All eleven patients were 'cured' within eight weeks of commencing treatment – there were no significant adverse reactions and subsequent informal reviews did not detect any relapses. More than thirty subsequent donovanosis patients were successfully treated with azithromycin. Subsequently, the 1995/1996 Australian Antibiotic Guidelines adopted azithromycin as the recommended treatment for donovanosis in males and in non-pregnant non-lactating females. The WHO and CDC also now recommend azithromycin for the treatment of donovanosis¹.

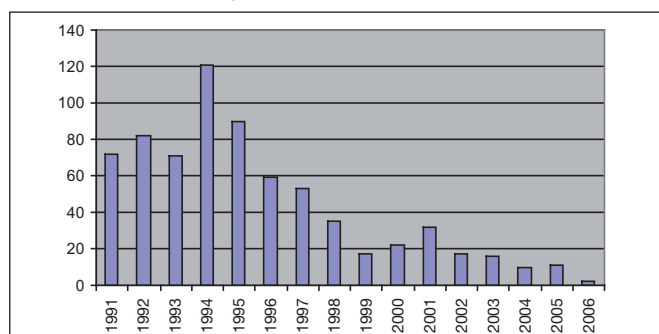


Figure 3: Notification of donovanosis to the Australian National Notifiable Diseases Surveillance System 1991-2006 (Data from http://www9.health.gov.au/cda/source/Rpt_2.cfm?RequestTimeout=500 on 28 November 2006).

Azithromycin can be used in effective and convenient regimens because of the drug's favourable pharmacokinetic properties (ie concentration within macrophages and long tissue half-life). Outpatients with small donovanosis lesions can receive supervised weekly doses (ie regimen A). In contrast, individuals with extensive disease can be admitted to hospital for dressings and daily azithromycin treatment (ie regimen B) that will produce therapeutic tissue levels up to four weeks after discharge.

Hope

The development of an acceptable reliable molecular test and the introduction of a convenient effective antibiotic treatment raised the possibility of eliminating donovanosis from Indigenous Australian communities. Community-based education and intervention strategies were of course also required to achieve this goal. Following a report commissioned by the Office for Aboriginal and Torres Strait Islander Health (OATSIH), the Commonwealth Department of Health established the National Donovanosis Eradication Advisory Committee (NDEAC) in 2001⁸. Four project officers were employed to assist primary care services with the management of all GUDs in northern Australia (where the majority of donovanosis cases occur). Syndrome-based treatment protocols and educational materials were developed, staff training conducted, access to the new PCR diagnostic test optimised, and enhanced active surveillance undertaken⁸.

A review of the Australian National Notifiable Diseases Surveillance System (NNDSS) shows a continuing downward trend in donovanosis notifications over the last decade (Figure 3). Only two cases have been reported in 2006 as of November. Elimination is defined as no new donovanosis notifications to NNDSS for three consecutive years. Achieving (and proving) elimination will be problematic as interest, expertise and funding in donovanosis wanes in parallel with the falling incidence of the disease. However, elimination is attainable through integration of the NDEAC initiatives into broader sexual health programmes.

The decline in donovanosis cases contrasts sharply with the rising incidence of other sexually transmitted infections (STIs), such as chlamydia, syphilis and gonorrhoea, that may very well be chronicled with pessimism in other chapters of this publication. The donovanosis experience provides hope that laboratorians and clinical staff working in partnership with primary health care providers and communities can successfully control STIs.

References

- O'Farrell N. Donovanosis. *Sex Transm Infect* 2002; 78: 452-7.
- Richens J. The diagnosis and treatment of donovanosis (granuloma inguinale). *Genitourin Med* 1991; 67: 441-52.
- Public Health Laboratory Network. Donovanosis laboratory case definition.
- Bastian I & Bowden FJ. Amplification of Klebsiella-like sequences from biopsy samples from patients with donovanosis. *Clin Infect Dis* 1996; 23: 1328-30.
- Carter JS, Bowden FJ, Bastian I, Myers GM, Sriprakash KS & Kemp DJ. Phylogenetic evidence for reclassification of *Calymmatobacterium granulomatis* as *Klebsiella granulomatis* comb. nov. *Int J Syst Bacteriol* 1999; 49:1695-700.
- Carter J, Bowden FJ, Sriprakash KS, Bastian I & Kemp DJ. Diagnostic polymerase chain reaction for donovanosis. *Clin Infect Dis* 1998; 28: 1168-9.
- Bowden FJ, Mein J, Plunkett C & Bastian I. Pilot study of azithromycin in the treatment of genital donovanosis. *Genitourin Med* 1996; 72: 17-9.
- Bowden FJ, National Donovanosis Eradication Advisory Committee. Donovanosis in Australia: going, going... *Sex Transm Infect* 2005; 81: 365-6