

# Granuloma inguinale (donovanosis) in South Africa

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## Summary

Granuloma inguinale is a chronic specific infection of the genitalia of both sexes. It is endemic in many parts of the world, including the Caribbean, the southern USA, India, New Guinea and tropical and subtropical Africa. Apart from a single patient diagnosed clinically, no cases of the disease have previously been reported in the RSA, and some have thought that it did not occur here. A series of 8 cases diagnosed on the Witwatersrand over the past 21 months is presented, suggesting that the disease is endemic in this country and has until now been overlooked by clinicians and pathologists.

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A biopsy specimen of an ulcer of the vulva, thought clinically to be malignant, was submitted for histological examination. Microscopic examination revealed granulation tissue with an inflammatory infiltrate of plasma cells and small numbers of neutrophils. On Warthin-Starry staining to exclude spirochaetes (which were absent) characteristic intracellular Donovan bodies, diagnostic of granuloma inguinale, were unexpectedly found.

The haematoxylin and eosin-stained section was re-examined and the histological changes of granuloma inguinale recognized. These changes consisted of granulation tissue heavily infiltrated with plasma cells, neutrophils and large histiocytes. Lymphocytes were conspicuous by their absence (Fig. 1). The histiocytes had a variable appearance, were large and had either an eosinophilic granular cytoplasm or an intracytoplasmic vacuole with eosinophilic granules concentrated at the periphery of the vacuole (Fig. 2). These parasitized histiocytes, although visible in haematoxylin and eosin preparations, are much more clearly demonstrated by Warthin-Starry staining, which shows the Donovan bodies as intracellular rod-shaped bipolar-staining organisms resembling closed safety-pins (Fig. 3).

Granuloma inguinale is a chronic specific infection of the genitalia of both sexes, which is endemic in many parts of the world, including the Caribbean, the southern USA, India and New Guinea, as well as tropical and subtropical Africa. Apart from 1 patient, diagnosed clinically,<sup>1</sup> no cases have previously been reported in the RSA.

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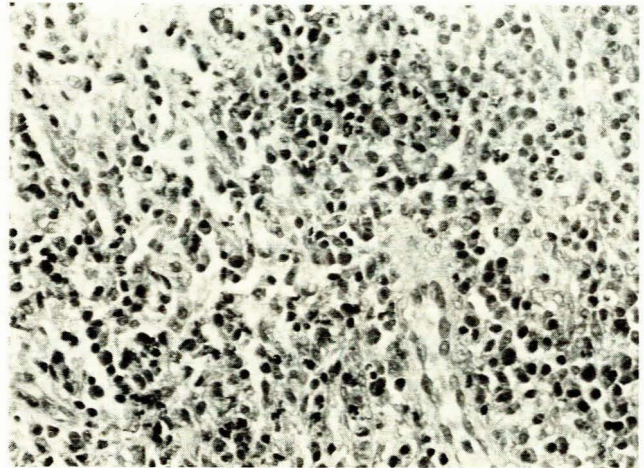


Fig. 1. Granulation tissue from the deeper portion of a biopsy showing the inflammatory infiltrate of plasma cells, neutrophils and large histiocytes. Lymphocytes are conspicuous by their absence (H and E x 720).

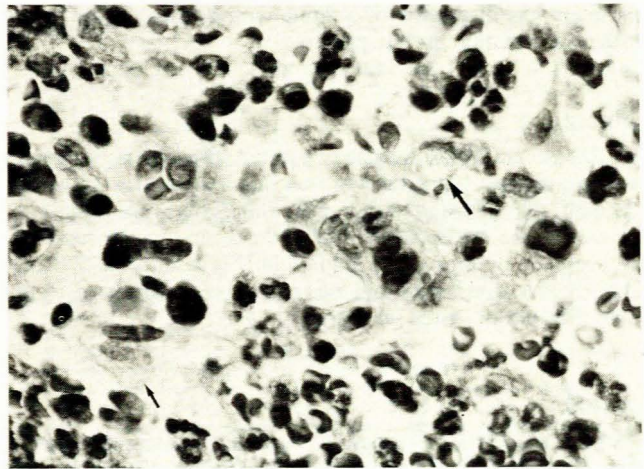


Fig. 2. The parasitized histiocytes, one with granular cytoplasm (small arrow) and one with an intracytoplasmic vacuole with granules concentrated at the periphery of the vacuole (large arrow) (H and E x 1800).

## Patients and methods

Following the initial diagnosis of granuloma inguinale in July 1980, all subsequent biopsy specimens of genital or inguinal ulcers showing the typical histological appearances were stained by the Warthin-Starry silver impregnation method and examined for the presence of Donovan bodies. Over the following 21-month period, from July 1980 to April 1982, 8 cases of granuloma inguinale were diagnosed. All the patients were young Black women whose ages ranged from 17 to 25 years. Five were seen at the Natalspruit Hospital, 2 at the Far East Rand Hospital and 1 at the Boksburg-Benoni Hospital.

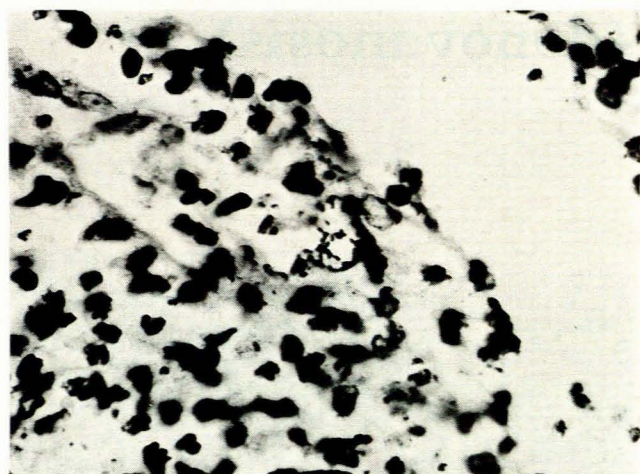


Fig. 3. The diagnostic intracellular rod-shaped Donovan bodies (Warthin-Starry stain x 1 800).

During this 21-month period a total of 9 757 histological specimens were examined in this laboratory; revealing invasive malignant tumours involving the cervix in 194 cases, the vulva in 13 and the penis in 19.

## Case reports

### Case 1

A 17-year-old Black woman had a vulval ulcer. The biopsy specimen was diagnostic of granuloma inguinale. There is no further information on this patient.

### Case 2

A 22-year-old Black woman presented with lower abdominal pain and contact bleeding. On examination she was 18 weeks pregnant, pyrexial, and had a tender cauliflower-like tumour, 6 cm in diameter, on the anterior lip of the cervix. Biopsy revealed the presence of granuloma inguinale. Erythromycin 500 mg 6-hourly was prescribed and the patient was permitted to go home. She has not been seen since.

### Case 3

A 19-year-old Black woman, who was 32 weeks pregnant, had large ulcers which had been present for 2 years on either side of the vulva, extending posteriorly towards the anus and into the vagina all the way up to the cervix. The inguinal lymph nodes on both sides were enlarged. Biopsies of the vulva and cervix both revealed granuloma inguinale. Erythromycin 500 mg 6-hourly was prescribed, and the patient has not returned for follow-up.

### Case 4

A 19-year-old Black primigravida was admitted to the labour ward and had a normal vertex delivery. There was a large kissing ulcer of the labia majora. The rapid plasma reagin test was positive to 16 dilutions. The white blood cell count was  $6,5 \times 10^9/l$ , the haemoglobin value 11,4 g/dl, and the erythrocyte sedimentation rate 46 mm/1st h. Biopsy of the ulcer on the 10th day after admission revealed granuloma inguinale. The patient was treated with intramuscular penicillin G and tetracycline 500 mg 6-hourly for 10 days. The lesion improved and she was discharged; she did not return for postnatal examination.

### Case 5

A 20-year-old Black woman had an ulcer of the right side of the vulva. She was treated with 8 ml penicillin. Six days later, biopsy revealed granuloma inguinale. There is no record of further therapy or follow-up.

### Case 6

In a 19-year-old Black woman biopsy of the vulva revealed the presence of granuloma inguinale. The case notes on this patient could not be found.

### Case 7

A 22-year-old Black woman in the first trimester of pregnancy presented on 8 December 1981 complaining of contact bleeding and continual spotting. An ulcer involving the left lateral fornix and anterior wall of the vagina, which bled readily, was noted. Biopsy at this stage revealed nonspecific vaginitis. On 21 January 1982 the patient was admitted to the antenatal ward having had a brisk haemorrhage, and on 5 February after further bleeding she received a blood transfusion. She continued to bleed a little, and on 15 February it was noted that the ulcer had increased in size. Biopsy at this stage revealed granuloma inguinale. The earlier biopsy specimen was reviewed but no Donovan bodies could be demonstrated. The patient was treated with erythromycin 500 mg 6-hourly for 2 weeks and was discharged when the bleeding stopped. Later in the pregnancy the ulcer, although smaller, was still found to be present, and repeat biopsy on 15 April again revealed Donovan bodies. A second course of erythromycin 500 mg 6-hourly for a further 2 weeks was prescribed. At term the ulcer was much smaller but still present, and the patient was delivered by elective caesarean section. After a third 2-week course of erythromycin, healing was complete and biopsy showed re-epithelialization of the cervix.

### Case 8

A Black woman aged 25 years complained of a blood-stained vaginal discharge. Examination showed slight vaginal bleeding and material within the vagina resembling products of conception. Histological examination showed this material to be granulation tissue containing Donovan bodies. This patient has not been seen again and has had no treatment.

## Discussion

Granuloma inguinale was first recognized in 1882 by McLeod in India. In 1905 Colonel Donovan described the intracellular rod-shaped bodies known since then as Donovan bodies. In 1913 South American investigators<sup>2</sup> named the organism *Calymmatobacterium granulomatis* (*calymma*, Greek for 'mantel' or sheath and *bakterion*, Greek for a 'small rod', thus *Calymmatobacterium*, the sheathed rodlet<sup>3</sup>). It was only in 1945 that organisms resembling Donovan bodies were successfully cultured in the yolk sac of chick embryos from aspirates of pseudobuboes of 3 patients with granuloma inguinale.<sup>4</sup> The same investigators also showed that serum from patients with granuloma inguinale contained antibodies against the organism.

Subcultures of the organisms from the yolk sac of chick embryos have been transferred to artificial media, but the organism has never been cultured directly from a lesion onto artificial media. Clinical disease has been transferred by the injection of aspirates of pseudobuboes from patients with granuloma inguinale into volunteers,<sup>5</sup> but experiments to transfer the disease to animals have not been successful, nor has clinical disease been produced by the injection of cultures of organisms into man.

Because of this inability to produce the disease in man or experimental animals from cultures of the organisms, Koch's postulates (which state the experimental evidence required to establish the aetiological relationship of a given micro-organism to a given disease) have not been completely fulfilled. Nevertheless, it is generally accepted that the causative organism of granuloma inguinale is *C. granulomatis*.

Electron microscopy suggests that the organism has a capsule and is a Gram-negative bacillus.<sup>6</sup> There is evidence that the organism may be antigenically related to certain members of the genera *Klebsiella*<sup>7</sup> and *Escherichia*.<sup>8</sup> The incubation period is variable, probably 8-80 days.<sup>9</sup> The lesion begins as an indurated nodule which enlarges, ulcerates and coalesces with satellite lesions to form extensive indolent beefy-red velvety granulations, often with a raised rolled edge. It is commoner in males, with a male/female ratio of 2,3:1.<sup>10</sup> The course of the untreated disease is prolonged, with recurrent episodes of ulceration and healing and eventual gross scarring and mutilation. An association with carcinoma has been suggested but never substantiated. Morbidity<sup>9</sup> appears to depend on attitudes and behaviour among the groups in which it occurs. With early treatment the infection is trivial, but patients usually delay for months before seeking treatment and then present with extensive disease; alternatively they may present with an ulcer which is regarded as a primary chancre without consideration of the differential diagnosis, and receive a single dose of penicillin. The patient then returns much later with more extensive disease.

The disease is not very contagious and occurs in the lower economic strata where it may be related to poor personal hygiene, combined with certain unknown intrinsic host susceptibility factors.<sup>11</sup> The mode of transmission is still disputed. The occurrence of the lesions, in most cases on the genitalia and in homosexuals, during periods of sexual activity, suggests that transmission is by sexual contact. In many cases this is true, but lesions may also occur in the very young and the sexually inactive. The disease does not always affect conjugal partners despite repeated contact, nor does it regularly occur in prostitutes. Goldberg<sup>12</sup> postulates that the organism occurs in the bowel, that the vagina is often infected by auto-inoculation from the rectum, and that clinical disease then occurs after sexual or non-sexual trauma of the infected site.

The diagnosis depends on the demonstration of the typical intracellular bipolar-staining rod-shaped organisms. The organism occurs extracellularly as well, but interpretation is then difficult unless the organisms are seen intracellularly. It is generally said that the examination of a crushed preparation of clean granulation tissue, air-dried and stained with Wright or Giemsa stain, is more sensitive than histological examination.

Recovery of the organism *in vitro* has been largely unsuccessful. Serological tests are of low specificity and not generally available. Apart from direct examination of tissues, therefore, laboratory assistance in the diagnosis of the disease and *in vitro* testing for sensitivity to antimicrobial agents is not generally available.

## Treatment

The organism is a Gram-negative rod and is usually inhibited by antibiotics that are active against these organisms.<sup>11</sup> There is no response to penicillin. Ampicillin and erythromycin have not been consistently effective. Tetracycline (0,5 g 6-hourly) appears

to be the drug of choice. Chloramphenicol, gentamicin and co-trimoxazole have been shown to be effective. The combinations of lincomycin and erythromycin as well as ampicillin and erythromycin<sup>13</sup> have been found satisfactory in the treatment of pregnant patients. Treatment should be continued until the lesions have healed completely, usually 2-3 weeks. Long-standing lesions may be so mutilating and extensive that surgical repair may be necessary.

The literature on granuloma inguinale in southern Africa is sparse. In 1950 Wilcox<sup>14</sup> reported 17 cases from Southern Rhodesia. Brain<sup>15</sup> and Kingsley<sup>16</sup> have each reported single cases from Southern Rhodesia, as has Veen<sup>17</sup> from Botswana. Bhagwandeem and Naik<sup>18</sup> have reported 40 histologically verified cases over a 3-year period from Zambia.

The only reference to granuloma inguinale in the RSA is the single case mentioned by Duncan *et al.*<sup>1</sup> among a series of 102 Black men in Soweto with genital ulcerations, diagnosed on Wright staining of smears of scrapings of the ulcer.

## Conclusion

Eight cases of granuloma inguinale diagnosed over a period of 21 months are presented. As there were no males in this series, the true incidence of the disease is probably higher than these figures would suggest. The disease appears to be endemic on the Witwatersrand and has previously been overlooked by clinicians and pathologists.

Granuloma inguinale must be considered in the differential diagnosis of all genital ulcers, particularly where histological changes appear nonspecific at first sight.

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