STUDY OF GRANULOMA VENEREUM

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Summary

Study is a comprehensive work on 62 patients with granuloma venereum. 16 of them were females and 46 were males. The predominant age group among males and females was 21-30 years and 15-20 years respectively. The incubation period varied from 3 days to 1 year. The duration of disease was from 3 days to 4 years. 55 patients had pure genital lesions. 4 had genital and extragenital lesions. 3 had extragenital lesions only. V.D.R.L. was reactive in 20 of these patients. Histopathological examination done in 6 patients did not reveal any abnormality. Malignancy as a complication was not encountered in this series. The duration of the treatment varied from 10-25 days.

Author has also given 7 case reports each representative of the varied clinical picture of this condition. He has also given the salient aspects of his observations regarding the morphology and life cycle of Donovania Granulomatis.

Ever since the condition of granuloma venereum has been described by McLeod in 1882 it has been a subject of much discussion and controversy. The number of synonyms like granuloma inguinale, donovanosis etc., which it has come to acquire, is itself an indication of prevailing confusion. Though Donovan discovered the causative organism in 1905[1] its pathogenesis and epidemiology is not yet completely elucidated. In fact there are authors who dispute its very venereal nature[2-4]. There are extensive reviews on this subject from Madras[5,6] Pondicherry[7-11] and Madurai[12]. From Andhra Pradesh most of the works reported so far are from coastal areas[13-17]. There is one statistical report from Telangana area also[18]. Except for the incidence which was reported in 1960[19], there are no comprehensive works on this subject from Rayalaseema area of this State and hence this communication. As mere presentation of statistical data does not reflect the morbidity and variegated clinical picture of this condition this communication will present brief accounts of selected cases which the author had the opportunity to observe. In addition the author would be presenting an account of morphology and probable life cycle of donovania granulomatis based on his observation.

The material for this study is provided by the cases which were diagnosed as granuloma venereum during a period of 14 months. After thorough scrutiny and review, 29 out of 91 such cases were discarded and the present review is confined to 62 cases.

Epidemiological Features

The total number of new cases with S.T.D. observed during the same period

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was 3,730. Thus granuloma venereum constituted 1.6% (Table-1) of new cases

TABLE 1
Table showing the Incidence of Granuloma Venereum

No. of cases Granuloma Venereum	No. of new cases	Incidence
62	3730	1.6%

attending the S.T.D clinic. This incidence is in agreement with that of 1.5% reported by Rajam and Rangaiah[5] and Rama Iyengar[12]; but far less than the incidence reported from Pondicherry[7,11] Guntur[13,15], Kakinada[17], and higher than the incidence of 0.3 and 0.9% reported by Vimalabai et al[18] from Hyderabad and Secunderabad respectively. From this institution Ramachander[19] reported an incidence of 1.3% in 1960 and the slight difference in the present work may be due to better communication facilities which developed during the last two decades.

Age sex distribution is given in table 2. Among males maximum number

TABLE 2
Age and Sex Distribution

Age group	Males	Females
15—20	7	7
21—30	22	5
31—40	13	3
41—50	4	1
Total	46	16
Sex Ratio :	2.8	1

of patients were in the age group of 21-30 years with 22 patients. The next predominant group was between 31-40 years with 13 patients. Among females the predominant age group was 15-20 years with 7 patients followed by 4 patients in the age group of 21-30 years. This disparity in the age group of sexes is well documented and is attributed to earlier onset of maturity in females. The youngest male patients in this series was 18 years old while the oldest was 50 years of age. The youngest female patient was 15 years old and the oldest was aged 45 years.

46 patients were males while 16 were females giving a M : F ratio of 2 8 : 1. This sex ratio is in rough agreement with the ratios reported from elsewhere [5,8,12,17].

Marital status of these patients is given in table 3. Among 46 males, 30

TABLE 3
Marital Status

	Males	Females
Married	30	11
Unmarried	10	2
Others	6	3

were married, 10 were unmarried and 6 were divorced, separated or widowed. Among 16 females, 11 were married, 2 were unmarried, and in another 3, 2 were widows while the third was a woman of questionable character with no definite spouse. While it would be easy to explain this predominant occurrence among married males on the basis of greater financial and sexual freedom it would not be possible to do so in case of females.

Based on the criteria of definite extra marital exposures incubation periods could be recorded only in 29 male patients. (Table-4). In 11 patients it ranged

TABLE 4
Incubation Period

Period	No. of patients
1—10 days ...	11
11—20 days ...	6
21—30 days ...	7
31—60 days ...	2
61—90 days ...	2
1 Year	1
Total	29

from 1-10 days, in 6 from 11-20 days and in 7 from 21-30 days. In 2 patients each it ranged from 31-60 days and 61-90 days respectively. In one patient it was 1 year. The minimum period was 3 days while the maximum was one year.

The duration of disease could be assessed correctly only in 60 patients (Table-5). The shortest duration was 3 days while the longest was 4 years.

TABLE 5

Duration	No. of patients
1—10 days ...	9
11—20 days ...	8
21—30 days ...	11
31—60 days ...	11
61—90 days ...	2
91—180 days ...	6
181—365 days ...	4
1—2 years ...	6
2—3 years ...	2
3—4 years ...	1
Total	60

Clinical features

The location of lesions are given in table 6. Out of 62 patients, exclusive genital ulceration was noticed in 55. Among 7 patients with extragenital lesions, associated genital lesions were present in 4. Thus 59 out of 62 had genital lesions. 3 patients had lesions in the genito inguinal region. One of these patients had bilateral inguinal scars with a granulomatous ulcer on genitalia. Another patient had ulcer penis with bilateral hypertrophic inguinal ulcers (Fig. 1). The 3rd patient had granulomatous ulcers on penis and left inguinal region with pseudobubo of right inguinal region. One each had inguinal, inguino-cruro-scrotal (Fig. 2) ano-genital and periano-perineal lesions.

TABLE 6

Location of Lesions

Region	No. of patients
Genital ...	55
Genito-inguinal ...	3
Inguinal ...	1
Inguinocruro-scrotal ...	1
Ano-genital ...	1
Perianoperineal ...	1

In table 7 the number of patients with different types of lesions are given. It could be said that on male genitalia the lesions were generally fleshy and exuberant while on female genitalia they were fleshy, exuberant or hypertrophic. The extragenital lesions in inguinal and perianal regions were hypertrophic. Thus both the types of lesions were seen sometimes in the same patient. The number of lesions on male genitalia was generally 1, though 2 or 3 were occasionally seen. Multiple lesions were more commonly observed in females. The order of frequency as regards sites of involvement of male genitalia was glans, prepuce, coronal sulcus and shaft in that order. In the females it was fourchette, labial folds and adjoining vagina and clitoris in that order. Periurethral ulceration was noticed in 1 case. 1 case of sclerotic form and 4 cases of necrotic form with secondary infection were noticed. In one case there

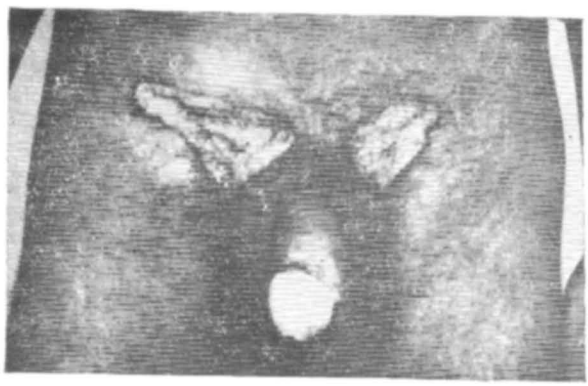

Fig. 1 Inguinogenital Location

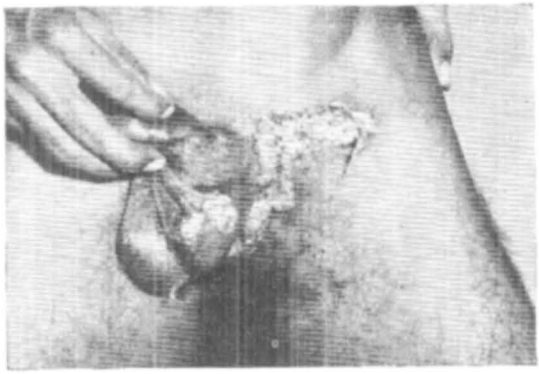

Fig. 2 Inguino-cruro-scrotal location

were extensive scars in inguinal region with granulomatous ulcer on genitalia and hence it is classified as sclerotic with fleshy exuberant type. Absence of conspicuous regional lymphadenopathy is indisputably one of the diagnostic hall marks of this condition. The initial lesion on male genitalia was generally in the form of an eroded papule while in the inguinal region it was in the form of a cystic swelling.

In 20 patients VDRL was reactive (table 8 & 9). 15 of them had latent syphilis. 3 had secondary syphilis. 1 of these 3 had granulomatous ulcer penis with partial phimosis and joint pains. The 2nd patient had ulcer genitalia with joint pains and generalised lymphadenopathy. The dark field examination from the ulcer was positive for treponema pallidum. After 10 days of treatment with procaine penicillin 8 lakhs daily, as the ulcer did not subside, tissue smear for Donovan bodies was done and found positive. The 3rd case had perianal granuloma extending on to perineal region which was positive for treponema pallidum and donovan bodies. His VDRL was reactive 1:64 dilutions. As the patient was a confessed pederast he was thought to have granuloma venereum supervening over condyloma lata or vice-versa. 1 patient had latent syphilis with L.G.V. Another patient had latent syphilis with stricture urethra. 2 of the VDRL non-reactive patients had molluscum contagiosum and warts respectively. Thus 22 out of 62 patients had some other S. T. D. disease or diseases.

Anatomical abnormalities were also noticed. Among males 9 had phimosis, 1 had para-phimosis and 4 had penile oedema with phimosis. One patient developed partial destruction of prepuce after treatment. 8 female patients had hypertrophy or pseudo-elephantiasis of vulva while 3 had vulval oedema. One of the patients with hypertrophy had perforation of left labial folds. Reports of 7 cases each unique in its own respect are appended below.

TABLE 7

Fleshy exuberant or ulcerative		49
Hypertrophic	..	7
Sclerotic	...	1
Necrotic	...	4
Sclerotic with ulcerative	...	1

TABLE 8

V. D. R. L. Reactivity

Titre	Males	Females	Total
1 : 2	1	—	
1 : 4	3	1	
1 : 8	2	—	
1 : 16	2	—	
1 : 32	3	—	
1 : 64	7	1	
Total	18	2	20

TABLE 9

Associated Venereal Conditions

Latent syphilis	...	15
Secondary syphilis	...	3
Latent syphilis with stricture urethra	...	1
Molluscum contagiosum	...	1
Warts	...	1
	Total	22

Fig. 3 Genital location

Case Reports

(a) Fleshy Exuberant Lesions :— An unmarried male aged 25 years, presented with two ulcers on genitalia of one year's duration. (Fig. 3). Patient acquired the disease six days after an exposure with a prostitute. On examination there were two ulcers, one on ventral surface of prepuce $\frac{1}{4}$" x $\frac{1}{4}$" in size and another on the dorsal aspect of shaft 2" x $\frac{1}{2}$" size. Prepuce was phimotic. There was no regional lymphadenopathy. Smear for Donovan bodies (D.B.) was positive and S.T.S. was non-reactive. Patient was administered streptomycin 1g I.M. and chloromycetin 1g. orally. He made complete recovery in 10 days.

(b) Hypertrophic Lesions with Pseudoelephantiasis : 30 years old female, a widow presented with multiple ulcerative lesions on genitalia of one month duration. On examination there were multiple hypertrophic ulcers on vulva and vaginal wall. There was no regional lymphadenopathy. There was elephantiasis of vulva with hypertrophy of clitoris (Fig. 4). Urinalysis, motion examination and blood counts were normal. VDRL was non reactive. Frei's test was negative. A/G ratio was 3/2.9 G%. Biopsy from the edge of ulcerated growth showed hyperkeratosis, acanthosis and chronic inflammatory cell reaction. Tissue smear from the ulcer showed Donovan bodies. The patient was administered the same regimen as mentioned in case 1. At the end of 15 days, ulcers subsided with some lichenification but pseudoelephantiasis persisted.

(c) Hypertrophic Lesions :— 45 years old married female presented with multiple hypertrophic lesions covered with whitish pellicle on vulva and perianal region of 10 days' duration. Though the first clinical impression was condyloma lata, tissue smear for D.B. was found to be positive and VDRL done twice was non-reactive. Biopsy from the lesion showed ulceration and epithelial hyperplasia with subepithelial round cell infiltration and fibrosis. As the patient was sensitive to streptomycin, she was administered tetracycline 2 g. daily orally for 15 days with complete relief.

(d) Sclerotic Form :—25 years old married male presented with subprepeutial ulcer and phimosis of 10 months' duration. He had an exposure 2 months prior to the onset of complaint. There was no conspicuous lymphadenopathy.

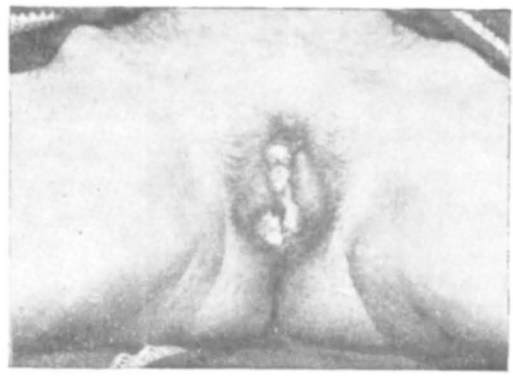

Fig. 4 Hypertrophic lesions with pseudoelephantiasis

His VDRL was non reactive. After administering sulphadiazine 4 g. daily for 3 days, circumcision was done. The prepuce was found to be fibrotic and hard. The fibrotic mass extended on to coronal sulcus and glans at 9-11 o' clock position, eating away part of the flesh. The fibrotic mass was excised as much as possible and circumcision completed. Part of the mass was subjected to microscopic examination for Donovan bodies and another part was sent for histopathological examination. Even after detailed scrutiny no Donovan bodies could be discovered. Histopathology showed a chronic inflammatory cell reaction with areas of haemorrhage. Postoperatively the patient was administered streptomycin 1g. + procaine penicillin 4 lakhs for 15 days with complete healing of the ulcer. In this case we thought of granuloma venereum, because the only alternative possibility was malignancy and that was not proved by biopsy. In addition the patient made complete recovery with antibiotics. It is known that Donovan bodies are rarely demonstrable from this type of lesions[5].

(e) Necrotic form :— 35 years old married male presented with the complaints of ulceration and oedema of penis of 20 days' duration. He gave history of multiple extramarital exposures. On examination there was a big ulcer of 1½" diameter at the junction of the prepuce with the shaft with oedema of penis and phimosis. The ulcer was necrotic, exuding foul smelling discharge. His V. D. R. L. was reactive 1 : 64 dilutions. After administering procaine penicillin 12 lakhs for 7 days, tissue smear examination showed Donovan bodies. Patient was treated subsequently with Chloromycetin 1 G orally and Streptomycin 1 G I. M. for 15 days. As the ulcer did not subside even then, based on the culture report patient was given Erythromycin 2 G. orally daily for another 10 days. At the end of such a heroic treatment for more than 1 month the ulcer healed, but the entire anterior part of prepuce was destroyed leaving only a tag at the distal portion. Later in the Urology Department the circumcision was completed (part of it was done by disease itself). He was found to have stricture urethra.

(f) Pseudo-bubo :— 25 years old male presented with the complaints of ulcer genitalia of 2 months' duration, ulcer in the left inguinal region of 1½ months' duration and swelling in the right inguinal region of 1 months' duration. He confessed to have an extramarital exposure 2½ months earlier. Patient was pyrexial. Routine urinalysis, motion examination and blood counts showed leucocytosis and E. S. R. of 85 mm/hr. His V. D. R. L. was non reactive. Frei's test was negative. A/G ratio was 3.7/3.1 G%. Tissue smears from genital ulcer and left inguinal region as well as the aspirated material from the right inguinal region all showed Donovan bodies. Patient was treated with Cap. Tetracyclin 2 G. daily orally for 15 days.

(g) Granuloma Venereum suspected to be a malignancy :—

50 years old married male, highly promiscuous with multiple extramarital exposures, was referred by a general practitioner with a recalcitrant ulcer genitalia of 2 months duration, not responding to any antibiotics — a probable malignancy. On examination there was a ¼" x ¼" sized ulcer at 6-0' clock position on the preputial margin. It was non-tender, margins were raised and indurated. There was no regional lymphadenopathy. Smear taken from the floor of ulcer showed Donovan bodies. His V. D. R. L. was non-reactive. The ulcer subsided by 10th day with 1 G. of Streptomycin and 1 G. of Chloromycetin daily.

Granuloma Venereum and Malignancy:

It is well documented that granuloma venereum can turn malignant[20]. However

Rajam and Rangaiah[5] feel that such a transformation is infrequent as only 0.25% in their series of 2000 cases showed such a change. Rama Iyengar[12] reported 2 instances of such an association. Goldberg and Annamunthodo[21] demonstrated antibodies to donovania granulomatis in 9 out of 62 cases of cancer penis. But greater danger lies in mistaking a case of granuloma venereum for malignancy. Rangaiah[6] emphasised this aspect on his retrospective study. In the present series malignancy was suspected in 3 cases (d, e, g,) clinically and in 1 case (b) histologically. But subsequent investigations, response to treatment and further follow up disproved it.

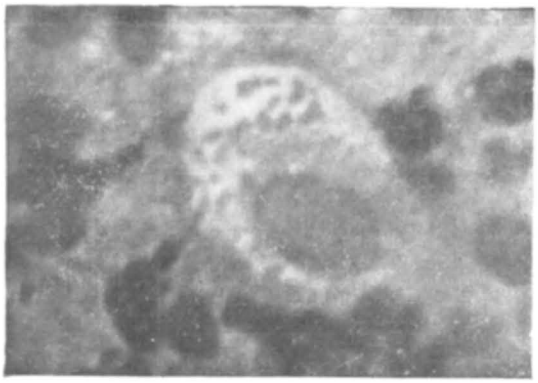

Fig. 6 Intra cellular capsulated donovan bodies

Histology

Biopsy pieces were examined in 3 cases of fleshy ulcerative type, 2 cases of hypertrophic type (case reports b & c) and one case of sclerotic type (case report d). No specific pathology was reported in any of these.

Donovania Granulomatis

Rajam and Rangaiah[5] have described in detail the morphologic characteristics of this organism. Davies[22] recently has described its ultrastructural features. However, in current Indian literature no stress is being laid on the pleomorphic nature of this organism. American authors mostly concentrate on capsulated forms, though it is the noncapsulated ones which are seen in profusion. In addition no effort is being made to construct all these stages into a probable life cycle. Author after observing number of slides in good number of patients has made the following salient observations. These observations are confined to smears stained with Leishman's stain only (Fig. 5 & 6).

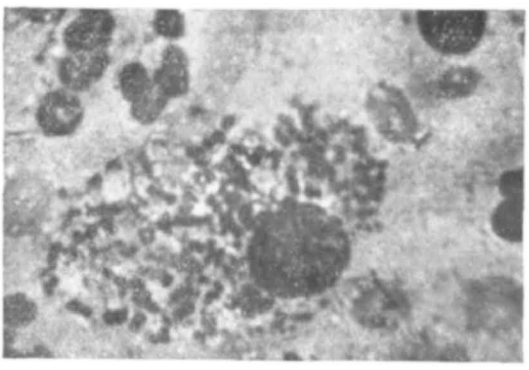

Fig. 5 Intra cellular capsulated and non capsulated donovan bodies

(1) The most pathognomonic feature in a smear is the presence of mononuclear cells with organisms inside. Sometimes organisms may be seen within vacuoles. Vacuoles may or may not have adjoining nucleus.

(2) Non capsulated form is generally diplococcoid though rarely interspersed in them coccoid and bacillary forms may be seen. Capsulated form may be bipolar stained (safety pin) or centrally stained. Occasionally it may be so densely stained that no details may be visible.

(3) The non-capsulated diplococcoid forms grown in size and after achieving 2-4 times

their original size become capsulated. Thus the transformation is gradual.

(4) The capsulated form continues to grow and assume even 10 times the size of original non-capsulated diplococcoid forms.

(5) Within the mono-nuclear cells, along with capsulated forms, dark blue stained structures, which are 20-25 times the original size of non-capsulated forms have been observed. These were probably described in the past as inclusions. After careful observation author is of the opinion that they are overgrown-sized capsulated forms.

(6) Author has observed very often organisms coming out of burst vacuole or cell. Though mostly these were non-capsulated, occasionally capsulated forms were noticed.

These observations naturally leads one to believe that there is a life cycle in the growth, development and multiplication of these organisms. The organisms are naturally not dividing by simple binary fission, as otherwise the presence of so many stages becomes irrelevant. Is it likely that the non-capsulated is the active infective form and the capsulated the resting reproductive form? Or is it possible that one of the forms of non-capsulated, and there are many, alone is infective? Is it possible that capsulated after assuming some size bursts to liberate non-capsulated forms? If not what is the provocation to become capsulated?

Unless these questions are properly answered, it is difficult to understand the vagaries in the epidemiology and pathogenesis of this condition.

Treatment and Follow-Up

4 therapeuticr egimens were followed.

1. Streptomycin 1 G I.M. daily with or without procaine penicillin 4 lakhs I.M. daily. ... 11 cases
2. Streptomycin 1 G I.M. daily + Chloromycetin 1 G orally daily. ... 17 cases
3. Streptomycin 1 G I.M. daily + Tetracycline 1 G orally daily. ... 9 cases
4. Tetracycline 2 G. daily orally ... 3 cases

With regimen No. (1) the duration of treatment ranged from 10–25 days. With regimen No. (2), (3) and (4) the duration of treatment among males varied from 10–15 days, while among females it was from 10–20 days. 3 patients under regimen No. (2) responded however differently. 2 of them were males. These patients had necrotic lesions. In these patients the treatment had to be prolonged for 7 and 10 days with chloromycetin and erythromycin respectively (Case-e.) In one female patient under the same regimen with extensive ulceration of genitalia the treatment had to be given for 25 days. One male patient (Case–a) with ulcers on genitalia and another female with multiple lesions were followed up after commencement of regimen No. (2) with tissue smears every alternate day. In the male patient the smear became negative after 4th day and ulcers healed by 10th day. In the female patient the smear became negative by 12th day and the ulcers healed completely by 18th day.

2 patients reported after 1 year with the same complaint and in both the instances it was considered reinfection. One was a widow and another a prostitute.

Comments

The argument that granuloma venereum is a sexually transmitted disease is based on the following points.

a) It is present in the age group which is most sexually active.

b) It follows very often extra marital exposure.

c) Lesions are mainly localized on genitalia.

d) The disease is associated with other venereal diseases.

On the other hand Goldberg and his associates[2-4] feel it to be a non-venereal condition. These authors have shown that Donovania granulomatis is intestinal in habitat, antigenicity and cultural characteristics. They have also demonstrated number of intestinal organisms in the vaginal tract of females. Consequently they feel that it could be caused by any infection or trauma. If this argument is accepted granuloma venereum must be seen more frequently with piles, fistula, pruritus ani, intestinal parasitic infections, tinea cruris, scabies, folliculitis etc which is not the case. This, the authors explain postulating individual susceptibility. If this postulate is accepted, there must be greater frequency of recurrences.

Venereal concept also suffers from certain snags. Mere presence of this condition in the age group of 15–30 does not make it venereal. Likewise the presence of history of extramarital exposure also does not prove it.

Obviously there are far too many puzzles in the epidemiology of granuloma venereum. Perhaps the answers for all these may be in the organism itself.

Acknowledgement

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TRUE

Although according to several publications, applications of 5-FU on normal skin results in neither clinical nor microspic alterations. Zelickson and coworkers[1] on E/M studies showed substantial ultrastructural changes. 5-FU has been implicated in the development of rapidly growing squamous cell carcinoma upon actinic keratoses so treated[2,3]. Hill[2] has reported squamous cell carcinoma developing after 6 weeks of topical applications of 5-FU to histologically verified basal cell epithelioma (BCE). Others who have extensive experience with 5-FU have also reported rare instances of apparent conversion of BCE to squamous cell carcinoma after topical application of the agent. Kurtis and Rosen[4] recently published a case in which squamous cell carcinoma developed in a clinically and histologically typical BCE treated with intralesional 5-FU.

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