Donovanosis

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Donovanosis is a chronic bacterial illness frequently associated with sexually transmitted infections (STI) and is under diagnosed both in endemic areas as well as in countries in which doctors have little experience with tropical diseases. The utilization of syndromic diagnosis and treatment of STIs in various parts of the world and the previous use of antibiotics make it difficult to find Donovan bodies in the cytodiagnostic and hystopathological exams, requiring the utilization of technology that is neither routine nor often accessible to confirm the hypothesized diagnosis. Therefore, it is necessary to bring medical professionals up to date about this infectious disease.
Key-Words: Granuloma inguinale, review, sexually transmitted diseases.

Donavanosis is a chronic bacterial illness, progressive and indolent, which normally attacks the skin and mucous membranes in the genital and perigenital regions. It is frequently associated with sexual transmission, although it is known to be only slightly infectious.

This disease was described in 1882 by McLeod in India. Donovan, in 1905, working in the same country, described the causal agent [1,2].

In 1913, two Brazilians, Aragão and Vianna, introduced the use of emetic tartar, the first effective medication used for the treatment of this disease, also known as granuloma inguinal because of its frequent involvement in these regions. However, of the 720 cases mentioned in a Peruvian study of this disease, only 10% demonstrated inguinal lesions, usually associated with concurrent genital lesions. Other synonymies reveal clinical epidemiologic aspects of the disease.

Etiology

Donovan described the agents as intracellular microorganisms. Later studies revealed that they are Gram-negative coccobacilli that whiten with greater intensity in the extremities than in the center, whether in capsules or not, intracytoplasmotic, and not moving. When in their initial phase, with something of the appearance of round coconuts, they measure between 0.02 to 0.2 μm in size. When they are roundcoccus, they measure between 1 to 2.5 μms in length. Aragão and Vianna [3] were the first authors to classify the agent of donovanosis, *Calymmatobacterium granulomatis*.

Although Anderson has suggested that the classification be changed to *Donovania granulomatis* in honor of Donovan, the name proposed by the Brazilians continued [4-8].

Similarities of the agent with *Klebsiella* spp. have been described using as their base the reactions of crossing serums and the ultra-structural aspects, as well as the similarities in the histological aspects of donovanosis and of rhinoscleroma, an infection caused by *K. pneumoniae rhinoscleromatis* [9].

Nevertheless, it was from the time of the study of Carter et al., in 1999, based on molecular aspects (genes 16SrRNA and phoE) that a proposal was made to reclassify the donovanosis agent as *Klebsiella granulomatis* comb. nov. [10]. Another study found a small phylogenetic relationship between the Donovan agent and the *Klebsiella* spp. [11]. In spite of this, recent works and official *guidelines* have reinforced the similarities and used the classification proposed by Carter et al. [12-19].

Epidemiology

Even though this illness has been described for more than a century, it is frequently neglected because of its occurrence in unspecified geographical locations and with infrequent incidences. Therefore, its pathogenesis and epidemiology are not completely understood and require more study [20].

This illness is more common in Afro-Americans, in individuals with a lower socio-economic status, and among those untrained in hygiene. It is endemic in tropical and subtropical climates, such as Papua New Guinea, South Africa (provinces of KwaZulu/Natal and East Transvaal), parts of India and Indonesia, and among the aborigines of Australia. Some cases have been reported in the countries of Central America and the Caribbean, Peru (where the first cause of chronic genital ulcers in patients with immune deficiency disorder have been found), Argentina, French Guiana and Brazil [1,2,8,9,21,22]. Brazil was not included as an endemic area in the 2006 guidelines for the treatment of sexually transmitted infections (STI) of the CDC (*Centers for Disease Control and Prevention*) [18]. It is possible that this classification is more related to the socioeconomic conditions than to racial or geographical factors.

Nevertheless, O'Farrell considered that the diagnosis of the illness had been underestimated in various places where the illness is prevalent [9]. Morrone et al. considered the possibility that even among developing countries, medical professionals have found it difficult to identify donovanosis cases due to lack of experience with tropical diseases [23]. Another possibility is that the illness has been treated and accidentally cured by the use of antibiotics which are being self administered more frequently than before [24].

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The introduction of the diagnosis and syndromic treatment in various areas of the world has made it more difficult than ever to statistically evaluate the prevalence of STIs, as can be seen in the example of the observations of O'Farrell in Durban, South Africa [25].

All of these things have contributed to the lack of understanding of the true prevalence of the illness. The incidence between the sexes varies from study to study [1], but there does not seem to be a predilection for a particular gender.

This is an illness which touches almost exclusively adults between the ages of 20 and 40 years [1,2]. There are no reports of congenital infections as a result of fetal infections [26]. However, cases have been reported in nursing and newborn babies [1].

Cases in children are frequently associated with contact with infected adults, though not necessarily because of sexual abuse [25].

Complications have been clearly observed in rural endemic areas, which reinforces the necessity of control of STIs by medical professionals [9]. Since the middle of the 20th century, there has been a consensus that donovanosis can be transmitted sexually. In spite of the occurrence in sexually inactive children and adults, and the disease being proportionately rare in sex workers, the arguments which this thesis will present are based on the fact that in the majority of cases, those with this illness have a history of sexual activity, and in the subcategory of those who are sexually active, there is a greater incidence of exclusively cervical lesions, anal lesions associated with the practice of sodomy, genital lesions in the majority of cases (80%-100%), concomitant STIs, sexual contact with sex professionals, and a high prevalence in the sexual partners of the cases studied [1,2,20,23,25,26].

It is supposed in some studies that the natural habitat of *K. granulomatis* could be the intestine and that the skin is affected by direct contact, during anal coitus, or indirectly, through contamination of the genitals by fecal organisms [27].

Clinical Manifestations and Classification

The period of incubation is explained as being 1 to 360 days. However, lesions induced in volunteers appear in an average period of 50 days [25]. The carrier of the disease is the human body [28].

Clinical manifestations of the disease begin with papules on the skin or subcutaneous nodes that can evolve into superficial ulcerations. The ulcers can be leticular with uneven borders and may present a slightly inflamed reaction. These ulcers grow slowly and centrifugally, without pain, and become well-defined, granulomatous, with a circular or snake-like appearance, and which bleed easily. They can be self-inoculated, and there are often multiple ulcers which may appear to be mirror images. They are commonly located in the folds of the skin, and can become extensive. Frequently, these lesions contain a super bacterial infection. The granulamatous tissue emits a rank odor [2,25].

Nodular lesions can appear to be lymphadenopathic, which is also known as "pseudobulbar". Typically, however, donovanosis does not occur together adenites [2,16,26,29].

As a general rule, the anatomical regions most commonly affected in men are the sulco coronal, the balanopreputial region and the anus, while woman are most affected in the labia minor, vaginal furcula and occasionally in the cervix and trato genital superior (where they appear as carcinomas). Ulcers are more frequent in uncircumcised men and in men with poor genital hygiene [9,25].

Extra genital lesions are almost exclusively secondary to lesions on the genitals or anus (Figure 1) [1].

In addition to the anal and perianal regions, other extra genital areas affected are: lips, gingiva, mucosa jugal, mandibles, palate, pharynx, larynx, neck, nose, ophthalmological regions, scalp, thorax (sulci inframammaries), abdomen, arms, legs, and bones (particularly the tibia). Oral lesions in general are the most frequent, and loss of teeth indicates that the bones have been compromised by donovanosis [1,2,9,25,30].

The occurrence of dissemination in the abdominal cavity, intestines, spleen, liver, lungs, uterus and ovaries has been recorded, and occurs more frequently in endemic areas. The following symptoms occur in these cases: fever, malaise, anemia, night sweats, weight loss and toxemia. These symptoms can lead to a risk of loss of life, because they are rarely associated with the diagnosis of donovanosis [1,2,9,31].

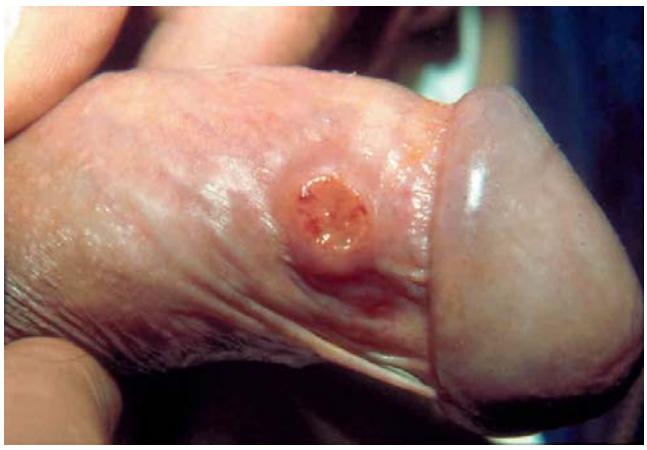
The following classification was proposed by Jardim [32]:

1. Genitals and perigenitals
   - 1.1 Ulcers:
     - 1.1.1 with hypertrophic borders
     - 1.1.2 with smooth borders
   - 1.2 Ulcerovegetative
   - 1.3 Vegetatives
   - 1.4 Elephantiasic
2. Extragenitals

In the ulcerovegetative form, which is also the most frequent, there is an abundance of granulated tissue crossing the limits of the borders. Dry or timorous vegetative forms are normally smaller and less noticeable. Elephantiasic lesions occur almost always after chronic ulcers form, which leave intense fibrosis scarring and lead to lymph deterioration. Normally, these are found in the female genitals, and only exceptionally in men. This is the most frequent complication of donovanosis. Other than dissemination, it has been recorded that after long periods of the illness, spinocelular carcinoma of the vulva develops. Other complications may include: phimosis, and stenosis of the urethra, vagina, and anus [20,26,28,32]. It can reoccur in a period of 6 to 18 months, even after effective treatment [25,31].

Donovanosis takes an aggressive course during gestation and women with atypical lesions in the genital area should consider this as a possible diagnosis when undergoing prenatal care [9].

Figure 1. Donovanosis: ulcerated lesion of the hypertrophic borders of the penis.



Little study has been done regarding the relationships of the effects of HIV on donovanosis. However, it is known that donovanosis increases the risk of acquiring HIV, which augments with the continuation of lesions [25,31].

Co-infection with HIV usually causes persistent ulcers for prolonged periods and requires intense and prolonged antibiotic treatment, in comparison with donovanosis patients that are HIV negative. The size of the ulcers and the clinical presentation do not differ significantly, as demonstrated in an Indian study conducted with patients co-infected with this retrovirus and those without this infection [33]. However, HIV positive patients experienced greater tissue damage and the average time needed for scarring of the ulcers was significantly greater. The confirmed diagnosis was the same for both groups. In co-infected patients, the resistance to the treatments fell within traditional ranges considered [31].

Differential and Laboratorial Diagnosis

The differential diagnosis of donovanosis should be done with primary syphilis and some secondary forms (such as condyloma), Ducrey's diseases (principally in its phagedenic form or with a cluster of papules), chronic herpes ulcers, condyloma acuminata (most importantly when large and in a common area), lymphogranuloma (when donovanosis is inguinal and elephantiastic) and spinocellular carcinoma [1,2,25,28].

Studies raise the possibility of co-infection, especially with STIs. Samuel et al., for example, described the concomitant relationship of donovanosis with syphilis and simple herpes [34].

Other aetiologies of granulomatosas ulcers should be considered, such as cutaneous tuberculosis, paracoccidioidomycosis, leishmaniasis, as well as pyoderma gangrenosum. In cases which exhibit extra genital location, it will be necessary to procure diagnoses differentials in accordance with the common forms of dermatosis in each region. In the nasolabial region, for example, possible diagnoses which should be considered are rhinoscleroma and medio-facial granuloma, among others [2].

Extra genital lesions can present themselves in an atypical form, which frequently makes diagnosis difficult [25].

Uncommon diagnoses, such as histiocytosis of cells of Langerhans and bipolar aftose can also require a diagnostic differential with donovanosis [35,36].

A clinical hypothesis can be confirmed in the laboratory by the discovery of Donovan bodies in the fragment of the lesion, using cytodiagnosis or pathoanatomical exams. When collecting the materials for cytodiagnosis, the first sample should be used to research Donovan bodies to obtain an adequate amount of cellular material [9].

Giemsa colorations of Leishman and Wright should be used. *Pari-Diff* is a quick version of Giemsa coloration and can be used as well. Histopathological exams are useful to establish diagnoses in rare cases in which the cytodiagnosis does not permit a confirmation of the clinical hypothesis. The exam should be conducted in extensive lesions with necrosis or sclerosis, to eliminate the possibility of malignancy, and less commonly, in lesions in the mouth, anus, cervix and uterus. The bacteria multiplies within the histocytes until they burst, liberating a new generation of bacterium. The corpuscles have been seen both inside and outside of the histocytes and are difficult to find in newly formed lesions [2,13,25,26,32].

Remaining techniques will be used in cases which have a limited number of Donovan bodies, such as happens when lesions have a shortened period of evolution or in cases in which patients previously used antibiotics [20,25,36].

Other than pathoanatomical exams, a transmitting electronic microscope may be used to evaluate the ultra-structural characteristics of *K. granulomatis* of different specimens [25].

Cultural agents are complicated, and are not routinely available. A co-culture with single-layered cells have been recorded using human monocytes, Hep-2 cells and macrophages peritoneal of mice [9,13,36].

The techniques of genetic detection by polymerase chain reaction (PCR), which permits a reclassification of the Donovan agent, has its diagnosis application restricted to programs of eradication the illness [9,13,14,25].

Indirect immunofluorescence is used in population studies in endemic areas, although there is not sufficient evidence to make any firm diagnosis [25].

The methods used in the past which do not have much relevance for the present are antigen detection, complement fixation, and cutaneous testing [2,25].

Treatment and Prevention

Protocols used for diagnosis and treatment of genital ulcer syndrome observe, in the majority of cases, simple herpes, syphilis and cancroids. Inadequate use of antibiotics, whether by dosage or by duration of treatment, makes it difficult or even impossible to diagnose donovanosis with certainty using routine and accessible cytodiagnosis techniques and pathoanatomical exams.

Table 1. Therapeutic programs proposed by the WHO, by the CDC, and by the Brazilian Ministry of Health, for the treatment of donovanosis [17,18,26].

	WHO (2003)	CDC (2006)	MH (2006)
Recommendations	**Azithromycin** 1g OR on the first day, and 500mg 1x/day after that or **Doxycycline** 100mg, OR, 2x/d	**Doxycycline** 100mg, OR, 2x/day	**Doxycycline** 100mg, OR, 2x/d
Alternatives	**Erythromycin** 500mg, OR, 4x/d or **Tetracycline** 500mg, OR, 4x/d or **Sulphametoxazol/Trimethoprim** 400mg/80mg 2 cp, OR, 2x/d/14 days (at least)	**Azithromycin** 1g, OR, per week or **Ciprofloxacina** 750mg, OR, 2x/d or **Erythromycin** 500mg, OR, 4x/d or **Sulfametoxazol/ Trimethoprim** 400mg/80mg 2 cp, OR, 2x/d	**Erythromycin** 500mg, OR, 4x/d or **Sulfametoxazol/Trimethoprim** 400mg/80mg 2 cp, OR, 2x/d or **Tetracycline** 500mg, OR, 4x/d or **Azithromycin** 1g OR on first day and 500mg 1x/day after that
Pregnant Women	- - -	**Erythromycin** 500mg, OR, 4x/d	**Erythromycin** 500mg, OR, 4x/d
Observations	The patient should be under clinical observation until the signs and symptoms disappear.	For at least 3 weeks or until complete scarring of the lesions.	For at least 3 weeks or until clinically cured.

OR: oral route.

Until recently, long-term antibiotic treatment had been recommended until the ulcer is completely healed over. Recently, shorter dosages are recommended, under clinical observation, for a minimum of six weeks [9].

A consensus has not been reached regarding which treatment of donovanosis is best. After the introduction of emetic tartar by Aragão and Vianna in 1913, and with the advent of antibiotics and the discovery of the bacterial etiology of donovanosis, various substances have been employed in the treatment of this illness, with better results and fewer side effects than with antimonials.

Streptomycin and gentamyacin were used. Recently, there is indication that only one aminoglycoside, in addition to another therapeutic regimen, for the treatment of patients co-infected with HIV, pregnant women, or in cases in which the patients do not respond within the first days of the other treatment regimen [18,26,31].

Tetracyclines have also been recorded as variable therapeutic regimens. In accordance with the CDC and the Brazilian Ministry of Health, doxycycline is the drug of choice for the treatment of donovanosis, and is one of the two best options recommended by the World Health Organization (WHO) (Table 1) [17,18,26].

Ampicillan, amoxicillin and chloraphenicol have already been used, and erythromycin continues to be the drug of choice for the treatment of pregnant women [8,18,26].

Azithromycin, according to some authors, is the drug of choice for the treatment of donovanosis, in spite of its high cost [9,17]. Its advantage is that it can be administered intermittently and on a weekly basis, while under supervision. However, this weekly schedule is considered as an alternative by the CDC and is not included as an option in the WHO *Guidelines* [17,18].

Jardim used thiamphenicol for the treatment of donovanosis in the following dosages: 2.5g (one envelope of the drug in granulated form) on the first day, and afterward, 500mg every 12 hours until completely cured, which was achieved at a maximum time of 3 weeks without significant side effects [8]. A study was published in 2007 which reported that this drug was used with the same dosages in ten patients with penile donovanosis. Of these ten, eight were cured within two weeks, including two HIV positive patients. The remaining two patients presented only partial regression by the second week, and were treated with 1g of azithromycin on the first day, and 500 mg during two weeks and were cured. There was no incidence of recurrence in any of the patients after three months. The cost benefit of treating donovanosis with thiamphenicol was emphasized [21]. Aside from this consideration, it is necessary to take into account that in clinical practice, this drug is indicated only for the treatment of STIs and

vaginosis, which, theoretically, could be useful for the prevention of resistant bacteria.

When the patient is not responsive during the first days of treatment, the addition of gentamycin is recommended at a dosage of 1mg/kg, administered intravenously, every eight hours during the chosen treatment plan [18,26,31].

For pregnant women and HIV positives, the addition of amnioglycosides should be considered from the beginning of the treatment [17,18,26].

The antibiotics most recently reported for the treatment of donovanosis and recognized as most effective are: ceftriaxone, norfloxacina, trovofloxacina [25].

Apart from antibiotic treatment, many times surgical intervention is necessary in order to correct some side effects of the disease [28].

References

1. Galarza C. Donovanosis. Dermatol. Peru **2000**;10(1):35-8.
2. Fonseca A., Souza E.M. Donovanose. Dermatologia Clínica. 1ª ed. Guanabara Koogan. p. 167-69. Rio de Janeiro, **1984**.
3. Aragão H.B., Vianna G. Pesquisas Sobre o Granuloma Venéreo. Mem. Inst. Oswaldo Cruz **1913**;5:211-38.
4. McIntosh J.A. The Etiology of Granuloma Inguinale. JAMA **1926**;87(13):996-1002.
5. Greenblat R.B., Torpin R. Experimental and Clinical Granuloma Inguinale. JAMA **1939**;113(12):1109-16.
6. Marmell M., Santora E. Donovanosis - Granuloma Iinguinale. Incidence, Nomenclature, Diagnosis. Am J Syph Gonor Vem Dis **1950**;34:83-90.
7. Anderson K. The Cultivation from Granuloma Inguinale of Microorganism Having the Characteristic of Donovan Bodies in Yolk Sac of Chick Embryos. Science **1943**;97:560-1.
8. Jardim M.L., Melo Z.O. Tratamento da Donovanose com o Tiamfenicol. An Bras Dermatol **1990**;65(2):93-4.
9. O'Farrell N. Donovanosis: an Update. Int. J. STD AIDS **2001**;12:423-7.
10. Carter J.S., Bowden F.J., Bastian I., et al. Phylogenetic Evidence for Reclassification of *Calymmatobacterium granulomatis* as *Klebsiella granulomatis* comb. nov. Int J Syst Bacteriol **1999**;49:1695-700.
11. Kharsany A.B., Hoosen A.A., Kiepala P., et al. Phylogenetic Analysis of *Calymmatobacterium granulomatis* Based on 16S Sequences. J Med Microbiol **1999**;48:841-7.
12. Bowden F.J. Donovanosis in Australia: Going, Going... Sex Transm Infect **2005**;81(5):365-6.
13. Richens J. Donovanosis (Granuloma Inguinale). Sex Transm Infect **2006**;82(4):21-2.
14. Mackay I.M., Harnett N.J., Bastian I., et al. Detection and Discrimination of Herpes Simplex Viruses, *Haemophilus ducreyi, Treponema pallidum* and *Calymmatobacterium* (*Klebsiella*) *granulomatis* from Genital Ulcers. Clin Infect Dis **2006**;42:1431-8.
15. Boye K., Hansen D.S. Sequencing of 16S rDNA of *Klebsiella*:Taxonomic Relations within the Genus and Other *Enterobacteriaceae*. Int J Med Microbiol **2003**;292:495-503.
16. Costa J.B., Domingues D., Castro R., Exposto F. Úlceras Genitais Causadas por Infecções Sexualmente Transmissíveis. Actualização do Diagnóstico e Terapêuticas, e a Sua Importância na Pandemia do HIV. Acta Med Port **2006**;19:335-42.
17. Organização Mundial da Saúde. Granuloma Inguinal (Donovanose) *in* Orientações para o Tratamento de Infecções Sexualmente Transmissíveis. p.48-9. Genebra, Suíça. **2001**, disponível no site http://www.who.int/hiv/pub/sti/STIguidelines2003_pt.pdf.
18. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. Granuloma Inguinale (Donovanosis) *in* Sexually Transmitted Diseases Treatment Guidelines. MMWR **2006**;55(11):20-1.
19. World Health Association. Global Strategy for the Prevention and Control of Sexually Transmitted Infections: 2006-2015. P.6 Geneva, Switzerland. **2007**.
20. Veeranna S., Raghu T.Y. A Clinical and Investigational Study of Donovanosis. Indian J Dermatol Venereol Leprol. **2003**;69(2):159-62.
21. Belda Jr. W., Velho P.E.N.F., Arnone M., Romitti R. Donovanosis Treated with Tiamphenicol. Br J Infect Dis **2007**;11(4):388-9.
22. Silva D., Salgado U., Macedo C., Neves C. Donovanose no Pará. Rev Soc Bras Med Trop **1991**;24(4):251-2.
23. Morrone A., Toma L., Franco G., Latini O. Donovanosis in Developed Countries: Neglected or Misdiagnosed Disease? Int J. STD AIDS **2003**;14(4):288-9.
24. Nadal S.R., Framil V.M.S. Diagnóstico das Úlceras Ano-retais Sexualmente Transmissíveis. Rev bras Coloproct **2005**;25:370-3.
25. O'Farrell N. Donovanosis. Sex Transm Infect **2002**;78:452-7.
26. Brasil, Ministério da Saúde, Secretaria de Vigilância em Saúde, Programa Nacional de DST/AIDS. Donovanose *in* Manual de Controle de Doenças Sexualmente Transmissíveis: DST. 4ª ed. Série Manuais nº 68, p. 50. Brasília, DF, **2006**.
27. Goldberg J. Studies on Granuloma Inguinale. Isolation of Bacterium from Faeces of a Patient with Granuloma Inguinale. Br J Vener Dis **1962**;38:99-102.
28. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Donovanose *in* Doenças Infecciosas e Parasitárias: Guia de Bolso. Ministério da Saúde, p.118-21. Brasília, DF, **2004**.
29. Ferreiro M.C., Rodríguez M.A., Léon C.P. Ulceras Genitales. Dermatol Venez **2004**;42(3):12-9.
30. Veeranna S., Raghu T.Y. Oral Donovanosis. Int. J. STD AIDS **2002**;13:855-6.
31. Wu J.J., Huang D., Pang K.R., Tyring S.K. Selected Sexually Transmitted Diseases and Their Relationship to HIV. Clin Dermatol **2004**;22:499-508.
32. Jardim M.L. Donovanose: Proposta de Classificação Clínica. An Bras Dermatol **1987**;62(3):169-72.
33. Jamkhedkar P.P., Hira S.K., Shroff H.J., Lanjewar D.N. Clinico-epidemiologic Features of Granuloma Inguinale in the Era of Acquired Immune Deficiency Syndrome. Sex Transm Dis **1998**;25:196-200.
34. Samuel M., Aderogba K., Dutt N., et al. A Hat Trick Ulcerating Pathogens in a Single Genital Lesion. Int J STD AIDS **2007**;18:65-6.
35. Magno J.C.C., D'Almeida D.G., Magalhães J.P., et al. Histiocitose de Células de Lagerhans em Margem Anal: Relato de Caso e Revisão de Literatura. Rev bras Coloproct **2007**;27(1):83-8.
36. Kaimal S., Thappa D.M. Methods of Specimen Collection for the Diagnosis of STIs. Indian J Dermatol Venereol Leprol **2007**;73(2):129-32.