

Review Article

## Leishmaniasis of the Penis: A Review and Update

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**Abstract** *Leishmania* parasites that are transmitted through bites of over 90 species of the infected female phlebotomine sand-fly. . Three main forms of leishmaniasis including cutaneous, mucocutaneous, and visceral leishmaniasis exist. The disease tends to affect some of the worlds poorest people. An estimated 700,000 to 1 million new cases and 20,000 to 30,000 deaths occur globally due to the disease. 24,200 deaths were attributed to leishmaniasis in 2015 and 4 million to 12 million cases of leishmaniasis have been documented to exist globally. Leishmaniasis of the penis (LOP) is extremely rare. LOP does present with: subcutaneous nodules of the penis, ulceration of penis, crust on penis, erythematous scaling plaque, crusty scar on penis. Clinical examination may reveal on the penis/glans penis: papules, crusts, serous or sero-haemorrhagic fluid secretion, usually painless ulcer(s), hyperkeratotic plates with induration of the penis or haemorrhagic crust lesion on the penis of a child or adult. Smears from the ulcer could typically demonstrate amastigotes, leishmania may be grown in culture of smears or specimens of the penile lesion. Histopathology features of LOP would show a granulomatous infiltrate containing some leishmania parasites. Histopathology examination of biopsies of the penile lesion may show ulceration of epidermis and a diffuse inflammatory infiltrate in the dermis composed of lymphocytes, histiocytes, plasma cells, giant cells with granuloma formation and presence of leishmania amastigotes histiocytes contain small oval organisms with bar shaped paranuclear kinetoplast. Haematoxylin and Eosin as well as Giemsa staining may be sufficient but with regard to positive staining for LOP, Wiegert ion haematoxylin could stain better than H&E or Giemsa stain and immunostaining with G2D10 antibody tends to be more sensitive in diagnosing LOP. The diagnostic methods available for the detection of LOP include: Intradermal delayed hypersensitivity test (Montenegro); Culture on NNN (Novy-McNeal-Nicolle) agar using smears from ulcer; ELIA; DNA probes; PCR. The Identification of parasites on H & E or smears by culture on specialized media, fluorescent antibody tests using patient's serum, or by PCR using specific primers. But polymerase chain reaction (PCR) results can be false positive, leishmanin intradermal skin test (Montenegro), positive culture for leishmania from specimen or smear, zymodeme analysis and monoclonal antibody to detect leishmaniasis. A high index of suspicion is required to undertake the most appropriate investigation to diagnose LOP. Resistance to various anti-leishmaniasis medicaments exist in various parts of the world therefore treatment of LOP should include utilization of recommended medicament appropriate to the geographical area of the world and could either

be (a) oral medication (doxycycline and others), (b) topical ointment (paromomycin and methylbenzethonium chloride), (c) intramuscular injection (meglumine antimoniate). With early diagnosis appropriate treatment and follow-up assessment cases of LOP should resolve and this should be followed up by appropriate steps to prevent leishmaniasis including use of nets impregnated with sand fly repellent and environmental spraying methods to ensure control of vectors of the disease.

**Keywords:** Leishmaniasis; Penis; Sand Fly; Haematoxylin and Eosin; Giemsa Stain; Novy-Mcneal-Nicolle Medium; Meglumine Antimoniate; Montenegro Test; Polymerase Chain Reaction

### Introduction

Leishmaniasis is a protozoan infection that is encountered in all continents globally with the exception of Australia and the Antarctica [1]. It has been stated that 1 million to 2 million new cases of various types of leishmaniasis are encountered globally per year [1]. Cutaneous leishmaniasis is an infectious disease which is caused by protozoa of the gender *Leishmania*, which is transmitted by stings/bites of female insects of the *Phlebotomus* gender in the Old World, and *Lutzomia* within the New World [2]. It has been stated that greater than twenty species of *Leishmania* that is pathogenic for human beings and other mammals have been identified globally [2] [3]. The clinical manifestations of leishmaniasis would depend upon the interaction between the typical virulence of the species of *Leishmania* and the immune response of the host [2] [4]. Within America, cutaneous leishmaniasis is caused by many species of the *Leishmania braziliensis* complex and *Leishmania mexicana* [5] [6] [7]. Cutaneous leishmaniasis which is caused by many species of protozoa belongs to the family of Trypanosomatidas that are flagellate protozoa which live within the tissues and within blood of the human host [8]. The vector of leishmaniasis is the sand fly and most commonly it is *Phlebotomus papatasi* and the commonest reservoirs include rodents, dogs, and cats [8]. The incubation period tends to be variable and this does range between 1 week to 12 weeks and the mean incubation period is 9 weeks [8]. Cutaneous leishmaniasis tends to be caused by five species of *Leishmania* including *Leishmania major*,

*Leishmania tropica*, and *Leishmania aethiopica*, which do cause old world leishmaniasis (in non-America countries) [8] [9], and *Leishmania mexicana* complex and *Leishmania braziliensis* complex which are responsible for causing new-world leishmaniasis (Leishmaniasis in the Americas).

Cutaneous leishmaniasis may be treated by means of utilization of cryotherapy, localized heating, as well as utilization of Leshcutan™ ointment [8] [10]. Severe cases of cutaneous leishmaniasis could be treated by means of systemic treatment with utilization of antimonial compounds, ketoconazole, allopurinol, dapsone, levamisole, and immunotherapy [8] [9]. Even though between 1 million to 2 million cases of leishmaniasis are reported each year globally, Leishmaniasis of the penis is extremely rare in view of this it would be envisaged that majority of clinicians globally within Leishmaniasis non-endemic and Leishmaniasis endemic regions would not have encountered the disease before and they would therefore probably not be familiar with the presentation, investigation procedures and management of the disease. A high-index of suspicion would be required in order to establish a quick, succinct, and accurate diagnosis of the disease through undertaking of appropriate investigations to be able to provide the most appropriate management of the disease armed with the knowledge of the medicament sensitivity pattern of leishmaniasis within their localities. The ensuing review article on leishmaniasis of the penis is divided into two parts (a) Overview, and (B) Miscellaneous narrations and discussions from some reported cases and series as well as studies on leishmaniasis of the penis.

**Aim:** To review the literature on leishmaniasis of the penis specifically and leishmaniasis in general

**Method:** Internet data bases were used including: Google; Google Scholar, and PUBMED. The search engines used included: Leishmaniasis of the penis, and Leishmaniasis. Thirty one references were identified and found suitable to write the review article which has been divided into two parts: (A). Overview and (B) Miscellaneous narrations and discussions from case reports, case series and studies related to the disease.

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**Result/ Literature Review**
**(A) Overview**

**Definition:** Leishmaniasis is a terminology that refers to a disease that is caused by parasites of the leishmania type and the disease is spread by certain types of sand flies [10]. Leishmaniasis can present in three different ways including cutaneous, mucocutaneous, and visceral leishmaniasis [10] [11]. Cutaneous leishmaniasis does present with skin ulcers, papules, skin encrustations, erythema or induration of the skin; the mucocutaneous form of leishmaniasis does present with ulcers of the skin, mouth, and nose; visceral leishmaniasis does start with ulcers of the skin which is ensued by fever, low red blood cell count, and hepato splenomegaly [10] [11] [12].

**General Comments on Leishmaniasis:** The ensuing summations have been made about Leishmaniasis in general [1].

- Leishmaniasis is a protozoan infection that is encountered in all continents globally with the exception of Australia and the Antarctica [1].
  - It has been stated that leishmaniasis in human beings is caused by more than 20 species of *Leishmania* [11].
  - More than 90 species of sand fly have been known to transmit the *Leishmania* parasites [13] [14].
  - Documented risk factors for the development of leishmaniasis include: poverty, malnutrition, deforestation, and urbanization [11].
  - All three types of leishmaniasis can be diagnosed by visualising the leishmania parasites under the microscope [13].
  - Visceral leishmaniasis can be diagnosed by means of blood test [12].
  - It has been stated that approximately 4 million to 12 million people are infected with leishmaniasis globally currently [13] [15] in some 98 countries [12].
  - It has been stated that 1 million to 2 million new cases of various types of leishmaniasis are encountered globally per year [1].
  - It has also been stated that between 20 thousand and 50 thousand deaths occur globally each year due to leishmaniasis [13] [14].
  - It has been documented that approximately 200 million people residing in Asia, Africa, South and Central America, and Southern European countries dwell in areas where leishmaniasis is common [12] [13]. It has also been stated that more than 90% of global visceral leishmaniasis cases do occur in six countries including India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil and furthermore; cutaneous leishmaniasis tends to be more widely distributed, with approximately one third of cases occurring in each of three leishmaniasis epidemiological regions: the Americas, the Mediterranean basin, and western Asia from the middle East to central Asia. The ten countries that had the highest estimated case counts of visceral leishmaniasis included Afghanistan, Algeria, Columbia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica, and Peru, which together account for 70% to 75% of the global estimated case incidence of cutaneous leishmaniasis. [16].
  - It has been stated that the frequency of leishmaniasis globally is between 4 million to 12 million [10] [13] [15].
  - It has been documented that globally in 2015 there were 24,200 deaths due to leishmaniasis [13] [17].
  - It has been stated that only a small fraction of individuals that have been infected by *Leishmania* parasites would develop the disease eventually [13].
  - It has been iterated that leishmaniasis could occur in a number of animals including dogs, and rodents [10] [13]. Furthermore, it has been documented that some 70 animal species, including human beings, had been found as natural reservoir hosts of the leishmania parasites [13].
  - It has been intimated that epidemics of leishmaniasis do occur from time to time within tropical areas of the world as well as leishmaniasis infections do afflict HIV positive patients [1].
  - It has been documented that leishmaniasis does occur generally in various parts of the body produce crusted, indurated papule which tends to enlarge slowly and also
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tends to be self-limited; nevertheless, leishmaniasis also on other occasions does manifest as a fatal systemic illness [1].

- It has been stated that the World Health Organization has obtained discounts on some medications to treat leishmaniasis [12] [13].
- It has been stated that leishmaniasis is classified as a neglected disease [1] [13].
- Three sub-types of leishmaniasis have been documented including: cutaneous leishmaniasis, muco-cutaneous leishmaniasis, and visceral leishmaniasis [1].
- In view of the fact that the clinical features of leishmaniasis are not specific to the disease, leishmaniasis generally tends to mimic other diseases which can be regarded as differential diagnoses of leishmaniasis. Some of the differential diagnoses of leishmaniasis include: Sarcoidosis; foreign body reaction; Granulomatous Rosacea; Granuloma annulare [1]. At times leishmaniasis lesion may mimic a malignant tumour.

#### **Cutaneous Leishmaniasis:**

- It has been stated that afflictions of cutaneous leishmaniasis tend to commonly involve the face, the scalp, the arms and other externally exposed parts of the body [1].
- Cutaneous leishmaniasis could be (a) a localized disease, (b) disseminated disease which does occur in the situation if the immune system of the patient does not respond to the presence of the invading leishmania parasite, (c) recurrent cutaneous leishmaniasis which is also called Recidivans Cutaneous Leishmaniasis, and (d) or post Kala azar disease which tends to be a rare disease and does occur years pursuant to the development of visceral leishmaniasis [1].
- It has been stated that cutaneous leishmaniasis is the commonest form of leishmaniasis which causes skin lesions that tend to be mainly ulcers, upon exposed areas of the body which tend to leave life-long scars and serious disability [13].
- It has been stated that approximately 95% of cutaneous leishmaniasis do occur in the Americas, the Medi-

terranean region, the Middle Eastern countries, and Central Asia [13].

- It has been recorded that in 2015 more than two thirds of new cases of cutaneous leishmaniasis did occur in 6 countries including; Afghanistan, Algeria, Brazil, Colombia, Iran, (Islamic Republic of Iran), and Syrian Arab Republic [13].
- It has been documented that it had been estimated that between 600,000 to 1 million new cases of cutaneous leishmaniasis do occur globally each year [13].

#### **Mucocutaneous Leishmaniasis:**

- It has been iterated that mucocutaneous leishmaniasis is usually regarded as a new world disease which does afflict individuals of Rural areas and Jungle areas [1].
- Muco-cutaneous leishmaniasis does occur in situations when primary *Leishmania braziliensis* infection becomes a disseminated disease with dissemination to the upper respiratory tract, with emanations of lesions of oral mucosa, pharyngeal mucosa, or anal mucosa, resulting on ulceration of the mucosa, mutilation or sometimes death of the individual [1].
- It has been documented that mucocutaneous leishmaniasis does lead to partial or total destruction of the mucous membranes of the nose, throat, and the mouth and that more than 90% of cases of mucocutaneous leishmaniasis do occur in Bolivia (the Pluri-national state), Brazil, Ethiopia, and Peru [13].

#### **Visceral Leishmaniasis:**

- Visceral leishmaniasis is also referred to as Kala Azar. It has been stated that in cases of visceral leishmaniasis, the leishmania parasites disseminate through out the reticuloendothelial system of the patient and this does lead to the development of fever, general malaise, enlargement of liver and spleen, anorexia, pancytopenia, and hypergamaglobulinemia [1].
- It has been documented that in Visceral leishmaniasis or Kala azar, the skin is usually spared of disease with the exception of the development of irregular areas of dark

pigmentation for which the terminology Kala Azar which means black sickness had been coined [1].

- Visceral leishmaniasis could be so severe that if it is not treated it could lead to the death of the patient [1].

- Visceral leishmaniasis has been divided into (a) old world disease that has included: tropical and sub-tropical Asia, India, Africa, and Mediterranean region; and (b) New World which includes the Americas [1].

- Old World – Within the old world, *Leishmania tropica* complex is the sub-type of leishmania disease that is encountered [1].

- New World – Within the New World, *Leishmania braziliensis* complex, and Leishmania Mexicana Complex are the sub-types of Leishmania encountered [1].

- It has been stated that *Leishmania braziliensis* could also produce espundia which is a destructive mucocutaneous form of leishmania [1].

- It has been documented that human infection by leishmania does occur by means of a bite of Phlebotomus Sand fly and on rare occasions human infection can occur through blood contamination [1].

- It has been stated that the clinical presentation of leishmaniasis and prognosis of leishmaniasis is variable and it depends upon the species of leishmania causing the disease, the duration of infection, and upon the immune status of the individual patient [1].

- It has been stated that leishmania infection with regard to the United States of America primarily occurs through global travel and HIV infection [1].

- It has been stated that visceral leishmaniasis if left alone untreated becomes fatal in over 95% of cases/ [13].

- It has been stated that majority of cases of visceral leishmaniasis do occur in Brazil, East Africa, and in South East Asia. It has also been documented that an estimated 50,000 to 90,000 new cases of visceral leishmaniasis do occur each year globally [13].

- It has been documented that in 2015, more than 90% of new cases of visceral leishmaniasis that had been reported to the World Health Organization (WHO) had occurred in 7 countries including: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan [13].

**Presentation of Leishmaniasis of Penis:** A patient who has LOP may present with

- Painless lump or nodule which had been present for few weeks to many months or years.

- Induration of the penis.

- Papule on the penis.

- Crusty eruption / eruptions on the penis

- Ulceration of the penis

- Serous discharge from lesions on penis.

- No pain associated with the penile lesions.

- Most of the time no problem associated with coitus

- When the penile lesion is large the lesion could be interfering with coitus.

- LOP could affect a child or an adult therefore any of the aforementioned would present in a child or adult.

- Patient could have been healthy and on no medication prior to the presentation.

- A history of living in or having lived in a leishmaniasis endemic zone or travelled from a leishmania endemic zone may be helpful to make a diagnosis.

- A lesion on the penis only, but it is possible there may be a cutaneous lesion elsewhere.

**Clinical Examination Findings:**

Generally the general and systematic examinations of the patient would tend to be normal but lesions would be found on the glans, foreskin, or any other part of the penis which may include: erythema, papule(s), ulceration, encrustation, sero-haemorrhagic crusts on the penis of varying sizes depending upon the size of the lesion. It is also possible that there may be a cutaneous lesion elsewhere on

the body but this would tend to be rare.

### Investigations

**Urine:** Urine analysis urine culture and sensitivity are general examinations that are carried out routinely as part of the general assessment of the patients but the results would not be diagnostic of the disease/infection of leishmaniasis.

### Blood Tests

**Haematology:** Full blood count, coagulation screen and erythrocyte sedimentation rate are general tests that are under taken as part of the general assessment of patients but usually the results would be normal but occasionally the erythrocyte sedimentation rate may be raised and the eosinophil count could be raised due to the fact that LOP is an emanation of a parasitic disease but the results would not be diagnostic of LOP.

**Biochemistry:** Serum urea and electrolytes, blood glucose, liver function tests and C-reactive protein are general tests that are undertaken but the results would not be diagnostic of LOP. The results generally would tend to be normal but rarely the C-reactive protein level may be raised.

**Microscopy features:** It has been stated that microscopy examinations of tissues that contain leishmania tend to show the following features:

- Dermal granulomatous inflammation with prominent lymphocytes. [1]
- Histiocytes that contain small oval organisms with bar shaped paranuclear kinetoplast. [1]

**Diagnosis:** The various ways by which leishmaniasis can be diagnosed include:

- Intradermal delayed hypersensitivity test (called Montenegro test); Culture on NNN agar using smears from the leishmania ulcer; ELISA; DNA probes; polymerase chain reaction (PCR) [1].
- Identification of parasites based up on microscopy examination of Haematoxylin and Eosin stained specimens of the tissue, or in smears; or by culture on specialized media; by leishmanin intradermal skin test (Montenegro test); fluorescent antibody tests using the patient's serum, or by PCR with utilization of species specific primer but it has pointed out that PCR results could be false positive [1].

### Positive Stains

- Wiegert iron haematoxylin – It has been stated that Wiegert iron haematoxylin could stain leishmania parasites better than haematoxylin and eosin or Giemsa stain [1].

- Immunohistochemistry staining with G2D10 antibody has been said to be more sensitive in comparison with Haematoxylin and Eosin in the detection of leishmaniasis [1].

**Diagnosis Specific to Leishmaniasis of the Penis:** The diagnosis of cutaneous leishmaniasis and leishmaniasis of the penis have been summated as follows [18]:

- The diagnosis of cutaneous leishmaniasis has been frequently made clinically. Nevertheless, the demonstration of parasites with utilization of laboratory methods is pertinent to the establishment of a diagnosis [18] [19] [20].

- The demonstration of amastigotes upon Giemsa staining of smears that had been taken from the edge of lesions represents the simplest and most efficacious diagnosis of the disease [18] [20].

- The illustration of plasma cells and Leishmania donovani within macrophages in the dermis by means of histopathology examination of specimens of the lesion represents another diagnostic tool that is utilized [21].

**Treatment:** There are many treatment options for the management of leishmaniasis globally but resistant problems have emerged therefore clinicians would need to rely upon the sensitivity pattern of the area of the world to effectively treat leishmaniasis sub-type that is involved; nevertheless, some of the available medications or treatments include:

- Meglumine antimonite and Sodium stibogluonate.
- Amphotericin B.
- Pentamidine.
- Pentavalent antimonial
- Miltefosine
- Fluconazole
- Ketoconazole

- Itraconazole
- Levamisole
- Allopurinol
- Doxycycline
- Paromomycin
- Azithromycin
- Dapsone and Rifampicin
- Doxycycline
- Immunotherapy/Immunomodulation

Mucocutaneous and diffuse cutaneous leishmaniasis could be refractory to treatment [1].

#### Treatment

- The planning and choice of treatment for leishmaniasis tends to be determined by where in the world the disease is acquired, the species of *Leishmania* that is causing the disease, as well as upon the type of leishmaniasis [11] [13].
- Some of the possible medicaments that are utilized in the treatment of visceral leishmaniasis include: liposomal amphotericin B, [13] a combination of pentavalent antimonials and paromomycin, [11] [13] and miltefosine [22].
- With regard to cutaneous disease, paramomycin, fluconazole, or pentamidine could be effective [13].

#### Prevention

- It has been stated the leishmaniasis can be partly prevented by sleeping under nets that had been treated with insecticides [11].
- It has also been documented that the spraying of insecticides to kill Sand flies as well as treating people who have leishmaniasis early to prevent further spread of leishmaniasis would prevent further spread of the disease [13].

Other documented ways of preventing leishmaniasis include:

- Effective disease surveillance [13].
- Control of animal reservoir hosts which is complex

and needs to be tailored according to the local situation of the county [13].

- Social mobilization and strengthening partnerships through mobilization and education of the community with regard to effective behavioural change interventions [13].

**Differential Diagnoses:** Some of the differential diagnoses of leishmaniasis of the penis include

- Squamous cell carcinoma of penis.
- Lymphoma of the penis may present as a painless ulcer on the penis.
- *Haemophilus ducreyi* infection of penis (a fastidious gram-negative coccobacillus bacterial infection which is characterized by painful sores or ulcers of the penis unlike leishmaniasis of the penis in which the ulcers generally are not painful.
- Syphilitic ulcers (chancres) of the penis which occur during the primary stage of the disease about 21 days after the initial exposure to *Treponema pallidum*, the gram negative spirochete bacterium responsible for syphilis. The chancres are generally painless just as leishmaniasis ulcers of the penis are also generally painless.
- Granuloma inguinale which is a genital ulcerative disease that is caused by gram negative bacterium *Klebsiella granulomatis* that used to be called *Calymmatobacterium granulomatis*. The ulcers in the genital region including the penis most commonly are painless which would simulate leishmaniasis of penis or glans penis which is also most commonly painless.
- Traumatic ulcer of penis.
- Viral infection of penis including Herpes genitalis and infections that are caused by human papillomavirus (HPV) which can cause genital ulceration, with evidence that many infections tend to asymptomatic similar to leishmaniasis of the penis.
- Other Bacterial infection of penis (non-specific and specific infections including tuberculosis of the penis.
- Fungal infection of penis including candida infec-

tion which can affect the glans penis and foreskin. .

- Parasitic infection including cutaneous larval migrans caused by hookworm infection.
- Other malignancies of penis including sarcoma, basal cell carcinoma, melanoma, and adenocarcinoma.
- Auto-immune bullous diseases of the penis including localized bullous pemphigoid of childhood as well as squamous cell carcinoma of penis with bullous pemphigoid masquerading as lymphogranuloma venereum.
- Immune and systemic diseases affecting the penis
- Drug reactions including fixed drug eruptions to penis due to oxcarbazepine, and ornidazole.
- Inflammatory diseases of the penis.
- Papulo-squamous diseases affecting the penis including psoriasis, Reiter syndrome, lichen planus, lichen nitidus, seborrheic dermatitis, secondary syphilis, fixed-drug eruption, erythroplasia of Queyrat, plasma cell balanitis of zoon, Bowenoid papulosis, discoid and lichenoid dermatosis of Sulzberger and Garbe.

**Outcome:** If visceral leishmaniasis is left untreated, majority of patients who have the disease would die because of the disease but patients who receive full treatment would be expected to recover.

With regard to cutaneous leishmaniasis, very few cases have been reported in the literature and following treatment the trend has been improvement / cure of the disease. One individual noticed great improvement but was lost to follow-up.

**(B) Miscellaneous Narrations and Discussions from some reported cases, Case Series and studies related to the disease.**

Gülüm et al. [23] reported a 45-year-old man who had presented a crusty scar on his penis which he had noticed for a period of about 4 years. He was asymptomatic otherwise. He also did not have any significant past medical history apart from having been having coital difficulties over the preceding one year. On examination, he was found to have hyperkeratotic plates which had fully spread all over his glans penis and which had a slight indurated base

and sometimes sero-haemorrhagic crust lesion and fissure. He had leishmaniasis smear test which was normal. He had excisional biopsies from the hyperkeratotic lesion and histopathology examination of the specimens had excluded benign and malignant skin conditions. He received treatment by means of intralesional meglumine antimoniate twice weekly for 8 eight weeks and pursuant to this the treatment was continued with utilisation of 20 milligrams per kilogram of meglumine antimoniate. Over the period of treatment, an improvement had been observed in the hyperkeratotic plates and shrinkage in the penile lesion had also been observed. There was a further plan to continue is treatment with utilisation of 20 milligrams per kilogram of meglumine antimoniate but unfortunately the patient subsequently failed to attend for follow-up assessment and treatment. This case is pertinent to clinical practice in that some lesions of the penis may look like malignant penile lesions but may turn out not to be malignant and knowledge that leishmaniasis is a differential diagnosis should make clinicians have a high-index of suspicion for leishmaniasis of the penis so that they can decide early to undertake a leishmania smear test.

Schubach et al. [24] reported a man who had presented with an ulcerated lesion of his glans penis which had subsequently been followed by the development of mucosal lesions of his nasal cavity and palate. He had investigations including leishmania skin test (Montenegro's test) and biopsy of the border of the ulcer which were submitted for histopathology examination and culture in Novy-McNeal-Nicole (NNN) medium. The results of the tests revealed the following:

- The leishmania skin test was positive.
- Histopathology examination of the specimen showed a granulomatous infiltrate that contained some parasites.
- Culture of the specimen was positive for leishmania sp- and this was subsequently identified by utilisation of zymodeme analysis and monoclonal antibodies as Leishmania (V.) Braziliensis.

With regard to treatment he received pentavalent antimony at a dose of 10 milligrams per kilogram per day for

30 days which resulted in healing of the lesions. Schubach et al. [24] made the ensuing summing iterations:

- With regard to men, especially those who are older than 50 years of age, ulceration of the glans penis would be highly suggestive of carcinoma of the penis.
- Precise differential diagnosis of penile ulcer is imperative in establishing the correct diagnosis.
- A lesion such as the one they had reported, could pose diagnostic difficulties when it does present in countries that are different from the source of infection, where the condition is very uncommon.
- In view of the current era of widespread travel the finding of leishmaniasis of penis has been frequently increasing.

This article is useful in illustrating to clinicians in countries where leishmaniasis is not common that leishmaniasis of the penis; therefore, clinicians should be alert and should consider leishmaniasis as a differential diagnosis of penile ulcers and to undertake tests that would confirm or exclude leishmaniasis of the penis.

Grunwald et al [25] reported a 30-year-old man who had presented with a lesion on his glans penis which had been present over the preceding 2 months. His clinical examination showed an erythematous scaling plaque which had measured 1.5 cm in diameter. His general and systematic examinations were otherwise normal. A smear was taken from the lesion which did show large macrophages that were filled by many amastigotes of *Leishmania* which are called Donovan bodies. He was treated by means of local application of paromomycin and methylbenzethonium chloride ointment (Leshcutan TM, Teva, Israel). There was marked improvement of the lesion.

**Cabello et al. [2] reported 2 cases as follows:**

**Case 1:** An 18-year-old gold mine worker from Venezuela had presented a 3-months history of an ulcerated lesion over his glans penis for which he had been treated with intramuscular injection of 2.4 million international units of Penicillin. On examination he was found to have an ulcer on his glans penis that measured 1 cm in diameter associated with an indurated base of the ulcer and raised infiltra-

tive borders. He did not have any palpable inguinal lymph node enlargement. Venereal Disease Research Laboratories (VDRL) test and Fluorescent Treponemal Antibody (FTA-ABS) test had been negative. He had Montenegro's intradermal test which was positive and had shown an indurated papule which measured 2.6 cm in diameter. Histopathology examination of biopsy specimens of the lesion which he had had shown ulceration of the epidermis and a diffuse inflammatory infiltrate within the dermis which had consisted of lymphocytes, histiocytes, plasma cells, and giant cells with formation of granuloma as well as presence of *Leishmania* amastigotes. He received daily 38-injections of meglumine antimoniate for 3 weeks and at the end of the treatment his glans penis lesion had fully healed.

**Case 2:** A 38-year-old man from Venezuela had had what he reported as a scrotal tumour for 5 months that was diagnosed as squamous cell carcinoma based upon clinical examination. An ulcerated tumour that measured 5 cm x 3 cm in diameter was found with an indurated base as well as raised, infiltrative borders and a yellowish exudate was found. He had a *Leishmania* skin test and the result was positive. The results of his HIV (enzyme-linked immune-sorbent assay [Elisa], and VDRL test were negative. Histopathology examination of biopsy specimen of the lesion did show pseudoepitheliomatous hyperplasia, a necrotic area as well as ulceration of epidermis and a diffuse inflammatory infiltrate within the dermis which had comprised of lymphocytes, plasma cells, polymorphonuclear cells as well as vacuolated histiocytes together with presence of *Leishmania* amastigotes. He received daily intramuscular injections of meglumine antimoniate for 3 weeks which had resulted in complete cicatrization of his lesion.

These two cases have illustrated that 3-weeks daily intramuscular injections of meglumine antimoniate is effective for the treatment of leishmaniasis of the penis and the scrotum.

Yesilova et al. [18] reported a 5-year-old boy who had presented with a 6-months history of an asymptomatic, persistent ulcer on his penis that had been treated by means of topical steroids, anti-bacterial agent, anti-scabetic agent, anti-viral preparations; nevertheless, none of the treatment approaches had been successful. He did not have any family

history of similar symptoms. His clinical examination revealed a 20 mm x 30 mm ulcer with a haemorrhagic crust on his glans penis. There was a mild painless enlarged bilateral inguinal lymph nodes. The results of his routine haematology and biochemistry blood tests and C-reactive protein as well as his erythrocyte sedimentation rate were normal. The results of the following tests were also normal or classified as negative:

- Venereal Disease Research Laboratory (VDRL) test.
- Fluorescent Treponemal Antibody Absorption (FTA-ABS) test.
- Serological tests for herpes simplex virus, cytomegalovirus, Epstein-Barr Virus (EBV), Chlamydia Trachomatis, Human Immunodeficiency Virus.

Examination of Giemsa stained smear obtained from his lesion did show amastigote forms that had been suggestive of Leishmaniasis. Promastigotes forms of the parasite had been observed in the Novy-McNeal-Nicole (NNN) culture medium. Pathology examination of biopsy specimens of his lesion had shown features that were compatible with the diagnosis of cutaneous leishmaniasis. With regard to treatment, he received two doses of intramuscular injections of meglumine antimoniate with a dose of 20 milligrams per kilogram weight, 20 days apart. He did not experience any complications. At his 20-day follow-up appointment, it was noticed that his penile lesion had appeared to be healing with a mild scar tissue. This case report is important in illustrating that leishmaniasis of the penis can occur in children and also that meglumine intramuscular injections given at 20 days interval for children is effective in the treatment of leishmaniasis of the penis affecting a child.

Herbert et al. [26] reported a 75-year-old Caucasian man who had presented with a severe recalcitrant ulcer on his glans penis which he had developed over the preceding 8 months. He did undergo circumcision one year earlier for phimosis as a sequel of lichen sclerosus with a good post-operative unremarkable recovery. Nevertheless, several months after his circumcision he developed penile ulcer which had continued to increase in diameter despite

his utilization of a variety of topical anti-inflammatory and anti-infectious treatments. He did not have any significant medical history and there was no discharge from the lesion. His examination did reveal an inflammatory crusty ulcer on his glans penis that had measured 25 mm in diameter. Based upon the history and clinical examination findings the provisional differential diagnoses that were made included: Erythroplasia Queyrat, squamous cell carcinoma of the penis, and balanitis circumscripta plasmacellularis zoon. The patient's systematic examination was unremarkable except for a painless enlargement of the left inguinal group of lymph nodes. Microbiology cultures of swabs taken from the ulcer and crust did not reveal a growth of any fungus or bacterium. The results of his routine haematology and biochemistry blood tests were normal except for a slightly elevated C-reactive protein level. The results of his syphilis serology (VDRL) were normal. He had biopsy of the border of the lesion and pathology examination of the specimen showed complete ulceration of the epithelium as well as granulomatous infiltrate that contained multinucleated giant cells, T lymphocytes and plasma cells. Microscopy examination of the haematoxylin and eosin stained specimen of the biopsy was inconspicuous for infectious causes of granulomatous diseases, especially amastigote leishmania parasites. Examination of the biopsy specimen that had been stained by PAS and Ziehl-Neelson staining were negative for any specific infection. Nevertheless, polymerase chain reaction (PCR) test result was positive for Leishmaniasis. Herbert et al. [26] iterated that their results had confirmed an earlier statement that polymerase chain reaction (PCR) might be useful for the diagnosis of leishmaniasis, especially in the scenario in which the leishmania parasite load is low.

Masmoudi et al. [27] reported a 41-years old man presented with 20 days history of nodular lesion on the anterior aspect of his neck, 2 juxta-apposed ulcerated nodular lesions on the left wrist, and subcutaneous nodules which had been arranged linearly and had extended to the root of his penis. The lesions had been covered by an erythematous or ulcerated skin. Examination of smears that had been obtained from the genital lesions of the penis did confirm the diagnosis of cutaneous leishmaniasis. The evolution of the disease became favourable pursuant to 21 days treatment

with doxycycline after an interval of 1 week. The case report of Masmoudi et al. [27] is pertinent for two reasons (a) it had illustrated that leishmaniasis of the penis can also occur as part of multiple lesions on some occasions and not as a single spot lesion localized to the penis as reported sporadically; (b) doxycycline which is an inexpensive medication which is taken orally as well as which is globally available is efficacious in the treatment of leishmaniasis of the penis.

Castro Coto et al. [28] reported 5 cases leishmaniasis in the genital organs of males that were farmers. Four of the five men were aged less than 30 years and one patient was older than 30 years. All five patients were residents of high leishmaniasis incidence zones. Majority of the lesions had affected the penis, and the lesions were of scabies ulcer type, destructive, painless, and of slow evolution. Castro Coto et al. [28] stated that with regard to the five cases, generally, the clinical diagnosis of leishmaniasis was difficult to corroborate by means of the habitual laboratory methods as well as they further iterated that the principal differential diagnoses of leishmaniasis of the penis are neoplastic processes of the genital area. They additionally stated that a high index of suspicion for the diagnosis of leishmaniasis of the penis is required even before initiating the most appropriate diagnostic / therapeutic tests that would provide the solution to this type of diagnostic dilemma.

The aetiopathogenesis of ulcers of the penis does include: trauma, viral infection, bacterial infection, fungal infection, parasitic infection, malignancies, auto-immune bullous diseases, immune and systemic diseases, drug reactions, inflammatory diseases, and papulo-squamous diseases. [18] Nevertheless, most of the ulcers of the penis tend to be caused by sexually transmitted diseases that include syphilis, genital herpes virus infection, lymphogranuloma venereum, and donovanosis [18]. Additionally, it has been documented that non-venereal infections including candida, Epstein Barr virus, bacteria, parasitic, and mycobacterial infections could emanate in formation of ulcers of the penis. [18] Furthermore, it has been documented that Syphilitic chancres tend to be painless and they also tend to be persistent in comparison with ulcers and vesicles which had emanated from genital herpes which tend to be painful as well as to be associated a high degree of inflammation. [18] [29] It is also known that *Haemophilus ducreyi* does

cause soft chancre, which is typified by painful ulcers of the penis and are associated with tender lymph node enlargement [18].

With regard to non-steroidal anti-inflammatory medications, it had been stated that sulphonamides, penicillin, tetracyclines, anti-epileptic medicaments, and anti-malarial medications could also cause erosive as well as ulcerative drug reactions within the genital mucosa [18]. It has been iterated that inflammatory and papulosquamous diseases inclusive of psoriasis, lichen sclerosus, angiokeratomas, lichen nitidus, lichen planus, behnet's disease, Reiter's syndrome, pyoderma gangrenosum, pemphigus, as well as inflammatory bowel disease could also affect the penis.

It has been stated that neoplastic diseases that cause ulcers of the penis include; erythroplasia of Querat, squamous cell carcinoma, basal cell carcinoma, extramammary Paget's disease, lymphoma, and leukaemia are malignant diseases that could cause ulcers of the penis [18].

It has been stated that on rare occasions, ulcers of the penis that are related to mechanical trauma, chemical trauma, thermal trauma, and factitial reasons could also be encountered [29] [30] [31].

### **Conclusion**

Leishmaniasis of the penis is a rare treatable disease which can affect children as well as adults and could easily be missed as a diagnosis due to its rarity and the fact that globally most clinicians would not have encountered the disease and would not be familiar with the clinical features of the disease. Leishmaniasis is endemic in few in all continents of the world except Australia and Antartica. Leishmaniasis is endemic in only few countries in the world but because of global travelling these days clinicians should be aware that they could encounter various types of leishmaniasis including leishmaniasis of the penis any time without notice. Leishmaniasis of the penis should be considered as a differential diagnosis of all the common lesions of the penis by having a high index of suspicion for the disease so that a history of travels must be obtained from all patients who present with ulcerative and crusty penile lesions and they should quickly undertake all the necessary tests to exclude a diagnosis of leishmaniasis of the penis if the diagnosis is not obvious.

**Conflict of Interest** – None

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