Amoebiasis of the Penis: A Review and Update

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Received date: September 24, 2020; Accepted date: December 23, 2020; Published date: December 27, 2020

Citation: Anthony K-G Venyo. (2020) Amoebiasis of the Penis: A Review and Update. Journal of Clinical Surgery and Research. 1(1)
DOI: 10.31579/2768-2757/001

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Abstract
Ulceration of the penis/foreskin which would tend to be painful, Swelling of the penis, Oedema of the penis, Discharge from ulcer or inflamed area of penis that could be purulent or may contain blood, Balanoposthitis, Exudation from a penile ulcer which could be mild, profuse, purulent or bloody, Sloughing off of part of the foreskin and other tissues with resulting hypospadias, indurated swelling of the penis which may initially involve one part of the penis but could quickly spread, A history of homosexual coital activity may be obtained, The spouse of a man who has Amoebiasis of the penis could also have Amoebiasis of vulva, cervix or endometrium, The prepuce may not retractable. There may be ulceration or swelling of the glans penis that may be irregular. Clinical examination findings in cases of Amoebiasis of the penis could reveal some of the ensuing: The general and systematic examinations may be normal. Examination of the penis may show: Tight non-retractile foreskin, Ulceration of foreskin, Swelling of the foreskin, Swelling of the glans penis, Ulceration and swelling of glans penis., Swelling and inflammation of the shaft of the penis, Ulceration on the shaft of the penis, Development of an iatrogenic hypospadia which was not there before, The inguinal lymph nodes may not be palpable but sometimes they may be enlarged on one side or on both sides, The penile swelling may involve part of the penis but at times on rare occasions the entire penis may be swollen, the penile swelling could on rare occasions extend to the supra-pubic area. On rare occasions the swelling of the penis could extend to include the scrotum but this is extremely rare, Amoebiasis of the penis does mimic various common conditions that affect the penis including: squamous cell carcinoma of the penis, chancroid, primary syphilitic ulcer of the penis, granuloma inguinale, balanoposthitis, and many other lesions affecting the penis. A high-index of suspicion is required to diagnose Amoebiasis of the penis. Clinicians need to be aware that male homosexuals who practice penetrative penis-anal coital activity have a higher risk of developing amoebiasis of the penis especially in Amoebiasis endemic countries. If an individual is suspected to have balanoposthitis or non-specific infection of the penis and is treated with antibiotics but the lesion does not respond to treatment, amoebiasis of the penis should be suspected. Secretions and discharges from the penile ulcer as well as biopsies of the penile lesion should be submitted for pathology examination which would demonstrate trophozoites, entamoebae as well as inflammatory cells. Even if carcinoma of the penis is initially suspected biopsy of the penile lesion would show features of Amoebiasis in the absence of any features of malignancy but in the very rare situation of a combination of Amoebiasis of the penis and carcinoma of the penis microscopic pathology examination of a biopsy specimen of the penile lesion would show features of Amoebiasis and carcinoma of the penis. Amoebiasis of the penis does quickly and effectively respond to anti-amoebic medications.

Key Words: amoebiasis of penis; amebiasis of penis; penile amoebiasis; penile amebiasis; entamoeba histolytica; balanoposthitis; trophozoites; microscopic examination; biopsy of penile lesion; metronidazole; anti-amoebic medicament; emetine; chancroid; syphilis; squamous cell carcinoma of penis. homosexuals. amoebiasis of cervix, amoebiasis of vulva, amoebiasis of endometrium; pcr.; amoebic liver abscess; metronidazole; granuloma; microscopy; biopsy; histopathology, prepuse; glans penis; hypospadias; urethroplasty

Introduction
It has been iterated that Amoebiasis of the penis is a rare clinical entity due to the fact that the penis is an unusual site for the manifestation of amoebiasis. [1] It has additionally been stated that homosexuals tend to have a higher risk for the development of amoebiasis of the penis. [1] Amoebic ulcers tend to mimic cutaneous lesions that had arisen from squamous cell carcinoma of the penis, chancroid, primary syphilis, granuloma inguinale, and many other causes of lesions involving the penis. [1] It had been recommended that Amoebiasis of the penis should be suspected when a patient with a penile lesion which has been clinically provisionally diagnosed as having balanoposthitis and treated with antibiotics has not responded to antibiotic treatment and such a situation biopsy of the penile lesion to isolate trophozoites to confirm the diagnosis of Amoebiasis of the penis should be necessitated. [1] It has been documented that most of the individuals that are afflicted by Amoebiasis tend to be asymptomatic; nevertheless, they tend to pass cysts and their condition has been referred to as asymptomatic intra-luminal Amoebiasis. [2] This document was stated to be true with regard to
Entamoeba Moshkovskii and majority of Entamoeba Dispar and up to 80% of cases of Entamoeba histolytica. [2] It has also been iterated that whilst Entamoeba dispar had generally been understood to be non-pathogenic, it had been reported in 2015 that Entamoeba Dispar could sometimes cause symptoms. [2] [3]  
Amoebiasis of the bowel which tends to be associated with diarrhoea without dysentery with absence of mucus or stool. [2]. With regard to Amoebic dysentery or colitis there tends to be an associated mucus with the diarrhoea or visible or non-visible blood [2] some of the manifestations that tend to be associated with the common Amoebic dysentery include:

- 15% to 33% of cases of Amoebic dysentery manifest with diarrhoea [2]
- Quite commonly the symptoms tend to develop insidiously over a period of 3 weeks to one month and associated with worsening diarrhoea and abdominal pain.
- The symptoms sometimes do present acutely and thus mimic the situation of an acute abdomen [2]
- Young children could develop intussusception or necrotizing colitis that could lead to perforation of the bowel that would necessitate acute surgical care.
- Rare complications of Amoebic dysentery include colonic amebomas and toxic megacolon. [2]
- Ameobic liver abscesses tend to be more common in males in comparison with females with a ratio of 10:1. [2]
- Ameobic liver abscess tends to be a solitary abscess [2]
- The symptoms of Ameobic liver abscess tend to include: fever, cough, and dull right upper abdominal pain or ache which also tends to be associated with referred pain to the right shoulder or the lower part of right chest. [2]
- Only one third of people who have amoebiasis of the liver tend to have gastro-intestinal symptoms. [2]
- The symptoms of Ameobicis of the liver tend to develop over a period of two to four weeks. [2]
- With regard to Ameobicis of the liver the liver tends to be tender as well as enlarged. [2]
- In Ameobicis of the liver, the leucocyte count would tends to be elevated as well as the results of the liver function tests tend to show elevation but these are non-specific and do not establish a diagnosis of Ameobicis.

Amoebiasis of the penis is a very rare condition that is sporadically reported and because of its rarity within Amoebiasis endemic areas clinicians within the Amoebiasis-endemic areas would tend not to be familiar with the manifestations of the infection. Additionally because of global travel and the practice of homosexuality Amoebiasis of the penis would be encountered in non-Amoebiasis endemic areas where most clinicians would not have encountered a case before and would also tend to be unfamiliar with the manifestations and treatment of the disease. Usually people who have Amoebiasis of the penis do not have symptoms of gastro-intestinal Amoebiasis. Amoebiasis of the penis would tend to present with non-specific symptoms including:

- Pain in the penis including: the foreskin, glans, or shaft of penis; ulceration of foreskin, glans penis, or shaft of the penis; swelling / induration of penis including foreskin, glans penis, or shaft of penis; discharge of purulent nature or blood from foreskin, glans penis, or shaft of penis; recently developed hypoplasias of unknown cause. The swelling and induration of the penis tends to be non-specific causes psychological trauma to most patients because their local practitioners have given them antibiotics presuming the symptoms have been related to infection but the symptoms have remained the same or are getting worse. The next thing is the patients worry about a strong possibility that they may have a malignancy of the penis. The ensuing article contains a review and update of the literature related to case reports, case series, and studies undertaken related to Amoebiasis of the penis as well as an overview documentations related to Amoebiasis in general.

**Aim**

To review and update the literature on Amoebiasis of the penis.

**Method**

Internet data bases were used to search for literature on Amoebiasis of the penis including Google, Google Scholar, Yahoo, and PUB MED. The search words that were used included Amoebiasis of the penis, Amebiasis of penis, penile amoebiasis, penile amebiasis, urogenital amebiasis, amoebiasis, amebiasis. Fifty references were identified which were used to write the paper that has been divided into (A) Overview which has discussed various aspects of amoebiasis in general and amoebiasis of the penis in general to provide a bird’s eye view of the subject and (B) Miscellaneous narrations, summations, and discussions from case reports, case series, and studies related to Amoebiasis of the penis.

**Result / Review and Update of Literature**

(A) **Overview**

Definition and general comments

- Amoebiasis refers to an infection that is caused by amoebae and overwhelmingly it tends to be caused by Entamoeba Histolytica. [2]
- Amoebiasis of the penis is a rare clinical entity which has been reported sporadically in Amoebiasis endemic and non-endemic areas globally because of migration to non-Amoebiasis endemic areas as well as travels from non-Amoebiasis endemic areas to Amoebiasis endemic areas and back home.
- Homosexual males and immunocompromised males would tend to have Amoebiasis of the penis more commonly than the ordinary population of males.
- The presentation and clinical signs associated with Amoebiasis of the penis are non-specific and these simulate more common lesions of the penis and hence a high index of suspicion for Amoebiasis of the penis is required to establish the diagnosis of the infection.
- Amoebiasis of penis can affect children as well as adults.

**Terminology**

- Amoebiasis is also referred to as Amebiasis.

**Epidemiology**

- It has been documented that the global estimate is that 10% of the world’s population has been infected with Entamoeba Histolytica. [2]
- It has been stated that Amoebiasis is endemic within the tropical and sub-tropical areas of the world. [2] Amoebiasis tends to be more common within areas or countries that have poor sanitation. [4]
- It has also been noted that within the temperate developed countries of the world, Amoebiasis tends to be encountered among individuals who are immigrants from Amoebiasis endemic areas of the world, individuals from temperate non-Amoebiasis endemic areas who had travelled to and back from Amoebiasis endemic areas, men who have coitus with men, as well as residents of institutions. [2]
- It has been iterated that other sources had suggested that many if not majority of individuals who are believed to be carriers of Entamoeba Histolytica could be carrying the non-pathogenic
Entamoeba Dispar, or Entamoeba Moshkovski which morphologically are identical to Entamoeba Histolytica. [2]

- It has been noted that the global estimate of Amoebiasis is that there are 50 million cases of Amoebic diarrhoea within the world yearly and out of these 100,000 deaths do occur as a sequel of Amoebiasis. [2]
- Extra-intestinal Amoebiasis including Amoebiasis of the penis, ano-genital region, and other parts of the body tend to be reported sporadically but these tend not to be common therefore a high index of suspicion is required to establish the diagnosis of extra-intestinal Amoebiasis.

Sites

- Amoebiasis commonly tends to affect the colon and the commonest part of the colon to be affected by the infection is the caecum, which is followed by the right side of the colon, rectum, sigmoid colon, as well as the appendix.
- The terminal ileum may also be involved by Amoebiasis. [2]
- Cases of recto-vesical fistula or fistula to the skin could on rare occasions be reported in relation to Amoebiasis [2]
- Amoebiasis may involve the liver as a spread of infection which can be likened to a metastatic liver involvement / abscess. [2]
- Amoebiasis could spread from the liver to the thorax and on rare occasions to the brain
- Other rare sites for the development of extra-intestinal Amoebiasis include: the penis, testis, epididymis, urinary bladder, the kidney, the uterine cervix, the vulva, the endometrium, the ovary in the form of tube-ovarian mass, the lungs forming pulmonary amoebiasis, the heart with the development of cardiac tamponade, the ocular tissues, the limbs causing cutaneous amoebiasis of the thighs and other areas.

Pathophysiology

- Transmission of Amoebiasis tends to occur through the faecal to oral route either directly from person to person contact or indirectly through drinking or eating water or food contaminated with faeces. The amoebic cysts most commonly tend to be ingested from food or water that has been contaminated and at times via sexual contamination. [2]
- Encystation to 8 motile trophozoites does occur within the small bowel. [2]
- The cysts tend to be resistant to gastric acid in the stomach and to chlorine that is in the water supplies. [2]
- The trophozoites potentially tend to be invasive and they also tend to multiply by binary fission. [2]
- It has been documented that 20% of Amoebiasis infections, invasion into the colonic wall with destruction of tissue does occur. [2]
- It has been stated that: [2]
  - Adherence to the mucosa of the colon tends to be mediated by lectin on the surface of Entamoeba Histolytica. [2]
  - The parasite then tends to induce apoptosis of epithelial cells via a channel forming pore protein.
  - The Entamoeba does ingest the remaining cells. [2]
  - Some trophozoites do undergo encystation via signalling pathways that complete the cycle. [2]
- It would be envisaged that the pathophysiology of Amoebiasis of the penis would be similar to what happens within the colon except that all the processes would be occurring within the penis or prepuce.

Clinical presentations

- Amoebiasis of the bowel tends to be associated with a clinical spectrum which does range from asymptomatic infection, or diarrhoea and dysentery to fulminant colitis and peritonitis as well as extra-intestinal amoebiasis. [4]
- Acute amoebiasis could manifest as diarrhoea or dysentery with frequent stools, small and bloody stools.
- Chronic amoebiasis of the colon could manifest with gastrointestinal symptoms as well as fatigue, loss of weight, and fever on rare occasions. [4]
- Amoebic liver abscess could manifest with fever, and right upper quadrant abdominal pain. [4]
- Amoebiasis of the penis would tend to present with:
  - Ulceration of the penis/foreskin which would tend to be painful.
  - Swelling of the penis.
  - Oedema of the penis.
  - Discharge from ulcer or inflamed area of penis that could be purulent or may contain blood
  - Balanoposthitis
  - Exudation from a penile ulcer which could be mild, profuse, purulent or bloody.
  - Sloughing off of part of the foreskin and other tissues with resulting hypospadias
  - Indurated swelling of the penis which may initially involve one part of the penis but could quickly spread
  - A history of homosexual coital activity may be obtained.
  - The spouse of a man who has Amoebiasis of the penis could also have Amoebiasis of vulva, cervix or endometrium.
  - The prepuce may not be retractable
  - There may be ulceration or swelling of the glans penis that may be irregular

Clinical examination findings

The general and systematic examinations of the patients who have Amoebiasis of the penis may be normal. However examination of the penis, genitalia and inguinal region may show:

- Tight non-retractile foreskin.
- Ulceration of foreskin
- Swelling of the foreskin
- Swelling of the glans penis.
- Ulceration and swelling of glans penis.
- Swelling and inflammation of the shaft of the penis.
- Ulceration on the shaft of the penis
- Development of an iatrogenic hypospadias which was not there before.
- The inguinal lymph nodes may not be palpable but sometimes they may be enlarged on one side or on both sides.
- The penile swelling may involve part of the penis but at times on rare occasions the entire penis may be swollen.
- The penile swelling could on rare occasions extend to the suprabubic area.
• On rare occasions the swelling of the penis could extend to include the scrotum but this is extremely rare.

The aforementioned features are non-specific and would not be diagnostic of Amoebiasis alone because many conditions would tend to present similarly.

Investigations

Urine
• Urinalysis urine microscopy and culture are general assessment investigations that tend to be undertaken on all patients that have Amoebiasis of the gut or extra-intestinal Amoebiasis as part of their general assessment but the results would not establish a diagnosis of Amoebiasis but if there is any urinary tract infection it would be treated accordingly to improve the general health of the patient.

Stool
• Microscopy examination of stool samples of individuals who have Amoebiasis of the colon would tend to show trophozoites and Entamoeba species and encompassing inflammatory cells and also with regard to those who might have had Amoebiasis of the penis through infection from stool there is the possibility that the stool examination would be normal in cases where the penile infection had been from homosexual coital activity.

Haematology investigations
• Full blood count, and coagulation screen are general tests that are undertaken as part of the assessment of patients who have Amoebiasis and the results would generally tend to be normal. Even if there is eosinophilia this would not be diagnostic of Amoebiasis but if there is evidence of anaemia this will be investigated appropriately and treatment would be provided to improve the general state of the patient.

Biochemistry Blood Tests
• Serum urea and electrolytes, liver function tests, and blood glucose are general assessment investigations that are undertaken as part of the general assessment of individuals who have Amoebiasis but generally the results would tend to be normal. Nevertheless, if there is any impairment of function it would be investigated and treated accordingly.

Radiology Investigations

Ultrasound Scan
• Ultrasound scan of abdomen and pelvis tend to be undertaken in cases of intra-abdominal Amoebiasis for instance if there is Amoebic liver abscess it would demonstrate the site, the size, and number of abscesses which could at times be potentially drained under ultrasound scan guidance.

Considering that the provisional clinical diagnosis that is made when many patients that have Amoebiasis of penis as seen, majority of the patients would tend to have ultrasound scan of abdomen and pelvis to establish if the possible tumour is associated with lymph node enlargement or metastasis. The results would generally turn out to be normal because the disease is an infection and not a malignant lesion. Nevertheless, there is the possibility that an incidental finding of a lesion not related to Amoebiasis could be found and investigated as well as treated occasionally that is not related to Amoebiasis.

• Ultrasound scan of the penis undertaken as part of the investigation of the penis would tend to show benign features and when contras-enhanced ultrasound scan (CEUS) of the penis is undertaken it would tend to show no significant enhancement. The ultrasound scan would also demonstrate the extend of the Amoebiasis of the penis.

Computed tomography (CT) scan
• CT scan of abdomen and pelvis tend to be undertaken in cases of intra-abdominal Amoebiasis for instance if there is Amoebic liver abscess it would demonstrate the site, the size, and number of abscesses which could at times be potentially drained under CT scan guidance.

Considering that the provisional clinical diagnosis that is made when many patients that have Amoebiasis of penis as seen, majority of the patients would tend to have CT scan of abdomen and pelvis to establish if the possible tumour is associated with lymph node enlargement or metastasis. The results would generally turn out to be normal because the disease is an infection and not a malignant lesion. Nevertheless, there is the possibility that an incidental finding of a lesion not related to Amoebiasis could be found and investigated as well as treated occasionally that is not related to Amoebiasis.

• CT scan of the penis undertaken as part of the investigation of the penis would tend to show benign features and when contrast-enhanced CT scan (CECT) of the penis is undertaken it would tend to show no significant enhancement. The CT scan would also demonstrate the extend of the Amoebiasis of the penis.

Magnetic Resonance Imaging (MRI) scan
• MRI scan of abdomen and pelvis tend to be undertaken in cases of intra-abdominal Amoebiasis for instance if there is Amoebic liver abscess it would demonstrate the site, the size, and number of abscesses which could at times be potentially drained under MRI scan guidance.

Considering that the provisional clinical diagnosis that is made when many patients that have Amoebiasis of penis as seen, majority of the patients would tend to have MRI scan of abdomen and pelvis to establish if the possible tumour is associated with lymph node enlargement or metastasis. The results would generally turn out to be normal because the disease is an infection and not a malignant lesion. Nevertheless, there is the possibility that an incidental finding of a lesion not related to Amoebiasis could be found and investigated as well as treated occasionally that is not related to Amoebiasis.

• MRI scan of the penis undertaken as part of the investigation of the penis would tend to show benign features and when contrast-enhanced MRI scan (CEMRI) of the penis is undertaken it would tend to show no significant enhancement. The MRI scan would also demonstrate the extend of the Amoebiasis of the penis.

Diagnosis

Diagnosis of Amoebiasis of the penis tends to be confirmed by the following:

• Microscopy examination of wet films of scrapings and discharge of from the penile ulcer that show trophozoites and Entamoeba and inflammatory cells or granulomatous reaction.

• Microscopy examinations of biopsy specimens of the penile lesions that show trophozoites, Entamoeba, granulomatous inflammation and absence of malignant tumour.

• It has been recommended that clinicians should use antigen detection or PCR based assays to differentiate Entamoeba Histolytica from non-pathogenic Entamoeba [2] [5]

• Patients who do have Amoebic liver abscess tend to have anti-amoebic antibodies and amoebic antigens in the serum [2]; however, this has not been studied in cases of Amoebiasis of the penis to the knowledge of the author.
Staining for Amoebiasis [2]

Positive stains

The positive stains for Amoebiasis include:
- PAS
- Trichrome.

Negative stains

The negative stain for Amoebiasis does include:
- CD68.

Update on laboratory diagnosis of amoebiasis: [6]

Amoebiasis caused by Entamoeba histolytica, is a public health problem in many developing countries which does cause up to 100,000 fatal cases globally annually. The detection of pathogenic Entamoeba histolytica and its differentiation from non-pathogenic Entamoeba spp. does play a vital role with regard to the clinical management of patients. Laboratory diagnosis of intestinal amoebiasis within the developing countries of the world does still rely upon labour intensive and insensitive methods that involve staining of samples of the stool and microscopy examination. Newer and more sensitive methods for the diagnosis of amoebiasis do include various antigen detection ELISAs and rapid tests; nevertheless, their diagnostic sensitivity and sensitivity does seem to vary between studies that had been undertaken, and some of the tests have not been able to distinguish from among the Entamoeba species. Molecular detection techniques are highly sensitive and specific and isothermal amplification approaches could be developed into field applicable tests; nevertheless, the cost would tend to be a barrier for their utilization as a routine laboratory method of testing for Amoebiasis in most developing poor countries where Amoebiasis is endemic. [6]

Entamoeba culture methods: [5]

- It has been documented that two types of culture media have been available that can be used to isolate Entamoeba spp, xenic and axenic media. Xenic cultivation refers to cultivation of the parasite with undefined/unknown flora. [5]
- Modified Boeck and Drbohlav egg diphasic medium, Balamuth’s medium, Jones’s medium and TYSGM-9 are examples of xenic medium that is used for the culture of Entamoeba spp. [5]
- Axenic cultivation refers to the growth of parasites with the absence of any unknown/ unidentified flora other than the protozoa that is intended to be grown or cultured. Examples of axenic cultivation include TP-S-1, TYI-S-33 and others which are used for the cultivation of Entamoeba histolytica. It is worth knowing that Entamoeba Bangledeshi and Entamoeba Moshkovskii have the capability of growing at 37 degrees centigrade and 25 degrees centigrade, which does help with regard to the differentiation of the aforementioned species from Entamoeba histolytica and Entamoeba dispar. [7]
- It has been stated that culture of Entamoeba histolytica for a diagnostic purpose does have poor sensitivity in comparison with microscopy examination, and it tends to be technically difficult, expensive, as well as difficult to maintain. [8] In view of this culture methods for the diagnosis of Entamoeba histolytica has not been in the list of available diagnostic tests for the diagnosis of amoebiasis.

ISO-ENZYME/MODEME ANALYSIS [5]

The ensuing summations have been made with regard to Iso-Enzyme Modeme Analysis: [5]

- When strains of Entamoeba do have the same electrophoretic pattern for many enzymes, they are referred to as zymodemes.
- It has been stated the enzymes which had been studied with regard to the detection and differentiation of the various species of Entamoeba include: hexokinase, malic enzyme, phosphoglucoisomerase and others, and that 24 different zymodemes had been identified. The zymode pattern analyses do clearly distinguish Entamoeba histolytica from Entamoeba dispar (which tends not to be pathogenic) and thus it has remained the gold standard for the diagnosis of amoebiasis in the pre-molecular era.
- It has been iterated that the disadvantages of utilizing iso-enzyme analysis do include its large consumption of time, the difficulties associated with the performance of the iso-enzyme analysis, the dependence of the procedure of the analysis on culture methods, and the low sensitivity of the analysis. [9] In view of the aforementioned difficulties, at present, molecular techniques have surpassed the iso-enzyme analysis with regard to the differential detection of Entamoeba species.

Serological tests [5]

Antibody detection [5]

Relevant summations related to antibody detection in relation to the diagnosis amoebiasis that had been made include: [5]

- It has been iterated that serological tests could be useful with regard to the diagnosis of amoebiasis within developed countries in view of the fact that this Entamoeba histolytica is not common. On the contrary, within developing countries, Entamoeba histolytica has remained endemic [10]
- This would make the definitive diagnosis of amoebiasis by utilization of antibody detection difficult in view of the difficulty to corroborate the present from previous infection. [11]
- Parija et al. [12] reported their study in which 41 patients out of 50 patients who had amoebic liver abscess (ALA) had tested positive for anti-amoebic antibodies undertaken by indirect hemagglutination test (IHA). Three of the patients that amounted to 12% did have other parasitic infections and not amoebiasis and this gave false positive reactions. The positive predictive value and the negative predicted value were reported to be 93.1% and 83.9% respectively. [12]
- It had been stated that IHA tends to be easy to undertake and standardise in comparison with other in-house assays and that among the antibody detection assays, ELISA had been the most widely utilized test to study amoebiasis. Hira et al. [13] reported a sensitivity and specificity of 97.9% and 94.8% respectively in patients who had ALA.
- With regard to amoebiasis, IgG antibodies tend to remain detectable for many years pursuant to amoebiasis infection, but on the contrary IgM antibodies do clear from the circulation within a short period of time and can only be detected in a current (newly developed) amoebiasis infection. Abd-Alla et al. [14] reported their use of an ELISA for the detection of anti-lectin antibodies from sera of patients who had amoebic colitis. Later on in 2000, Abd-Alla et al. [15] did report a test for the identification of anti-lectin antibodies of individuals and they did find it more sensitive and specific in comparison with serum IgG detection.
- It has been documented that ELISA has played an important part with regard to the diagnosis of patients who have invasive amoebiasis in that it does not have cross-reactions with other
non-pathogenic Entamoeba species and it does contribute to high specificity. [5]

- Indirect immunofluorescence assays have been illustrated as a rapid, reliable as well as reproducible method of detecting antibody that differentiates amoebiasis from non-amoebic diseases as well as previous amoebic infections from current amoebic infections. [5]
- Jackson et al. [16] did report that the monitoring of IgM level was useful with regard to the diagnosis of extra-intestinal/invasive amoebiasis. [16]
- With regard to extra-intestinal/invasive amoebiasis, especially, amoebic liver abscess (ALA) the sensitivity and specificity of IFA was reported to be 93.6% and 96.7% respectively by Haque et al. [17]
- In developing countries where amoebic infections tend to be endemic the disadvantage of antibody detection relates to its low sensitivity. [5]

**Detection of antigen [5]**

Summations relating to the detection of antigen in amoebiasis have included the following: [5]

- Antigen detection methods have been stated to have many advantages in comparison with the aforementioned detection modalities, like specific detection of Entamoeba histolytica from Entamoeba dispar/moshkovskii infection, they also have better sensitivity and specificity, as well as, they tend to require less expertise and large scale screening tools. [5]
- The antigens which had been used and reported with regard to the diagnosis of amoebiasis include: [5]
  - Gal/Gal-NAc lectin,
  - Lipophosphoglycan,
  - And 29 kDa surface antigen.
- Haque et al. [18] did study in 1995, 1996, and 1998, the use of Gal/Gal-NAc detection in stool specimen of asymptomatic individuals as well as in patients who had acute colitis. The reports of these studies had documented high sensitivity (80% to 94%) and specificity (94% to 100%) with good correlation with molecular methods. [18]
- Haque et al. [17] did report that 96% and 100% of patients who had amoebic liver abscess (ALA) did have demonstrable levels of Gal/Gal-NAc lectin antigen in their sera and liver abscess pus respectively preceding their treatment with metronidazole, but on the contrary, only 33% and 41% after a few days of undergoing metronidazole treatment.
- Parjia et al. [12] used counter-current immunoelectrophoresis test the detection of amoebic antigen in the sera of patients who had amoebic liver abscess (ALA) and they reported that the antigen was detected in 38 out of the 50 patients they had studied that amounted to 76%. 
- Karki and Parjia [19] used Co-agglutination assay to detect amoebic antigen in 50 patients and detected the antigen in 45 out of 90 patients which amounted to 90%.
- An immunochromatographic card assay had been designed to identify 29kDa surface antigen for Entamoeba histolytica/Entamoeba dispar and this assay had also been designed to identify other stool pathogens including Giardia and Cryptosporidium spp from stool specimen. With regard to the sensitivity of this assay, controversies have been reported. [20]
- Some of the disadvantages of this study that had been observed included the inability to utilise the test to distinguish Entamoeba histolytica, Entamoeba dispar, Entamoeba moshkovskii, the requirement of obtaining fresh, unfixed stool specimens.
- Many vaccine candidate antigens had been found including: - 25 kDa serine-rich Entamoeba histolytica protein (SREHP), 260 kDa Gal/GalNac inhibitable lectin, lipophosphoglycans, cysteine proteases and peroxiredoxins.
- Studies had been reported relating to animal models like gerbils, as well as severe combined immunodeficiency mice did reveal SREHP and Gal/GalNac lectin as having the potential as well as being promising vaccine candidates for the prevention of invasive amoebic diseases. [21] There is the need to establish studies on these antigen targets in order determine their role with regard to the diagnosis of amoebiasis.

**Molecular Methods**

Summations related to utilization of molecular methods diagnosis and management of amoebiasis have been summarised as follows: [5]

- Over the last one and half decades molecular biology-based procedures for the diagnosis of various infections that had included amoebiasis have become important in order to circumvent problems related to the older conventional techniques and these molecular-based procedures have been associated with increased sensitivity, specificity, as well as simplicity. [5]
- The accurate distinguishing of pathogenic Entamoeba histolytica from non-pathogenic Entamoeba spp is pertinent with regard to the treatment of patients as well as with regard to the epidemiological study of outbreaks of amoebiasis. [5]
- Molecular-based techniques have been demonstrated to be adequate with regard to satisfying these needs and thus had emerged as the gold-standard diagnostic methods of testing in current times. [5]
- The most important step with regard to the diagnosis of intestinal amoebiasis relates to standardisation of DNA extraction procedure from samples of faeces. [5]
- DNA isolation from samples of faeces tends to be associated with difficulties in view of presence of various polymerase chain reaction (PCR) inhibitors including: heme, bile salts, bilirubin, and complex polysaccharides. [5] [22]
- There are various in-house methods for DNA extraction from stool that had been published out of which the commonest had been the phenol-chloroform method. [5]
- The disadvantages pertaining to the in-house methods relate to the large amount of time consumption and the procedure tends to be laborious to undertake. [5]
- Commercial kits like QIA amp DNA stool kit had been successfully as well as reliably utilized in the extraction of DNA from samples of faeces thus overcoming the disadvantages that had been associated with the in-house/conventional methods of extraction. [5] [23]
- It had been pointed out that the transportation as well as storage of faeces, or pus from liver abscess at room temperature does lead to rapid degeneration of the target DNA. The sensitivity of PCR undertaken on a non-preserved samples does fall with improper storage temperature and the storage duration and therefore, the specimens do need to be preserved at minus 20 degrees. Fixatives of stool had also been utilized; nevertheless, the studies did reveal that freezing a fresh specimen at minus 20 degrees Celsius preceding DNA extraction does constitute a better strategy due the results being reproducible and sensitive. [5] [24] [25]

**Conventional polymerase chain reaction (PCR)**

Summations related to the utilization of conventional PCR in the detection / diagnosis of amoebiasis include: [5]
A large spectrum of PCR methods had been described relating to the differentiation of the Entamoeba species. The genes which had been studied well including 18S rRNA (small sub-unit rRNA) had been utilised widely in view of the fact that they are present in multiple copies of extrachromosomal plasmids which make it more easily detected in comparison with a DNA copy. [26]

Mirelman et al. [27] had reported that PCR targeting 18S RNA did have a very high sensitivity in comparison with the best ELISA that was available within the market.

Dis-correlation between microscopy examination findings and the results of PCR (microscopy examination positive for Entamoeba cysts and PCR results negative) could arise if the primers of narrow specificity are utilized. In view of this, primers that have broader specificity (for example small subunit rRNA) should be used to reduce having dis-correlation results. Additionally, the use of such primers with broad specificity had led to the finding of newer species of Entamoeba like Entamoeba Bangladeshi. [7]

Two different nested PCR studies, one of which had been reported by the International Centre for Diarrhoeal Diseases and Research, Dhaka, Bangladesh [28] and another study from JIPMER, Puducherry, India on faecal samples on faecal samples that target 16S-like rRNA were found to differentiate accurately between the infections that had been caused Entamoeba histolytica, Entamoeba dispar, and Entamoeba moshkovskii with a specificity of 100%. [29]

Parija and Khaimar [30] in 2007 used the conventional PCR assay for the detection of Entamoeba histolytica 16 S rRNA gene from the urine and saliva in patients who had amoebic liver abscess (ALA). The assay did demonstrate Entamoeba histolytica DNA in 4 out of 23 urine specimens (which amounted to 17.4%) that were collected preceding the administration of metronidazole, but the DNA had been demonstrated in 17 out of 30 urine specimens (which amounted to 56.7%) that were collected pursuant to the metronidazole treatment. In view of this it would be said that the detection of Entamoeba histolytica gene from urine could be utilized as a prognostic marker to assess the treatment of invasive / extra-intestinal amoebiasis. [30] Khaimar and Parija [31] in 2008 reported similar results in studies undertaken using saliva samples of patients who had invasive cases of amoebiasis.

Despite the fact that conventional PCR assays had been utilised increasingly for the detection as well as differentiation of Entamoeba species, the disadvantages that had been had been encountered were consumption of time when large-scale processing of samples was necessitated, cost of the procedure, inability to produce quantitative results and false-positive results as a result of carry-over contamination. [5]

REAL-TIME POLYMERASE CHAIN REACTION [5]

Parija et al. [5] summarized salient points related to utilization of Real-Time Polymerase Chain Reaction as follows:

- It had been noted that Real-time PCR (RT-PCR) assay, which had succeeded PCR had gained attraction for the laboratory diagnosis of infections in view of its characteristics of enhanced sensitivity, eliminating post-PCR manipulation that had led to short turn-around times, minimised laboratory environment contamination with amplicons and quantitative analysis. Even though the estimation of parasite burden could not be relevant with regard to cases of amoebiasis because parasite content does vary between, and even within specimens that had been obtained from the same patient, it could be utilised in environmental sampling. [32]
- A variety of chemistries are available which detect the amplicon in RT, that involve fluorescent labelled oligonucleotide and probes. The three chemistries that are widely utilised include: the hydrolysis probes (Taqman chemistry), hybridization probes (molecular beacons and FRET probes) and SYBR Green assay. [5]
- At present RT-PCR has become the “gold standard” test relating to the differential detection of Entamoeba spp and epidemiological study of amoebiasis. [5]
- Since the World Health organization had redefined amoebiasis, many diagnostic techniques are being introduce in order to accurately detect and differentiate Entamoeba. Molecular methods, especially the newly introduced RT-PCR has been of assistance regarding the accurate diagnosis and specific selection of patients for treatment with anti-amoebic medication. Wang et al. [33] studied DNA microarray technology in the diagnosis of amoebiasis and they reported that their utilization of microarray technology to detect Entamoeba histolytica, Entamoeba dispar, Giardia lamblia, and Cryptosporidium parvum with high sensitivity and specificity.
- Shah et al. [34] in 2005, developed a microarray-based genotyping assay utilising sequence DNA clones of Entamoeba histolytica HM1: IMSS strain which did reveal capability for distinguishing DNA clones of non-pathogenic Entamoeba dispar, to detect genes that are present only in virulent strains of Entamoeba virulent strains and to ascertain the potential phenotypic-genotypic association.
- The aforementioned recent tools for the detection of amoebiasis are promising and their scope of use within the field of amoebiasis as diagnostic technologies needs to be further assessed. [5]

Treatment

Treatment of Amoebiasis of the penis tends to be by utilization of anti-amoebic medicaments which tends to result in quick resolution of the infection and some of the medicaments include:

- Metronidazole (Flagyl).
- Tinidazole
- Emetine
- Nitazoxanide
- Iodoquinol (Diquinol and others)
- Paromycin (Humatin)
- Diloxanide furoate (Furamide)

In situations when destruction of tissue has resulted in the formation of hypospadias then utilization of the most appropriate surgical procedure to repair the hypospadias would need to be adopted including pedicle island flap repair.

Differential Diagnosis of Amoebiasis of penis.

Some of the differential diagnosis of Amoebiasis of the bowel include:

- Appendicitis.
- Balantidium coli
- Crohn’s disease
- Histiocytes
- Non-pathogenic Amoeba
- Pseudo-membranous colitis
- Pyogenic abscess of the liver
- Tuberculosis of the bowel
Ulcerative colitis.
Some of the differential diagnosis of Amoebiasis of the penis include:
- Carcinoma of the penis.
- Chancreid.
- Granuloma inguinale.
- Syphilitic penile ulcer.
- Balanoposthitis.
- Non-specific bacterial infection.

Outcome
When Amoebiasis of the penis is diagnosed accurately, treatment with utilization of anti-amoebic medications for one to two weeks does result in resolution of the infection completely but if there was any structural damage like hypospadias that would need to be repaired surgically.

(B) Miscellaneous narrations, summations and discussions from some reported cases, case series, and studies related to amoebiasis of the penis.

Thomas and Antony [35] in 1976, reported a case of amoebiasis of the penis. They stated that cases of amoebiasis of the penis are very rare and that cases of amoebiasis of the penis had tended to be mistaken clinically a malignant lesion or cancer as well as an ulcerative venereal disease affecting the penis. Furthermore, Thomas and Antony [35] iterated that prior to the publication of their case report only 8 cases of Amoebiasis of the penis had been reported within the 51 years preceding their publication which had included publications by: Shih, Wu, and Lieu in 1939 [36]; Hermann and Berman in 1942 [37]; Camacho and Beirana in 1959 [8]; Mylius and Ten Seldam in 1962 [39]; Talwaker in 1962 [40]; Quevedo and Elias Dib in 1963 [41]; Purpon Jimenez and Engelking in 1967 [42].

Shih et al. [36] reported a 54-year-old Chinese man who had presented with an ulcerative lesion of his penis of 5 months duration. The clinicians provisionally considered the lesion to be either a malignant lesion or a pyogenic lesion. Shih et al. [36] reported also that examinations of the exudate of the ulcer as well as the superficial layers of the ulcer did reveal amoebae which had the characteristic features of Entamoeba Histolytica. The patient did not have any history of dysentery. Examinations undertaken repeatedly of the patient’s faeces did not show any evidence of Entamoeba. Additionally the patient had denied having had extraneous intercourse. He was treated with utilization of Emetine which resulted in a speedy cure. In view of the fact that his home was too far for his wife to come for examination the possibility of the amoebiasis being an emanation from amoebic dysentery which the wife might have had could not be ruled out and that meant the source of amoebiasis of the man’s penis could not be established. Shih et al. [36] cases of cutaneous amoebiasis usually tend to arise either from an abscess (for example liver abscess) discharging on to the abdominal wall or from extension from the bowel content.

Sosa Camacho and Beirana [38] in 1959 reported a case of dermatosis in which an ulcerated lesion of the penis with abundant secretion was found in young male who had practiced active pederasty. The lesion had been reported in Papua New Guinea, the author, did find lesions of the ano-genital region as the most common form of amoebiasis that had been found within the laboratory which was in sharp contrast to the findings in other parts of the globe where ano-genital amoebiasis had been a very rare disease.

In 1973, the experience of a pathologist called Cooke who had worked in Papua New Guinea were summated in the Journal of the Medical Association of Thailand summated as follows: [45]

- During a period of 4 years working in Papua New Guinea, the author, did find lesions of the ano-genital region as the most common form of amoebiasis that had been found within the laboratory which was in sharp contrast to the findings in other parts of the globe where ano-genital amoebiasis had been a very rare disease.
- The most common lesion was a painful, ulcerated, purulent area encompassing the anus and the commonest clinical provisional diagnosis of the lesions almost invariably had been squamous cell carcinoma.
- With regard to males, amoebiasis lesions of the penis tended to be common and they normally did start with infection underneath the prepuce and they then did spread to the penile shaft and even up to the scrotum as well as to the supra-pubic region.
- With regard to females, they had encountered vaginitis and cervicitis.
- Microscopy examinations of ano-genital amoebiasis did reveal the organisms within the purulent exudate upon the surface of the epithelium and the microscopy examinations also tended to show an inflammatory reaction within the dermis but the amoebae were not visualized within the deep tissues of the ano-genital region.
• Treatment of amoebiasis of the ano-genital region with utilization of any of the recognised anti-amoebic medicaments did result in rapid cure of the amoebiasis.
• The cause of the unusual prevalence of amoebiasis of the ano-genital organs had not been established.

Jayaweera [46] in 1975 reported a case of amoebic ulceration of the cervix in a female as well as a case of amoebiasis of the penis in a male. They stated that amoebiasis of the cervix and amoebiasis of the penis can closely mimic or simulate carcinoma of the cervix and carcinoma of the penis. A lesson to be learnt from this case report is that amoebiasis of the cervix and amoebiasis of the penis do exist and they are treatable diseases and for this reasons clinicians in amoebiasis endemic areas as well as globally show be aware that amoebiasis of the cervix and amoebiasis of the penis though they are generally uncommon because of global travel can be encountered anywhere in the world because of this a high-index of suspicion for amoebiasis of the cervix and the penis should be borne in mind.

Hejase et al. [1] reported a case of amoebiasis of the penis in 1975 in which they summated pertinent aspects related to amoebiasis of the penis as follows:

• Amoebiasis of the penis is a rarely recognised clinical entity in view of the fact that the penis is not the usual site of manifestation of amoebiasis.
• Homosexual men tend to have a higher risk to acquire amoebiasis of the penis.
• Amoebiasis ulcerous lesions of the penis tend to simulate cutaneous lesions that arise from squamous cell carcinoma, chancroid, primary syphilis, granuloma inguinale, as well as many other causes of ulcers of the penis.
• An amoebic ulcer of the penis should be expected with regard to a patient who develops balanoposthitis which resists antibiotic medicament utilization.
• Biopsy of the penile lesion is fundamentally necessitated with regard to the isolation of the trophozoites in order to confirm the diagnosis of amoebiasis of the penis.
• Utilization of metronidazole and hydrochloric emetine still remain the treatment of choice for amoebiasis of the penis.
• The diagnosis of amoebiasis of the penis should be especially be considered with regard to individuals who practice anogenital coitus or who are immunocompromised.

Mohanty et al. [47] reported a 47-year-old man who did present with a very painful ulcer of 15 days duration that had developed over the glans of his penis and which had encompassed his external urethral meatus. The penile ulcer did have a well-demarcated border and a raised erythematous rim (see figure 1). The whole penis was oedematous as well as associated with foul-smelling haemo-purulent exudates. He did have bilateral inguinal lymph node enlargements. The penile lesion did commence as multiple superficial ulcers that had coalesced to constitute a spreading ulcer. He did have a history of homosexuality. His local practitioner had already treated him with utilization of ciprofloxacin and azithromycin without any response of the penile lesion to treatment. The results of his stool examination, urine examination, blood routine haematology and biochemistry tests were normal. The results of his Venereal Disease Research Laboratory (VDRL) as well as Human Immunodeficiency Virus (HIV) tests were also non-reactive. A scrape cytology examination of the penile lesion was undertaken and its examination did reveal presence of inflammatory cells, and no atypia, or dysplastic cells. A wet mount of the haemo-purulent discharge did show presence of trophozoites of Entamoeba histolytica. The stool examination was normal and did not reveal any parasite. He was prescribed a two week course of metronidazole and after one week his ulcer had regressed and complete regression ensued in 2 weeks (see figure 2).
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Abdolrasouli et al. [48] reported 4 cases of Amoebiasis of the penis in 4 individuals who had presented as genital ulcerative lesions in 4 individuals who had practised unprotected anal coital activities by the identification of trophozoites of amoebae within their lesions. They were treated with metronidazole which led to resolution of the lesions (see journal for the report of the case series). With regard to the diagnosis of the infection, motile trophozoites of Entamoeba histolytica were found in the lesions which were examined by wet mount microscopy. The ulcers were solitary, painful, irregular, discharging as well as increasing in size. Three heterosexual men and one bisexual man had practiced insertion anal intercourse within the two weeks preceding the diagnosis. There was bilateral inguinal lymph adenitis with regard to one case. Direct examination of the lesions was positive for presence of trophozoites of Amoeba. There was complete resolution of the lesion pursuant to treatment with oral metronidazole 800 mg three times per day for 7 days to 10 days.

Abdolrasouli et al. [48] made the ensuing conclusions:

- Clinicians should be aware of cutaneous amoebiasis in sexually active men who do practice unprotected insertion anal intercourse in areas where intestinal amoebiasis is endemic.
- Wet mount microscopy is a useful and rapid diagnostic test for amoebiasis of the penis.

Parkash et al. [49] in 1982, reported a 50-year-old man who had presented with a 10 day history which included a painful swelling of his penile prepuce, that was a foul smelling, as well as blood stained sub-preputial discharge. His prepucce could not be retracted. A dorsal slit of his foreskin was undertaken as well as a biopsy of the tissue was taken for examination in view of a suspicion of a malignancy. Within a week it had been observed that his entire prepucce (foreskin) had been destroyed by an ulcer that had eaten away the ventral three quarters of his glans penis as well as the skin of the distal one third of the shaft of his penis. His whole penis was oedematous. There was no evidence of any significant regional lymphadenopathy. Histology examination of the biopsy specimen did show an amoebic granuloma with many trophozoites. He did not admit to any history that had suggested an amoebiasis infection including alimentary and extra-alimentary amoebiasis as well as any history of any extra-marital contact. He had been having an active sexual life. Pursuant to receipt of the histology report which had confirmed the diagnosis of amoebiasis of the penis, the wife of the patient was examined and was found to have an asymptomatic granulomatous lesion on her cervix. She did not have any discharge from her vagina. Histology examination of specimens of her cervical granulomatous lesion showed many trophozoites of Entamoeba Histolytica. Additionally, amoeba was not grown or isolated from the stool specimens of the man and his spouse as well as from smears of the granulomas. Anti-amoebic therapy was instituted for 2 weeks which resulted in the disappearance of the slough and discharge as well as the ulcer had regressed. With regard to the man, his surviving glans penis had been resting a peninsula that had less than 1 cm of an isthmus on the dorsal aspect. One centimetre of the ventral aspect of his urethra had been lost with the resultant creation of a large coronal ventral hypospadias. The penile defect was surgically reconstructed by utilization of an antero-lateral dartsos based scrotal flap that had been tunneled as a one-staged surgical procedure that had been supplemented with utilization of skin which was removed in the de-epidermizing of the buried part of the flap. A lesson to learn from this case report is the fact that amoebiasis of the foreskin can cause extensive destruction of the foreskin as well as glans penis and cause hypospadias. Additionally utilization of anti-amoebic medicament can lead to eradication of the infection and it is also important that the spouse or sexual partner of each patient who develops amoebiasis of the penis should also be screened quickly and treated with ant-amoebic medicament in order to prevent subsequent re-infection by amoebiasis.

Veliath et al. [50] in 1987, reported five cases of amoebiasis of the genital tract which had involved the cervix, vulva, and the penis. All five cases did present as an ulcerating mass and each of them was clinically provisionally suspected to be a malignant tumour. With regard to two cases, the amoebiasis did co-exist with a carcinoma, and an association which is very rare. The spouse of a man who had amoebiasis of the penis was found to have amoebiasis of the cervix had suggested a sexually transmitted mode of infection of amoebiasis. Veliath et al. [50] emphasized the need for histopathological confirmation of all suspected malignancies of the genitalia in view of the striking resemblance of amoebiasis of the genitalia to a carcinoma. Veliath et al. [50] additionally stated that the coexistence of amoebiasis with carcinoma would be of interest and would suggest a possible aetiological relationship between amoebiasis and carcinoma.

Conclusions

Amoebiasis of the penis is a very rare infection of the penis which is reported sporadically in Amoebiasis endemic and Amoebiasis non-endemic areas of the world. Amoebiasis of the penis does mimic various common conditions that affect the penis including: squamous cell carcinoma of the penis, chancroid, primary syphilitic ulcer of the penis, granuloma inguinale, balanoposthitis, and many other lesions affecting the penis. A high-index of suspicion is required to diagnose Amoebiasis of the penis. Clinicians need to be aware that male homosexuals who practice penetrative penis-anaI coital activity have a higher risk of developing amoebiasis of the penis especially in Amoebiasis endemic countries. If an individual is suspected to have balanoposthitis or non-specific infection of the penis is treated with antibiotics but the lesion does not respond to treatment, amoebiasis of the penis should be suspected. Secretions and discharges from the penile ulcer as well as biopsies of the penile lesion should be submitted for pathology examination which would demonstrate trophozoites, entamoebae as well as inflammatory cells. Amoebiasis of the penis does quickly and effectively respond to anti-amoebic medicaments.

Conflict of interest – None

Funding - None

Acknowledgements

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