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Unusual presentations of cutaneous leishmaniasis in clinical practice and potential challenges in diagnosis: a comprehensive analysis of literature reviews

Jombo GTA[1*], Gyoh SK[2]

[1]*Department of Medical Microbiology & Parasitology, College of Health Sciences, Benue State University, PMB 102119 Makurdi, Nigeria*
[2]*Department of Surgery, College of Health Sciences, Benue State University, PMB 102119 Makurdi, Nigeria*

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ABSTRACT

Cutaneous leishmaniasis is regarded as a re-emerging disease due to its increase in spread and rate of transmission over the past decade due to a proportionate increase in global human movements. This study was therefore carried out to review epidemiology, laboratory diagnosis and treatment with in-depth discussion on some of the rare clinical presentations of the disease capable of influencing its control. The study was based on literature review on clinical and laboratory features of cutaneous leishmaniasis from original research articles, review articles, short communications, letters to editor and case reports on the disease for the past 10 years (April 2000 to April 2010). The results were analysed using simple descriptive methods. The rarest presentations of leishmaniasis encountered were peritibial ulcerations, hard painful nipple in a male, swollen upper lip, dermatofibro sarcoma protuberans, sternal proliferative growth, turban tumour, post operative granuloma, chalazion-like 0.00%, and cutaneous sterile pyogranuloma with asymmetrical alopecia 0.00% each. Others include infected sebaceous cysts 0.45%, syphilis 0.19%, yaws 0.13%, thrombotic ulcerations 0.40%, mycetoma 0.90%, sarcoidosis 0.67%, painless nasal solitary nodule 0.00%, tuberculous lymphadenopathy 0.25% and unilateral erythema nodosum 0.28%. Physicians practicing in cutaneous leishmaniasis endemic, but most especially in the non-endemic areas should bear in mind that the disease may not be that rare in the context of the present global village phenomenon; and that, the next case could just be that of cutaneous leishmaniasis, the clinical picture of the patient notwithstanding.

1. Introduction

Leishmaniasis is an arthropod borne zoonotic disease transmitted through the bites of female sandflies. The old world leishmaniasis is caused principally by *Leishmania donovani(L. donovani)*, *Leishmania infantum* (*L. infantum)*, *Leishmania tropica(L. tropica)*, *Leishmania majoy (L. major)* and *Leishmania aethiopica(L. aethiopica)*are transmitted by Phlebotomus species while parasites of the new world infections principally *Leishmania peruriana (L. peruriana)*, *Leishmania chagasi (L. chagasi)*, *Leishmania mexicaca (L. mexicaca)* complex and *Leishmania braziliensis (L. braziliensis)* complex are transmitted by sandflies of the genus *Lutzomyia* and *Psychodopygus*[1,2]. Leishmaniasis is broadly grouped into cutaneous, mucocutaneous and visceral types in line with the clinical manifestation of each infection. Cutaneous leishmaniasis is commonly caused by *L. tropica*, *L. major*, *L. aethiopica*, *L. mexicana* complex, *L. braziliensis* and *L. peruviana* while visceral leishmaniasis is caused by *L. donovani*, *L. infantum* which causes infantile visceral leishmaniasis and *L. chagasi* that causes the American type[3,4].

There have been several reports of unusual clinical presentations of cutaneous leishmaniasis which often put to test both the clinical and laboratory competence of the management teams involved. Apart from presenting as pyrexia of unknown origin with attendant difficulties in diagnosis especially in climes where the disease is barely known, and also as tuberculous granulomatous skin lesions and non infectious sarcoid lesions, the disease may as well present with features mimicking malignant tumours[5-7]. In the present era of AIDS, leishmaniasis has also been found to be proportionately on the increase where the prevalence of AIDS is also high with more of its unusual clinical features expected[8-10].

In view of the present global upsurge in the incidence of

*Corresponding author: Jombo GTA, Department of Medical Microbiology & Parasitology, College of Health Sciences, Benue State University, PMB 102119 Makurdi, Nigeria.
Tel: +2348039726398
E-mail: jombogodwin@yahoo.com

cutaneous leishmaniasis with accompanying challenging clinical features, the disease could no doubt be classified as a re-emerging disease. This study was therefore set up to review the epidemiology, laboratory diagnosis and treatment of cutaneous leishmaniasis with in-depth discussion on unusual clinical presentations of the disease from available literatures on the disease in the tropical and sub-tropical parts of the world. This is to help raise the index of suspicion among clinicians who may be confronted with its myriad of complex clinical presentations[11-13].

It is estimated that at least 14 million people globally are currently infected by Leishmania parasites in not less than 82 countries. The annual infection rate is put at 2 million while at least 350 million (5.0%) of the world's estimated 7 billion people are still at risk of acquiring leishmaniasis[14,15]. Also there are presently at least 1.5 million new cases of cutaneous leishmaniasis alone each year. The disease is common in central Asia, Middle East, Indian sub-continent, Africa especially around Ethiopia, Eritrea and Somalia, Central America and western Peru[16-18].

The classical clinical picture of cutaneous leishmaniasis is the formation of raised papules leading to formation of ulcers with clean cut margins and raised indurated edges called sores with accompanying varying degrees of immunosupression[19,20]. Post Kala-azar dermal leishmaniasis (PKDL) is caused by *L. donovani*, a causative agent of visceral leishmaniasis after about two years of treatment for the original disease. It presents as hypopigmented macules and indurations anywhere in the body especially the upper trunk[20-22].

Laboratory diagnosis of cutaneous leishmaniasis is by detection of the amastigote forms of the parasites in macrophages from material obtained by puncture of indurated edge of the sore and stained by Wright or Giemsa stains. Promastigotes of the parasites may also be recovered from Novile Nicole Mc Neil (NNN), Hockmeyer's or Schneider's insect culture media inoculated with ulcer aspirates. The leishmanin skin test based on intradermal injection of leishmanin (killed promastigotes of *L. tropica* in 0.5% phenol saline) is also sensitive and specific[24,25]. PKDL is diagnosed by microscopical examination of amastigote form of *L. donovani* by Leishman-stained smears of biopsy material from a nodular lesion[24-26]. Other diagnostic methods include: nested polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP) and other molecular methods, histology and cytology, chromatographic and immunohistochemical procedures[25,26].

Leishmania parasites respond well to several antimicrobial agents, these include: pentavelent antimonials (sodium stibogluconate, megbumine antimoniate), aromatic derivatives (pentamidine), and other drugs such as monomycin, paromomycin, amonosidine, amphotericin B and allopurinol[26].

2. Clinical presentation of cutaneous leishmaniasis

From 6 689 cases of cutaneous leishmaniasis in 778 literature reviews studied, 76.80% (5 135) presented with classical cutaneous features of papules, nodules and ulcers while 23.20% (1 554) presented with unusual features.

The less common modes of presentation of cutaneous leishmaniasis were as: pyrexia of unknown origin (PUO) 5.19% (347), Non-specific cutaneous granulomatous dermatoses 1.17% (78), cutaneous myiasis 2.16% (145), mycetoma 0.90% (64) and lymphoproliferative malignancies 0.99 (66) and post kala azar dermal leishmaniasis (PKDL) 3.09% (207) (Table 1).

The most rare presentations of cutaneous leishmaniasis encountered were peritibial ulcerations, hard painful nipple in a male, swollen upper lip, dermatofibro sarcoma protuberans, sternal proliferative growth, turban tumour, post operative granuloma and cutaneous sterile pyogranuloma with asymmetrical alopecia 0.00% each (1-2) (Table 1).

Other unusual presentations of cutaneous leishmaniasis were chalazion-like 0.14% (10), infected sebaceous cysts 0.47% (32), syphilis 0.19% (13), yaws 0.13% (9), thrombotic ulcerations 0.40% (27), multiple myeloma 0.46% (31), sarcoidosis 0.67% (17), painless nasal solitary nodule 0.00% (2), tuberculous lymphadenopathy 0.25% (11), and unilateral erythema nodosum 0.28% (19) (Table 1).

3. Unusual clinical presentations of cutaneous leishmaniasis

The most unusual clinical presentations of cutaneous leishmaniasis presently documented are: peritibial ulcerations, hard painful nipple in a male, swollen upper lip, dermatofibro sarcoma protuberans, sternal proliferative growth, turban tumour, post operative granuloma and cutaneous sterile pyogranuloma with asymmetrical alopecia 0.00% (<5) each. Similarly, chalazion-like 0.00%, infected sebaceous cysts 0.47%, syphilis 0.19%, yaws 0.13%, thrombotic ulcerations 0.40%, multiple myeloma 0.46%, sarcoidosis 0.67%, painless nasal solitary nodule 0.00%, tuberculous lymphadenopathy 0.25% and unilateral erythema nodosum 0.28% were other rare clinical pictures of cutaneous leishmaniasis. This is in addition to the usual classical presentations of the disease which were found in 76.80% of cases as well as presentations as PKDL and as PUO. Fever, headache, weight loss, loss of appetite and varying haematological abnormalities were common features associated with various forms of presentation.

The association of symptoms such as fever, headache, weight loss and loss of appetite may delay or make diagnosis of the disease difficult especially in most tropical and subtropical regions of the world where several other infectious diseases such as malaria, typhoid, tuberculosis and human immunodeficiency virus (HIV) are still common and often present with similar symptoms as cutaneous leishmaniasis[27-29]. The disease may become more difficult in diagnosis in isolated imported cases occasioned by easy global integration and movement, and where index of suspicion may be extremely low among the local clinicians due to its absence in some communities[30-32]. Presentations in form of PUO and PKDL which were found to be common in India and Pakistan may even be more confusing where clinical history may not link with any immediate source of the infection hence making its early and immediate diagnosis difficult[32-34].

Leishmaniasis has been found to create varying degrees of diagnostic dilemmas in different parts of the world: in Canada, leishmaniasis was found to present as cutaneous myiasis caused by *Dermatobia hominis*[34]; in Tunisia, erythema nodosum was the presenting feature[35]; while in Brazil, pyrexia of unknown origin (PUO) were found to be common presentations[36]. Also in USA, cutaneous leishmaniasis was found to present as sebaceous cysts

Table 1

Clinical presentations of cutaneous leishmaniasis in 778 literature reviews on 6 689 cases [*n*(%)].

Clinical presentations		Number
Usual presentations	Papules, nodules, ulcers	5 135 (76.80)
Unusual presentations [1 554(23.20)]	Pyrexia of unknown origin	347 (5.19)
	Post-Kala azar dermal leishmaniasis (PKDL)	207 (3.09)
	Unilateral erythema nodosum mimicking allergic reactions	19 (0.28)
	Non-specific cutaneous granulomatous dermatoses	78 (1.17)
	Peritibial ulcerations	1 (0.01)
	Mimicking tuberculous lymphadenopathy	17 (0.25)
	Painless nasal solitary nodule	2 (0.01)
	Asymetrical alopecia	2 (0.00)
	Mimicking cutaneous diphtheria	67 (1.00)
	Mimicking cutaneous tuberculosis	45 (0.67)
	Mimicking tropical ulcers (buruli ulcer)	32 (0.47)
	Non-specific pyodermas (caused by *Staphylococcus aureus* and β-haemolytic streptococci)	54 (0.81)
	Boggy superficial indurations	33 (0.49)
	Sarcoidosis	45 (0.67)
	Multiple myeloma	31 (0.46)
	Gauchers disease	11 (0.16)
	Lymphoproliferative malignancies(hodgkins and non-hodgkins lymphoma)	66 (0.99)
	Perisinusoidal fibrosis + intrasinusoidal megakaryocytes+ kupffer cell hypertrophy	47 (0.70)
	Chorioretinitis, uveitis	36 (0.54)
	Central retinal vein thrombosis, flame shaped retinal haemorrhages	13 (0.19)
	Papillitis, keratitis	41 (0.61)
	Chalazion-like	10 (0.14)
	Hard painful nipple in a male	1 (0.01)
	Swollen upper lip	1 (0.01)
	Thrombotic ulceration	27 (0.40)
	Yaws	9 (0.13)
	Syphilis	13 (0.19)
	Dermatofibro sarcoma protuberans	1 (0.01)
	Cutaneous + visceral leishmaniasis co-infection	29 (0.43)
	Sternal proliferative growth	17 (0.25)
	Hepatomegaly, splenomegaly, hepatosplenomegaly	83 (1.20)
	Turban tumour	1 (0.01)
	Cutaneous myiasis	145 (2.16)
	Post-operative granuloma with no leishmania	1 (0.01)
	Mycetoma	64 (0.90)
	Infected sebaceous cyst	32 (0.47)
	Cutaneous sterile pyogranuloma with asymmetrical alopecia	1 (0.01)
	Leishmaniasis of the Lid (chalazion-like, ulcerous, phagedenic, cancer-like forms, Unilateral chronic granulomatous blepharitis)	10 (0.14)
	Non-specific dermal lesions	27 (0.40)
*Constitutional symptoms [4 176(60.04)]	Fever	2 291 (54.86)
	Headache	1 558 (37.30)
	Wasting	1 875 (44.89)
	Weakness	993 (23.77)
	Cachexia	77 (1.84)
	Anorexia	685 (16.40)
	Cough	131 (3.13)
*Laborataory findings [2 779(39.96)]	Anaemia	2 344 (84.34)
	Pancytopaenia	433 (15.58)
	Elevated plasma cell count	178 (6.41)

NB: Different features reported in same patient were grouped separately.

caused by *Staphylococcus aureus* and *Streptococcus pyogenes*[37], and as boggy induration mimicking malignancy[38]; while in the Netherlands, the disease was found to mimic buruli ulcers from immigrants[39]. The presentation of leishmaniasis as chalazion in Iran[40], mycetoma in India[41], and as a post-operative granuloma in Scotland[42] all constituted varying difficulties arriving at the exact diagnosis with delays in proper management of the patients.

The main factors responsible for the delays or difficulties in arriving at the diagnosis of cutaneous leishmaniasis from the various studies were usually as a result of the presentations mimicking other diseases known for such presentations, and also the fact that, the amastigotes forms of the parasites were difficult to detect in several cases on microscopy[43-45]. In other instances of diagnostic dilemma of cutaneous leishmaniasis, genetic methods such as PCR and RFLP still failed to establish diagnosis of cutaneous leishmaniasis until therapeutic trials were commenced which turned out to be the way forward[46,47]. The fact is that in classical cases of cutaneous leishmaniasis, parasites may be detected by microscopy or histology of biopsy specimens in less than 70% of cases[48,49]. The finding of some of these cases in areas where leishmaniasis was rare or scarcely a public health issue further contributed to the difficulty in arriving at diagnosis[50-52].

In view of the present global mass or individual movement of people and the increasing transmission of leishmaniasis, the disease is no doubt re-emerging with probably no territorial or geographical boundaries. Physicians practicing in regions where the disease is unknown or rare should consider it a possible encounter at any time in the course of their practice.

Adequate facilities for laboratory diagnosis of leishmaniasis as well as that of other emerging diseases should be provided at clinics and hospitals especially in the developing world; these include histology/cytology, immunohistochemistry, polymerase chain reaction (PCR) and other genetic methods, culture and microscopy, so as to shorten the time and lighten the clinical and laboratory rigour towards arriving at definitive diagnosis. Regional governments should be sensitised towards influencing health policies so as to achieve these goals.

In patients presenting with PUO where amastigotes prove difficult to detect with all available laboratory facilities, therapeutic trial should be considered a veritable treatment option. Physicians should always be aware and conscious of this fact. Physicians may need to look, and look again when carrying out physical examination of even very familiar cutaneous lesions and accommodate as many possibilities as possible especially in the present global changes in epidemiology of diseases.

The authors wish to note that the data presented on cutaneous leishmaniasis in the present study is subject to certain variables and may not represent the most accurate up to date information on the disease. These include under-diagnosis of the disease due to probably poor infrastructure from the developing world, under-reporting from health institutions due to varying degrees of competence in data management, unwillingness or inability to publish scientific findings, and also authors' preference of specific data on the disease to present with greater clarity and accuracy in journal articles. These limitations are nevertheless well noted and should also be considered in the utilization of this piece of clinical information.

4. Conclusion

The present study has shown that cutaneous leishmaniasis, in its myriad of unusual presentations are capable of confusing the most experienced physicians. Physicians therefore, while attending to patients with simple and often common cutaneous lesions should as well broaden their thoughts to accommodate possibly both immediate and remote possibilities such as cutaneous leishmaniasis so as to forestall probable ophthalmic, medical as well as surgical pitfalls.

Conflict of interest statement

We declare that we have no conflict of interest.

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