Diffuse Cutaneous Leishmaniasis in North-western Nigeria: A Case Series

Jamila MOHAMMED MBBS, FWACP, **Sirajo H TAMBUWAL** MBBS, FMCP,[2]
Salisu A BALARABE MBBS, M.Sc., FWACP,[1] **Kabir B MUHAMMAD** MBBS, FWACP[2]

[1]Department of Medicine, Usmanu Danfodiyo University Sokoto, Nigeria.
[2]Department of Medicine, Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria.
Corresponding author: Dr Jamila Mohammed
Email: jmkamfani@gmail.com; **Phone number**: +234 8035864875

ABSTRACT

Diffuse cutaneous leishmaniasis (DCL) is a rare form of cutaneous leishmaniasis that is seen in patients with defective cell-mediated immunity to the leishmanin antigen. The condition is characterized by the presence of numerous non-ulcerated nodules and plagues, an abundance of the parasite in the skin, a negative leishmanin skin test and an absence of visceral involvement. It was first reported by Convit and Lapenta from Venezuela in 1948. It is a chronic and often severe disease that responds poorly to treatment and relapses frequently. DCL occurs as isolated cases in parts of the world where the New World leishmaniasis is endemic. We report 5 cases of DCL among patients attending a dermatology clinic at a tertiary health centre in North-western Nigeria.

Keywords; Diffuse cutaneous leishmaniasis, rare, defective cell-mediated immunity, North-western Nigeria.

ABSTRAIT

Contexte: La leishmaniose cutanée diffuse (LCD) est une forme rare de leishmaniose cutanée observée chez les patients présentant une immunité à médiation cellulaire défectueuse contre l'antigène leishmanine. L'affection est caractérisée par la présence de nombreux nodules et fléaux non ulcérés, une abondance du parasite dans la peau, un test cutané négatif à la leishmanine et une absence d'atteinte viscérale. Il a été signalé pour la première fois par Convit et Lapenta du Venezuela en 1948. Il s'agit d'une maladie chronique et souvent grave qui répond mal au traitement et rechute fréquemment. Le DCL se produit sous forme de cas isolés dans les régions du monde où la leishmaniose du Nouveau Monde est endémique. Nous signalons 5 cas de DCL parmi des patients fréquentant une clinique de dermatologie dans un centre de santé tertiaire dans le nord-ouest du Nigeria.

Mots-clés; Leishmaniose cutanée diffuse, immunité à médiation cellulaire rare et défectueuse, Nord-ouest du Nigeria.

Introduction

Leishmaniasis is a vector-borne disease caused by the obligate intracellular protozoa of the genus leishmania.[1] The disease is transmitted exclusively by the bite of an infected female phlebotomine sandfly of the genera *phlebotomus* in the Old World and *lutzomyia* in the New World.[1-3] More than 20 species of leishmania are known to be pathogenic to man, the clinical manifestation of which depends on the species' virulence and the host's immune response.[3,4] Leishmaniasis is a neglected tropical disease mainly affecting people from underdeveloped countries. An estimated 350 million are at risk of leishmaniasis worldwide and 0.7 to 1.6 million cases occur yearly.[4,5] Cutaneous leishmaniasis (CL) is the commonest form of leishmaniasis with an annual incidence of 0.7-1.2 million cases worldwide.[6] The disease mainly manifests as limited cutaneous or mucocutaneous disease.

Diffuse cutaneous leishmaniasis is a very rare and unusual manifestation of cutaneous leishmaniasis that occur in anergic patients with defective cell-mediated immunity.[1,7] This form of CL is seen as isolated cases predominantly in areas where American (New World) leishmaniasis is endemic.[1] It was first reported by Convit and Lapenta from Venezuela in 1948.[8] In the New World, the commonest cause of DCL is L.amazonensis while L.aethiopica is the commonest cause in the Old

World[7]. The disease starts as a nodule usually on a limb that rarely ulcerates.[9] After a few months to years, it spreads slowly locally and also metastasizes to distant areas like the ears, face, legs and trunk sometimes resembling lepromatous leprosy.[10] The disease may affect the mucosal surfaces and lymph nodes but does not invade the viscera.[7,9] Leishmanin skin test is negative in DCL, and histology shows intense dermal infiltration with vacuolated and parasite stuffed macrophages.[10] Treatment of DCL is often unsatisfactory and most of the patients will experience a relapse of the disease. Most reports of DCL are from The Americas and East Africa.[1,9] Although CL is proposed to be endemic in a belt running from Mauritania, Gambia and Senegal to the west, to Nigeria and Cameroon to the east, there are very few reports of DCL from Senegal, Mali and Burkina Faso in West Africa.[1,7,11,12] Furthermore, DCL is rarely reported from Nigeria. We, therefore, report 5 cases of DCL among patients attending dermatology clinic at a tertiary health centre in North-western Nigeria to sensitize us of the possibility of this rare manifestation of CL that may be easily missed.

Case Series

Case 1

The first case is a 37-year-old male civil servant with HIV infection diagnosed about 6 years prior and with a CD4 count of 53 cells/ul. He presented with painless nodular rashes and plaques involving the hands, forearms, arms, face, lower limbs and ear lobes. He subsequently developed progressive hoarseness of voice. There was no history of cough or difficulty in breathing. Flexible laryngoscopy revealed asymmetry of arytenoids and reduced mobility. About 4 months later, he developed conjunctivitis with photophobia, excessive lacrimation and poor vision. Ocular examination showed bilateral keratitis, anterior uveitis and secondary glaucoma.

Laboratory investigations were done which included a full blood count, liver and renal function profiles, hepatitis B surface antigen, anti-hepatitis C antibody, abdominal ultrasound scan and chest radiograph and were essentially normal.

The patient was diagnosed clinically to have Lepromatous Leprosy with Type II Lepra reaction and commenced on anti-leprosy multi-drug therapy with no improvement. A skin biopsy was done and histopathology of nodules revealed atrophic epidermis, expanded dermis with loose sheets of macrophages and cytoplasm containing basophilic Donovan bodies. A diagnosis of Diffuse Cutaneous Leishmaniasis was made.

He was placed on oral Itraconazole 200 mg twice for 28 days following which some of the lesions regressed in size. His vision continued to deteriorate, and hoarseness of voice improved but did not resolve completely.

The patient had first-line antiretroviral therapy (TDF/3TC/EFZ) failure and deteriorated clinically and died.

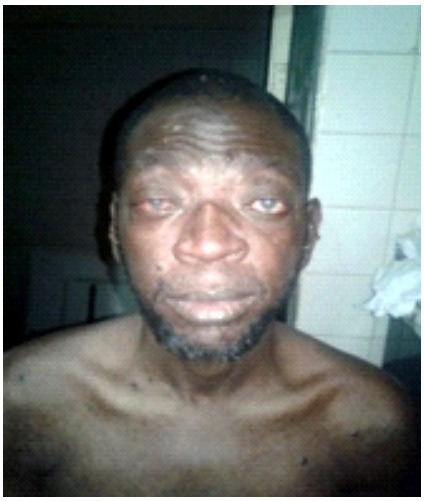

Fig 1: Conjunctivitis/corneal haziness

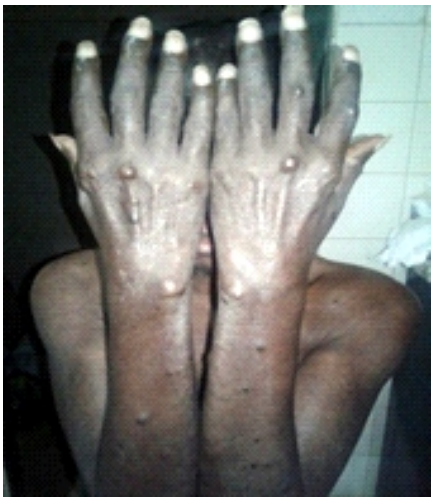

Fig 2: Nodules on hands

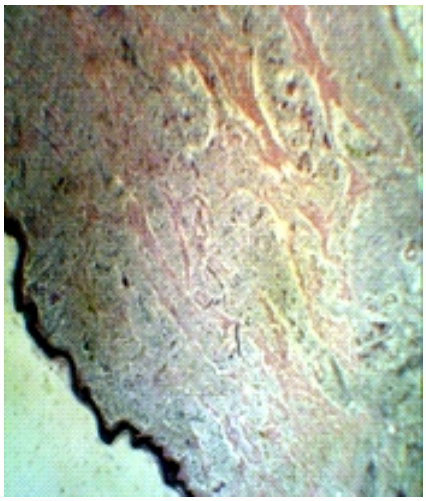

Fig 3: Atrophy of epidermis/ Donovan bodies in the dermis

Case 2

A 48-year-old woman who was diagnosed with HIV infection about 3 years ago with an initial CD4 count of 24 cells/ul presented with a 1-year history of nodular rashes on the hands, forearms, face and ear lobes. Three months later she developed progressive hoarseness of voice. There was no history of a cough or fever, no hepatosplenomegaly and no history of skin ulcers. There was an associated difficulty in swallowing both solid and liquid substances. Examination of the oral mucosa revealed widespread nodules on the pharynx and palatal tonsils. A diagnosis of Kaposi's sarcoma was entertained, but biopsy of the cutaneous nodules showed stratified squamous keratinized epidermis overlying a fibro-collagenous dermis within which were numerous granulomata consisting of lymphocytes, plasma cells and numerous histiocytes containing Leishman-Donovan bodies. She received oral Itraconazole 200mg twice daily for 28 days with no improvement in her symptoms. She achieved sustained HIV viral load suppression on anti-retroviral medications TDF/3TC/ATZ/r but was however lost to follow up.

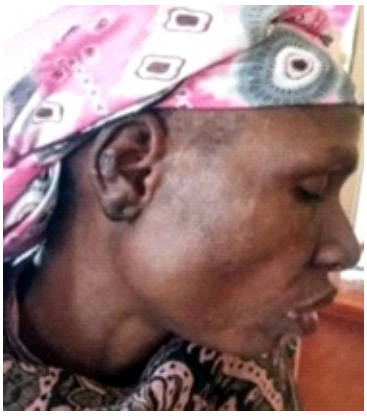

Fig. 4: Nodules on the ear

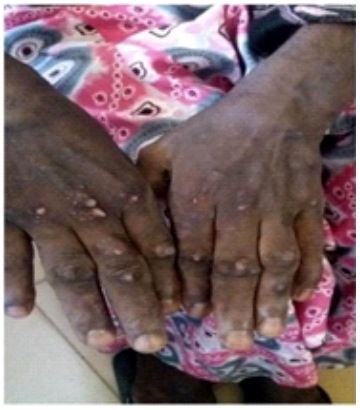

Fig. 5: Nodules on hands

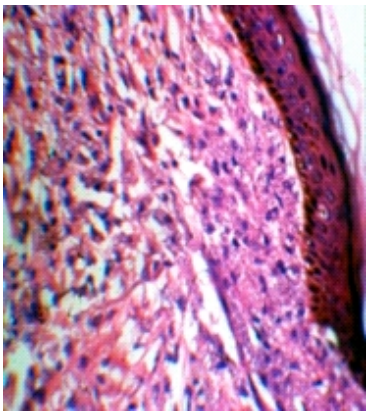

Fig. 6: Donovan bodies in dermis

Case 3

A 25-year-old man who was diagnosed HIV positive about 7 months before presentation with an initial CD4 count of 81 cells/ul presented with 4 months history of widespread nodular rashes on the face, hands, back and trunk with more predisposition to the extensor areas. These lesions were preceded by a single ulcer on the left upper arm that was clinically diagnosed to be cutaneous leishmaniasis.

Biopsy of the lesions reveal macrophages with Leishman-Donovan bodies. The patient was placed on oral Itraconazole 200mg twice daily for 4 weeks without any improvement. The patient failed first-line antiretroviral therapy, was switched to second-line but succumbed and died.

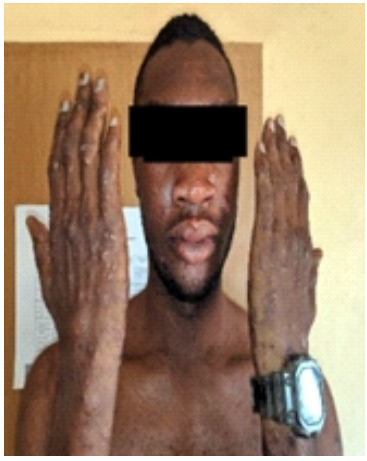

Fig. 7: Nodules on hands, face & lips

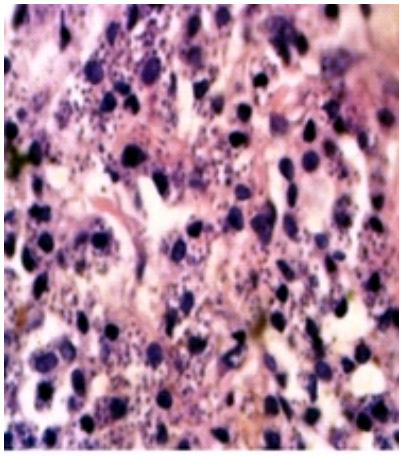

Fig. 8: Macrophages containing Donovan bodies

Case 4

A 22-year-old lady presenting with 13 years history of itchy generalised nodules/plaques. The problem started with a single ulcerated plaque on the abdomen that progressed to involve other parts of the body and face including the ear lobes. Subsequently, the patient developed scaling of the scalp, palms and soles. There were no features to suggest the affectation of other systems. A diagnosis of cutaneous lymphoma was initially entertained. The full blood count was essentially normal except for eosinophilia, retroviral screening was non-reactive, liver and renal function tests were essentially normal. Skin biopsy histopathology showed acanthosis, infiltration of the dermis with multiple granulomas consisting of histiocytes, plasma cells and multiple Leishman-Donovan bodies. She was admitted and placed on IV amphotericin B 30mg daily for four weeks. She was discharged home on tabs fluconazole 200 mg b.d, tabs dapsone 100mg daily and tab levocetirizine 10 mg daily. There was an initial improvement but a few weeks later, she represented with worsening of her symptoms and associated lacrimation and haziness of the conjunctiva but no affectation of buccal mucosa and no dysphagia. Fluconazole was increased to 400mg b.d and rifampicin was added at a dose of 600mg daily without any further improvement.

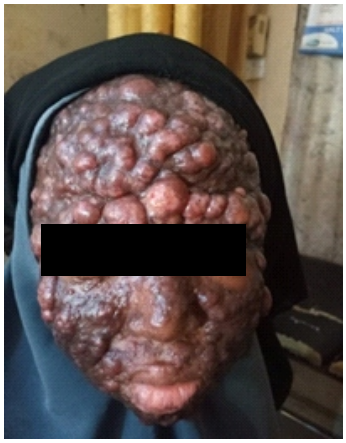

Fig. 9: Nodules and plaques on the face, corneal haziness

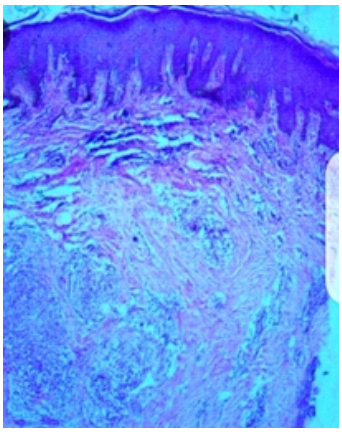

Fig. 10: Acanthosis, granulomas containing Donovan bodies

Case 5

A 25-year-old housewife, known HIV patient for 1 year with a CD4 count of 27 cells presenting with 2 months history of itchy hyperpigmented papules, nodules and crusted plaques on the face, upper chest, back and upper limbs. There was an associated cough that was productive of whitish mucoid sputum and weight loss, no haemoptysis or drenching night sweats. Initial diagnosis of cryptococcosis was entertained. However, serum cryptococcal antigen (CrAg) was non-reactive and the chest radiograph was essentially normal. Full blood count parameters showed anaemia and leucopenia while skin biopsy histology showed atrophy of the epidermis with an expansion in the dermis containing numerous Leishman- Donovan bodies.

The patient was admitted and placed on intravenous amphotericin B 30mg daily for 4 weeks with significant improvement in her clinical status. She was discharged on oral fluconazole 200mg daily for 2 weeks. However, she complained of an eruption of new rashes in the previous scars 2 weeks later. The dose of fluconazole was increased to 400mg twice daily and 100mg of dapsone daily was added with some improvement but she was subsequently lost to follow up.

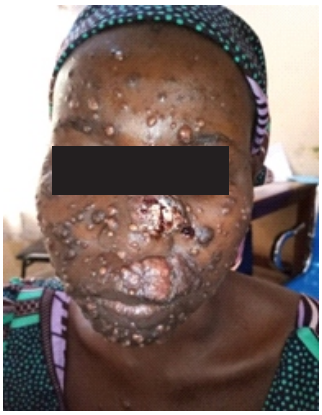

Fig. 11: Papules, nodules, plaques on the face at presentation

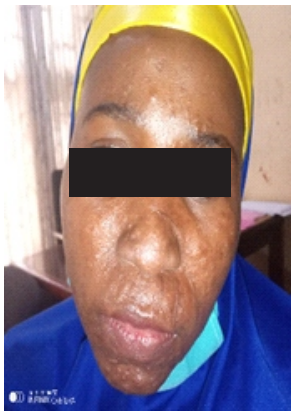

Fig. 12: 4 weeks later

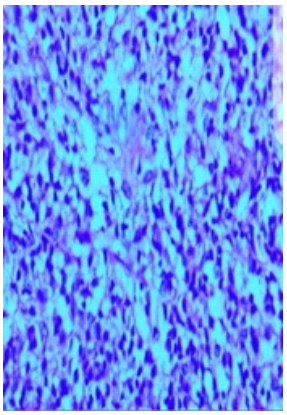

Fig. 13: Donovan bodies in the dermis

Table 1: Summary of Patient's Demographism and Clinical Profile

No	Age	Gender	Duration	HIV status	CD4	Type of lesions	Area of body affected	Mucosal affectation	Histology
1	37	M	6 months	+ve	53	Non-ulcerated papules, nodule, plaques	Ears, face, limbs, upper trunk	Keratitis, Uveitis, conjuctivitis, glaucoma, asymmetry of aretenoids	Atrophic epidermis, expanded dermis with loose sheets of macrophages with clear cytoplasm containing basophilic Donovan bodies
2	48	F	1 year	+ve	24	Non-ulcerated nodule/plaques	Upper limbs, ears, face	Nodule on tonsils / pharynx)	A fibro collagenous dermis within which are numerous granulomata consisting of lymphocytes, plasma cells and numerous histiocytes containing Leishman Donovan bodies.
3	25	M	4 months	+ve	81	Non-ulcerated papules nodules/plagues	Face, lips, upper limbs, trunk	Nil	Normal epidermis, however, there is diffuse infiltration of the dermis with numerous macrophages containing Leishman-Donovan bodies
4	22	F	13 years	-ve	-	Nodules & plaques	Generalised	Nil	Acanthosis, infiltration of the dermis by multiple granulomas containing, lymphocytes, histiocytes and plasma cells containing multiple Leishman-Donovan bodies
5	25	F	2 months	+ve	27	Crusted papules, nodules & plaques	Face, upper trunk, upper limbs	Nil	Atrophic epidermis, infiltration of the dermis with numerous macrophages Donovan bodies.

Discussion

Diffuse cutaneous leishmaniasis is a rare manifestation of leishmaniasis that is seen in patients who are anergic to leishmania antigen due to defective cell-mediated immunity. This leads to the progression and dissemination of localized disease via tissue, blood and lymph.[1,13] The disease is commoner where American leishmaniasis is endemic. However, because of the increasing prevalence of HIV-AIDS in Africa and other parts of the world, migration and urbanization, cases of DCL have been reported outside the Americas.[1,7,11,12] Leishmaniasis-HIV co-infection is associated with Th2 response especially in those with low CD4 count.[14] Activation of Th2 response results in the production of interleukin 4(IL-4), IL-5, IL-10 and transforming growth factor β(TGFβ). These cytokines are associated with impaired phagocytosis, intracellular killing and chemotaxis by macrophages and cytotoxic T cells leading to uncontrolled parasite growth.[15] It is therefore not surprising that four of our five patients are HIV positive with a CD4 count of <200copies/ml Similarly, many pieces of literature on the clinical course of HIV-CL coinfection have shown atypical and severe manifestation.[16]

Clinically, DCL presents with multiple nodules and plaques on exposed areas of the body which may or may not ulcerate. Lesions are seen on the face, ears, extremities, buttocks and sometimes mucous membranes.[13] All our patients presented with non-ulcerated papules, nodules and plaques predominantly on the face, extremities and upper trunk. In one of the patients, the rashes were generalized with scaling of the scalp, palms and soles. This patient had the lesions for more than 13 years which may be responsible for the extensive nature of the disease in her. Two of the patients had papules and nodules on the pinna and auricle. Similar findings have been reported from Ecuador and Ethiopia.[1,] Three patients had mucosal involvement: two had nodules on the pharynx and palatal tonsils while the other one had asymmetry of the arytenoids with reduced mobility, conjunctivitis, photophobia, poor vision, excessive lacrimation, bilateral keratitis, anterior uveitis and secondary glaucoma. Mucosal affectation has been reported to be more common in disseminated cutaneous leishmaniasis (where up to 50% of cases may have mucosal involvement) compared to mucocutaneous leishmaniasis.[9] Bruno et al reported a similar case of nodules on the palate of a patient with DCL from Mexico.[17] Ocular involvement is very rare in leishmaniasis.[19] However, it may occur in the setting of contiguous spread from eyelid margin or dissemination of cutaneous lesion in an immunocompromised host like our index patient.[18] Cases of blepharoconjunctivitis and dacryocystitis have been reported.[18] Additionally, Gonjito et al isolated L.braziliansis in aqueous humour and vitreous body of a patient with CL.[19]

Histology of most of our patients showed expansion of the dermis and infiltration by macrophages containing Leishman-Donovan bodies and a few lymphocytes. This is in keeping with what reports from other parts of the world.[1,9] However, histology of 2 of the patients showed granulomata made up of lymphocytes, plasma cells and histiocytes containing Leishman-Donovan bodies. This may be as a result of improvement in the patient's immune status following commencement of ARVs while the other one is HIV negative.

Treatment of DCL is often not satisfactory and most of the patients relapse after therapy.[1,9] Due to the non- availability of the first-line drugs in this part of the world and coupled with financial constraints, our patients were placed on antifungals, dapsone and antihistamines without much improvement. Two of the patients that received intravenous amphotericin B deoxycholate improved initially but later relapsed.

Limitations

This study is limited because of the small number of patients involved, our inability to isolate the species of leishmania in these patients as well as carry out Leishmanin skin tests.

Conclusion

Diffuse cutaneous leishmaniasis is present in the north-western part of the country. This study also showed that the condition is commoner among HIV positive patients with low CD4 counts and mucosal affectation is common in patients with DCL.

Histologically, infiltration of the dermis with numerous macrophages containing Leishman-Donovan bodies and absence of granuloma formation are the predominant features of DCL.

Recommendations

1. The government, World Health Organization and other stakeholders should pay more emphasis on the prevention of neglected tropical diseases like leishmaniasis
2. Procurement of first-line drugs for the treatment of leishmaniasis by the government
3. Early detection and treatment of cutaneous leishmaniasis
4. Health education on preventive measures of cutaneous leishmaniasis
5. Effective management of HIV infection to improve their immune status and avoid dissemination of a localized disease

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