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Case Report

Atypical Presentation of Post-Kala Azar Dermal Leishmaniasis in Bhutan

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1. Abstract

This article describes an atypical case of post-kala azar dermal leishmaniasis associated with complications due to delayed diagnosis and poor case management. The grave consequences of the prolonged disease process, which included facial disfigurement, visual impairment and distress both to the patient and the family with increased the risk of infection spread in the community are elaborated.

Bhutan is a member of the leishmaniasis elimination network in Asia and the government continues to invest in maintenance of the national healthcare system. The case study highlights the gaps in the healthcare system with hardships faced by a patient to access quality healthcare and poor patient outcome used as proxy indicators. It also point towards the key challenges faced by a resource poor nation like Bhutan in achieving universal health coverage and reaching the set goals for disease elimination unless the national health care system is carefully reviewed and deficiencies are adequately addressed.

2. Key words

Leishmania donovani; Skin lesions; Neglected tropical disease; Indian subcontinent; Asia; Kala azar elimination; Cutaneous leishmaniasis

3. Introduction

Bhutan plans to achieve Universal Health Coverage (UHC) early [1] and to eliminate leishmaniasis by 2020. However, leishmaniasis surveys have not been conducted since 2006 [2]. Therefore, the existing VL incidence data [3] are unreliable and are based on clinical suspicion while the actual cases may go unrecorded due to the dearth of healthcare professionals. The causative agent of VL in Bhutan is *Leishmania donovani*, closely related to the Indian subtype with several *Phlebotomus* spp. identified as probable vector(s) [4].

This article reports the first case of Post-Kala Azar Dermal Leishmaniasis (PKDL) from Bhutan with an atypical presentation. Its complex nature, prolonged history and resultant complications underscore the need for careful review of the healthcare delivery system in Bhutan, with a focus on successful control of Neglected Tropical Diseases (NTDs). This case adds to the evidence that leishmaniasis, unless diagnosed early and treated effectively may result in considerable debility and devastating socio-economic consequences and therefore, poses as a formidable challenge to achieve UHC in Bhutan.

4. Methodology

Patient consent was sought as per study protocol and ethics approval granted by Research Ethic Board of Health, Bhutan. We collected information through review of medical records, laboratory reports and prescriptions maintained since 1999 and patient and family member interviews.

5. Case Description

We present the case of a 37-year-old female, a mother of three children from the eastern part of Bhutan, seen by a dermatologist in 2014 at Jigmi Dorji Wangchuck National Referral Hospital (JDWNRH). The patient presented with extensive erythematous plaques on forehead, central face, peri-oral, cheeks that extended

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to both ears (Figure 1a). The left eye was damaged and marked swelling was observed of the right eye-lid with lid scarring and lagophthalmos. There were plaques extending to the nasal mucosa without intra-oral involvement. Other skin and system examinations were apparently normal. Blood investigations showed hemoglobin of 11.7 g/dl, total leukocyte count of 6390 mm^3; lymphocyte 28%, monocyte 4%, neutrophil 62%, eosinophils 5%, platelet count 191,000 mm^3. ESR 39 mm/1st hour, SGOT 35 units/L, SGPT 68 units/L, serum bilirubin 1mg/dl, urea 21mg/dl, creatinine 0.8mg/dl, fasting blood sugar 80mg/dl. Tests for HIV, hepatitis B and C and syphilis were negative. Chest radiograph, ECG and ultrasound scan of abdomen were normal. Slit-Skin Smear (SSS) stained with Giemsa showed numerous Leishman-Donovan (LD) bodies. Kala azar dip stick test (rk-39) was positive. Skin biopsy was done, which showed granulomatous inflammation with predominant infiltration of lymphocytes, a few histiocytes and LD bodies (Figure 2).

She was treated with Sodium Stibogluconate (SSG) 20mg/kg/day, intra-muscularly on alternate days; total 28 doses. Her lesions markedly improved but with residual scarring (Figure 1b). She again presented in 2017 with new dermal plaques over old healed lesions (Figure 1c). Both SSS and skin biopsy were positive for LD bodies. She responded to liposomal amphotericin B injections 2mg/kg/day for 28 days.

Her clinical history dated back to February 1999, when she presented at a medical clinic with fever, weight loss and anemia. She was 4 months pregnant, had low hemoglobin (6.5mg/dl), total leukocyte count of 3500 mm^3, with 57% Polymorphs and 43% lymphocytes, ESR 43mm/1st hour and elevated liver enzymes. Aldehyde test was positive. Ultrasound scan of abdomen showed hepatomegaly. Bone marrow aspirate report was unavailable. She was diagnosed as VL and treated with SSG injections 850mg/day for 20 days with 4 units of blood transfused. Her condition improved. Seven months later, erythematous lesions appeared on her forehead that spread over the face. In 2002 a dermatologist saw her with papules and plaques over cheeks, peri-orbital and peri-oral areas that were suspected as chronic dermatitis or cutaneous lupus erythematosus. She was treated with corticosteroids topical therapy initially but subsequently given intra-lesionally and orally. In 2007 she was seen by a WHO-consultant for kala azar who suspected PKDL. By this time, she had lid edema with left corneal scarring. Aldehyde test was positive and ultrasound scan of abdomen was normal. She was again treated with SSG 850mg/day for 20 days. Her lesions improved only transiently. Skin biopsies in 2006, 2010 and 2013 failed to confirm leishmaniasis, therefore, no firm diagnosis was recorded. Her eye lesions progressed with the development of Phthisis bulbi on left side with swelling and scarring of the right eye lid.

She again visited the JDWNRH for follow-up in February 2019. New plaques were seen on the nostrils and chin with marked perioral scarring limiting the mouth movements (Figure 1d). SSS was negative for *Leishmania* parasites and skin biopsy showed dense granulomatous inflammation in dermis with lymphocytes, histiocytes and multi nucleated giant cells with histiocytes containing small particles suggestive of LD bodies. PKDL was diagnosed and oral miltefosine 100mg/day was started but reduced to 50 mg/day after a month due to severe nausea and elevated liver enzymes (transaminases). Treatment continued with the reduced dosage for further 2 months with clinical improvement (Figure 1e) and no major side effects.

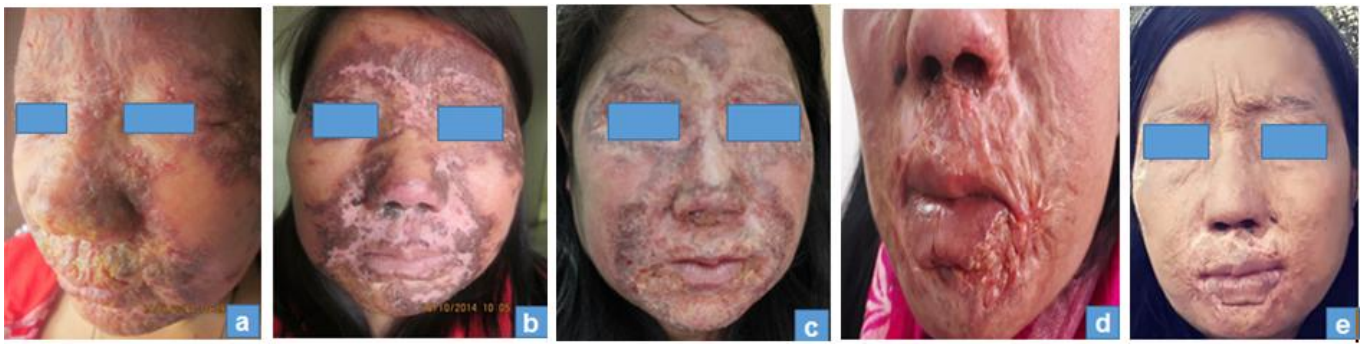

Figure 1: a) First presentation in 2014 with erythematous plaques with crusting and loss of left eye
b) Marked improvement in 2014 after 28 doses of sodium stibogluconate (SSG)
c) 2017, reappearance of plaques over old healed areas
d) 2019, relapsed and diagnosed (and subsequently treated) as post-kala azar dermal leishmaniasis
e) 2019, after treatment with miltefosine.

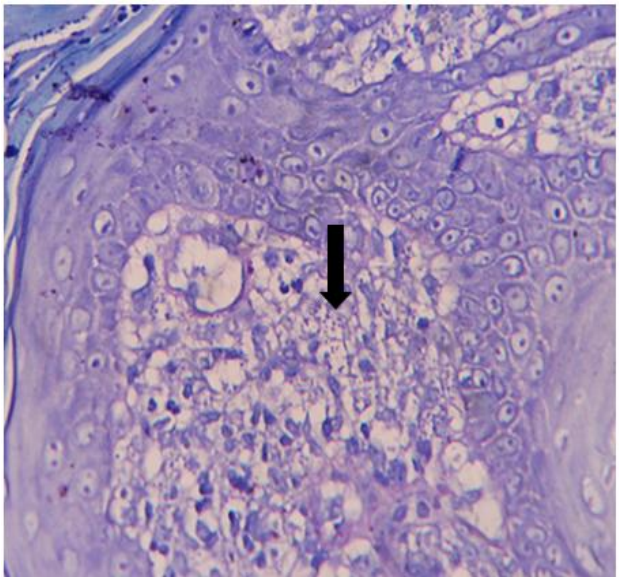

Figure 2: Microscopic image (X1000) of punch biopsy tissue section stained with hematoxylin and eosin (H and E). Arrow points to Leishman-Donovan parasite bodies

6. Socio-Economic Aspects

The patient lives with her children and parents in a remote village of Kalapang. Her husband is a cook and lives away from home in another district. The family lives by subsistence farming. A narrow walking path leads to the village. Residents walk for 4-5 hours to reach the nearest town to hire a taxi to reach Mongar, where the eastern regional referral hospital is located. It takes a further two day-bus rides to reach Thimphu, the capital city to access services of the dermatologist. Over a period of 20 years (1999 to 2019), she has visited multiple health centers incurring a considerable cost that the family could barely afford. Chronic and debilitating form of disease has had devastating impact on her and her family in terms of economic, social stigmatization and isolation.

7. Discussion

PKDL that manifests as painless macular and/or papulo-nodular skin lesions may be a rich source of parasites, promoting transmission. Therefore, early patient management with appropriate drugs is critical to contain the infection spread [5]. Its pathophysiology is obscure and associated risk factors remain debatable [6, 7]. As per records 10-20% in the Indian subcontinent [6, 8] and almost 50% in Sudan are affected [9] months to years after apparent drug-cure of VL or as a sequel of asymptomatic infections [6]. Mucosal involvement rarely occurs [10-12]. Blephero-conjuctivitis and uveitis as sequelae are known with organisms demonstrated in extra/intra ocular and adnexal muscles [13]. Associated eye inflammation may have grave consequences (aptly demonstrated through this case study). Diagnosis of PKDL is based on clinical picture and epidemiological pattern as confirmation through parasite isolation has low sensitivity [14] nevertheless can be improved with the use of molecular techniques [6]. Serological diagnosis (rk39 or ELISA) though useful to detect exposure to infection, the interpretation of its results may be difficult due to post-VL persistence of antibodies. Availability of effective treatment options in endemic areas remains important to minimize both the resultant morbidity due to PKDL and the risk of further community spread. The latter is due its potential to act as a reservoir for VL and trigger the emergence of infection in non-endemic areas or its re-emergence in areas that have successfully eliminated the disease. PKDL is, therefore, of considerable public health significance in the region [15].

8. Conclusion

This case portrays the challenges faced by patients and clinicians in PKDL management, particularly in resource-poor settings where the disease is generally prevalent. It highlights areas that need attention within the healthcare system, including the need for national-level guidelines for leishmaniasis treatment and more effective disease-awareness programs for public as well as healthcare personnel. Active case detection studies to assess the true burden of leishmaniasis (including PKDL) will also help to understand the magnitude of the problem. The apparent hurdles to achieve UHC in Bhutan highlight the need for remodeling of services based on primary healthcare principles to ensure equality in access to quality healthcare.

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