

PKDL Development after Combination Treatment with Miltefosine and Paromomycin in a Case of Visceral Leishmaniasis: First Ever Case Report

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Received Date: Jan 29, 2018; Accepted Date: Feb 12, 2018; Published Date: Feb 21, 2018

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Citation: Pandey K, Goyal V, Das VNR, Verma N, Rijal S, et al. (2018) PKDL Development after Combination Treatment with Miltefosine and Paromomycin in a Case of Visceral Leishmaniasis: First Ever Case Report. J Med Microbiol Immunol Res 2:1.

Abstract

We report for the first time the occurrence of post kala-azar dermal leishmaniasis (PKDL) after successful treatment of visceral leishmaniasis (VL) with a combination of miltefosine and paromomycin. This 10-year-old male patient from Bihar, India developed maculopapular lesions on the face and trunk one year after successful treatment of VL. PKDL was confirmed by parasitological diagnosis (slit skin smear) of skin lesions for *Leishmania donovani*. He was treated with amphotericin B deoxycholate injections for PKDL and recovered completely.

Keywords: Post kala-azar dermal leishmaniasis; Visceral leishmaniasis; Miltefosine; Paromomycin

Background

Post kala-azar dermal leishmaniasis (PKDL) is a skin disease which occurs following the treatment of visceral leishmaniasis (VL) caused by *Leishmania donovani*. PKDL usually develops within 6 months of VL treatment in Sudan, and between 2 months and several years in India [1]. A small proportion of PKDL cases develop without any past history of visceral leishmaniasis. PKDL presents with skin lesions which are macules (hypo-pigmented patches), papules, and nodules, or a combination of these, known as polymorphic skin lesions [1]. PKDL is a disease of major public health importance post-VL, as it is thought that PKDL could be a reservoir of *L. donovani*

infection and hence transmit to the sand fly vector. PKDL usually occurs after treatment of VL, which explains the higher number of PKDL cases where the number of treated VL cases is high. However, cases have also been reported without a documented history of VL in 10-23% of patients [2].

Ethics Statement

Consent was obtained from the guardian of the patient for investigation and treatment of PKDL and publication of the case report.

Case Report

A 10-year-old male with a past history of visceral leishmaniasis presented to the outpatient department of Chapra District Hospital, Bihar, in May 2014 with hypopigmented lesions. PKDL was suspected, and he was referred to Rajendra Memorial Research Institute of Medical Sciences (RMRI), a specialized referral institute for visceral leishmaniasis, for confirmation of diagnosis. He had multiple maculopapular lesions on the face and trunk, and these lesions were non-anesthetic to touch and pain. On palpation, the ulnar and common peroneal nerves were not thickened thus ruling out leprosy. He reported to have suffered from VL in February 2013 and was treated with a combination therapy of paromomycin injection (11 mg/kg for 10 days IM) and miltefosine capsules (2.5 mg/kg body weight, 50 mg capsule orally B.D. for 10 days) at Chapra District hospital, Bihar. He had become afebrile after completion of VL treatment and was followed-up after 6 and 12 months, at which points he had no symptoms of relapse. He did not suffer from any other complaints such as fever or weakness. The rapid diagnostic

test rk39 gave a positive result, as expected from a former VL case, meanwhile routine haematology and biochemistry tests were within the normal range. Microscopy of skin snip smear on Giemsa staining demonstrated Leishman-Donovani (LD) bodies confirming PKDL. He was treated with amphotericin B deoxycholate (1 mg/kg I.V. infusion in 5% dextrose, 15 injections on alternate days) and needed 3 courses at 15 day intervals for complete disappearance of lesions. Skin snip after 3 courses was negative for LD bodies. He was followed up at 12 and 24 months, and has remained symptom free with no recurrence of skin lesions.

Discussion

As has already been stated, PKDL may prove to be a reservoir of VL, thereby causing new epidemics [3]. The vector is the same as that for VL, i.e. the female phlebotomine sandfly, *Phlebotomus argentipes*. As per the Kala-azar Elimination Program (KAEP), there should be less than 1 case/10,000 population at the sub-district level. Most of the Indian states appear to be moving in this direction, with early detection, diagnosis and complete case management of VL cases. The number of cases has come down considerably, even in Bihar which contributes to about 70-80% of the total number of Indian cases. However, PKDL is not properly included in this program, as both diagnosis and management of the disease is very challenging. Besides, the lack of trained clinicians, dermatologists and pathologists compounds this pre-existing problem. These aspects of PKDL, in addition to its pathophysiology, have to be taken into consideration at this juncture, particularly when we are knocking at the door of VL elimination. PKDL occurs in the same areas which are known to be endemic for leprosy and so clinical examination has to be very meticulous. History of previous VL, or its treatment, and intact sensation over the lesions, along with non-enlargement of the peripheral nerves such as the ulnar or common peroneal and great auricular, virtually rule out leprosy. Further confirmation can be obtained by histopathological differentiation by skin snip/smear, which will demonstrate acid-fast bacilli in leprosy and LD bodies in PKDL. Electromyography (EMG) and nerve conduction velocity (NCV) can help in the confirmation of leprosy by showing signs of peripheral neuropathy, like wrist or foot drop, sensory loss or tingling, and slowing of nerve conduction velocity.

A trained clinician and a dermatologist can rule out leprosy, as well as other common fungal infections such as pityriasis versicolor for the macular form of PKDL, and additionally autoimmune disorders such as psoriasis or vitiligo. Histopathological diagnosis can be made by skin snip or biopsy of the lesion and demonstration of LD bodies. PCR, including real time PCR from the skin lesions, can prove to be a very useful diagnostic tool for confirmation of PKDL. However, it requires trained personal, a well-equipped laboratory, and is costly. Serological tests in the blood, such as rk39 RDT, may be used for screening; it is not clear whether antibodies may persist from previous VL or indicate the diagnosis of PKDL [2]. Even sputum and urine have been found to report positive in VL cases [4,5]. PKDL has been found to occur after VL

treatment with SAG, amphotericin B, liposomal amphotericin B, miltefosine, and paromomycin when given as monotherapy treatment [6-9]. The Indian national program revised its treatment policy in August 2014 and combination regimens are now considered as an alternative treatment option for the management of cases of VL in India [10]. This is the first case to be reported in which PKDL occurred after treatment of VL with paromomycin and miltefosine combination therapy.

As per the National Vector Borne Disease Control Programme (NVBDCP), the first line of treatment strategy for PKDL is 12 weeks of miltefosine. Other treatment options include amphotericin B (1 mg/kg, 3-4 courses with 20 injections on alternate days) and liposomal amphotericin B (5 mg/kg, twice weekly for 3 weeks). In this case, since miltefosine was used for VL treatment previously, we used amphotericin B for PKDL treatment. The patient responded well to treatment and was completely cured.

At present, we have no treatment for VL that can prevent progression to PKDL. Therefore, it is important to investigate the relationship between the various VL treatments and the incidence of PKDL. Furthermore, treatment options using existing drugs for PKDL have to be broadened and future combination therapies based on new chemical entities (NCEs) need to be developed.

Conclusion

In conclusion, it is clear that measuring the burden of PKDL, the rates of PKDL according to the drug used in the VL episode, and mapping all PKDL cases and getting them treated is important for the control of VL, especially in terms of achieving the KAEP target in the Indian sub-continent.

Acknowledgements

We express our gratitude to the patient who participated in the case report and to his family, without whom this case report would not have been possible.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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