Para-kala-azar dermal Leishmaniasis cases in Indian subcontinent – A case series

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Introduction

Leishmaniasis is a vector-borne disease caused by approximately 20 species of genus leishmania and is transmitted by female phlebotomine sand flies. Transmission may be anthroponotic or zooponotic. In India transmission is anthroponotic. Leishmaniasis is a major public health problem in tropical, subtropical, temperate, and Mediterranean region, the living area of sand fly. Leishmaniasis occurs over 98 countries and more than 1.5 million cases occur annually, of which 0.7–1.2 million are cutaneous leishmaniasis and 0.2–0.4 millions are visceral leishmaniasis (VL). More than 350 million people are at risk, with an overall prevalence of 12 million.[1] Leishmaniasis occurs in three forms, VL (lethal inflammation of liver and spleen), destructive mucocutaneous leishmaniasis, and cutaneous leishmaniasis of skin where it heals spontaneously.[2] In India the parasite *Leishmania donovani* is responsible for VL as well as post-kala-azar dermal leishmaniasis (PKDL).[3] Both the diseases have different clinical manifestation; in VL, patients experience fever, hepato-splenomegaly, weight loss, weakness, and pancytopenia, whereas PKDL appears in the skin as macular, papular, and nodular lesions or combination of these. PKDL is a stigmatizing disease having significant socioeconomic burden and almost no mortality as compared to VL. It is prevalent in two endemic zones, namely South Asia (India, Nepal, and Bangladesh) and East Africa, mainly Sudan.[4] PKDL develop in 50% cases in Sudan and 5–10% cases in India after treatment of VL. Time interval of PKDL development after VL is 0–6 month in Sudan and 2–3 years or more in India. In India 15–20% cases have no history of VL. Nandy et.al study has shown that active cases of VL develop after successful treatment of PKDL.[5] In Sudan PKDL heals spontaneously and does not need treatment except in chronic cases of more than 6 months to one year duration. In India patients need treatment, as PKDL serves as reservoir for VL. So eradication of PKDL is very important to bring down the annual incidence of VL. In India VL occurs among the poorest of poor people from the rural community and the co-association of active VL in PKDL patients may further impoverish them and increase the health care burden. The simultaneous occurrence of PKDL in active VL patients is also known as para-kala-azar dermal leishmaniasis(para-KDL).[6] Co-association of active VL in PKDL patient was reported in East Africa, but In Indian subcontinent it was rarely reported.[6] A case of co-association of VL and PKDL was found in a patient who relapsed with miltefosine in Bihar, India.[7] Another case of para-kala-azar dermal leishmaniasis was reported by Shamim et.al. 2013 in Bangladesh[8]; however, detailed clinico-epidemiological profile and treatment of this case was unknown. Here in this study, we are reporting a series of nine such cases with detailed clinico-epidemiological profile along with its management. The increasing number of such cases, especially when we are knocking at the door of kala-azar elimination demands special attention to understand the various clinical and epidemiological aspects to cope up in future.

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Case summary

Here, we are presenting a series of nine cases; who were residents of Bihar, India. The details of clinical features,

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Table 1 The clinical features, diagnosis, and treatment outcome of cases

Case	Age (year)	Sex	P/H VL	Past Treatment history	Fever	Spleen size (cm)	Liver size (cm)	Lesion Type	Diagnostic method			Treatment outcome*
									BMA/SA	Skin smear	rK39	
1	25	F	No	_	Yes	1	1	M, P	BM+ 4ve	+ 3ve	+ ve	Cured
2	20	M	Yes	SAG	Yes	1	1	M,P	BM+ 4ve	+ 2ve	+ ve	Cured
3	14	M	No	_	Yes	6	2	M	BM+ 3ve	+ 2ve	+ ve	Cured
4	50	M	Yes	Mil.	Yes	4	1	M	BM+ 2ve	+ 4ve	+ ve	Cured
5	36	M	Yes	SAG	Yes	5	2	M	SA+ 4ve	+ 1ve	+ ve	Cured
6	40	M	Yes	Mil.	Yes	8	4	M,P,N	SA+ 3ve	+ 2ve	+ ve	Cured
7	15	M	No	_	Yes	5	1	M	SA+ 3ve	+ 1ve	+ ve	Cured
8	18	F	No	_	Yes	14	1	M	SA+ 4ve	+ 1ve	+ ve	Cured
9	25	F	yes	SAG	Yes	10	2	M,P	SA+1ve	+ 4ve	+ ve	Cured

Notes: BMA: Bone marrow aspiration, SA: Splenic aspiration, P/H: Past history, VL: Visceral Leishmaniasis, PKDL: Post-kala-azar dermal leishmaniasis, SAG: Sodium antimony gluconate, SDA: Single-dose AmBisome, Mil.: Miltefosine PS: Parasitic score, M: Macular, P: Papular, N: Nodular, M: Male, F: Female.

*Each case was first treated for VL with single-dose AmBisome (10 mg/kg) and followed by Miltefosine (2.5 mg/kg/daily) 50 mg twice a day for 12 weeks for PKDL.

Table 2 Clinical, biochemical, and hematological parameters of all the nine patients before, one-month follow-up and after treatment

Parameter	Mean (SD) value		
	Baseline value	One-month follow-up (Post-VL treatment with SDA)	End of treatment
Body Temperature (°F)	100.3(1.79)	97.65(0.44)	97.66(0.49)
Weight (kg)	41(1.17)	43.11(1.14)	44.55(1.04)
Spleen (cm below left costal margin)	6(4.2)	2.1(3.14)	1(0.86)
Liver (cm below right costal margin)	1.6(1)	0.33(0.50)	0.33(0.55)
Hemoglobin (g/dl)	8.35(2.43)	9.4(1.89)	10.2(1.17)
WBC (Per micro-liter)	2811(1.49)	5831(9.15)	5170(1.07)
Neutrophil (% of leucocytes)	32.11(9.18)	40.78(6.32)	61.66(8.30)
Lymphocyte (% of leucocytes)	60.22(9.39)	53(4.840)	37(7.35)
Eosinophil (% of leucocytes)	3.22(3.56)	2.66(2.18)	1.33(1.22)
Platelet (per micro-liter)	1.24(3.46)	1.81(4.40)	2.20(6.85)
Albumin (g/dl)	3.72(0.17)	3.84(0.19)	3.91(0.105)
Globulin (g/dl)	3.63(0.20)	3.38(0.21)	3.13(0.17)
Serum Creatinine (mg/dl)	1.05(0.30)	0.94(0.21)	0.88(0.08)
Serum Urea (mg/dl)	26(3.74)	24(3.31)	25.33(3.53)
Serum total bilirubin (mg/dl)	0.96(0.17)	0.85(0.07)	0.78(0.10)
Aspartate amino transferase (U/liter)	1.16(1.32)	39.5(1.27)	34.55(4.24)
Alanine amino transferase (U/liter)	85.66(7.95)	40.11(1.21)	36.55(1.04)
Serum NA^+ (mmol/liter)	138(3.85)	139(2)	139(1.09)
Serum K^+ (mmol/liter)	3.95(0.23)	3.63(0.22)	3.67(0.14)
Parasitic score(skin smear)	2.2(1.2)	1.2(0.44)	0
Parasitic score(SA/BMA)	3.1(1.05)	0	0
Prothrombin time (patient value)	14.4(1.7)	13 (1.1)	12.5 (1.1)
Result of HIV	Negative	Negative	Negative
HBsAg	Negative	Negative	Negative
HCV	Negative	Negative	Negative

Notes: SA: Splenic aspiration, BMA: Bone marrow aspiration
SDA: Single-dose AmBisome(10 mg/kg)
End of treatment was the completion of 12 weeks courses of Miltefosine for PKDL.

diagnosis, and treatment outcome are depicted in Table 1. All the cases were admitted in Rajendra Memorial Research Institute and Medical Sciences, Patna, India and treated with single-dose AmBisome (10 mg/kg) for VL. At one-month follow-up signs and symptoms of VL subsided and splenic/bone marrow aspiration demonstrated the absence of Leishmania Donovani (LD) bodies for all the patients, however, skin lesions persisted. Parasitic evaluation of skin snip examination revealed the presence of LD bodies in all patients; though parasitic score decreased as compared to baseline values (parasitic score was done by the procedure developed previously by Bryceson and Chulay[22]). All of them were treated with miltefosine 50 mg twice a day for 12 weeks for PKDL. Upon treatment completion all the cases were cured clinically as well as parasitologically. The detailed clinical, biochemical, and hematological parameters of all the cases at various stage of treatment are shown in Table 2. Written informed consent was taken from all the patients.

Discussion

The etiopathogenesis of PKDL is limited and unexplained. How the viscerotropic parasite becomes dermatotropic and manifests as PKDL is controversial. But immunological

hypothesis is considered by most researchers.[6,9] In PKDL mixed Th1 and Th2 responses are activated, whereas in VL, Th2 alone plays a role.[10,11] Th2 response is characterized by strong humoral response with high antibody titer, leishmanial skin test (LST) remains negative and there is absence of cellular response. Th1 usually shows cellular immune response and LST positive. After cure from VL Th1 immune response are involved. During VL cytokine profile shows high level of IL10 but after recovery interferon gamma level is predominant.[12] But in the immunocompromised patient restoration of immune system is immunopathological and causes immune restoration disease. Immune reconstitution syndrome after antiretroviral therapy in HIV patients is most common.[13–15] It is clear that VL and PKDL have different etiopathogenesis but how VL and PKDL developed simultaneously needs to be explored. Diagnosis of VL, mainly by splenic/bone marrow aspiration is considered as gold standard. Splenic aspiration is more sensitive (85–90%) as compared to bone marrow aspiration (50–60%)[16]. However, these days PCR/rt-PCR with splenic aspiration can be more sensitive and specific. Similarly, the diagnosis of PKDL is also tedious and requires the services of trained pathologist and dermatologist. LD bodies demonstration in the skin snip is very low in macular(about 30–40%), whereas it is higher in papular and nodular lesions (60–70% or higher).[17] Therefore, PCR/rt-PCR (qPCR and immunohistological analysis) can be very helpful for macular lesions. However, these require expensive equipment, well-equipped laboratory, trained personnel, and cannot be done in the field conditions.

A case of VL associated with PKDL was reported by Rabi Das et.al, where the patient was treated with Amhotericin B for both the episodes (VL & PKDL).[7] A similar case was reported from Kenya, where sitamaquine was used at a dose of 2 mg/kg body weight for 28 days.[21]

However, in our study all the cases have received treatment for VL and PKDL separately. As VL is more fatal than PKDL, VL was treated earlier than PKDL. A study by Mandal et al. reported that single-dose AmBisome is safe and effective (cure rate 98%) in the treatment of VL. Owing to its convenient single-dose administration, high compliance compound with excellent efficacy and low toxicity profile National Vector-Borne Disease Control Program/World Health Organization (NVBDCP/WHO) has adopted this drug as a first-line choice for kala-azar. Hence, we have used single-dose AmBisome for the treatment of VL. After one month of VL treatment, we started miltefosine for PKDL as per the recommendation of NVBDCP/WHO.

VL associated with PKDL is rare and limited to some specific geographical areas. According to some reports active VL in PKDL was rarely reported in the Indian subcontinent, but it was reported in East Africa.[6,18] How the PKDL developed from VL after treatment or without treatment in asymptomatic carriers is not clear. Due to unknown reasons parasite resides in fibroblast or keratinocytes during latent period after treatment of VL, but when reactivated becomes PKDL.[19] Survival of parasite in PKDL is longer than VL hence, PKDL cases needs higher dose and prolonged treatment. The previous treatment guidelines for PKDL included SAG at 10 mg/kg for 90–120 injections intramuscularly. This is very long and has numerous side effects like cardiotoxicity and arthritis. The present treatment guideline includes miltefosine in the dose of 2.5 mg/kg/day or 100 mg/day for 12 weeks. The other alternative treatment is with amphotericin B in the dose of 1 mg/kg in 5% dextrose IV, on alternate days for 20 injections in 3–4 courses at 15-day intervals. This treatment regimen is very lengthy, requires prolonged hospitalization, and has severe side effects including nephrotoxicity and hypokalemia. With regards to VL elimination program, PKDL is not addressed well in the program. There are very few drugs used for the treatment of PKDL as per National Vector-Borne Disease Control Program (NVBDCP). Further combination studies are needed so that the treatment duration is shortened with high efficacy and safety, similar to VL where Paromomycin and Miltefosine of 10 days duration was found highly effective, safe, and affordable with 98.7% efficacy.[20] In our study all para-KDL patients had mixed clinic-pathological pictures different from VL or PKDL alone. These patients presented with history of fever for few weeks to months, constitutional symptoms like loss of appetite, weight loss, weakness, maculopapular or macular skin lesions, hepatomegaly, splenomegaly, and pancytopenia. Skin lesions in our all para-KDL cases were of three types macular, papular, and nodular or mixture of these. Macular lesions were predominant in most of the patients either in isolation or in combination with papular or nodular lesions. Lesions most commonly appeared around the mouth and spreading to other part of face, upper arm, chest, back, and thigh. All the patients were rK39 positive and none of them was immunocompromised (negative for HIV, HBsAg, anti-HCV, and absence of tuberculosis). Diagnosis of VL was confirmed by demonstration of LD bodies in bone marrow/splenic aspirate and PKDL by presence of LD bodies in skin smear in the same patient. There is no specific treatment guideline available currently for co-association of active VL in PKDL. There were few more unpublished cases with VL and PKDL diagnosed simultaneously, however, after one month of receiving AmBisome therapy for VL, skin smear demonstrated absence of parasites but lesions persisted (mainly macular). How these patients can be managed is a question of future research. These patients are at high risk of relapse to either VL or PKDL. In East Africa, usually these cases do not require treatment till severe disfigurement and self-healing. Treatment is needed if this persists for more than 6 months to 1 year.

Conclusion

Increasing burden of active VL in PKDL cannot be neglected. More attention is required to understand the

clinico-pathological, diagnosis, and treatment aspects of these emerging cases of para-kala-azar dermal leishmaniasis. This in turn can be helpful for elimination of VL from the Indian sub-continent as well as future eradication. This case series will further guide clinicians/dermatologists in recognizing and treating these combinations of diseases.

Disclosure statement

No potential conflict of interest was reported by the authors.

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