Original Article

Rising visceral leishmaniasis in Holy Himalayas (Uttarakhand, India) – A cross-sectional hospital-based study

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Abstract

Background: Apart from the rarity of the visceral leishmaniasis (VL) cases in high altitude (>2000 ft), the combination triad of VL, hemophagocytic lymphohistiocytosis (HLH) syndrome, and Himalayas is rarely being reported. Here, we studied the triad in the Himalayan region, attending a single tertiary care hospital over a period of 2 years. **Methods:** The study was a cross-sectional analysis of case records of seven confirmed VL patients. A systematic master chart review analyzed the demographic, clinical, laboratory, treatment, and outcome details of these patients. **Results:** These cases were diagnosed as VL by clinical findings and confirmed by rk-39 anti-body and demonstration of LD bodies in bone marrow smears. All cases without any travel history to endemic regions presented with prolonged fever (>1 months duration), anorexia, weight loss, and having hepatosplenomegaly and bi-or pan-cytopenia. All cases were having HLH, confirmed based on the HScore system (online calculation), and liver injury having transaminitis. Kidney involvement was seen in 27% cases. All cases improved with liposomal amphotericin-B, but one had cardiac arrest after blood transfusion reaction. **Conclusion:** Clinician of the non-endemic zone should suspect VL in patients with fever of unknown origin and have a high suspicion in cases of HLH and liver involvement and vice versa. Kidney involvement is seen in one-third of the VL cases. Liposomal amphotericin-B is recommended in this region. The leishmaniasis prevalent in these areas should further be subject to comparison with endemic parts, and a large-scale study is needed to find the reason of the rising vector from the holy Himalayas.

Keywords: Endemicity, Hemophagocytic lymphohistiocytosis (HLH) syndrome, High altitude, Kala-azar, LD bodies, Liver injury

Introduction

Visceral leishmaniasis (VL), a systemic parasitic vector borne disease, is prevalent in low-altitude areas having river belts attributing to preferential habitat of its vector, i.e. sand fly. It does rarely occur in altitudes over 2000 ft (600 m).[1] However, in the last quarter of the twentieth century, migration of disease has been noticed and new niches being reported from previous non-endemic regions. One of them is across the Himalayas (Southern) from Pakistan to Bhutan through India. Considering Uttarakhand Himalayas of India, sporadic cases have been reported from the natives of Himalayan region such as Kumaon (350–900 m above mean sea level) and Garhwal (1500–2500 m above mean sea level) region.[2,3] This phenomenon of migrations of the disease from Indian endemic locality such as Bihar and West Bangel towards the hilly regions of Himalayas points towards the new endemicity of the disease.

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The disease pattern of this region also varies slightly from rest of the world as documented in the few published case reports/series. Almost all cases present as VL rather than cutaneous leishmaniasis, and the common association of VL and hemophagocytic lympho-histiocytosis (HLH) syndrome is being found.[4] HLH-associated VL is more malignant and difficult to diagnose as features of both overlap and lead to delayed treatment. Both require aggressive and early treatment for better outcomes in terms of morbidity and mortality.

This needs a study to know the demography and clinical details of VL patients in this so-called non-endemic area. Thereby, we do a cross-sectional hospital-based study of all adult VL cases who are coming from Uttarakhand state of India and admitted in our hospital (General Medicine Department) during the last two years.

Materials and Methods

This cross-sectional study was conducted during July 2017 to June 2019 in a referral 1000-bedded tertiary health center in Rishikesh, located in the base of Uttarakhand (state full of Himalayas), India.

Case records of all patients (n = 10) with VL (confirmed diagnosis), admitted to the Department of General Medicine of the hospital in the last two years, were scrutinized. Seven patients were included in the study after the inclusion criteria of Uttarakhand residential address.

The demographic, clinical, laboratory, treatment, and outcome details of all seven patients were entered in a systematic master chart excel. HLH was diagnosed based on diagnostic criteria and HScore calculated by online software *http://saintantoine.aphp.fr/score* predicted the percentage of possibility of HLH [Table 1].[5,6] Diagnosis of acute kidney injury (AKI) was made based on the KDIGO definition. Either or both hyperbilirubinemia (total bilirubin >2.5 mg/dL) and transaminase elevation (more than twice the upper limit of normal) were used to classify as acute liver injury (ALI) after excluding the prior history of liver diseases.

Results

During the last two years, we found seven cases of VL proven by rk-39 (point of care test for leishmaniasis) and later confirmed by bone marrow examination. Majority of them (except few having atypical features) presented with prolonged (>1 months) high-grade fever with chills, rigors, malaise, anorexia, and unintentional weight loss without the history of any localizing symptoms [Table 2]. None of them gave any history of IV drug abuse, exposure to STDs, or travel to endemic region of VL (within a period of 1 year). Most of them had pancytopenia and hepato-splenomegaly.

Other local causes of prolonged fever like malaria, enteric fever, scrub typhus, tuberculosis, HIV, HCV, and HBV were ruled out except case 7 that had HBsAg positive. Bone marrow examinations showed LD bodies confirming VL [Table 3]. During further evaluation, serum ferritin and triglyceride were found to be raised, so possibility of HLH syndrome was suspected and HScore calculated. All had >90% probability of HLH (secondary to VL). However, NK cell activity and sCD25 level could not be done due to unavailability. Final diagnosis of VL with secondary HLH was considered. All cases except one improved after treatment with either plain amphotericin-B (never alone) and or liposomal amphotericin-B depending upon affordability and preferences. Positive response was considered to have informed of absence of fever, decrease in spleen size, and improving hematological parameters. All were discharged on due course and doing well on follow up except one who died during hospital course.

Few atypical findings were observed. All cases had liver involvement in the form of transaminitis and three had jaundice. Two cases had anasarca and kidney injury. One had gastrointestinal manifestation. Although case 6 had been diagnosed as VL 4- 5 months before by haematology department, but she deferred treatment and after 2 months she presented with intermittent bleeding lips and progressive anasarca. She developed transfusion reaction after the transfusion of packed RBC with acute lung injury and suddenly went to irreversible cardiac arrest.

Discussion

The present study focuses on cases, presenting as fever of unknown origin (FUO) from hilly regions of Southern Indian Himalayas, and later on unexpectedly proven to be VL. These cases were native of Uttarakhand (mainly areas near the river belts, especially Ganga), neither visited to endemic zone nor having any contacts with people of that zone except case 3 and 7 having h/o contact with Bengali and Bihari laborers, suggesting the possibility of expansion of endemicity [Figure 1]. All cases were proven to have HLH (>95% chance based on Hscore) and liver involvement. Hence, expansion of disease territory and variation in disease manifestations are more concern.

Previous case reports of VL from different regions of Uttarakhand are mainly distributed along the banks of river Ganges [Table 4].[2,3,7-12] But there is lack of data and research regarding whether the parasite and its vector have developed as a new species in these areas or introduced de novo by migrant population. Although the latter appears more likely, as one study suggests the possibility of ecological changes causing an environmental shift in favor of vector proliferation, due to the development of Tehri dam reservoir and migration of laborers from endemic areas.[3] Also, the possibility of the upstream move of sandflies along the Ganges from endemic zone cannot be excluded as has been suspected in our study in the map. Each primary care physicians should consider this possibility now in this non-endemic region.

Table 1: HLH diagnostic criteria and online software version to predict HLH[5,6]

At least five of the following eight findings required for diagnosis:	Following points are considered in online score calculation:
Fever ≥38.5°C	Known underlying immunodepression
Splenomegaly	Yes
Peripheral blood cytopenia, with at least two of the following:	No
Hemoglobin <9 g/dl (for infants <4 weeks, haemoglobin <10 g/dl for others)	Maximal Temperature (C)
Platelets <100,000/microL	Unknown
Absolute neutrophil count <1000/microL	Less than 38.4 C
Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or	38.4-39.4 C
hypofibrinogenemia (fibrinogen <150 mg/dL)	>39.4 C
Hemophagocytosis in bone marrow, spleen, lymph node, or liver	Hepatomegaly
Low or absent NK cell activity	Unknown
Ferritin >500 ng/mL (>3000 ng/mL as more indicative of HLH)	Yes
Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations	No
above age-adjusted laboratory-specific norms	Splenomegaly
	Unknown
	Yes
	No
	Lower Hemoglobin level
	Unknown
	Less than equal to 9.2 gm/dl
	More than 9.2 gm/dl
	Lower Leucocytes count
	Unknown
	Less than equal to 5000
	More than 5000
	Lower Platelets count
	Unknown
	Less than equal to 11,000
	More than11,000
	Higher Ferritin level (ng/ml)
	Unknown
	Less than equal to 2000
	Between 2000 to 6000
	More than 6000
	Higher Triglyceride level (mmol/L)
	Unknown
	Less than 1.5
	Between 1.5 and 4
	More than 1.5
	Lower Fibrinogen level (g/L)
	Unknown
	Less than or equal to 2.5
	More than 2.5
	Higher SGOT/AST level (U/L)
	Unknown
	Less than 30
	More than or equal to 30
	Hemophagocytosis features on bone marrow aspirate
	Unknown
	Yes
	No

Clinical presentation of cases varies compared to endemic cases. For example, most of the cases till now, reported from this area, are of VL rather than cutaneous leishmaniasis similar to our study. Liver function derangement is infrequent in VL although the parasite primarily infects the reticuloendothelial system and hepatomegaly is common. In previous Indian studies, biochemical evidence of hepatitis was found in 25%, 17%, and 51% of VL patients, respectively.[13,14] In our study, 43% had direct hyperbilirubinemia, 70% had hypoalbuminemia, and all had transaminitis (100%), although none had evidence of other causes of hepatitis except case 7 having positive HBsAg. This 100% liver involvement could be a part of HLH since all of our cases had the same. This supports HLH goes hand in hand with VL in this region.

VL is one of the major infective causes of HLH. The clinical picture of both is often overlapping and bone marrow may fail to reveal LD bodies. Consequently, VL might be missed and intense immunosuppression for HLH without specific antimicrobial therapy may be administered with disastrous

Table 2: Clinical characteristics of seven cases of visceral leishmaniasis

case	Age/sex	Occupation	Height from sea level (ft)	Duration of illness	Symptoms and signs other than fever, anorexia, and weight loss	Treatment	Outcome
1	28/male	Auto driver	4436	1 month	Pallor Hepatosplenomegaly B/L pleural Effusion Ascites	Liposomal amphotericin B (10 mg/kg single dose)	Improved
2	40/female	Housewife	5740	6 months	Jaundice Hepatosplenomegaly B/L pitting leg edema B/L pleural Effusion Ascites	Started with plain amphotericin B, but because of anaphylactoid reaction, switched to liposomal, with dose 10 mg/kg	Improved
3	26 y/male	Mason Contact with co-worker coming from West-Bengal	1030	4 ½ months	Pallor Dragging sensation in left upper abdomen Massive splenomegaly Hepatomegaly	Liposomal amphotericin B (10 mg/kg single dose)	Improved
4	35/male	Labourer	1030	First illness - 4 months Relapse - 1 week	Loose stool Recurrent vomiting Massive splenomegaly	First episode - plain amphotericin B (1 mg/kg, 14 days) Second episode - Liposomal amphotericin B (10 mg/kg - single dose) and 14 days course of plain amphotericin B	Improved
5	61/male	Retired postman	5413	3 months	Pallor Jaundice Hepatosplenomegaly Breathlessness	Liposomal amphotericin B (10 mg/kg single dose)	Improved
6	34y/female	Housewife	3000	5-6 months	Bleeding lips Epistaxis Breathlessness Jaundice Pallor B/L pitting leg edema	Liposomal amphotericin B (3 mg/kg/day for 5 days and then on day 14 and 21)	Improving trend, but during second blood transfusion developed breathlessness and irreversible cardiac arrest
7	45/male	Labour Contact with co-worker coming from Bihar	1030	4-5 months	Pallor Hepatosplenomegaly	Liposomal amphotericin B (10 mg/kg single dose)	Improved

consequences. Till date only few cases have been reported to have this combination.[4] In our study, all cases have strong association with HLH. If it comes true, we need aggressive approach for VL in these areas since the main treatment of secondary HLH is the treatment of primary cause. This will help all clinicians in this region to work up for HLH in the suspected cases of VL and vice versa. The common association is yet to be studied on large database so as to conclude the exact relationship and association between the two.

Kidney involvement is also unusual in VL. According to a prospective study, kidney impairment found in 11% cases of VL, but in our study, two cases (27%) had AKI (case 4 and 7).[15] We could not find out the exact cause of AKI, but case 4 had diarrhea (pre-renal AKI). We need further detail study and more data to conclude the cause. VL-associated lymphadenopathy is seen in hilly area as per one study, but our study could not establish this relationship.[16] Case no 6 had epistaxis and bleeding lips, mostly due to thrombocytopenia or deficient clotting factor as suggested by Sigdel *et al.*[17] Bilateral pleural effusion is also a very rare finding in immunocompetent VL cases and has been reported only in few cases from endemic cases.[18]

Treatment for VL and associated HLH is mainly amphotericin-B either as a single dose of liposomal one or multiple doses of plain one.[19] An efficacy of 95.7% is seen with a single-dose regimen of liposomal amphotericin B at a dose of 10 mg/kg, along with the lower toxicity and shorter duration of therapy. However, multiple doses of 18–21 mg/kg plain amphotericin-B have 90%–100% efficacy in southern Europe with many adverse effects, which necessitate close monitoring and hospitalization for 4–5 weeks, which ultimately increases the cost of therapy.

Table 3: Laboratory (initial) characteristics of seven cases diagnosed as visceral leishmaniasis

Parameters	1	2	3	4	5	6	7
Hemoglobin (gm%)	7.8	9.6	7.0	10.6	6.7	6.2	8.08
Total leukocyte count (cells/mm^3)	2500	2290	2200	1500	3000	4200	3.500
Platelets	50,000	1.2 lakh	21,000	63,000	42,000	35,000	1.23 lakh
Total bilirubin (mg/dL)	1.15	2.1	1.2	1.05	2.46	4.3	0.54
Direct bilirubin (mg/dL)	0.52	0.4	0.13	0.21	1.22	1.2	0.25
Serum albumin/globulin (mg/dL)	2.13/3.7	2.78/2.68	2.5/3.12	3.1/4.1	2.1/3.7	1.9/3.2	3.74/4.85
AST (IU)	734	385	57	65	136	98	80
ALT (IU)	651	152	245	156	412	132	116
Urea/creatinine (mg/dl)	45/0.56	40/1.12	56/0.9	51/2.36	25/0.72	46/2.3	36/0.5
Triglycerides (mg/dl)	251	219	266	239	242	342	Unknown
Serum ferritin (ng/dl)	>1650	>1650	>1650	>1650	>1650	>1650	>1650
USG - abdomen	Hepatosplenomegaly, mild bilateral pleural effusion, and ascites with subcentimetric abdominal lymphnodes	Hepatosplenomegaly, mild bilateral pleural effusion, and ascites	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly
BM findings	Leishman Donovan (LD) bodies	LD bodies and hemophagocytosis	LD bodies	LD bodies and hemophagocytosis	LD bodies and hemophagocytosis	LD bodies	LD bodies and hemophagocytosis
HScore	219/96.03%	238/96.74%	235/98.49%	225/97.23%	243/99.076%	219/96.03%	235/98.4%

Figure 1: Terrain map showing distribution of seven visceral leishmaniasis cases (in orange colored) and previous published studies (in blue colored) in Uttarakhand Himalayas and trace of river Ganga along with endemic locations (inlet, Indian map having colored states: Uttar Pradesh, Bihar, Jharkhand, and West Bengal) of leishmaniasis. Map courtesy: Terrain map scaled down from Google Map^R – modified in compliance with in-app permissions and policies

Amphotericin-B may inhibit macrophage function, cytokine expression, antigen-induced proliferation of T and B cells *in vitro*, and the function of cytotoxic T cells. Therefore, it may have exerted a dual effect on both HLH and VL in our study. All our cases respond to liposomal molecule including one case that failed from plain amphotericin-B. This suggests importance of liposomal over plain amphotericin-B, especially a note for physicians in this community.

Our study had its own set of limitations. First, this study was of small sample size and short follow up. However, in a non-endemic area, this may be significant. Second, the data collected were dependent on medical records. Third, our work is based on the characteristics of the study population, which was from a tertiary care center and most likely represents a more severe disease spectrum. Therefore, the disease prevalence might have been underestimated. Lastly, the study did not account negative diagnostic test results during the study period. Since pointers to think for VL/HLH depend upon experiences of concerned doctors of this study, good documentation quality and knowledge capacity of the doctors are to be taken care in future studies to answer this question. Findings in our study are similar to few studies done before, adding validity to the data.[20] Since this study was done in non-endemic zone for VL, the result is valid to whole Himalayas where VL may be a rising threat. This may serve as a benchmark for further epidemiological study for case detection.

In summary, in cases presenting with FUO from hilly regions of Uttarakhand, VL should be considered as one of the differentials. It is alarming that so-called non-endemic areas for VL are converting to endemic zone. The possible reason may be migration of vectors along the upstream belts of Gange. High index of suspicion of VL is to be kept in cases of HLH and vice

Table 4: Summary of published articles on leishmaniasis in Uttarakhand Himalayas[2,3,7-12]

Citations	Sample size	Location	Agent details	Host details	Vector details	Environmental factors studied	Nearby river	Authors Conclusion
Ahmad S, *et al.* 2016	33 (excludes 14 pediatric cases as below)	Garhwal region of Uttarakhand (India)	Leishmania, species not identified	CP: VL - prolonged fever, hepato-splenomegaly, pancytopenia, negative HIV status, and Hemophagocytosis. Rx: Sodium stibogluconate, both types of amphotericin-B, and miltefosine Outcome: one relapse and cured with lip amph-B. Survival of all cases except one who succumbs.	Not documented	Altitude: 1500-4000 m above sea level. The patients had never visited any of the endemic areas. Development of Tehri dam reservoir, migration of labors from Bihar and endemic areas, and the ecological changes have apparently caused an environmental shift in favor of vector proliferation	Ganges	The protozoan is de novo from Uttarakhand. However, molecular mapping is needed to confirm the ancestry.
Bhatt NK, *et al.* 2016	14	Garhwal region of Uttarakhand (India)	Leishmania, species not identified	CP: VL - prolonged fever, hepato-splenomegaly, lymphadenopathy, pancytopenia, negative HIV status, and Hemophagocytosis (HLH - 7 cases). Rx: Sodium stibogluconate Outcome: Survival of all cases except one who succumbs before starting the treatment.	Not documented	-do-	-do-	The protozoan appears to have established a local transmission cycle, although local vector and probably an animal reservoir remain elusive. Epidemiological studies are needed to identify the vector and animal reservoir if any.
Chandra H, *et al.* 2014	Seven	Different areas of Uttarakhand (India)	Leishmania, species not identified	CP: VL - fever, hepato-splenomegaly, hemophagocyticlymphohistiocytosis (HLH) syndrome. Rx: plain Amphotericin B Outcome: Survival of all cases.	Not documented	Altitude??	Ganges	In all HLH cases, leishmaniasis should be suspected. HLH diagnosis criteria may be modest while applied. VL with HLH respond well to amphotericin.
Mathur SB, *et al.* 2014	Six	Nainital (3), Champawat (1) and Pithoragarh (2) of Uttarakhand (India)	Leishmania, species not identified	CP: VL - prolonged fever, hepato-splenomegaly, pancytopenia. Rx: Liposomal (4 cases) and plain (2 cases) Amphotericin B Outcome: 5 survived and 1 death	Not documented	Altitude: 258-1760 m from sea level. Patients never traveled to or migrated from endemic areas.	Ganges	Highlight the changing geographic distribution and the need for detailed epidemiological surveys in nonendemic regions for assessing the impact of climate change and the possibility of a zoonotic reservoir of VL in India.

Contd...

Table 4: Contd...

Citations	Sample size	Location	Agent details	Host details	Vector details	Environmental factors studied	Nearby river	Authors Conclusion
Kumar A, *et al.* 2013	10	Kumaon region of Uttarakhand (India)	Leishmania, species not identified	CP: VL - fever, hepato-splenomegaly, weight loss, and pancytopenia. Rx: Intravenous sodium Stibogluconate (2, then shifted to ampho due to failure), Lip ampho-B Outcome: Survival (6 cases), lost to follow up (3), and death (1)	Not documented	-do-	Ganges	Highlights the changing geographic distribution and spread with implications for its control as a public health problem. Epidemiological work is required in this area to substantiate the presence or absence of any zoonotic reservoir.
Verma SK, *et al.* 2007	Nine	Garhwal region of Uttarakhand (India)	Leishmania, species not identified	CP: prolonged fever, hepato-splenomegaly, pancytopenia and hypergammaglobulinaemia. Rx: Sodium stibogluconate Outcome: Survival of all cases	Preponderance of Phlebotomusargentipes (77%), which is mainly confined to cattle sheds and mixed dwellings in villages	Altitude: 1500-4000 m above sea level. The patients had never visited any of the endemic areas.	Ganges	Sodium stibogluconate-sensitive VL is emerging in the non-endemic Garhwal region, India, and urgent and effective vector control measures may be warranted to prevent the disease from becoming a major health problem in this region.
Rao JS, *et al.* 2001	None	Kumaon region (Almora&Nainital) of Uttarakhand (India)	Not applicable	Not applicable	Ph. argentipes (77%), Ph. papatasi (6.9%), Ph. major (2.9%), and sergentomyia (13.2%)	-do-	Ganges	Ph. argentipes mainly confined to cattle sheds and mixed dwellings in the villages, mainly zoophilic, and highly susceptible to DDT (mortality, 98-100%).
Singh S, *et al.* 1999	Five	Kumaon region (Almora and Nainital) of Uttarakhand (India)	Leishmania, species not identified	CP: VL - fever, hepato-splenomegaly, weight loss, and pancytopenia. Rx: Intravenous sodium Stibogluconate Outcome: Survival of all cases except one death	Not documented	Altitude: 350-960 meters from sea level.	Ganges	This advices for further research into the epidemiology of vector and warns about the emerging pattern in non-endemic areas.

versa. Similarly, liver involvement is to be considered in VL/HLH cases and vice versa. Kidney involvement is seen in one-third of the VL cases. Liposomal amphotericin-B is recommended over plain one in VL cases in this region. Furthermore, VL cases should further be subject to comparison with those found in other endemic parts of India so as answer and fill the gap of knowledge about increasing prevalence and variances of VL in this region.

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Conflicts of interest

There are no conflicts of interest.

Authors' contribution

Sweety Kumari and Piyush Dhawan searched the literature, collected the data, drafted, reviewed, and approved the study. Prasan K. Panda, Mukesh Bairwa, and Venkatesh S. Pai searched the literature, drafted statistically, critically reviewed, and approved the study.

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