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Subclinical tumor lysis-like syndrome during treatment of visceral leishmaniasis with low-dose intermittent liposomal amphotericin B

Research Article

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Abstract: We retrospectively evaluated the rate of renal dysfunction during treatment with liposomal amphotericin B (L-AmB) (3-4 mg/kg, for 7-10 days) in nine consecutive patients with visceral leishmaniasis (VL). During the first week of treatment, 5 patients (56%) experienced transient deterioration of renal function, with a rise in serum creatinine to 1.27-2.44 times the baseline level, and a parallel elevation of uric acid levels without other metabolic or electrolyte disturbances. Serum renal function parameters were restored to normal levels after the completion of therapy, on day 21. These 5 patients had presented with prolonged fever and/or significant spleen enlargement, reflecting high parasite load. This observation suggests that treatment of VL with intermittent L-AmB causes a subclinical tumor lysis-like syndrome, especially in patients with high parasite load.

Keywords: *Visceral leishmaniasis • Liposomal amphotericin B • Renal function • Uric acid • Tumor lysis syndrome*

1. Introduction

Visceral leishmaniasis (VL) is an endemic disease in the tropics, subtropics, and southern Europe with a broad range of manifestations. Typically it represents a life-threatening disease with fever, cachexia, hepatosplenomegaly, pancytopenia, hypergammaglobulinaemia and hypoalbulinemia [1]. Renal dysfunction is an important feature of VL, associated with important morbidity and mortality [2]. Case reports and small case series have described renal involvement in VL appearing as glomerulonephritis and/or interstitial nephritis [3-7]. Agents with activity against VL include amphotericin B (AmB), pentavalent antimonial drugs, paromomycin and miltefosine [1].

Liposomal amphotericin B (AmBisome, L-AmB) is a lipid-associated formulation of the broad-spectrum polyene antifungal agent AmB. It was developed to improve the tolerability profile of AmB deoxycholate, which, for many decades, was considered the gold standard of antifungal treatment [8]. Despite the improved safety features, patients receiving L-AmB may still experience infusion reactions such as fever, chills and rigors and renal toxicity. A recent meta-analysis demonstrated that the probability of experiencing nephrotoxicity during treatment with daily L-AmB (doses 3-10 mg/kg) for invasive fungal infections (IFIs) in patients with hematological malignancies ranged from 2.8 to 32% [9].

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Moreover, in a recent prospective observational study, the rate of deteriorating renal function during treatment with L-AmB, among patients hospitalized in hematology and oncology wards, was 28.6% [10].

During the past decade, liposomal amphotericin B, which was the first drug approved for the treatment of VL by the U.S. Food and Drug Administration [11], has been used with increasing frequency to treat VL [12]. The aim of this study was to retrospectively evaluate the rate of renal dysfunction in all patients treated with L-AmB for VL in our centre during the last two years.

2. Material and Methods

We report a series of 9 consecutive cases of Greek-Caucasian white patients with VL admitted to Laikon General Hospital, Athens, Greece, between 2008 and 2010. The mean age was 40.4 years (range 23 to 68 years) and 5 of them were male. Typically, all of them presented with fever, cytopenias, hepatosplenomegaly, diffuse hypergammaglobulinaemia, and weight loss. Diagnosis was established based on the presence of abundant *Leishmania* parasites in bone marrow aspirate, Giemsa-stained smears in six patients, and positive PCR for the detection of the *Leishmania* genome in the peripheral blood of the remaining three patients. One patient was positive for human immunodeficiency virus infection (HIV) (A3, CDC stage) and was treated with 4 mg/kg L-AmB on days 1 to 5, 10, 17, 24, 31, and 38 for a total dose of 40mg/kg. All the remaining patients had negative prior medical history of primary or secondary immunodeficiency and were treated with L-AmB with the standard dose 3 mg/kg on days 1 to 5, 14, and 21 for a total dose of 21 mg/kg. None of them had pre-existing renal disease, reported any other co-morbidities (for example, diabetes, hypertension, peripheral vascular disease) or were concomitantly treated with nephrotoxic drugs. Specifically, all patients had normal serum blood urea nitrogen /creatinine at baseline and received pre-hydration (1 to 2 litres of isotonic saline) prior to each L-AmB infusion. Daily monitoring of blood urea nitrogen, creatinine, uric acid and electrolytes levels was performed during the first week of treatment. The study was approved by the International Review Board of the Laikon General Hospital, Athens, Greece. All participants gave their informed consent.

3. Statistical Analysis

Data were analyzed by an unpaired t-test, a x^2 test (two by two with Yates' correction) and Fisher's exact test where applicable. A two-sided P-value <0.05 was considered statistically significant.

4. Results

During the first week of treatment, 5 patients (56%) experienced transient deterioration of renal function which returned to normal levels after completion of therapy. Specifically, there was a rise in serum creatinine up to 1.27-2.44 times the baseline value, which returned to normal by the post-treatment evaluation on day 21 (Table 1). Moreover, these 5 patients showed elevation in uric acid levels above upper normal limits (an increase of more than 25% from baseline) without other metabolic or electrolytes imbalance. All five patients presented with prolonged fever (duration > 1 month), or significant spleen enlargement (>15 cm, assessed by ultrasonography), or both. By way of comparison, only one out of the four patients who had no deterioration of renal function had prolonged fever and only one had significant spleen enlargement. No other serious adverse events were reported. Moreover, two patients had microscopic hematuria and another one mild proteinuria prior to L-AmB initiation, and it was no longer present

Table 1. Patients' characteristics during treatment with intermittent low-dose, liposomal amphotericin B.

Patient	Sex	Age (years)	Creatinine (mg/dl)			Urea (mg/dl)			Uric Acid (mg/dl)			Potassium (mEq/L)			Calcium (mg/dl)			Successful treatment
			day 1	day 5	day 21	day 1	day 5	day 21	day 1	day 5	day 21	day 1	day 5	day 21	day 1	day 5	day 21	
1	Male	62	0.9	1.0	1.0	30	32	29	4.0	4.2	4.2	3.9	4.2	4.0	8.8	9.0	8.9	Yes
2	Female	25	**1.1**	**1.4**	1.05	**29**	**67**	22	**4.0**	7.7	5.0	4.3	4.2	4.1	8.6	8.6	9.1	No
3	Male	23	1.0	1.0	1.0	38	25	30	**5.5**	7.1	4.3	3.9	4.3	4.2	8.4	8.7	9.8	Yes
4	Female	50	0.5	0.6	0.5	29	23	25	3.5	4.3	2.1	4.2	4.3	3.8	8.1	7.8	8.9	Yes
5	Male	45	**0.9**	**2.2**	1.0	**29**	**82**	31	**3.7**	**8.4**	**7.0**	4.6	4.1	4.1	8.6	7.9	10.0	Yes
6	Female	38	0.6	0.7	0.7	24	41	30	**6.3**	**8.0**	**7.1**	4.2	4.2	4.0	9.6	9.1	9.1	Yes
7	Female	25	**0.8**	**1.1**	0.7	10	20	23	6.1	7.4	7.0	3.8	4.1	4.0	8.4	8.8	9.1	Yes
8	Male	68	**0.7**	**1.0**	0.8	**36**	**49**	50	**4.3**	**6.4**	**6.4**	4.3	4.1	4.6	8.0	9.3	8.6	Yes
9	Male	28	**0.8**	**1.7**	1.1	**24**	**44**	20	**3.3**	**5.4**	4.5	4.3	4.2	4.4	7.5	8.2	8.5	Yes

at the treatment re-evaluation (2 of those 3 patients presented a rise in serum creatinine level during the first week of treatment).

All study patients responded well to initial treatment and all signs and symptoms of VL resolved.

5. Discussion

In our small case series of patients with VL, a transient modest deterioration of renal function was observed frequently (56%) during the first week, following 1 or 2 doses of intermittent low dose of L-AmB; this renal dysfunction abated as patients clinically improved with therapy. Moreover, these 5 patients showed elevation in uric acid levels above upper normal limits (or more than 25% increase from baseline value). All these patients had normal renal function at baseline, were young (average age 40 years) and had received no concurrent nephrotoxic agents.

In accordance with our results, in a previous study, evaluating short-course treatment with L-AmB for VL (total dose 12-24 mg/kg) in 88 immunocompetent patients, a statistically significant rise in mean serum urea level that reached its peak at day 5, and was completely resolved by day 21 was noticed during treatment. In addition, the mean change in serum creatinine concentration on day 5 was smaller, suggesting that some of the rise in serum urea concentration was due to increased hepatic urea synthesis [13].

Interestingly, in hematological patients with invasive mold infections, a prospective randomized trial comparing a high-dose regimen (10 mg/kg per day in 94 patients with average age 50.4 years) with a standard-dose regimen (3 mg/kg per day in 107 patients with average age 50.9 years) of daily L-AmB showed that nephrotoxicity occurred at 27% in the high dose group and 10% in the low dose group, respectively [14]. Likewise, in another observational, multicentre study in hematologic patients evaluating the nephrotoxicity of various amphotericin B formulations, the rate of worsening of renal function was 28.6% in the L-AmB treated group (totally 112 patients were included with mean age 45.1 ± 15.7, and 9.8% had abnormal renal function at baseline) [10]. Patients in the L-AmB group were treated with a significantly higher total dose than the VL patients of our series (cumulative dose 3093.6 ± 3019.3 mg versus 1466 ± 509 mg, respectively). Thus, it should be noted that although in the two above studies, patients were immunocompromised, with higher mean age than our patient group, frequently receiving concomitant nephrotoxic agents (for example aminoglycosides, immunosuppressants and cytotoxic agents), and generally treated with higher total dose of daily L-AmB, the rate of deterioration of renal function was notably lower in comparison to our study group.

Because of the fact that renal deterioration was observed only in patients with high disease burden, we believe that a tumor lysis-like syndrome (TLS) could be associated with successful treatment of VL. Thus, in patients with high parasite loads, massive death of parasites and amastigote-containing mononuclear phagocytes could follow onset of treatment [15,16]. TLS is an oncologic emergency that is caused by massive tumor cell lysis with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation, after the initiation of chemotherapy for rapidly proliferating lymphoid malignancies. Catabolism of the nucleic acids to uric acid leads to hyperuricemia, and a marked increase in uric acid excretion can result in the precipitation of uric acid in the renal tubules and acute renal failure. Nevertheless, none of our patients with renal dysfunction showed laboratory evidence of hyperkalemia, hyperphosphatemia, or hypocalcemia (or 25% change from baseline for all the above parameters) although all had transient hyperuricemia or more than 25% increase from baseline uric acid value, according to the TLS Cairo-Bishop definition [17].

Of interest, in vitro studies with THP1 cells (human acute monocytic leukemia cell line) showed that L-AMB could mediate effective parasite clearance due to strong induction of free radicals and proinflammatory cytokines [18]. Moreover, other studies showed that the process of parasite apoptosis is important for successful survival of *Leishmania* spp. amastigote within the macrophages [19]. There are several reports showing that anti-leishmanial drugs, including amphotericin B, precipitate *Leishmania* apoptosis inducing caspase-like activity in both axenic amastigotes (generated in the laboratory by subjecting the promastigotes to changes in *p*H and temperature) and promastigotes of *L. donovani* and resulting in DNA fragmentation [19]. Thus, a reasonable hypothesis would be that mass *Leishmania* apoptosis after initiation of L-AmB treatment in patients with high parasite load could lead to selective renal cell injury via proinflammatory signals.

Researchers evaluated the efficacy and safety of L-AmB in the treatment of VL especially in endemic countries, with no significant reports of nephrotoxicity or other adverse events [20-23]. It should be noted however that in none of these studies were patients submitted to frequent monitoring of renal function during the initial period of treatment (i.e. first week). Therefore, as patients were usually re-evaluated 15-30 days after the completion of therapy, variations of serum urea nitrogen and creatinine levels could have not been ascertained. Similarly, all patients in our series had normal renal

function within 21 days after initiation of treatment as well (Table 1).

Although the number of our patients was too low to draw firm conclusions, our data indicate that close monitoring of renal function during the initial phase of treatment for VL may reveal a significant trend of transient deterioration of laboratory parameters in patients without intrinsic renal disease. This change is both reversible and of limited clinical significance. Although the mechanism of this phenomenon remains to be explained, a subclinical TLS-like in cases with high parasite load is suggested. Larger prospective studies with close monitoring of renal function parameters during the initial phase of VL treatment are needed to verify our observation and evaluate the potential need of allopurinol prophylaxis.

Declaration of interest

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