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Use of Liposomal Amphotericin B in Kala-Azar

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Abstract

We report a case of 23-year old male from Tangail who developed intermittent fever and blackening of skin 7 months back. He was locally diagnosed as a case of kala-azar and was treated with Cap Miltefosine 50 mg 12 hourly for 28 days. But within 4 months after completing the treatment he again developed the symptoms. Referred from the local hospital he presented to us with fever, weight loss and discoloration of skin. He was anemic and had splenomegaly. Laboratory investigations showed pancytopenia, elevated Erythrocyte Sedimentation Rate (ESR). Leishman-Donovan body was found inbone marrow biopsy. In our hospital he was treated with injection Liposomal Amphotericin B 15 mg/kg in 6 divided doses. His anemia was corrected, spleen size became normal and bone marrow aspiration showed no Leishman-Donovan body on discharge and he remained symptoms free in the outpatient department.

Introduction

In a third world country like Bangladesh disease like Visceral Leishmaniasis quite common and a matter of great concern which is very rare in western modern world. Leishmaniasis (VL), also known as Kala-azar or black fever, is a vector-borne parasitic disease [1]. In Bangladesh it is popularly known as kala-azar. It is a severe chronic disease caused by parasites of the *Leishmaniadonovani* complex. There are more than 20 leishmanial species and is transmitted to humans by ~30 different species of phlebotomine sandflies [2]. It causes a huge burden to the society in terms of morbidity, mortality and economic burden (loss of productivity and treatment cost). It becomes lethal if left untreated and affects approximately half a million new patients annually worldwide, with 60% of new cases on the Indian sub-continent [3]. WHO report on control of Leishmaniasis 2010 showed it is endemic in 98 countries or territories, with more than 350 million people at risk. The global incidence is estimated to be 2 million new cases per year (0.5 million of and Visceral Leishmaniasis l.5 million of (Cutaneous Leishmaniasis). Visceral Leishmaniasis/Kal-azar causes an estimated 50,000 deaths annually, a rate surpassed among parasitic diseases only by malaria, and 2,357,000 disability-adjusted life years lost, placing Leishmaniasis ninth in a global analysis of infectious diseases [4]. Alvar et al. described that approximately 0.2 to 0.4 million Visceral Leishmaniasis cases and 0.7 to 1.2 million Cutaneous Leishmaniasis cases occur each year. More than 90% of global Visceral Leishmaniasis cases occur in just six countries: India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia. They found case-fatality rates ranged from 1.5% (93 deaths/6224 Visceral Leishmaniasis cases from 2004–2008) in Bangladesh to 2.4% (853/34,918) in India and 6.2% (91/1477) in Nepal [5]. The history of Kala-azar in Bangladesh is quite old. Kala-azar was first described in 1824 in Jessore district of the country [6]. Epidemic peaks were recorded in the 1820s, 1860s, 1920s, and 1940s. After achieving good control of the disease during the intensive vector control efforts for malaria in the 1950s-1960s, Bangladesh experienced a Kala-azar resurgence that has lasted to the present. Surveillance data show an increasing trend in incidence since 1995. The disease is highly clustered geographically, and Mymensingh district is the most highly endemic district out of 45 affected districts in Bangladesh [7]. The patients with Kala-azar usually present with fever, asthenia, weight loss and splenomegaly. Various drugs had been used for the treatment of Kala-azar. In a review article 2008 Ahsan et al. described nearly 25 compounds are reported to have anti-leishmanial effects. The first classical drug, antimony, is already useless as a result of drug resistance [8,9]. A report by Olliaro et al. [10] in an article concluded that "unresponsiveness to antimony has developed steadily in the past to such an extent that antimony must now be replaced" [10]. The emergence of resistance led to the use of other compounds like amphotericin B, pentamidine, paromomycin, miltefosine etc [10]. In the Indian subcontinent pentavalent antimonials (sodium stibogluconate) was replaced by oral treatment with miltefosine (MIL) in 2006 [11].

Miltefosine has been recommended as the first choice of drug in Bangladesh for treatment of Kala-azar at a dose of 50-100 mg capsule (~2.5 mg/kg body weight) in two divided dose by mouth in the morning and evening after meal for 28 days [12]. Miltefosine has a median long terminal half-life of 154 h, which could encourage development of clinical resistance [10,11]. The Miltefosine has a very good efficacy in Kala-azar but it is becoming resistance day by day. In an open-label, noncomparative study on 567 patients who received oral Miltefosine, 100 mg in divided doses daily for 28 days) the researchers found the initial cure rate was 97.5% and 6 months after the end of treatment the final cure rate was 90.3% and 6.8% of the patients redevelop symptoms of Visceral Leishmaniasis (relapse) within 6 months [12]. Rijal et al. in a cohort study of 120 Kala-zar patients treated with Miltefosine in Nepal found that the initial cure rate was 95.8% and the relapse rate at 6 and 12 months was 10.8% and 20.0% respectively [13]. Another drug that have shown huge promise in the field of treatment of Kala-azar is Amphotericin B. Amphotericin B is a polyene antibiotic and it is believed to be leishmanicidal due to its capability to bind ergosterol which is a major sterol in Leishmania [14]. Amphotericin B (AmB) and its formulations are increasingly being used and are considered as the best existing drugs against Visceral Leishmaniasis [15]. This drug is showing a significant improvement in treatment of Kala-azar including in treatment of relapse and resistant cases.

Amphotericin B has excellent cure rate (~100%) at a dose of 0.75-1 mg/kg for 15-20 daily or alternate days intravenous infusions. At present, three formulations have been tested extensively in kala-azar: liposomal amphotericin B (AmBisome; Gilead Sciences), amphotericin

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B lipid complex (ABLC; Abelcet®, Enzon Pharmaceuticals) and amphotericin B cholesterol dispersion (ABCD; Amphotec™, InterMune Corp) [16]. In Bangladesh liposomal amphotericin B (Ambisome) is available through the center for disease control under the Kala-azar control program. This drug remains as the last hope for thousands of poor patients who are suffering from this disease.

Case Presentation

A 23-year-male from Ghatail of Tangail district one of the kala-azar endemic areas of Bangladesh, presented to a local hospital (Thana health complex) with a history of fever with rigor and chills, night sweats and weight loss 7 months back. He was diagnosed as a case of Kala-azaron the basis of clinical presentation and lab investigations-hematological investigations revealed pancytopenia, ICT for Kala-azar was positive. He was treated with Cap Miltefosine 50 mg 12 hourly for 28 days. His symptoms subsided. But within 4 months of completing the treatment these symptoms reappeared. Then he was referred to the outpatient department our hospital (Bangabandhu Sheikh Mujib Messdical University hospital) and was admitted on 01-12-11. The fever was high grade, intermittent associated with chills and rigor and subsided by taking Paracetamol, the fever was not associated with evening rise or night sweating. His highest recorded temperature was 103° F. He complained about anorexia and lost about 6 kg weight in the last 4 months. His skin became darker. He remained in low mood in most of times most of the days, did not like to talk with others, the onset of his sleep was delayed with early awakening for the last 1 month. He was frustrated about his future and began to think it would be better if he died. In his personal life he was a married rickshaw puller who lived in a house made of mud in a rural area in a joint family. He was nonsmoker and there was no history of substance abuse. He did not have any history of blood transfusion or contact with tuberculosis patient. He had dry, rough, dark skin. He was anemic but not icteric. Abdominal examination revealed spleenomegaly which was 6 cm from left costal margin towards its right axis, firm in consistency, non-tender. There was noother organomegaly, spider nevi, palmar erythema or gynecomastia or palpable lymphnode. On mental state examination his mood and affect was depressed, volume and rate of speech was low, hallucination and delusion was absent, suicidal idea was present but there was no specific plan. Initial laboratory investigations showed pancytopenia (Haemoglobin-8.9 gram/deciliter), erythrocyte sedimentation rate- 120 mm in the first hour, peripheral blood film showed significant rouleaux formation. Alkaline phosphate and lactate dehydrogenase were high. Serum createnine was 1.6 milligram/deciliter and serum albumin was 26 gram/Liter. Examination of the bone marrow aspiration revealed presence of amastigote form of Leishmaniadonovani.

After confirming the diagnosis of Kala-azarthe patient was treated with Liposomal Amphotrecin B. Patient's weight was 40 kg and we decided to give him 2.5 mg/kg/day (100 mg/dose) 1 to 5th day and 14th day intravenously so he got total 15 mg/kg. His tolerance of amphotericin was excellent with no significant changes in his kidney and liver functions. After the therapy his general feeling of well-being increased, easy fatigability reduced, his food intake and sleep increased, the discoloration of skin gradually disappeared. On mental state examination before the day of discharge his mood was euthymic, speech was normal and there was no suicidal idea. There was also evidence of gradual weight gain. His spleen size reduced at the time of discharged it was just palpable. Laboratory investigation revealed- hemoglobin level became normal pancytopenia corrected, erythrocyte sedimentation rate came to 20 mm in the first hour. Serum creatininewas 1.4 milligram/deciliter, serum albumin increased to 34 gram/liter. Examination of the bone marrow aspiration on discharge revealed suggestive of secondary reactive marrow and Leishman-Donovan was absent. He was follow up in outpatient department and during the 9 months follow up he remained symptoms free his weight increased from 40 kg to 48 kg.

Discussion

Kala-azar is one of the chronic infectious diseases that are affecting the poor rural population in the endemic areas of Bangladesh. Many drug had been used and some of them now no more in use like Antimonis. Cap Miltefosine is one of the first line drugs in the treatment of kala-azar in Bangladesh [17]. But the relapse of Kala-azar with Miltefosine in this patient is matter of great concern for the Kala-azar treatment and its eradication program of the country. In this institution this was first reported case of Miltefosine resistance as far the knowledge of the researchers. The treatment with liposomal Amphotericin B for relapse case of Kala-azar with Miltefosine is quite new. The patient was poor so we had to collect this from government source. The drug is available in Bangladesh through the government chain free of cost under the National Kala-azar program. But the collection of the drug is troublesome procedure. The drug is so costly that most of the people are not able to afford this drug. In a study in Bangladesh in 2004 found that the median direct cost of health care for 1 patient with Kala-azar totaled 80% of the yearly per capita income, representing a catastrophic economic burden for affected households [18].

Another important aspect of this case was the features of depression. Chronic medical illness is consistently associated with an increased prevalence of depressive symptoms and disorders [19,20]. When we explore his mental condition we found that he met the criteria of depression due to general medical condition according to DSM-V [21]. Though he improved without any antidepressant after liposomal amphotericin B we are not sure whether the drug contains any antidepressant property or not? No pair review article was found during our search the quest of finding the answer of this question? How many people of Kala-azar are suffering from comorbid depression in Bangladesh and what is the effect of depression on the course of Kala-azar? We hope future researchers will find out the answer of these questions.

Recommendation and Conclusion

We recommend a complete mental state examination for all patients suffering from chronic medical illness including Kala-azar. The experience of the case safe and effective use of liposomal amphotericin B without any adverse effect will encourage the further use this drug in Bangladesh.

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