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CASE REPORTS

UNRESPONSIVENESS TO MILTEFOSINE IN VISCERAL LEISHMANIASIS (VL) - AN EXPERIENCE OF SEVEN CASES

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Introduction:

Visceral Leishmaniasis (VL) is prevalent in more than 80 countries in Asia, Africa(Leishmania Donovani),Southern Europe(L.infantum) and South America(L.chagasi).[1] L.donovani is the main causative parasite for VL and worldwide 5,00,000 new cases of VL(Kala-azar) occur in five countries of the world namely India,Sudan,Bangladesh,Nepal and Brazil. [1] These five countries account for 90% of the global VL cases.[2] A small focus has also been reported from Bhutan.[3] Historically VL was first described in 1824, in Jessore district of the then Bengal now Bangladesh.[4] VL or kala-a-zar is endemic in Bangladesh. Ongoing national Kala-azar elimination program recently introduced Miltefosine as the first line of drug for Kala-azar.[5] This first oral anti leishmanial agent has been approved in India for the treatment of Indian VL in 2003 and has achieved 94% cure rate after 6 months up in India.[1]In this paper we report seven known cases of Kala-azar who received full course of Miltefosine initially but presented to us with treatment failure.

Patients and Methods:

Seven patients from different upazilla of Tangail and Gazipur were admitted to the Medicine and Pediatrics department of Dhaka Medical College, Dhaka from November, 2007 to April, 2008 with the history (symptom and sign) compatible with Kala-azar.The cases were confirmed by the presence of Leishmania Donovan (LD) bodies on splenic smear. All of them received full course of Anti-leishmanial (Cap.Miltefosine) treatment before presented to us. We diagnosed them as treatment unresponsive to Miltefosine as all the relapse occurred with in one year of completion of initial treatment. They were treated with Inj.Stibogluconate and Inj.Amphotericin-B with successful outcome (clinical and parasitological cure).The cases were analyzed meticulously to see the age and sex distribution of the patient along with clinical feature, laboratory findings and lag period between completion of initial treatment and reappearance of symptoms. All the observations have been presented in this paper.

Results:

Out of seven patients four were male and three female. Their age ranged from 4 to 35 years (Table I). On admission most common features were Fever(7),Loss of weight (5),Loss of appetite (4),Abdominal mass (4),Anemia (7),Hepatomegaly (6) and

Table I

Age and Sex distribution along with Analysis of Drug Received (n=7)

Case No	Age in years	Sex	Thana, District	Previously received medication	Lag period between completion of treatment & development of Symptoms(in months)	Finally treated with
01	35	M	Modhupur,Tangail	Stibogluconate,then Miltefosine	06	Amphotericin-B
02	04	F	Rosulpur,Tangail	Miltefosine	5.5	Stibogluconate
03	16	M	Modhupur,Tangail	Stibogluconate,then Miltefosine	02	Amphotericin-B
04	04	F	Mirzapur,Tangail	Miltefosine	02	Stibogluconate
05	10	M	Mirzapur,Tangail	Miltefosine	02	Stibogluconate
06	04	M	Sreepur,Gazipur	Miltefosine	03	Stibogluconate
07	04	F	Sreepur,Gazipur	Miltefosine	09	Stibogluconate

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Splenomegaly(7).We found Leucopenia in five patients and Thrombocytopenia in three patients. All patients were anemic and got LD bodies on splenic smear. The lag period between completion of initial treatment and reappearance of symptom ranged from 2 months to 9 months. Two patients also received Inj.Stibogluconate before the Miltefosine therapy and found to be unresponsive. In these cases we used Inj.Amphotericin-B with successful outcome. Others were treated with Inj.Sibogluconate.Repeat splenic aspiration done and all of them found LD bodies negative. Patients were on regular follow-up for six months with good outcome.

Table II

Frequency of Common Symptom, Sign and Laboratory findings (n=7)

Symptom	No. of Patients
Fever	07
Loss of Appetite	04
Loss of Weight	05
Abdominal mass	04
Sign	
Anemia	07
Hepatomegally	06
Splenomegally	07
Laboratory findings	
Decrease Hemoglobin	07
Leucopenia	05
Thrombocytopenia	03
LD bodies on Splenic smear	07

Discussion:

Nearly 25 compounds are reported to have anti-leishmanial effects but not all are in use. The pentavalent antimony compounds have remained as mainstay of treatment for nearly 75 years.[6-8] But it has some serious side effect and required a prolong course. Moreover treatment unresponsiveness is already been reported from India and Nepal.[9-11] 37–64% of patients currently fail to be cured by antimony treatment in India.[12] Since all previous treatments required injections or infusions, the importance of establishing the effectiveness of an oral agent cannot be overemphasized. Newer oral drug Miltefosine is a potent antileishmanial drug with longer half-life. It is an active phospholipids derivative which has undergone different phases of study on India and Bangladesh. A multicentric phase IV study sponsored by Indian Council of Medical Research (ICMR)/WHO (TDR)/Zentaris at 13 sites was conducted in India. There were 57 relapse cases out of 1167 and 52 dropouts.[1] In Bangladesh a multicentric Phase IV clinical trial was also conducted. The result of this trial is yet to be published. In this case series we encountered seven patients during the last ten months who were treated with full course of capsule Miltefosine but failed to respond. Relapse occurred in all cases with in two to nine months. According to our national guideline we noted all the cases as treatment failure to Miltefosine as it happened with in one year of completion of therapy.[5] Oral miltefosine has a direct leishmanicidal property and is not dependant on host immune response. Though miltefosine is the only oral effective agent against VL, its long half life of about 150 hours may create problem of resistance and relapse when used indiscriminately as monotherapy.[1] Miltefosine resistant lines of L. donovani promastigotes have been generated in the laboratory. Mechanism of resistance is due to defective uptake of miltefosine through point mutations on a plasma membrane aminophospholipid translocase.[1] Recently National Kala azar Elimination Program has advocated miltefosine as the first line drug for the treatment of kala azar in Bangladesh.[5] But it is still debatable whether this drug can replace SSG as first line drug for Bangladesh as there was no such data or research work done in Bangladesh before regarding decreasing efficacy of Sb. It is also noticeable that five (5) patients out of seven (7) in this case series were successfully treated by this drug. Rests of the two patients were treated with Amphotericin-B. This drug now extensively used in India and primary unresponsiveness and relapses were uncommon though recently unresponsiveness to Liposomal Amphotericin was noted in some Sudanese patient.[13]

So in near future treatment of Kala-azar will be a great challenge for the physicians.Immidiate future strategies should be to save two new potent antileishmanial drugs, Miltefosine and Paromomycine acquiring resistance in VL. To solve the problem of resistance, relapses and to reduce the length of treatment, combination of two antileishmanial drugs might be the desirable solution. Researcher of our country should come forward to make extensive study and find out the best possible combination.

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