

Continuing Medical Education

DIAGNOSIS AND TREATMENT OF KALA-AZAR

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Kala-azar (KA) continues to be a major public health problem in endemic areas despite valuable advances in its diagnosis and treatment during the last two decades. The problem is further compounded by ever increasing reports of resistance to the commonly used drug, sodium stibogluconate (SS). The disease has assumed a magnitude of grave proportion by crossing the epidemiological limits and posing diagnostic and therapeutic problems even in non-endemic areas(1-5). This communication presents a review of current recommendations on diagnosis and management of KA.

Diagnosis

KA is usually suspected in a case from endemic area presenting with prolonged fever, anemia, hepatosplenomegaly and cachexia. However, over-reliance on earlier epidemiological profile of the disease may

result in delay or even missing the diagnosis in a patient from non-endemic area. Since the reappearance of KA in North Bihar in 1977-78, cases have been reported from various parts of India including New Delhi, Jammu and Kashmir, Himachal Pradesh, Tamil Nadu, Meghalaya and Uttar Pradesh(3-6). The current epidemiology should, therefore, be known and the diagnosis should be considered even in cases from non-endemic areas if otherwise the clinical presentation warrants.

Screening Serological Tests

Table I shows various tests used for the diagnosis of KA. Aldehyde (Formel-gel) test is an initial investigation which is positive in 35-94% cases. Since there are many conditions giving false positive results, it is regarded as a screening test(7,8). Aldehyde test is not positive if the duration of illness is less than 3 months(9). Various serological tests including complement fixation test, ELISA, CIEP and monoclonal antibodies are now available. They have 80-100% sensitivity (*Table I*) and are fast becoming preferred tests for large scale use(10-13). Montenegro reaction (Leishmanin test) is a dermal reaction but it is not commonly used for diagnostic purposes(8).

Confirmatory Tests

Confirmation of the diagnosis comes from demonstration of amastigote forms of the parasite *Leishmania donovani* (LD bodies). For this purpose bone marrow aspiration was traditionally recommended. Use of 21 gauge needle for splenic aspiration has made this procedure simpler, safer, quicker and less traumatic as compared

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TABLE I—Investigations for Diagnosis of Kala-Azar.

Test	Sensitivity (%)	Comments
A. Serological Tests		
a. Aldehyde test	35-94	- Not positive in early phase, used for screening as there are many false positive results(7,8,13).
b. Complement fixation test	96	- Cross reactions with tuberculosis, leprosy and Chagas disease(7,8)
c. ELISA	100	- 100% specificity(11)
d. dot-ELISA	98	- Visually read, useful for field use(10)
e. CDEP	80-100	- Positive in normal individuals in endemic areas(13)
f. Monoclonal antibody (using RIA, ELISA)	98	- No false positive results(12)
B. Confirmatory test		
a. Bone marrow aspiration	68-70	- (7,9)
b. Splenic aspiration	70	- Safer, quicker, simpler than bone marrow aspiration(7,15-17)
c. Culture of bone marrow/splenic aspirate	100	- More time consuming(3)

to bone marrow aspiration. In addition, pathologic process in the spleen makes it firm and less likely to tear. It is a more sensitive test and is currently regarded as the best method for demonstration of LD bodies(14-16). Splenic aspiration should be done in patients with normal prothrombin time (not more than 5 seconds over the control) and platelet count of more than 40 thousand/mm³(16,17). Quantitation of the parasite in splenic aspiration should be done for assessing the parasitic load and response to therapy(14).

Bone marrow or splenic aspirate culture is usually done when the parasite can

not be demonstrated because of low parasitic load(3). Occasionally, LD bodies can be seen in peripheral blood from the smears of buffy coat and in some patients, a short course of corticosteroids may help in demonstration of parasite when otherwise the bone marrow is negative. Lymph node aspiration and liver biopsy are seldom required for demonstration of LD bodies(2,9).

Apart from the tests for diagnosis, these patients should also be investigated for tuberculosis and other infections to which they are more prone because of impaired immunity.

Treatment

Sodium stibogluconate (SS)

SS has been used as the first line drug for KA in India. The recommendation for dose and duration of therapy have been changing over the last few years. With the initially recommended dose of 20 mg/kg/day for 10 days schedule, resistance and relapses were observed. Hence in 1984, WHO recommended an increase in the duration of treatment to 20 days(1). However, even with 20 day schedule, reports of resistance and relapse started appearing(19-22). At the same time it was demonstrated that higher initial dose and longer duration of therapy not only minimize initial unresponsiveness, but also decrease the chances of relapse(23-25). Initial inadequate treatment may be an important factor for subsequent resistance(26). It is now recognized that the duration of SS therapy which can be termed "adequate" varies in different geographical areas, the Indian KA requiring longer duration of treatment(2). Currently, a dose of 20 mg/kg for 20 days is recommended, which can be extended to 30 or 40 days without interruption if parasites persist(2,25).

During treatment, all cases should be assessed with daily temperature record and splenic size. Hemoglobin and blood counts should be done weekly. Disappearance of fever, decrease in splenic size, rising hemoglobin and blood counts, increasing serum albumin and decreasing number of parasites on splenic aspirate are indices of good response(1,17). The cases should be examined at 3 months and 12 months after successful treatment.

Persistence of fever, splenomegaly, anemia, leucopenia and parasites in the splenic or bone marrow aspirate indicate

resistance(20). Resistance to SS therapy in Indian patients is usually reported in 5-8% cases though from referral centres, 35-45% resistance is reported(9,19-22).

Pentamidine Isethionate (PI)

PI is usually recommended as the second line drug(27). PI is a parenteral drug and has many side effects even in usually prescribed doses (*Table II*). Although the response to PI is regarded inconsistent, recent Indian series have reported good response in SS resistant cases(18-20). It is given in a dose of 4 mg/kg/day. Ten injections are given on alternate days. Longer therapy upto 25-38 weeks can be used if required(2,8,24,28).

Allopurinol

After the first report of its antileishmanial activity, allopurinol has been used for treatment of KA; but allopurinol shows good response only when it is used following or alongwith SS. Only partial response is seen when allopurinol is used alone(29-32). Advantages with allopurinol use are its oral administration and it is cheap and well tolerated. The dose of allopurinol for KA is 16-24 mg/kg/day for varying lengths from 7-54 days(9,17,29).

Ketoconazol

Ketoconazol is an antifungal drug which is used for cutaneous leishmaniasis. A trial with 600 mg daily in adults has shown it to be effective in Indian KA(33).

Amphotericin B

Amphotericin B is an effective anti-leishmanial drug. But its infrequent availability and toxicity has prohibited its wide use. This drug is usually reserved for cases who do not respond to multiple courses of SS and PI(9,27,30).

TABLE II -Anti Leishmanial Drugs

Drug	Dosage schedule Route of administration	Side effects	Comments
Sodium stibogluconate	20 mg/kg/day IM Injection for 20-40 days	Minimal, local discomfort, generalized weakness, liver enzyme elevation, transient ECG changes	Increasing resistance being reported (19-22)
Pentamidine isethionate	4 mg/kg/day IM 10 injections on alternate days	GI symptoms, headache, paresthesias, tachycardia, hypotension, ECG changes, metabolic abnormalities. Side effects are less in children	Longer duration therapy upto 25-39 weeks can be given if required. Not easily available but can be procured from National Malaria Eradication Programme, New Delhi
Allopurinol	16-24 mg/kg/day oral in 2-3 divided doses	Hypersensitivity reactions, transient leucopenia, leucocytosis, eosinophilia, headache drowsiness, nausea	Usually well tolerated, better efficacy when used with or following sodium stibogluconate
Amphotericin-B	0.5-1.0 mg/kg/day IV infusion	Anorexia, nausea, vomiting, fever chills, azotemia, thrombophlebitis, agranulocytosis, anemia	Costly drug, not readily available
Ketoconazole	600 mg daily in adults. In children 3-15 mg/kg/day oral	Nausea, vomiting, anorexia, rash, hepatic enzyme elevation, hepatitis	Not frequently tried in children

Other Drugs : Urea stibamine is used by some as an alternative to SS.

In search of an effective oral drug; metronidazole, co-trimoxazole, isoniazid, ethambutol, rifampicin, and clofazimine have been used and are shown to have no or partial response(34,36). Rifampicin when used in combination with isoniazid was found ineffective by Thakur and Sinha while in a recent report, use of rifampicin alongwith co-trimoxazol, resulted in 70% response rate(35,37). Addition of interferon gamma to SS has helped some SS resistant cases and use of gold salts has been shown to produce excellent response in some resistant cases(38,39). Liposome incorporated antimonials are being tried to deliver higher doses of drugs without increasing the side effects(9,17).

Splenectomy

Splenectomy has been advocated in cases who remain symptomatic inspite of multiple courses of antileishmanial drugs. It helps by reducing the parasite load and better efficacy of drugs to kill the residual parasites(27,40,41).

Of all the above drugs, SS is still recommended as the first line drug for treatment of KA. Pentamidine is usually recommended as the second line drug. However, its infrequent availability, cost and toxicity necessitated use of other drugs. At present there are no clear guidelines for their use.

After reviewing the subject a protocol for the drug management of KA is suggested in *Fig. 1*.

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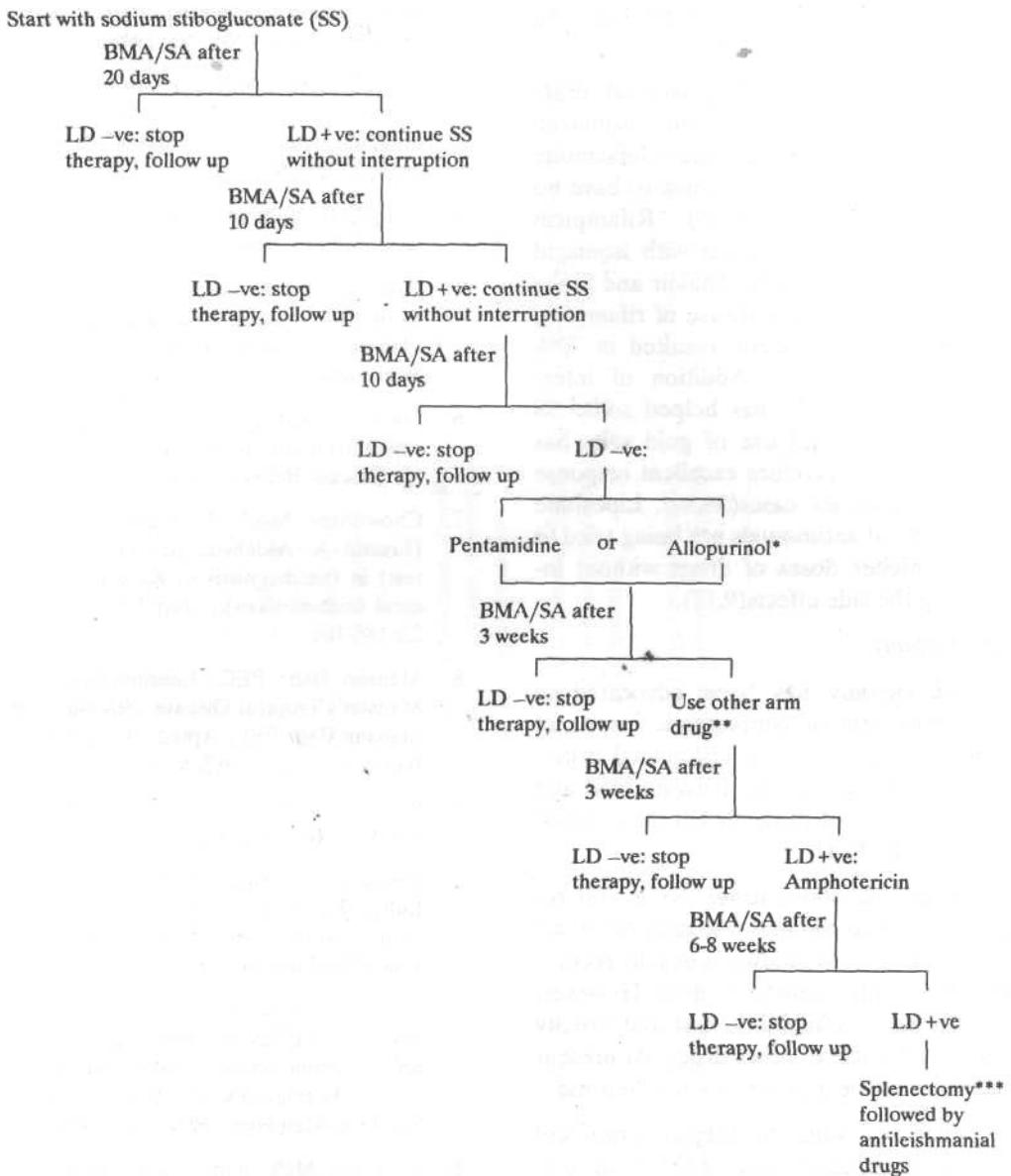


Fig. 1. Suggested protocol for treatment of Kala-Azar.

BMA=bone marrow aspiration, SA = splenic aspiration.

* Allopurinol can be used alone or alongwith SS.

** If partial response is seen with either drug, longer duration therapy may be considered otherwise if pentamidine is used initially, allopurinol can be tried and vice versa.

*** Other drugs like ketoconazole, rifampicin with co-trimoxazol may be tried before splenectomy.

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