CASE SCENARIO

20-year-old agricultural labourer with a history of recurrent **fever**, progressive weakness and **abdominal discomfort** associated with loss of appetite for six months followed by **petechial hemorrhages** over body.

O/E -**hepato-splenomegaly**.

- CBC – pancytopenia
- CXR – normal

BM – Bone marrow aspiration cytology – L Donovani

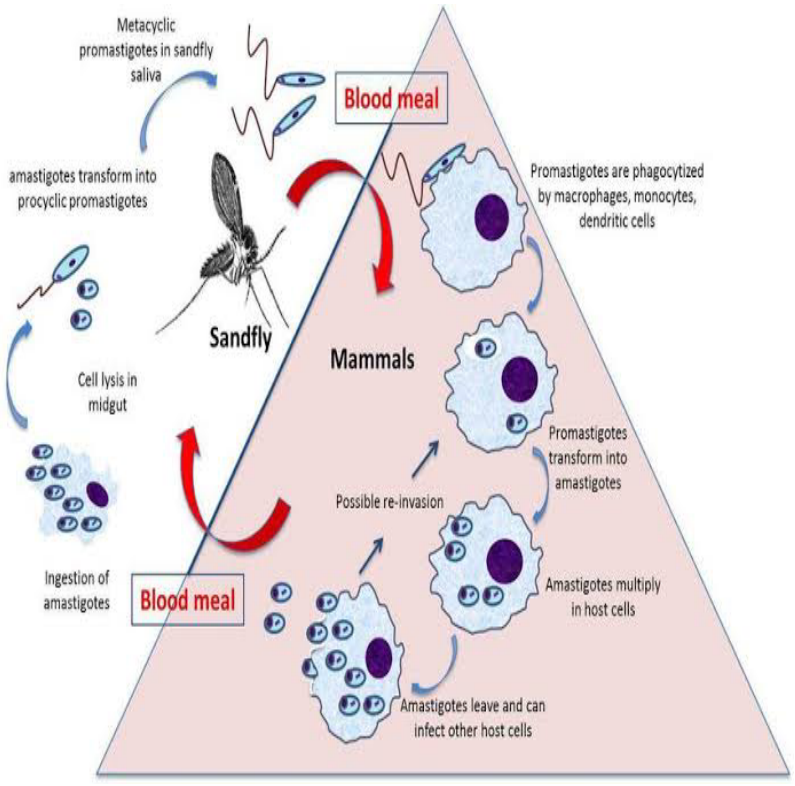
Rx - Amphotericine B

LEISHMANIASIS

- Zoonosis
- caused by leishmania - **unicellular flagellate intracellular protozoa**
- Vector - phlebotomine sandfly vectors
- **Only Reservoir (India)- Humans**

- **Three** important clinical syndromes
  - **i) Visceral leishmaniasis (VL, kala-azar)**
  - **ii) Cutaneous leishmaniasis (CL), and**
  - **iii)Mucosal leishmaniasis (ML).**

LIFE CYCLE



Two forms

- Flagellar **Promastigotes** (10 to 20 µm), found in **vectors**, and
- **Aflagellar Amastigotes** (2 to 4 µm) in **vertebrate hosts** including humans.
- Promastigotes are introduced through the proboscis of the female sandfly into vertebrate hosts.
- Neutrophils take up the promastigotes where they transform into amastigotes and undergo apoptosis, and released **parasites are taken up by macrophages.**
- Once inside the macrophages, they multiply, ultimately causing rupture and invasion of another cell.
- While **feeding on infected hosts, sandflies pick up amastigotes,** which transforms into the **flagellar form.**
- It multiplies by binary fission in the gut of the vector and infects a new host by migrating to the proboscis.

Amastigote form of the parasite primarily **infects the reticuloendothelial system and may be found in abundance in the bone marrow, spleen and Liver**

VISCERAL LEISHMANIASIS (KALA-AZAR)

- **Aka kala-azar (Hindi word for black fever)**
- Caused by L Donovani
- 90% of it occurs in India(North eastern states), Sudan, Bangladesh and Brazil.

Immunology and Pathogenesis

- **Tropism for RES**
- able to evade immunity by stimulating **immunosuppressive cytokine IL 10**
- Reticuloendothelial involvement = spleen, liver, bone-marrow and lymph nodes
  - **Lymphadenopathy is rare in India**.
- Other unusual modes of transmissions are in **utero, through blood transfusion, through needle sharing in drug addicts.**
- **Immunosuppression due to HIV infection or immunosuppressive medications makes these patients vulnerable** to development of VL.

Clinical Features

- **Except in Indian subcontinent** where all age groups are affected, it is a **disease of infants and small children**,
- Succeptinility = , HIV infection and Poor living condition
- Incubation = **weeks to months**.
- **Clinical history – above scenario**
  - **Fever + splenomegaly + pancytopenia**
- **Initially** there is **leishmania specific immunosuppression,** in **later stages profound immunosuppression occurs leading to secondary infections**
  - like tuberculosis, pneumonia, herpes zoster, chicken pox, recurrent gastrointestinal infection.
  - Skin infections like boils, cellulitis and scabies are common.

Features

- Pancytopenia
- Polyclonal hypergammaglobulinaemia in advanced disease
- Patients are **anergic to leishmanin antigen skin test (LST), which recovers after successful chemotherapy.**

Diagnosis

- Tissue smears from **spleen, bone-marrow or lymph nodes**.
  - **Splenic smear - Parasites (amastigotes)**

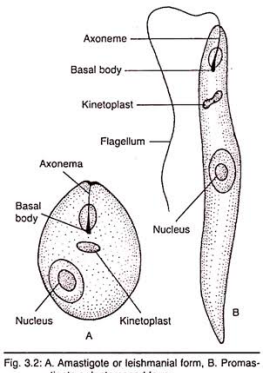


Fig. 3.2: A. Amastigote or leishmanial form, B. Promastigote or leptomonad form

        - Risk of serious haemorrhage
    - In HIV co-infected, **buffy coat smears may demonstrate parasites**

Serologic techniques

- ELISA
- IFAT
    - INDIRECT IMMUNE FLUORESCENT ANTIBODY TEST

Rapid immunochromatographic test – rK 39

- based on the **detection of antibodies to a recombinant antigen (rK39)** consisting of 39 amino acids **conserved in the kinesin region of L. infantum**
- Require only a drop of fingerprick blood or serum
- Turn over time = 15 min.
    - **sensitivity ~98% and**
    - **specificity is ~90%. (Except in East Africa)**

Drawback

- remain positive for years after cure, they **cannot be used for measurement of cure or detection of relapse.**
- In **Sudan**, an RDT based on a **new synthetic polyprotein, rK28, was more sensitive (96.8%) and specific (96.2%) than rK39-based RDTs.**

Qualitative detection of **leishmanial nucleic acid** by

- polymerase chain reaction (PCR) or
- by loop-mediated isothermal amplification (LAMP) and

Differential Diagnosis

Fever + Splenomegaly

- Malaria.
- **Typhoid fever**
- **Tuberculosis,**
- **Brucellosis,**
- **Schistosomiasis, and**
- **Histoplasmosis.**

****Rx**

- DOC = **pentavalent antimonial**
- **If Resistance**
    - **Amphotericin B (AmB)—deoxycholate or liposomal—or miltefosine** / Paromomycin

PENTAVALENT ANTIMONIAL COMPOUNDS

- Two preparations
    - Sodium stibogluconate (100 mg of SbV/mL) and
    - Meglumine antimoniate (85 mg of SbV/mL).
- The daily dose is **20 mg/kg by IV infusion or IM injection**
- Duration = 28–30 days.
    - **<50% in Bihar, India, as a result of resistance.**
- **Adverse reactions**

- Arthralgia, myalgia, and elevated serum levels of aminotransferases.
- ECG - QTc prolongation
- Pancreatitis occurs in immunosuppressed patients.

AMPHOTERICIN B (FIRST LINE IN INDIA)

- AMB = 0.75–1.0 mg/kg on alternate days for a **total of 15 infusions**. (**1 MONTH)**
- **Lipid > Deoxycholate formulation**
  - **Preferentially taken by Reticuloendothelial system**
  - **Long t ½ = 150 hr**
  - **Less S/e**
  - **Dosage = For immunocompetent patients, recommended total doses are – in the Indian subcontinent 10-15 mg/kg**
    - **Day 1-5 and 14 and 21 (FDA regimen)**
    - **Single dose regimen in India cure rate = 96%**
      - **Dosage = 10 mg/kg**
- **Adverse reaction**
  - Fever with chills
  - thrombophlebitis
  - **Renal dysfunction and hypokalemia**

PAROMOMYCIN

- Aminocyclitol-**aminoglycoside** antibiotic with antileishmanial activity.
- IM dose =**11 mg of base/kg daily for 21 days**
  - Cure rate = 94.6%.
- safe drug,
- S/e
  - hepatotoxicity, reversible ototoxicity, and (in rare instances) nephrotoxicity and tetany.

MILTEFOSINE

- Alkylphosphocholine
- First oral compound
- long half-life (150–200 h)
- Weight based
  - < 25 kg = Daily dose of 50 mg for 28 days
  - ≥25 kg = 50 mg BD for 28 days
  - 2.5 mg/kg for 28 days for children 2–11 years of age.
- Cure rate of 94%
- Because of its long half-life, **miltefosine is prone to induce resistance in Leishmania.**
- **Adverse effects**
  - GI S/e
  - contraindicated during pregnancy and (unless contraceptive measures are strictly adhered to for at least 3 months after treatment) in women of childbearing age.

MULTIDRUG THERAPY – NOT CURRENTLY USED ; FUTRURISTIC

ADVANTAGES in VL include

(1) better compliance and lower costs associated with shorter treatment courses and decreased hospitalization,

(2) less toxicity due to lower drug doses and/or shorter duration of treatment, and

(3) a reduced likelihood that resistance to either agent will develop.

Prognosis

- Recovery - quick.
- **Within a week after the start** of treatment, **defervescence, regression of splenomegaly, weight gain, and recovery of hematologic parameters are evident.**
- With effective treatment, no parasites are recovered from tissue aspirates at the post-treatment evaluation.
- Continued clinical improvement over 6–12 months is suggestive of cure.
- Small percentage = Relapse

KALA AZAR IN HIV

- May present with atypical features due to loss of immunity and involvement of **unusual anatomic locations—e.g., infiltration of the skin, oral mucosa, gastrointestinal tract, lungs, and other organs.**
- Serodiagnostic tests may be **negative in up to 50% of patients.**
- Parasites can be recovered from unusual sites such as bronchoalveolar lavage fluid and buffy coat.
- **Rx**
  - **LAmB is the drug of choice for HIV/VL co-infection—both for primary treatment and for treatment of relapses**.
  - **FDA APPROVED REGIMEN**
    - A total dose of **40 mg/kg, administered as 4 mg/kg on days 1–5, 10, 17, 24, 31, and 38**
  - Risk of relapse
- If LamB not available ; Pentavalent antimonials and AmB deoxycholate
- Restoration of the CD4+ T cell count to >200/µL does decrease the frequency of relapse, antiretroviral therapy (in addition to antileishmanial therapy) is a cornerstone of the management of HIV/VL co-infection.
- **Secondary prophylaxis with pentamidine or lipid AmB has been shown to delay relapses, but no regimen has been established as optimal.**

Post–Kala-Azar Dermal Leishmaniasis

- Seen in Indian subcontinent and Africa
- **2–50%** of patients develop **skin lesions concurrent with or after the cure of VL.**
- **MCC** –

- **hypopigmented macules, papules, and/or nodules or diffuse infiltration of the skin** and sometimes of the oral mucosa.

FEATURE	EAST AFRICA	INDIAN SUBCONTINENT
Most affected country	Sudan and South Sudan	Bangladesh
Incidence among patients with VL	~50%	~2–17%
Interval between VL and PKDL	During VL to 6 months	6 months to 3 years
Age distribution	Mainly children	Any age
History of prior VL	Yes	Not necessarily
Rashes of PKDL in presence of active VL	Yes	No
Treatment with sodium stibogluconate	2–3 months	2–4 months
Natural course	Spontaneous cure in majority of patients	Spontaneous cure in minority of patients

Abbreviations: PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.

- In PKDL, **parasites are scanty in hypopigmented macules** but may be seen and cultured more easily from nodular lesions.
- **Cellular infiltrates are heavier in nodules than in macules.**
- Cells = **Lymphocytes > histiocytes and plasma cells.**
- The diagnosis is based on history and clinical findings, but rK39 and other serologic tests are positive in most cases.

Rx

- Indian PKDL was treated with **prolonged courses (up to 120 days) of pentavalent antimonials.**
  - This prolonged course frequently led to noncompliance.
- The alternative—several courses of **AmB spread over several months—is expensive and unacceptable for most patients.**
- **Oral miltefosine for 12 weeks,** in the usual daily doses, cures most patients with Indian PKDL.
- In those with persistent lesions, the **response to 60 days of treatment with a pentavalent antimonial is good.**