Leishmaniasis

Michael Libman MD
J.D. MacLean Centre for Tropical Medicine
McGill University Health Centre
Thanks:
Alan Magill
Bjorn Blomberg

Leishmaniasis - Many names...

- Bagdad boils
  - >700 US soldiers
- Sandfly disease
- Black Fever
- Kala Azar (Sanskrit: Black fever)
- Oriental boils
- Dum-Dum fever (town near Kolkata)
- Espundia (Spanish: esponja - "sponge")
- Leishmaniac: person obsessed with leishmaniasis

History

- Old disease
- Leishmania-like features in art from pre Inca time in Peru and Ecuador (ca 100 AD)
- Known in India since ancient times
- Genus Leishmania described 1903
  - Ross, BMJ 1903:2:1261-62

It’s a bit complicated...

- 3 diseases in one
- >17 species pathogenic to humans

3 Major Clinical Syndromes

- Visceral Leishmaniasis
- Cutaneous Leishmaniasis
- Mucosal Leishmaniasis

The Leishmaniases

- A diverse group of protozoan parasites
- Intracellular pathogens of the macrophage
- Different clinical syndromes
- Zoonosis
  - Sand fly insect vector
  - Mammalian reservoir(s)
  - Man is incidental host
- Anthroponosis (human reservoir)
  - Indian VL cause by L. donovani
  - Cutaneous leishmaniasis caused by L. tropica
Impact of the Leishmaniasis

- 2.4 million DALYs
- 1 - 1.5 million cases of CL / year
- 500,000 cases of VL / year
- 350 million at risk
- Actual case-load 10-20 X higher

<table>
<thead>
<tr>
<th>SubGenus</th>
<th>Species</th>
<th>Tropism</th>
<th>VL</th>
<th>DCL</th>
<th>LCL</th>
<th>MCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leishmania</td>
<td>L.donovani</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.infantum (=chagasi)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.tropica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.amazonensis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.mexicana</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.aethiopica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.major</td>
<td></td>
<td></td>
<td></td>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.killicki</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viannia</td>
<td>L.lainsoni</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.naiffi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.peruviana</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.venezuelensis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.guyanensis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.panamensis</td>
<td></td>
<td></td>
<td></td>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.brazilensis</td>
<td></td>
<td></td>
<td>HIV</td>
<td>HIV</td>
<td></td>
</tr>
</tbody>
</table>

Parasite, disease, geography

<table>
<thead>
<tr>
<th>Disease</th>
<th>Area</th>
<th>Parasite</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>Old world</td>
<td>L.major, tropica, aethiopica</td>
</tr>
<tr>
<td>CL</td>
<td>New world</td>
<td>L.brazilensis, amazonensis, mexicana</td>
</tr>
<tr>
<td>MCL</td>
<td>New world</td>
<td>L.brazilensis, panamensis, guyanensis</td>
</tr>
<tr>
<td>VL</td>
<td>Old world</td>
<td>L.donovani, infantum</td>
</tr>
<tr>
<td>VL</td>
<td>New world</td>
<td>L.infantum (= L.chagasi)</td>
</tr>
</tbody>
</table>

Parasite Morphology

• Parallel venation on wings
• Feathered edges (fine hairs)
• Characteristic V shape at rest

Promastigotes in sand fly

Amastigotes in mammalian host
Two different forms

- Macrophages eathing promastigotes
- Amastigotes in mouse macrophages

Q1: *Leishmania* parasites can be transmitted in all the following ways except?

1. Sand flies
2. Sexual intercourse
3. Kissing
4. Congenital (Mom to baby)
5. Needle sticks
6. Blood transfusion

Other routes of transmission

Epidemiology of Leishmaniasis

Cutaneous Syndromes

- Cutaneous leishmaniasis
  - Localized, ulcerative
  - Nodular
  - Other: Psoriaform, verrucous, plaque, macules
- Diffuse cutaneous leishmaniasis
- Leishmaniasis recidivans
- Post Kala Azar Dermal Leishmaniasis (PKDL)

Cutaneous Leishmaniasis

- Self healing
- Incubation period of days to years
- Slowly enlarging nodule at bite site
- Crust forms centrally leading to ulceration with raised margins
- Healing leaves a hypo-pigmented and depressed scar
- Characteristic but inconstant clinical differences between species
Geographic distribution of Main species of Old World Cutaneous Leishmaniasis

Parasite             Reservoir          Characteristics
L. tropica           Rats/man          Cities > rural
L. major             Kangaroo-rat     April-June
L. aethiopica        Mountain rabbit, hyrax
L. braziliensis, peru, panam, guayanasis Rodents, mules Deforestation, timber-workers, after rainy season, april-may + sporades

Geographic distribution of Main species of New World Cutaneous Leishmaniasis

CL reservoir

Parasite             Reservoir          Characteristics
Rat                  Hyrax             "Volcano" edge

Ulcerative lesion

"Volcano" edge
No pain unless 2nd infection
Leishmania aethiopica (3 years old) (pre Rx)

Turkey (Anatolia) post fluconazole, pre antimony

Leishmania 2 years old from India or Saudi Arabia treated with ketoconazole

Sinai peninsula
Jan 2006 – 16 months post-Majorca
Visits a dermatologist in Germany; Dx mastocytosis
Rx. hydrocortisone cream x 3 weeks; no change

Sept 2005 – 12 months post Majorca

September 2006 (24 months post Majorca)
after 3 months of hydrocortisone cream, 4-5 months
of increased fatigue and “growing pains”

Features of different species causing CL
(“rule of thumb”)

L. major (Arabia, north Africa, South Sahara)
- Aggressive
- Incubation: 1w - 2m
- Big sores: 3-6 cm
- Scar after 3-5 months
- Lips, nose (not mucosa)

L. aethiopica (East Africa)
- Small papules, often multiple
- Long duration 2 - 5 years

L. Tropica (Greece, Turkey, Middle East)
- Less aggressive
- Incubation: 2m - 2y
- Sores: 1-2 cm (max size 8-12m)
- Heals in 10-14m
- Face
- Children

L. infantum (West Mediterranean, Latin Am.)
- Least aggressive
- Nodules, sometimes without sores
- Duration 3 years
- Face

Leishmania residivans – L.tropica
- Central scar (previous lesion)
- New lesions around
- Few parasites
- Intense immune response
- Non-healing / relapsing
Diffuse cutaneous Leishmaniasis

- Rare, looks similar to Lepromatous lepra
  - L. aethiopica (Africa)
  - L. amazonensis, mexicana (Americas)
- Associated with immune defect (CMI)
- HIV: more DCL (L.major, infantum, braziliensis)
- Primary lesion does not ulcerate
  - Months - years
  - spread (local, via blood)
  - To other parts of the skin, face, extensor-tendons
- Nodules, plaques, hypo-pigmented areas
- Chronic - many years
- Difficult to treat

So now what do I do?

Diagnosis

- Travel history
- Birth history
- Residence history
- Occupational exposure
- Blood transfusions
- Congenital

Q2: All the following are useful methods for the diagnosis of CL except:

1. In vitro culture
2. Smear diagnosis
3. Molecular detection (PCR)
4. Histopathology
5. Detection of specific antibodies (serology)
6. In vivo culture (amplification) in animals

Diagnosis: Scraping Method
Processing of diagnostic material for Leishmaniasis evaluation

- Touch preps Giemsa staining
- Schneiders, MMI, NNN culture media
- Promastigotes in culture
- Electrophoresis for speciation
- PCR

Lesion biopsy or aspirate

\[ \Delta R_n \]

- L. major
- L. V. panamensis
- Negative control

rRNA Probe for Genus Level Identification

Species identification

- Isoenzyme analysis
  - Comparison of unknown to reference standards
  - Requires cultured promastigotes
  - Patients usually treated before result is known
- Molecular / PCR

Leishmania Culture

- “Science” versus “art”
- Complex lab skills
- Asking the intracellular amastigote to transform into a promastigote and expand
- Parasite species growth differences

PCR

- Genus specific and / or species specific
- Sensitivity / specificity with different species, targets, probes, specimens, geographic locations
- Who does it?
- Where is it done?
So how do I treat this?

Amastigotes seen, kinetoplast confirmed!

No standard treatment regimen for cutaneous leishmaniasis

- Different treatment for
  - Different species
  - Same species in different locations

Spectrum of CL lesions and Rx options

Severity of disease

Local
- Systemic oral
- Systemic parenteral

Topical
- Paromomycin
- Intralesional injections – SbV

Physical
- Thermal Rx
- Cryotherapy
- Traditional
  - Battery acid

Local Treatment for CL

Cryotherapy

- Widely used in the Middle East
- Poor quality trials to support use
- Little experience in USA with Leish
- Consider LN2 for small lesions, non-facial
- Dermatologists very familiar with LN2

Topical paromomycin + gentamicin

Topical treatment of non-severe and uncomplicated, primarily ulcerative lesions in patients with cutaneous leishmaniasis (CL) caused by L. major

Safe, efficacious, easy to use, inexpensive new first line treatment option in phase 3 trials

Panama (L. panamensis): Sosa N. AJTMH 2013
Tunisia (L. major): Ben Salah A. NEJM 2013
Q3: The optimal systemic treatment for CL is:

1. Intravenous sodium stibogluconate (Pentostam)
2. Amphotericin B deoxycholate (Fungizone)
3. Liposomal amphotericin B (AmBisome)
4. Fluconazole
5. Miltefosine
6. Depends

Systemic Treatment for CL

- **Parenteral**
  - Amphotericin B deoxycholate (Fungizone®)
  - Liposomal amphotericin B (AmBisome®)
  - Pentavalent Antimony (SbV)

- **Oral**
  - Ketoconazole
  - Itraconazole
  - Fluconazole
  - Miltefosine

Advantages:
- Oral route of administration
- Widely available
- Relatively safe
- Most MDs familiar with drug

Limitations:
- Modestly efficacious
- Optimal dose and regimen not established
- Unless given DOT, effective ness likely to be low
- No FDA indication for Leish

Rationale / Data:
Recommendation:
- Not recommended as first line
- Part of Rx toolbox
- Occasional patients
- Want Rx, don’t want SSG
- Poor candidate for heat Rx

Advantages:
- Oral route of administration
- Widely available
- Relatively safe
- Most MDs familiar with drug

Limitations:
- Modestly efficacious
- Optimal dose and regimen not established
- Unless given DOT, effectiveness likely to be low
- No FDA indication for Leish

Example of cutaneous ulcer caused by L. (Viannia) braziliensis treated with AmBisome

Clinical presentation - VL

- Incubation period 2-6 months (10d-10ys)
- Subclinical - acute - subacute - chronic
- Fever, rigors, chills, 38-39(>41), 2 peaks a day, continuous or intermittent
- **Splenomegaly** (firm, mobile, non-tender)
  - Impression of big abdomen
  - Mild hepatomegaly ... -> jaundice (bad sign)
- **Pancytopenia** (hypsersplenism, bleeding)
  - Fatigue, palor, greyish skin in Indian Kala-Azar
- **Cachexia**
- **Hyperggammaglobulinemia**
- **Adenopathy**: 85% Africa - 5% India

Visceral Leishmaniasis & HIV

- **VL+HIV**: 90 % - CD4 < 200
  - Reactivation of latent infection
  - Poor immune response to new infection
- (muco)dermotropic species -> VL (Brazilensis)
- Unusual disseminated forms (major, braziliensis)
- Unusual transmission: contaminated needles (IVDU)
- Unusual clinical presentation: Lung, digestive system, parasites in healthy-looking skin
- Southern Europe: Spain, Southern France, Italy
  - HIV & L. infantum are endemic
- Spain: 50 % adults with VL are HIV+
  - But only 3% of all HIV+ have VL

VL - Clinical findings

- Patient from North-India (Uttar Pradesh)
- Fever and wasting last two years.
- Treated for malaria and for tuberculosis without resolution of fever.

Anemia

- Bone marrow suppression
- Anemia -> 7g/dl -> 4 -> heart failure
- Leukopenia (1-3 x 10^9 pr mm3)
- Thrombocytopenia (100-150 x 10^9 pr mm3), < 40 - bleeding
Dark pigmentation of skin
Sanskrit (Hindi?): Kala azar = “Black sickness”

Indians 70%
Europeans 0%
Africans?
Face
Hands
Chest

90% of visceral leishmaniasis in 3 areas

- Ganges river area (North East India) + neighboring areas in Nepal (terai) and Bangladesh
- Sudan
- Brazil

Ganges & surroundings

- India – the world’s biggest VL focus
- 3 major epidemics in Assam
- Bihar: 1977-90: >300,000 cases 2% mortality
- Leishmania donovani
- Human reservoir (including PKDL)

Sudan

- VL epidemics since 1900s
- Civil war 1983
- Upper Nile outbreak 1988 ->
- >100,000 deaths in 280,000 pop!
- L. donovani
- Scarcely populated, zoonotic reservoir?
- 56% PKDL – human reservoir

VL - reservoir

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Reservoir</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. donovani</td>
<td>Humans (anthroponotic)</td>
<td>Kala-azar, PKDL Age 10-30ys Male:female 6:1</td>
</tr>
<tr>
<td>L. infantum</td>
<td>Dog, fox, chicken (zoonotic)</td>
<td>Children &lt;5ys young men Tourists</td>
</tr>
</tbody>
</table>

Prognosis of Leishmaniasis

- Without Tx ... 90% fatal
Visceral leishmaniasis
Diagnosis & sample collection

- Detectable parasites in aspirate
  - Spleen >95% (risky? Surgery back-up?)
  - Liver 75%
  - Bone marrow 75% (65-85)
  - Lymph node 65%
  - Buffy coat from blood 50%
  - NB: Skin biopsy in HIV + patients
- Immunological diagnosis
  - ELISA >97% sensitivity
  - Sudan lower

Persistent Leishmania Infection

- Intracellular pathogen of the macrophage
- Lifelong, persistent infection
- Treat disease, never eradicate parasites
- Mycobacteria: TB, leprosy
- Bacteria: Brucella
- Fungal: Histoplasma
- Viral: HIV

Chemotherapy for VL: Current Issues in Returning Travelers

- AmBisome® is Drug of choice for VL Rx
- FDA approved August 1997
- 3.0 mg / kg days 1-5, 14, 21
  (Immunocompetent)
- 4.0 mg / kg days 1-5, 10, 17, 24, 31, 38
  (Immunocompromised)

Miltefosine (Impavido®)

- 1st oral Rx for VL
- Licensed in India for VL in March 2002
- Initially developed as an anticancer drug
- Broadly effective in many Leish syndromes
- Limitations
  - Teratogenic
  - Long oral course / adherence / long half life / emergent resistance
  - GI side effects
- Future likely in combination chemotherapy

Current Treatment Options for Visceral Leishmaniasis

- IM / IV SbV
- IV Amphotericin B
  - Deoxycholate salt (Fungizone®)
  - Liposomal (AmBisome®)
- Oral miltefosine (Impavido®)
- IM paromomycin
Combination Tx
Sundar, Lancet 2011

• 634 VL patients, Bihar, June 2008–July 2009

<table>
<thead>
<tr>
<th>Tx</th>
<th>Cure at 6m</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmpB 1mg/kg, alt. days 30 d</td>
<td>93.0% (146/157)</td>
</tr>
<tr>
<td>AmpB 5mg/kg once + Miltefosin 50mg/d for 7d</td>
<td>97.5% (156/160)</td>
</tr>
<tr>
<td>AmpB 5mg/kg once + Paromomycin 11mg/kg for 10d</td>
<td>97.5% (154/158)</td>
</tr>
<tr>
<td>Paromomycin 11mg/kg for 10d + Miltefosin 50mg/d for 7d</td>
<td>98.7% (157/159)</td>
</tr>
</tbody>
</table>

Combi-Tx = Efficacious, safe, shorter duration

Leishmaniasis as an OI in Persons with AIDS: Drug Therapy

• Clinical course is chronic and relapsing
• Eradication of parasites not possible
• Optimal drug or regimen not clear
• Principles of Rx are induction chemotherapy followed by maintenance regimen
• HAART with immune reconstitution

3 Major Clinical Syndromes

Cutaneous Leishmaniasis
Visceral Leishmaniasis
Mucosal Leishmaniasis

Mucosal Leishmaniasis

• Nodular and ulcerative lesions of the oral-nasopharyngeal mucosal surfaces
• Days to years (43!) following primary infection with L. braziliensis
• Healed scar of primary CL infection usually present
• Nasal septum lesion or hoarseness often first symptom or sign

MCL

• Suspect if previous CL and symptoms from nose/mouth/pharynx/larynx
Prevention of Leishmaniasis

- Microhabitats lead to focal areas of high risk
- Sand flies are evening and night time biters
- Sandflies are poor fliers
  - Windy areas safer
  - No vegetation
- Air-conditioned sleeping quarters
- Rodent control
- Area or barrier insecticide use
- Education
- DEET based repellents
- Impregnated bed nets
- Rx of human reservoirs of L. tropica and PKDL
- Pyrethroid impregnated dog collars