Leishmaniasis
Jan Hajek

Cutaneous
Mucocutaneous
Visceral

Disclosures

• I have no conflicts of interest to disclose
Introduction

Gorgas courses
Peru

Kala-azar project with MSF
North-western Ethiopia

Outline

Leishmaniasis overview
– Parasite, vector, life cycle, epidemiology

Cutaneous (CL) and Mucocutaneous Leishmaniasis (MCL)
– Clinical manifestations, diagnosis, treatment

Visceral Leishmaniasis (Kala-azar)
– Clinical manifestations, diagnosis, treatment
What you should know...

1. Where does leishmaniasis occur?
2. How is leishmaniasis transmitted?
3. What are the 3 main presentations of leishmaniasis?
4. What is the natural history of cutaneous leishmaniasis?
5. Why is *L. braziliensis* special?

Leishmaniasis

- Tissue/blood protozoa
  - Like malaria and toxoplasma
  - More closely related to trypanosomes
The pathogen
Leishmania

• Live in phagolysosome in macrophages

Amastigote stage

- kinetoplast (black arrow)
- nucleus (red arrow)

CDC/DPDx
The vector

• Sandfly
  – *Phlebotomus* - Old World
  – *Lutzomyia* - New World

• Characteristics:
  – Small (1/3 the size of mosquito)
    • Gets through most mosquito nets
  – Generally bites in the evening and night
    • Can be urban or rural
  – Poor flying ability
    • Uses hopping movements, can’t fly in the wind

Parasite life cycle

<table>
<thead>
<tr>
<th>Sandfly Promastigotes</th>
<th>Human Amastigotes</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image of sandfly" /></td>
<td><img src="image2.png" alt="Image of human amastigote" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Image of sandfly promastigote" /></td>
<td><img src="image4.png" alt="Image of human amastigote" /></td>
</tr>
</tbody>
</table>
Life cycle

Can be zoonotic or anthroponotic
3 characteristic syndromes

<table>
<thead>
<tr>
<th>Cutaneous</th>
<th>Mucocutaneous</th>
<th>Visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative skin lesions</td>
<td>Destructive, progressive</td>
<td>Systemic febrile illness</td>
</tr>
<tr>
<td>Painless</td>
<td>Painless</td>
<td>Wasting and splenomegaly</td>
</tr>
<tr>
<td>Most self-cure (6-18 months)</td>
<td>Associated with New World</td>
<td>Fatal without treatment</td>
</tr>
</tbody>
</table>

Clinical manifestations after infection with *Leishmania* parasites depend on:

1. Species of *Leishmania* parasite
2. Region acquired
3. Vector - type of sandfly (vary geographically)
4. Host immune response
Classification
Clinical syndrome and species

Visceral leishmaniasis
- \( L.(L) \) Donovani
  - Indian subcontinent and East Africa
- \( L.(L) \) infantum / chagasi
  - Mediterranean, and Latin America

Cutaneous Leishmaniasis
Old world
- \( L.(L) \) Major
  - Rural, zoonotic, inflammatory
- \( L.(L) \) Tropica
  - Urban, anthroponotic, dry, slow evolving
- \( L.(L) \) Aethiopica

New World
- \( L. \) Viannia - \( L.(V) \)
  - \( L(V) \) Braziliensis complex
- \( L. \) Leishmania – \( L.(L) \)
  - \( L.(L) \) Mexicana complex

Risk for Mucosal Leishmaniasis – MCL (5%)
Classification
Clinical syndrome and species

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New World
• L. Viannia - L (V)
  – L(V) Braziliensis complex
• L. Leishmania – L (L)
  – L. (L) Mexicana complex

Risk for Mucosal Leishmaniasis – MCL (5%)
+ indicates risk for MCL

4 important features shared by all Leishmania infections
1. Transmitted by sandflies
2. Intracellular pathogens
   – Amastigotes target macrophages and can survive and replicate within the phagolysosome
3. Clinical manifestations are dependent on host immune response
   – Subclinical infections are common
4. Persistent infection (even after effective treatment of disease)
   – Risk of relapse in patients with HIV/AIDS
Global burden of disease

- 350 million people at risk
- 300,000 cases of VL per year
  - Over 20,000+ deaths
  - Endemic in East Africa, NE India, and Brazil
    - Over 90% in just 6 countries
- 1-2 million cases of CL per year
  - CL burden is more widespread than VL
  - Most occur in:
    - **Latin America**: Brazil, Colombia, and Peru
    - **Middle East, Central Asia**: Afghanistan, Iran, Syria
    - Algeria and Mediterranean
  - MCL: 1-5% of NWCL cases
  - 90% of cases of MCL in just 3 countries
    - Bolivia, Brazil and Peru

WHO, fact sheet 2016

Visceral Leishmaniasis

Status of endemicity of visceral leishmaniasis worldwide, 2015

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New World Cutaneous Leishmaniasis

Which of following countries is not endemic for Leishmaniasis?

A. Costa Rica  
B. Cambodia  
C. Pakistan  
D. Iran
Cutaneous Leishmaniasis

Typical presentation

1. Papule develops at the site of sandfly bite
   - Incubation period 2 – 8 weeks (may be years)
   - Usually face, arms, legs (exposed sites)

1. Papule enlarges into nodular or plaque-like lesion with a soft center that breaks, forming an ulcer

2. Ulcer is painless, round, with a well-demarcated raised border

1. Heals slowly, over 6 – 24 months, often leaving a scar

OWCL

• L. major
  - Rural (zoonotic)
  - Inflammatory, faster time course
  - Larger lesions
  - May be multiple lesions
**OWCL**

- *L. tropica* - Urban (anthroponotic)
  - Predilection for the nose
  - Smaller, single
  - Slower time course

**NWCL**

- Typically more severe and last longer than OWCL + risk of MCL

- *L. (V) braziliensis* complex
  - Aggressive
  - Only 10% resolve within 3 months
  - May have lymphadenopathy
  - Associated with MCL

- *L. (L) mexicana* complex
  - Milder version
  - 75% resolve within 3 months
  - Not associated with MCL
  - Chiclero ulcer (ear)
Natural history of CL
Most lesions self-cure

L. major

Figure 6. Duration of the lesions in 134 cases of L. major infection. (From reference 5 with permission.)

L. tropica

Figure 10. Duration of the lesions in 454 cases of L. tropica infection. (From reference 3 with permission.)

6 months

Lancet 2005; 366: 1561–77

Epidemic of CL (L. tropica)
Kabul, Afghanistan

photo from: http://afghanistanmylasttour.files.wordpress.com
Epidemic of CL in Syria

Epidemic of CL in Yemen
Impact on women and girls

International Journal of Women’s Dermatology 2 (2016) 93–101
Stigma

Typical CL | Atypical

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**Atypical cutaneous**

**Diffuse cutaneous leishmaniasis (DCL)**

- Multiple, nodular, non-ulcerative
  - Gradually progressive over months – years
  - Polyparasitic, anergic immune response (no granulomas)
  - Mimics lepromatous leprosy


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**Atypical cutaneous**

**Leishmaniasis recidivans and lupoid**

- Plaque, scar-like, non-ulcerative forms
  - Typically involve the face
  - Strong cell-mediated response (no/few parasites)
  - Mimics tuberculoid leprosy

*Global Skin Atlas*

*Dermatol Ther* (2011) 1(2):36-41
**Cutaneous Leishmaniasis**

- 1 – 5% of all patients with *L(V)*braziliensis
- Bolivia, Peru, Brazil

- Generally occurs after an episode of CL
  - May occur years later
  - 5% occur *at the same time* as CL
  - 10% have no previous episode of CL

- Nose almost always involved first > pharynx, palate, larynx, lip
  - Nasal itch or stuffiness
  - Progressive ulceration can be very destructive
  - Does not heal spontaneously

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**MCL**

**Clinical features**

- 1 – 5% of all patients with *L(V)*braziliensis
- Bolivia, Peru, Brazil

- Generally occurs after an episode of CL
  - May occur years later
  - 5% occur *at the same time* as CL
  - 10% have no previous episode of CL

- Nose almost always involved first > pharynx, palate, larynx, lip
  - Nasal itch or stuffiness
  - Progressive ulceration can be very destructive
  - Does not heal spontaneously
MCL
Progressive, slowly destructive

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MCL
45F from Peru, old scar on leg

Gorgas Course in Tropical Medicine

Tropical and Geographic Medicine Intensive Short Course 2018
MCL
26M from Peru, old scar on leg

Gorgas Course in Tropical Medicine

Diagnosis

Maintain high index of suspicion if:

- Chronic skin or nasopharyngeal lesion
- Exposure to an endemic area
Diagnosis

• Sample collection for PCR analysis with Cervisoft® cytology brush:
  – As sensitive as scraping (CL) or tissue biopsy (MCL) (96%)

PloS ONE 7(11): e49738,(2012)
Diagnosis

- Sample collection for PCR analysis with filter paper

Clinical Infectious Diseases 2010; 50:e1–6

If the natural history of CL is to resolve on its own, why treat?

1. Practical aspects; to accelerate healing of the lesions
   - Cosmetically disfiguring
     - > 4 lesions; > 4 cm in size
     - Not getting better on their own

2. Immunocompromise

3. To decrease the risk for mucosal disease
   - New world, especially Bolivia, Peru or Brazil
   - *L.(V) braziliensis*
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Treatment options for CL

1. Wound care only

2. Local therapy
   – Cryotherapy
   – Thermotherapy
   – Topical paromomycin cream
   – Intralesional injections of pentavalent antimony (Sb⁵⁺)

3. Systemic therapy
   – Oral
     • Fluconazole
     • Miltefosine
   – Parenteral
     • Pentavalent antimony (Sb⁵⁺)
     • Amphotericin B

Cryotherapy

• Efficacy ~60 – 80%
• Typically used for small, old world CL lesions
Thermotherapy

• Efficacy ~60 – 80%
• Leishmania are heat sensitive

Valencia et al. PLoS NTD 2013

Topical paromomycin cream

• Efficacy ~20 – 80%
• Formulation/carrier may make a difference

• Several formulations:
  – Paromomycin with methylbenzethonium chloride (Leshcutan)*
  – Paromomycin with gentamicin (WR279,396)*
  – a compounding pharmacy can prepare a topical preparation using 15% paromomycin in soft white paraffin

Intralesional pentavalent antimony (Sb$^{5+}$)

- 1-3 ml infiltrated in the lesion, every 5-7 days, until better

Source: Paula Bronstein/Getty Images AsiaPac
Pentavalent antimony (Sb\(^{5+}\))

- Heavy metal
- Toxic and poorly tolerated
- Historical standard (1940s)
- **70 – 80% effective** for CL

  - Two “brands”:
    - Sodium stibogluconate (SSG) – Pentostam
    - Meglumine antimonate (MA) – Glucantime

  - Administration:
    - 20mg/kg IV or IM x 20 – 30 days
    - Can also be given **intralesional** for CL

  - Side effects:
    - Arthalgia, myalgia, GI upset
    - **Pancreatitis**; Monitor amylase
    - **Arrhythmia**; Monitor QT

Systemic treatment options
Recommended for complex CL

- **Pentavalent antimony (Sb\(^{5+}\))**
  - 20mg/kg IV or IM x 10 – 20 days

- **Liposomal amphotericin (L-amB)**
  - 3mg/kg IV x 6 - 10 doses

- **Miltefosine**
  - 2.5mg/kg (50mg PO TID x 28 days)

- **Fluconazole**
  - 600mg PO x 6 weeks

Also used for Mucocutaneous and Visceral leishmaniasis
Fluconazole

- RCT in Saudi (L. major)
  - 200 patients, 200mg fluconazole/day x 6 weeks
  - 80% cure vs 30% with placebo at 3 months


Cutaneous Leishmaniasis
Expect a slow response to treatment

- At least 50% re-epithelialization in 4-6 weeks
- 100% re-epithelialization by 12 weeks

- Clinical cure not parasitological cure
Choosing treatment options

• Difficult choice:
  – Variable clinical syndrome
  – Trial results vary by species and by region
  – Lack of well-controlled clinical trials

  – Cochrane review: “No general consensus on optimal treatment has been achieved”

Treatment of MCL

1. Sb5+ (20mg/kg x 28 days)
2. L-amB (40 - 60mg/kg total dose)
3. Miltefosine (50mg tid x 28 days)
Case
Yoga retreat in Costa Rica

- 35F, previously well
  - Developed painless lesion under her left eye
  - Persisted for 2 months
  - Saw dermatologist, biopsy taken
    - Histopathology = nonspecific inflammation, no organisms seen

Questions

- Is it leishmaniasis?
  - How would you investigate?
Questions

• Scrapings taken for PCR
  • Positive → Leishmania present, subgenus Viannia
  • L(V)panamensis

• How would you treat?
  A. Cryotherapy
  B. Fluconazole
  C. L-amphotericin
  D. Watch and wait

Outcome

• Scrapings taken for PCR
  • Positive → Leishmania present, subgenus Viannia
  • L(v)panamensis

• Treated with L-amB 3mg/kg x 7 days
  • Slow, but significantly better by 4 weeks
Which of these is most likely to mimic cutaneous leishmaniasis?

A. Ecchyma
B. Buruli ulcer
C. Anthrax
D. Fungal (e.g., Sporotrichosis)
E. Pyoderma gangrenosum

Ecchyma

- “Deep impetigo”
- Typically Strep pyogenes and Staph aureus
Buruli ulcer

- Mycobacteria ulcerans
- Painless and undermining of edges

http://www.who.int/buruli/photos

Sporotrichosis
*Sporothrix schenkii*

- Rose-cutters, tropical regions
  - 25% do not have classic lymphonodular spread
- Painless nodules that ulcerate

Gorgas course, Peru
Pyoderma gangrenosum

- Painful
- Associated with systemic illness

Cutaneous anthrax

- Painless, necrotic ulcer with extensive edema
  - More acute, may become very unwell
Young girl with CL
Kabul, Afghanistan

A. Topical paromomycin
B. Cryotherapy
C. Fluconazole
D. Miltefosine
E. IL pentavalent antimony

photo from: http://afghanistanmylasttour.files.wordpress.com

Tropical and Geographic Medicine Intensive Short Course 2018
Visceral leishmaniasis
Kala-azar

Clinical triad
1. Fever for ≥ 2 weeks
2. Weight loss
3. Splenomegaly
4. Pancytopenia

Gradual wasting and immunocompromise
– Lethal if not treated

VL
Epidemiology
• ≥ 300,000 cases per year
  – ≥ 30,000 deaths
    • Many cases may be missed
    • In some areas > 90% of VL deaths may go undetected

• 90% of all cases in just 6 countries
  – India (Bihar), Bangladesh
  – Sudan, South Sudan and Ethiopia
  – Brazil

Lozano et al, Lancet 2012
Trop Med Int Health. 2006 Apr;11(4):509-1
Global burden
Visceral Leishmaniasis

Strong association with poverty

Lancet 2005; 366: 1561–77
**VL Diagnosis**

**Clinical suspicion**

- **Serological tests**
  - rK39

- **Parasitological tests**
  - Sample collection:
    - Splenic aspirate
    - Bone marrow aspirate
    - Lymph node aspirate
  - Detection tests:
    - Microscopy
    - Culture
    - PCR

**Fever**

**Weight loss**

**Splenomegaly**

**Pancytopenia**

**Serology**

**Very useful test for VL**

- **rK39**
  - Simple, Rapid test
  - 10 minutes – uses a dipstick

- **Drawbacks:**
  - Remain positive for years after cure
  - Detect asymptomatic infections
Diagnostic algorithm for VL Indian subcontinent

Kala-azar suspect:
- Fever > 2 weeks
- Splenomegaly
- Weight loss

rK39

Not kala-azar
- search for other diagnosis

Kala-azar
- treat

Splenic aspirate
Treatment options

1. **Sb\textsuperscript{5+}**
2. L-amB
3. Miltefosine

**Sb\textsuperscript{5+}**

Has been standard of care for years, but...

1. In India (Bihar), very high rates of resistance
   - 30% failure rates in 1980
   - 50% failure rates in 2000

2. In East Africa, side effects and poor efficacy in patients with HIV
   - 30% mortality – if HIV positive
**Sb\textsuperscript{5+}**

Has been standard of care for years, but...

Photo: James Nachtwey

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**Miltefosine**

Breakthrough – an effective oral drug for VL

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**ORAL MILTEFOSINE FOR INDIAN VISCERAL LEISHMANIASIS**

Shyam Sundar, M.D., T.K. Jha, M.D., C.P. Thakur, M.D., Juergen Engel, Ph.D., Herbert Sannermann, Ph.D., Christina Fischer, Klaus Junge, Ph.D., Anthony Bryceon, M.D., and Jonathan Berman, M.D., Ph.D.

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- RCT of 299 patients with VL in Bihar, India
  - AmB x 15 doses on alternate days
  - Miltefosine x 28 days
  - **100% initial cure rate at 1 month**
    - 3% relapse at 6 months in miltefosine group
    - 0% relapse in AmB group

L-amB
Single 10mg/kg dose effective in India

- RCT of 410 patients in India
  - L-amB 10mg/g IV x 1 dose
  - AmB deoxycholate 1mg/kg x 15 doses every other day
  - 96% cure rates at 6 months
    - Less adverse effects in the L-amB group


Combination therapy?

- L-amB + miltefosine
  - For patients with HIV
  - To prevent drug resistance
Case
Migrant worker in Ethiopia

- 45M, migrant worker in Northern Ethiopia
  - 2 previous episodes of TB
  - 1 previous episode of VL
  - Recently diagnosed with HIV
    - CD4 count 175, not yet on treatment

- Presents with
  - Fever x 3 weeks
  - Weight loss
  - Splenomegaly
  - Generalized weakness, cough, diarrhea

Questions

- Initial investigations
  - Malaria smear negative
  - Pancytopenia

- Should we order rK39 blood test?
Questions

• Initial investigations
  – Malaria smear negative
  – Pancytopenia

• Should we order rK39 blood test?
  – Cannot distinguish between relapse and active disease vs positive from prior episode 3 months ago

• Next step?

He underwent splenic aspirate

• Microscopy:
He underwent splenic aspirate

- Microscopy: > 100 parasites per HPF

Diagnosed with relapsed VL, HIV+

- How should he be treated?
  - He started combination treatment:
    - L-amB IV every other day x 6 dose
    - Miltefosine PO x 28 days
- After 2 weeks he was feeling better, fevers reduced, but coughing persisted

- Other issues:
  - Starting ARV
  - Secondary prophylaxis to prevent relapse
Diagnosed with relapsed VL, HIV+

- How should he be treated?
  - He started combination treatment:
    - L-amB IV every other day x 6 dose
    - Miltefosine PO x 28 days

- After 2 weeks he was feeling better, fevers reduced, but coughing persisted

After 2 weeks he was feeling better but still coughing

- Sputum AFB negative x 3
- CXR left lower lobe infiltrate
- Next steps...
  - Sent for GeneXpert...
Leishmaniasis

- Vector borne (sandfly)
- Intra-macrophage protozoan infection
- 3 main clinical manifestations:
  - Visceral
  - Cutaneous
  - Rx - L-amB

Additional slides
Deltamethrin-impregnated dog collars

**Effect of insecticide-impregnated dog collars on incidence of zoonotic visceral leishmaniasis in Iranian children: a matched-cluster randomised trial**

A S Mazrouei Gargari, M H Hozati, H Mohit, C R Davies

Villages that used the collars had:
- 50% ↓ in seroconversion in dogs
- 50% ↓ in seroconversion in children

Lancet 2002
Substances in sandfly saliva may influence disease manifestations

• L. infantum/chagasi infections occur in both Brazil and Costa Rica
  – In Brazil they cause VL - not CL
  – In Costa Rica they cause CL - not VL

• The sandflies in the two countries are different
  – Costa Rica sandflies:
    • have very low amounts of maxadilan (vasodilatory peptide) they induce very little erythema and may increase the risk for cutaneous infection
  – Brazil sandflies:
    • have more maxadilan, more erythema, and may increase the risk for disseminated infection
PKDL
Post-Kala Azar Dermal Leishmaniasis

- East Africa (Sudan)
  - Occurs early, can start during treatment
  - Occurs frequently (50%)
  - Often heals spontaneously

- Indian subcontinent (Bihar)
  - Occurs years later
  - Occurs infrequently (5%)
  - Rarely heals spontaneously
Amphotericin B

- Effective for VL, MCL, and CL
- May have highest therapeutic index of any anti-leish medication
- 85% cure rates for CL

- Liposomal amphotericin B (L-amB)
  - WHO = 2-3mg/kg per day to a total of 20-40mg/kg
    - for L(V) braziliensis
  
  Other dosing options
  - 3mg/kg days 1–5 and 10
  - 3mg/kg days 1–7

L-amB vs SbV

Israeli travellers to Bolivia

- Up until 2004, everyone at their clinic with CL was treated with pentavalent antimony (Sb⁵⁺). They then switched to liposomal amphotericin (L-amB)

  - Observational study
    - Sb⁵⁺ (n=34): 20mg/kg x 21 days
      - 70% cure, 29% relapse
    - L-AmB (n=34): 3mg/kg days 1-5, 10
      - 85% cure, 3% relapse

Leishmanization

Leishmanization, as a live vaccine, was used in Middle East and C. Asia over 2 million people during the Iran-Iraq war of 1982-86

- It worked, but fell out of favour, perhaps due to limited efficacy and reports of chronic wounds

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- **L. Leishmania - L.(L)**

Risk for Mucosal Leishmaniasis – MCL (5%)

New 2016 IDSA Guidelines

Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH)

Clinical Infectious Diseases 2016;63(12):e202–64