Skin ulcers in travelers and migrants

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Case A
- 37 y.o male, healthy
- 1 month touristic travel to Morocco (all over the country)
- Vaccines: typhoid fever, hepatitis A+B, no malaria prophylaxis
- Sexual relations without preservatives
- Close contact with camels
- Insect bites ++
- Multiple non-painful skin ulcers (x5: forearm, calves, foot) appeared before returning and growing progressively

Case B
- 39 yo male, healthy, researcher biologist
- 3 weeks travel to French Guyana (jungle)
- Vaccines: yellow fever, rabies, no malaria prophylaxis
- Insect bites ++
- Last week before returning he noticed an increasing non-painful crusty ulcer in the left calve. Treated as tropical ulcer with local treatment and antibiotics (amoxycillin-clav) without improvement
- One moth later: a new 5 cm ulcer + satellite lesion in the chest
### Leishmaniasis: diagnostic procedure

- **Serology?**
- **Biopsy or needle aspirate (edges)?**
  - Giemsa stain
  - Culture: NNN medium, Schneider’s medium
  - PCR

Is it important to determine the *Leishmania* sp involved or just to classify as "Old world cutaneous leishmaniasis" (first case) or as "New world cutaneous leishmaniasis" (second case)?

- **Should we know the geographical origin and the *Leishmania* sp involved?**

### Skin/mucosal leishmaniasis

- **Cutaneous leishmaniasis (CL)**
- **Mucocutaneous leishmaniasis (MCL)**
- **Disseminated cutaneous leishmaniasis**
- **Diffuse cutaneous leishmaniasis**
- **Leishmaniasis recidivans**
- **Post-kala-azar dermal leishmaniasis**

#### Old World (South of Europe, Middle East, Asia and Africa)

- *L. tropica*, *L. major*, *L. infantum*, *L. donovani* and *L. aethiopica*

#### New World (Latin America)

- *L. mexicana* complex (*L. mexicana*, *L. amazonensis*)
- *L. braziliensis* complex (*L.(V) braziliensis*, *L.(V) peruviana*)
- *L. guyanensis* complex (*L.(V) guyanensis*, *L.(V) panamensis*)
- *L. chagasi/infantum* complex
Case A

- **L. major**
- In Morocco there are: *L. major*, *L. tropica* and *L. infantum*
- Intralesional antimonials (Glucantime®: meglumine antimoniate 85%): 0.3-0.5 ml per lesion, twice a week for 4 weeks
- Improvement
- One month later: forearm and calf lesions resolved, but still some activity in the foot lesion. New infiltration and cure

Case B

- **L. major**
- Multiple ulcers.
- Wet inflammatory, rapidly growing.
- Could self-heal in 3-6 months.

**2-10% risk for mucocutaneous spread if not treated properly.**

Case B

- **L. braziliensis**
- Liposomal Amphotericin B (Ambisome®): 3 mg/kg/d (7 doses), days 1, 2, 3, 4, 5, 14, 21 for a total dose of 21 mg/kg = 2.1 g.
- Slight improvement during treatment but worsening at the end with an increase in size of the metastatic thoracic lesion.

Case B

- Pentavalent antimonials (Glucantime®: meglumine antimoniate 85%): 20 mg 5×7 kg/d, i.v, for 28 days.

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INTRODUCTION

Leishmaniasis

Cutaneous leishmaniasis (CL) is frequent in travelers/migrants
- Bolivia, Afghanistan and Costa Rica are the main places of acquisition
- CL in travelers to South and Central America (60%).
- CL in European travelers to the Mediterranean basin
- CL in soldiers to Iraq, Afghanistan, Middle East and Belize
- CL in immigrants from areas of the New and Old World
- MCL rare in travelers (Bolivia, Suriname, French Guiana)
- MCL in immigrants from South American (Bolivia, Ecuador)

Visceral leishmaniasis (VL) is rare in travelers/migrants
- VL in travelers to Southern Europe: Greece, France, Spain, Italy, Portugal, Turkey and Croatia.
- VL in migrants from Northern Africa, Middle East and Asia

Prevention of leishmaniasis in travelers
- no prophylactic medications
- no vaccines
- personal protective measures (PPM)
  - protective clothing
  - insect repellents (DEET)
  - permethrin applied to clothing
  - insecticide-impregnated bed nets
- Healing of CL may be associated with some protection from clinical disease with subsequent exposure to the same Leishmania species/strain
Leishmaniasis

- Diverse group of syndromes caused by protozoa of the genus Leishmania (Leishmania and Viannia subgenera); >20 of which are pathogenic for humans
- Transmission by sandflies (Phlebotomus, Lutzomyia)
- Mammalian hosts (zoonotic cycle) or human hosts (anthroponotic cycle)
**Taxonomy of Leishmania sp**

- **Old World** (South of Europe, Middle East, Asia and Africa)
  - L. tropica
  - L. major
  - L. infantum
  - L. donovani
  - L. aethiopica

- **New World** (Latin America)
  - L. mexicana complex
    - L. mexicana
    - L. amazonensis
  - L. braziliensis complex
    - L(V) braziliensis
    - L(V) peruviana
    - L. guyanensis complex
      - L(V) guyanensis
    - L(V) panamensis
    - L. chagasi/infantum

**Leishmaniasis**

- Main clinical syndromes
  - Visceral leishmaniasis (VL)
  - Mucosal leishmaniasis (ML)
  - Cutaneous leishmaniasis (CL)
  - Diffuse cutaneous leishmaniasis
  - Disseminated cutaneous leishmaniasis
  - Leishmaniasis recidivans
  - Post kala-azar dermal leishmaniasis (PKDL)
Cutaneous leishmaniasis (CL)

- Incubation period: several weeks
- In exposed skin areas
- Single or clustered or satellite or distant lesions
- Lesions typically begin as papules, progress in size, and often ulcerate (well-defined ulcer with indurated borders)
- Small or large
- Lesions may be chronic ulcers, papules, nodules, verrucous lesions, or plaques
- May be subcutaneous nodules (sporothrichoid)
- Usually painless
- No purulence, unless superinfected.
- May be regional adenopathy

The morphologic characteristics and natural history depend on the infecting Leishmania species and the host’s response

Muco-cutaneous leishmaniasis (ML)

- ML after healing of CL (months-decades) or concomitantly with CL
- ML can progress to cause destructive lesions of the naso-oropharyngeal/laryngeal mucosa.
- Coryza, epistaxis, pruritus, mass sensation, obstruction, hyposmia, bleeding, dysphagia/odynophagia; dysphonia
- Examination of the naso-oropharyngeal mucosa even if they do not have any mucosal symptoms
- Erythema, edema, hyperemia, infiltration, nodules, erosion, ulceration, and tissue destruction (perforation of the nasal septum).

Typically from the New World
Amazonian Bolivia, Brazil and Peru (regions up to an altitude of 2000 meters)
L.(V).braziliensis mainly
L.(V).guyanensis, L.(V).panamensis, Also reported from the Old World

CL/ML in immunosuppressed hosts

- May be opportunistic infection in immunocompromised hosts (HIV+, drugs: anti-TNF, transplantation, cancer, etc)
- Likelihood of atypical, multifocal, diverse, persistent, progressive, mucosal, and relapsing lesions
- Pleomorphic, nonulcerative, papulonodular lesions

CL differential diagnosis

- bacterial skin abscesses, infected arthropod bites, impetigo
- cutaneous fungal and mycobacterial infections
- cutaneous actinomycosis/nocardiosis
- yaws
- skin cancer
- pyoderma gangrenosum
- sarcoidosis
- venous stasis ulcers
- cutaneous myiasis
- spider bites
- tropical ulcers
- prurigo nodularis
- lichen simplex chronicus
- fixed drug eruptions
- vasculitis
ML differential diagnosis

- paracoccidioidomycosis
- histoplasmosis
- rhinosporidiosis
- rhinoscleroma
- leprosy
- tuberculosis
- syphilis
- tertiary yaws
- neoplastic diseases
- Wegener’s granulomatosis
- sarcoidosis
- intranasal cocaine use

**Diagnosis**

- Clean the lesion, remove debris and take tissue samples:
  - Scratch, needle aspiration
  - Full biopsy (ML biopsy specimens obtained by an otolaryngologist)
- Light-microscopic examination of a Giemsa stained samples
- Histopathology (granulomatous inflammation)
- Parasite isolation by culture (NNN medium, Schneider’s medium)
- **Molecular detection of parasite DNA**: the most sensitive method and allows to determine the *Leishmania sp*
- Serology neither sensitive nor specific
- Leishmania skin testing is not recommended or available

**TREATMENT**

- amastigotes
- promastigotes
Treatment of imported leishmaniasis is complex

Management may vary from no treatment, to local or to systemic treatment

- Leishmania strain/species involved
- Area of acquisition of the infection
- Known response rates for anti-leishmanial in the geographic region
- Potential adverse events of anti-leishmanial drugs
- Drugs interactions
- Immunosuppression
- Pregnancy
- Overweight
- Hepatic, pancreatic, renal, and cardiac comorbid conditions
- The rapidity of healing, daily activities
- Drug availability, cost, insurance reimbursement
- Patient’s preferences

Cutaneous leishmaniasis (CL): spontaneous healing

OWCL
- The natural history is usually slow spontaneous (months to years) healing with residual scarring as cell-mediated immunity develops
  - L. major: 40%-70% (3m), 100% (12m)
  - L. tropica: 1% (3m), 68% (12m), 100% (3y).

NWCL
- Frequency of spontaneous healing observed for one species should not be generalized to other Leishmania sp
- 26% of all heal spontaneously (without treatment) after 3-9 months
  - L. mexicana: 44% (19%-72%)
  - L. braziliensis: 6-7% (0.2%-20%)
  - 20% relapse with initial healing

Simple CL lesions

- Single or few lesions (<5)
- Small size (<1cm)
- Location feasible for local treatment
- No mucosal involvement
- No local subcutaneous nodules
- No lymphatic spread (<1 cm regional lymphadenopathy)

Complex CL lesions

- ≥ 5 lesions
- Large size (≥ 5 cm)
- Lesion on face including ears, eyelids, lips; fingers, toes, genitalia
- Location non feasible for local treatment
- Mucosal/laryngeal involvement
- Local subcutaneous nodules
- Lymphatic spread
**Indications for local treatment (or no treatment)**

- Simple CL lesions
- Immunocompetent persons
- *Leishmania sp* not associated with increased risk for ML
- *Leishmania sp* not known but acquired in a non-ML-risk region
- Preferred for simple OWCL lesions
- Useful for NWCL caused by *Leishmania sp* not associated with ML-risk

**Indications for systemic treatment (oral or parenteral)**

- Complex CL lesions
- Immunosuppression
- *Leishmania sp* associated with increased risk for ML
- *Leishmania sp* not known but acquired in an ML-risk region, even with healing/recently healed CL lesions
- Mucocutaneous leishmaniasis
- Leishmaniasis recidivans (*L. tropica*)
- Diffuse CL (*L. mexicana, L. amazonensis, L. aethiopica*)
- Disseminated CL (*L (V). braziliensis*)
- PKDL (*L. donovani*)
- When healing does not progress with local treatment (2-3 months post)

**Increased risk mucosal leishmaniasis areas** are south of the Amazon in Peru, Brazil and Bolivia

**Moderate risk areas** are south of Nicaragua to Amazon

**Local treatment options**

- Thermotherapy
- Cryotherapy
- Photodynamic or laser treatment
- Topical ointments/creams with paromomycin and other ingredients
- Intraleisional injections of pentavalent antimonials or pentamidine

**Local treatment options: Thermotherapy/Cryotherapy**

- Thermotherapy by ThermoMed TM device (local) applied at 50°C for 30 seconds in one session
- Thermotherapy by radiofrequency (local) applied at 50°C for 30 seconds once weekly for 4 weeks
- Thermotherapy by Laser of CO2 (local) single session
- Cryotherapy (local) freeze for 10-30 seconds and thaw, applied 2-3 times in each session, repeated every 1-4 weeks to complete healing (usually 2-4 sessions, but some require an additional session)
- Photodynamic or laser treatment
Local treatment options: Thermotherapy/Cryotherapy

Topical ointments/creams with paromomycin and other ingredients

- 15% Paromomycin sulphate + 12% Methylbenzothonium chloridre ointment (topical) twice a day for 20 days
- 15% Paromomycin sulphate + 0.5% Gentamicin sulfate in a hydrophilic base ointment (topical) twice a day for 20 days
- 15% Paromomycin sulphate + 10% Urea ointment (topical) twice daily for 4 weeks

Local treatment options: Topical paromomycin

Local treatment options: intralesional antimonials / pentamidine

- Intralesional injections of pentavalent antimonials
  Sodium stibogluconate or Meglumine antimoniate il. 0.5-3 ml repeatedly administered (1-3 times a week) for 4-5 consecutive weeks

- Intralesional injections of pentamidine
  Pentamidine isethionate il. 120 μg/mm² lesion area, 3 injections over 5 days

Lesions should be debrided before administration of local therapy
Risk of secondary bacterial infection
### Systemic treatment options

- Fluconazole
- Miltefosine
- Pentavalent antimonials (SSG, MA)
- Amphotericin B deoxycholate
- Lipid formulations of amphotericin B
- Pentamidine
- Paromomycin
- Combination therapies

### Oral treatment options: Azole drugs

- **Fluconazol** (oral) 200 mg/day for 6 weeks.
- **Ketoconazole** (oral) 600 mg/day for 6 weeks.
- **Itraconazole** (oral) 200 mg/day for 6 weeks.
- **Itraconazole** (oral) 400 mg/day for 3 weeks.

### Oral treatment options: Miltefosine

- **Miltefosine** (oral) 2.5 mg/Kg/day for 28 days
  - 150 mg/d for 28d in adults
  - 150 mg/d for 28d in ≥12 years with body weight >50Kg
  - 100 mg/d for 28d in ≥12 years with body weight ≥25Kg
  - 50 mg/d for 28d in ≥12 years old with weight <25Kg

### Systemic treatment options: Pentavalent antimonials

- **Sodium stibogluconate** or **Meglumine antimoniate** (im or iv) 20 mg Sb⁺⁺/Kg/d for 20-30 days
- **Sodium stibogluconate** or **Meglumine antimoniate** (im or iv) 20 mg Sb⁺⁺/Kg/d for 20 days +/- **Allopurinol** (oral) 20 mg/Kg/day for 20 days
- **Sodium stibogluconate** (im or iv) 20 mg Sb⁺⁺/Kg/d for 20 days as above + **Pentoxifylline** (oral) 400 mg/8h for 20 days
Systemic treatment options: Amphotericin B

- **Amphotericin B deoxycholate**
  0.5–1.0 mg/kg iv. every other day for 20–30 days

- **Liposomal Amphotericin B**
  2-3 mg/Kg/day i.v, for 7-10 doses, up to 20-40mg/Kg total dose

Systemic treatment options: Pentamidine

- **Pentamidine isethionate**
  2–4 mg/kg iv./im. daily or every other day for a total of 4–10 injections

**Treatment options for ML**

The choice of anti-leishmanial agent, dose, and duration of therapy for persons with ML should be individualized

- **Pentavalent antimonials +/- pentoxyfilline (oral 400mg tid x 30 days)**
  20 mg SbV/kg daily, IV or IM for 28–30 days

- **Amphotericin B deoxycholate**
  0.5–1.0 mg/kg per dose, IV, daily or every other day, for a cumulative total of ~20–45 mg/kg

- **Liposomal amphotericin B [L-AmB]**
  Cumulative total dose ranging widely from ~20–60 mg/kg

- **Miltefosine**
  ~2.5 mg/kg per day [maximum, 150 mg/day] for 28 days

- **prophylactic corticosteroid therapy** for persons with laryngeal/pharyngeal disease

**Immunosuppressed hosts**

- Increased risk for suboptimal therapeutic response, for post treatment relapses, and for cutaneous, mucosal, or visceral dissemination

- HIV/AIDS (CD4+ T-lymphocyte <200–350 cells/mm3)

- Associated with TNF-alpha antagonist therapy

- ART should be initiated

- Withdrawal of TNF-α antagonists during antileishmanial therapy?

- Systemic therapy is recommended

- Chronic maintenance therapy if multiple post treatment relapses of CL/ML?
CL Follow-up

- Response is assessed by clinical criteria
- Repeat parasitologic testing is not recommended if appears to be healing
- Therapeutic failure is initially seen at the border of a healed lesion

- By 4–6 weeks the lesion should have decreased by >50%, ulcerative lesions should be reepithelializing, and no new lesions
- Ulcerative lesions are healed in approx. 3 months (healing continues after completed treatment)

- Consider additional therapy by 3rd month if failure is suspected

- CL follow-up for 6–12 months after treatment
- ML follow-up for 2 years after treatment
- Examination of the naso-oropharyngeal/laryngeal mucosa (NWCL)