SAWADEEKA

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Division of Infectious Diseases, the Ottawa Hospital

Director Tropical Medicine and International Health Clinic

National Coordinator Canadian Malaria Network

Site Director Ottawa GeoSentinel Site

My “Medical” history

- Medical School – Memorial University of Newfoundland
  - Joined Canadian Military in 1982
- Internship – University of Toronto – York Finch
- General duty medical officer – CFB Summerside Prince Edward Island
- Internal Medical Residency University of Ottawa
- Infectious Diseases Fellowship University of Ottawa
- DTM&H London School of Hygiene and Tropical Medicine
- Repeated Gorgas Expert Courses in Peru – excellent bedside experience
- ID/Internal Medicine Staff National Defense Medical Centre
- ID and Tropical Medicine the Ottawa Hospital
- Tropical Medicine Content Expert Health Canada
- Longstanding membership on CATMAT – Canadian committee to advise on tropical medicine and travel
- National coordinator Canadian Malaria Network
- Geosentinel site - Since 1995; ASTM Clinical Group; ISTM Review course lecturer
- Asian Clinical Tropical Medicine Course co-Director – Mahidol, UOttawa, UMinnesota, UGeorgia
  - **Next course June 2020**

University of Ottawa

- Medical school – English and French
  - Nursing, Physio, Occupational Medicine, Health Sciences
- Strong research at University and OHRI Ottawa Health Research Institute
- Faculty of Medicine with 65 specialty training programs

The Ottawa Hospital
3 Campuses
including Heart Institute and Research Institute

The Ottawa Hospital – 3 Campuses – 1202 beds

3rd Hospital
in Canada for peer-reviewed funding from the *Canadian Institutes of Health Research*

5th Hospital
in Canada for overall research funding

1,585
Scientific papers published in 2016

59,369
Patient admissions

51,701
Surgical cases

1,174,879
Ambulatory care visits

174,360
Emergency visits

20 years in the Canadian Armed Force the reason I do Tropical Medicine….

Leishmania and the Canadian Military

20 military members seen

18 from deployment to Afghanistan

1 from Jordan

1 on vacation to Costa Rica

In the military who is at risk?

Likely NOT people living here

The soldiers living and sleeping in the dirt – at the “pointy end”

Sandflies like tattoos??

43 year old soldier
Seen July 2007
Lesions since Sept 2006

Afghanistan, Aug 2006-Feb 2007. Outside Kandahar
Sleeping and working in mountains and dirt
Lots and lots of sandfly bites

Papules -> ulcers - with exudate/purulence then scabbing
Recurrent cycle

Bx - histology - dense diffuse mixed inflammatory cells - suppurative and granulomatous
Granulomas with plum histiocytes with numerous intracellular bodies compatible with leishmania

37 year old soldier
Afghanistan Aug 2006-Feb 2007
Seen in clinic Apr 2007
Mid January 3 small papules on his forehead
Blistered, became pruritic, increasing size

In Afghanistan on patrol - routinely sleeping outside
No bed nets, minimal PPM/insect precautions
Sleeping on mattress in sleeping bag
During daytime - always wearing headdress

Pathological diagnosis leishmania - lot of giemsa stained organisms in histiocytes

Initial - delayed treatment due to career course
Stibogluconate - limited response - pancreatitis
Lipid ampho B - poorly tolerated - excellent results

35 year old male seen July 2007
Afghanistan Sept 2006-March 2007
Multiple sandfly bites day 21 and 22 of deployment
Living in hills, sleeping on ground, no bednet, minimal use of PPM
Painless ulcer left upper arm since mid Oct (month after arrival)

Biopsy - histologically proven
1 week post biopsy less indurated

Treated stibogluconate - lots ADRs
Much improved with treatment, small flare off therapy, then ongoing healing

US Military Experience in Iraq ASTMH 2004; NE Aronson, et al

- Localized cutaneous leishmaniasis, generally *L. major,* frequently diagnosed in US military deployed in support of Operation Iraqi Freedom during 2003-2004

- Over 500 cases – many presented at local communities in the US, not to military medical facilities

- Eventually 1500-200 cases – taught us a lot about cutaneous leishmaniasis
  - Can look like almost anything, cutaneous can behave like visceral in the correct host – similar to leprosy – your cell mediated immunity is important

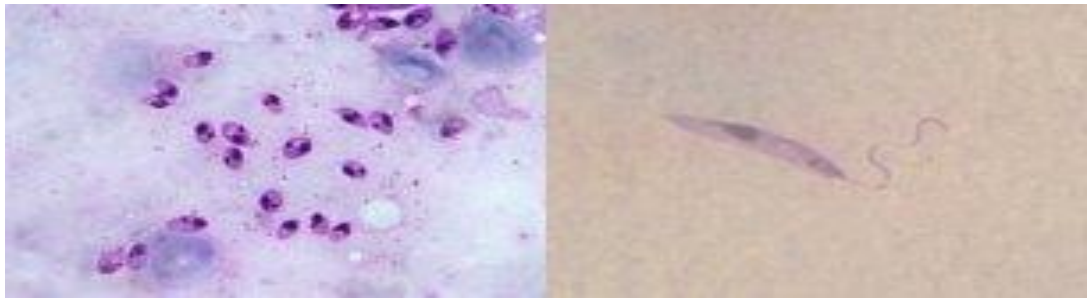
Leishmaniasis

Vector-borne disease

Protozoa of the genus *Leishmania*

Transmitted by sandflies

Obligate intracellular organism

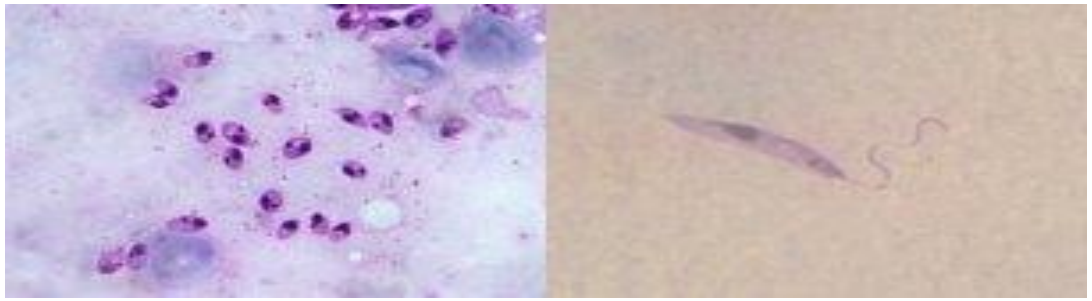


Leishmaniasis

Human infection - about 21 of 30 species that infect mammals.

Lots of mammals reservoirs in different areas of the world – including domestic dogs

Dog reseevoirs have led to increase in urban transmission in many regions



Public health impact

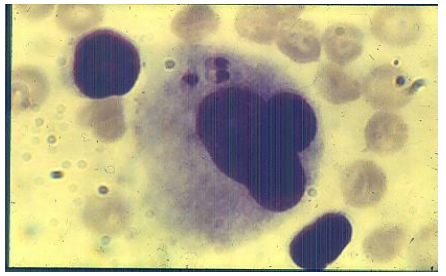
- The global annual incidence is estimated at 1.5-2 million new cases per year:
  - 1-1.5 million cases of CL
  - 500,000 cases of VL.
- Overall prevalence of 12 million cases.
- Approximately 350 million people live in risk areas.

- More than 90% of the VL cases are reported from Bangladesh, Brazil, India & Sudan.

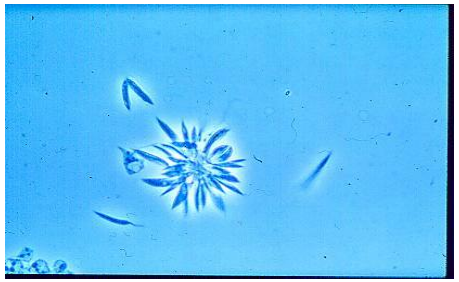
- More than 90% of CL cases occur in Afghanistan, Iran, Saudi Arabia (Old World), Brazil and Peru (New World).

Leishmanial parasites

- The species of genus *Leishmania* are in the family *Trypanosomatidae.*
- They alternate between two hosts:
  - Vertebrate: amastigotes (only intracellular forms)



  - the invertebrate vector (insect): promastigotes.



Epidemiology

- Leishmania infection occurs as consequence of the interaction :
  - Reservoir
  - Vector (sandfly)
  - Human (behaviour)
- All are closely related with ecological conditions
- Man is normally infected by the bite of an infected sandfly

Leishmaniasis - EPIDEMIOLOGY

Only small fraction of those infected get disease

Associated with poverty, malnutrition, population displacement, poor housing, weak immune system, lack of financial resources.

Linked to environmental changes – deforestation, building of dams, irrigation systems and urbanization.

Leishmaniasis - EPIDEMIOLOGY

Endemic in 88 countries on 4 continents.

Americas: from southern Texas to northern Argentina (not Chile and Uruguay).

Africa: mostly North and East Africa, sporadic cases elsewhere.

Europe and Asia: Mediterranean littoral, the Middle East, the Indian subcontinent, northeastern China, and many other Asiatic countries, **excluding Southeast Asia.**

Recenlty increased or reached epidemic proportions:

state of Bihar in northeast India, southern Sudan, Eritrea, Ethiopia, and Afghanistan, in particular the city of Kabul.

RISK FACTORS

Missionaries; Bird watchers and naturalists; People taking tours into the jungle; military

Transmission in urban centers is emerging in many areas of the world, including Afghanistan (Kabul), Brazil, and parts of Central America.

Cumulative risk - Risk increases with length of stay in the endemic area, however, cases with as short as single day

MODE OF TRANSMISSION

Bite of an infected female phlebotomine sandfly

genus *Phlebotomus* in the Old World

genus *Lutzomyia* in the New World.

Sandflies are **noiseless** fliers measuring only 2 to 3 mm in length, or approximately one-third the size of most mosquitoes

Regular bed nets might not be protective against these vectors.

Characteristically rest in cracks on the walls of human habitations or in **animal holes in the ground** and tend to be **more active in the evening and night hours**.

Occasional cases of transfusional, transplacental, and laboratory transmission also have been reported.

Leishmania - Lifecycle

Transmitted by the bite of female phlebotomine sandflies.

Sandflies inject the infective stage, **promastigotes**, during blood meals.

Macrophages phagocytized promastigotes -> **amastigotes**.

Amastigotes multiply in infected cells and affect different tissues
the *Leishmania* species and where they multiply results in the manifestations of leishmaniasis.

Within sandflies – infection from taking aa blood meal from infected person – ingest **amastigotes** – then in the sandfly's midgut, the parasites differentiate into **promastigotes**, which multiply and migrate to the proboscis.

Immunology

Outcome – depends on species, inoculum and host immune response (similarities to leprosy)

Progressive Visceral Leishmaniasis

- impaired TH1 response

Resolution/protection

Leish specific CD4+ t-cells

TH1 (IFN gamma) -> macrophage activation to kill intracellular amastigotes through nitrous oxide; IL12 is also important

Clinical Forms

- Cutaneous
- Mucocutaneous
- Diffuse cutaneous
- Visceral

INCUBATION PERIOD

Extremely variable.

Visceral leishmaniasis, it is 3 to 9 months on average, 10 days – 34 months reported.

Cutaneous leishmaniasis, the incubation period averages several weeks, but cases in which the person actually notices the infecting bite, and it uninterruptedly evolves into a typical leishmanial lesion.

> In a series of U.S. travelers who acquired American cutaneous leishmaniasis, the median incubation period was **30 days**.

Mucosal leishmaniasis - sequela of New World cutaneous leishmaniasis, usually a **few years** after resolution of the original cutaneous lesions. However, this is also variable and in some cases it can appear while cutaneous lesions are still present or decades after they have healed.

Clinical Features of Cutaneous Leishmaniasis

- Location and number of lesions depends on human and sandfly behavior
- Size varies : growing more during the first two months (3-4 cm in *L. braziliensis*)
- Morphology varies, more common ulcer (approx. 80% with majority of *Leishmania* species)

CLINICAL PRESENTATION

Cutaneous leishmaniasis

Has many names - Aleppo boil, Aleppo evil, Bagdad boil, Delhi boil, oriental sore, tropical sore, chiclero's ulcer, uta, pian bois

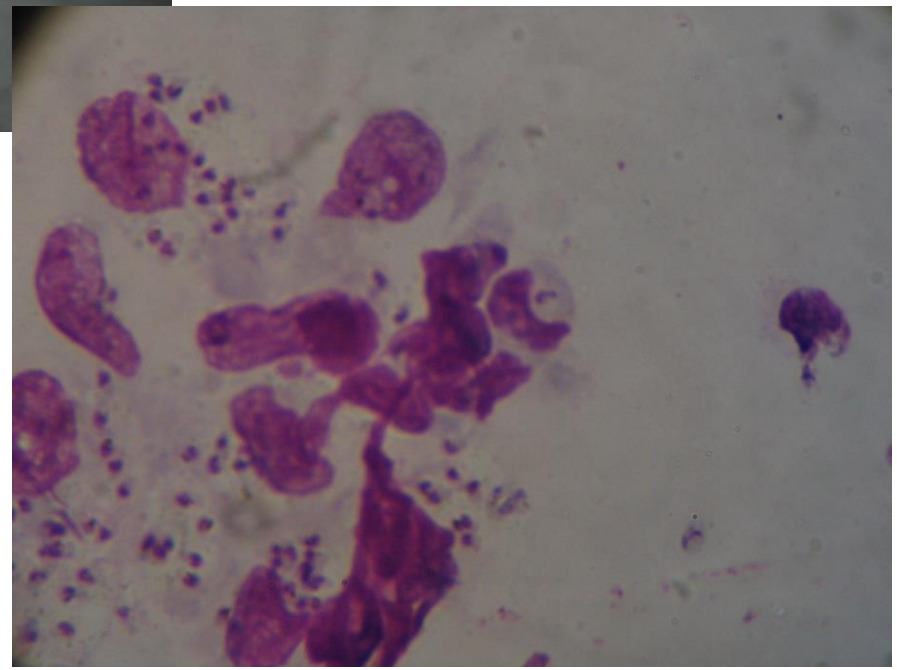
Classically presents with one or multiple lesions that evolve from papules to nodules to ulcers with a central depression and indurated, raised borders.

Atypical presentations with crusted, nodular, non-ulcerated lesions may also occur.

Left untreated, cutaneous leishmaniasis lesions resolve over a period of up to 2 years, leaving behind an atrophic scar. AUTOHEALS

Diagnosis

- Impression smear: 27.9%
- Dermal scraping: 32.7%
- Histopathology: 21.4%
- Culture (aspirate): 85% special medial NNN
- Culture (biopsy): 72.7%
- Hamster (aspirate): 61.2%
- Hamster (biopsy): 77.8%



Leishmania- Diagnosis

My approach – 6 mm punch –
send for routine, fungal and mycobacterial culture, pathology and to PHL for leish PCR testing:

Examination of Giemsa-stained slides of the relevant tissue is still the technique most commonly used to detect the parasite.

Culture with special media – NNN drosophila media

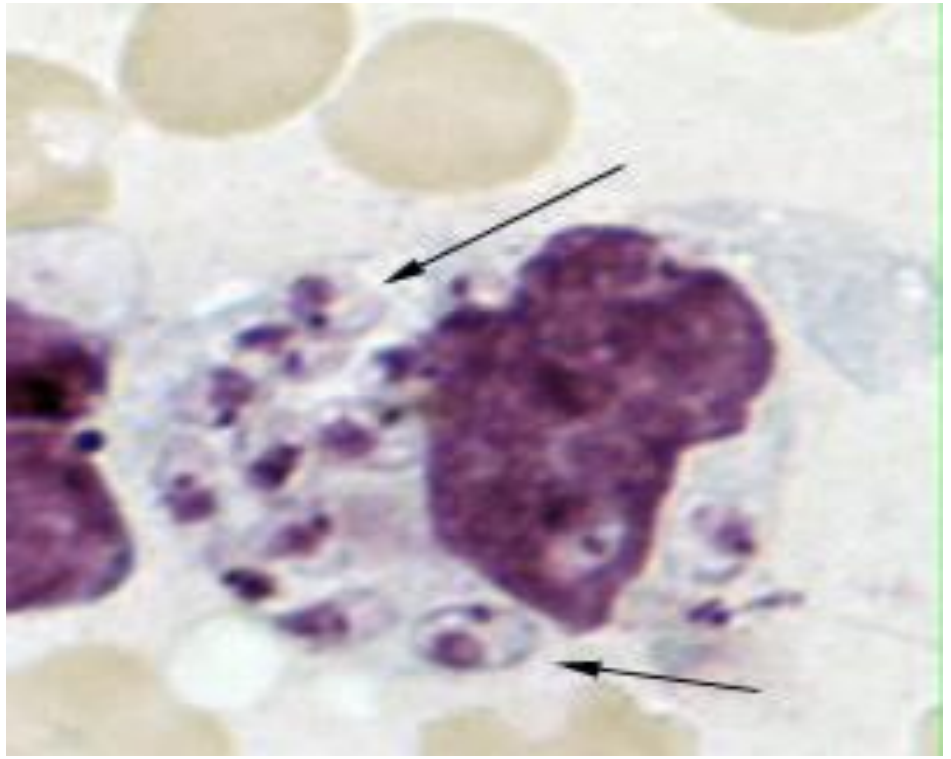
PCR for speciation

Amastigotes from an impression smear of a biopsy specimen from a skin lesion.

Intact macrophage filled with amastigotes (arrows), several with clearly visible nucleus and kinetoplast.

Patient had traveled to Egypt, Africa, and the Middle East.

Based on culture in NNN medium, followed by isoenzyme analysis, the species was *L. tropica*.



Leishmania – Treatment ….

Heat

Watchful waiting

Antimonal agents – sodium stibogluconate

Polyenes – lipid amphotericin

Pentamidine – some VL failures

Miltfosine - phosphocholine cytidylyl transferase (CTP) inhibitor with antimetastatic properties that induces apoptosis in cancer cells. The antiprotozoal effect is poorly understood.

Therapy… long list – variable results

- Pentavalent antimonials
- Amphotericin B dexycholate (Fungizone^{R})
- Pentamidina isothionate (Pentacarinat^{R})
- Aminosidine (paramomycin sulphate)
- Ketoconazole, Itraconazole
- Allopurinol
- Miltefosine
- Imiquimod (Aldara^{R})

Leishmania – Treatment ….

Clinical Infectious Diseases IDSA GUIDELINE 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)

https://www.idsociety.org/globalassets/idsa/practice-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.pdf

PREVENTION STRATEGIES

No clinically proven vaccine; no chemoprophylaxis

TREATED screens and bednets of sufficiently fine mesh to keep out sandflies

PLUS standard insect protective measures (DEET)

PREVENTION STRATEGIES

Cutaneous leishmaniasis is known to induce high-level protective immunity to the *Leishmania* species after spontaneous resolution. (urban myth?? some mothers use this to prevent unsightly scars – natural vaccine)

Old World Cutaneous Leishmaniasis

- Included those cases from Canadian Military
- Many of these may not need therapy – if single lesion – not on face or over a joint, they will autoheal

Leishmaniasis recidivans (observed in and around Iran and Iraq and we are seeing more in our Syrian refugee population)

Hyperergic, oligoparasitic form of Old World cutaneous leishmaniasis

Presents as a slowly enlarging, centrally healing usually solitary facial lesion.

- From Syria – lesion on forehead – started as papule
- Biopsied in Saudi Arabia
- Is painful


0mm 10 20 30 40 50 60 70 80
Santé publique
Ottawa
Public Health

New World Cutaneous Leishmaniasis

Here really worried about possibility of developing mucocutaneous disease

Really want to know the species responsible


0mm
10
20
30
40

How little exposure do you need?

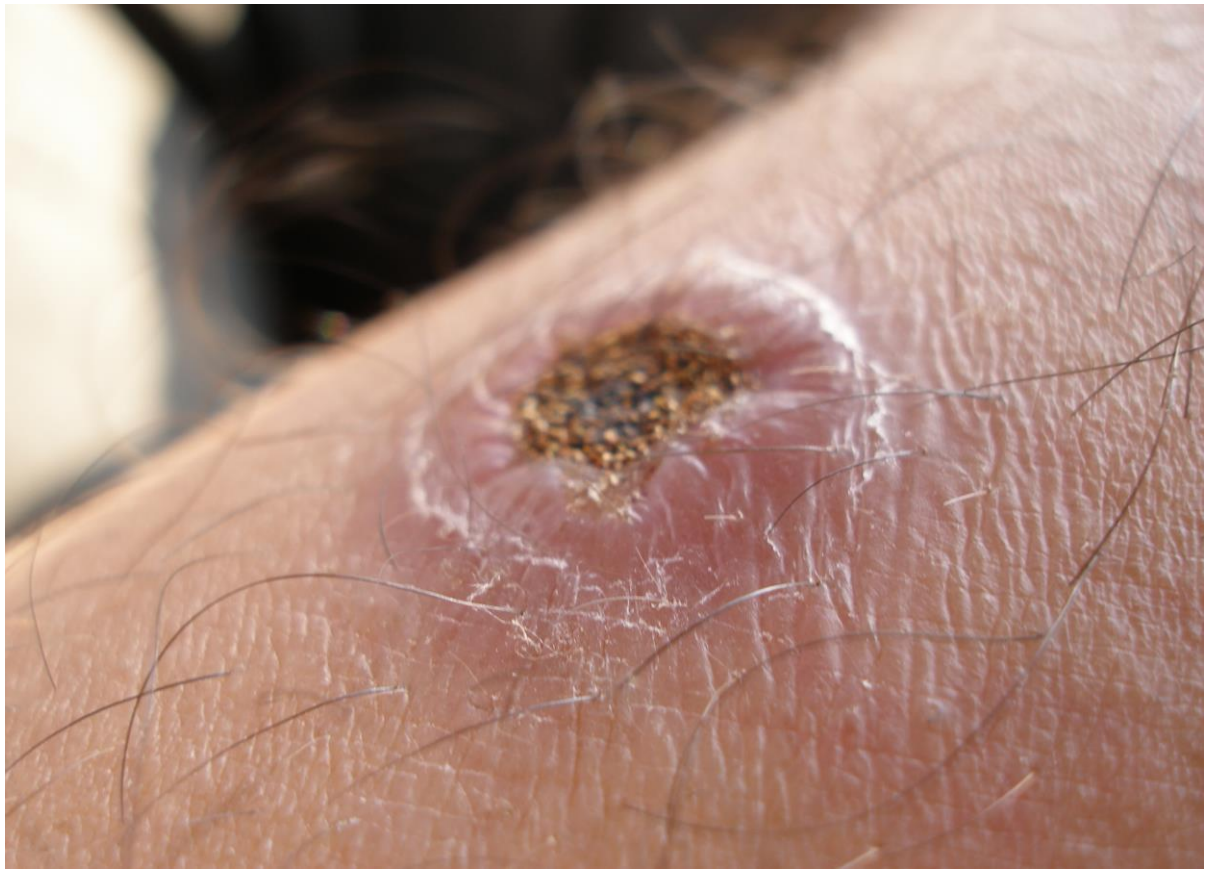
- 18 month history
- Caribbean cruise
  - Day trips to Mexico
  - Day trip to Belize – cave tubing in the jungle
- Seen by Derm
  - Repeated biopsies
  - Dapsone
  - Prednisone
  - Cellcept

Lives and plays in Panama
House in city and house in country
Recurrent lesions over 1 year – lymphatic spread up the arm
Repeated treatment with antimony
3rd treatment dose – out of supply
So “home” to Canada

- Kayaking in Costa Rica – roommates at eco lodge

Another Costa Rican Traveller

Our Peruvian Guide…



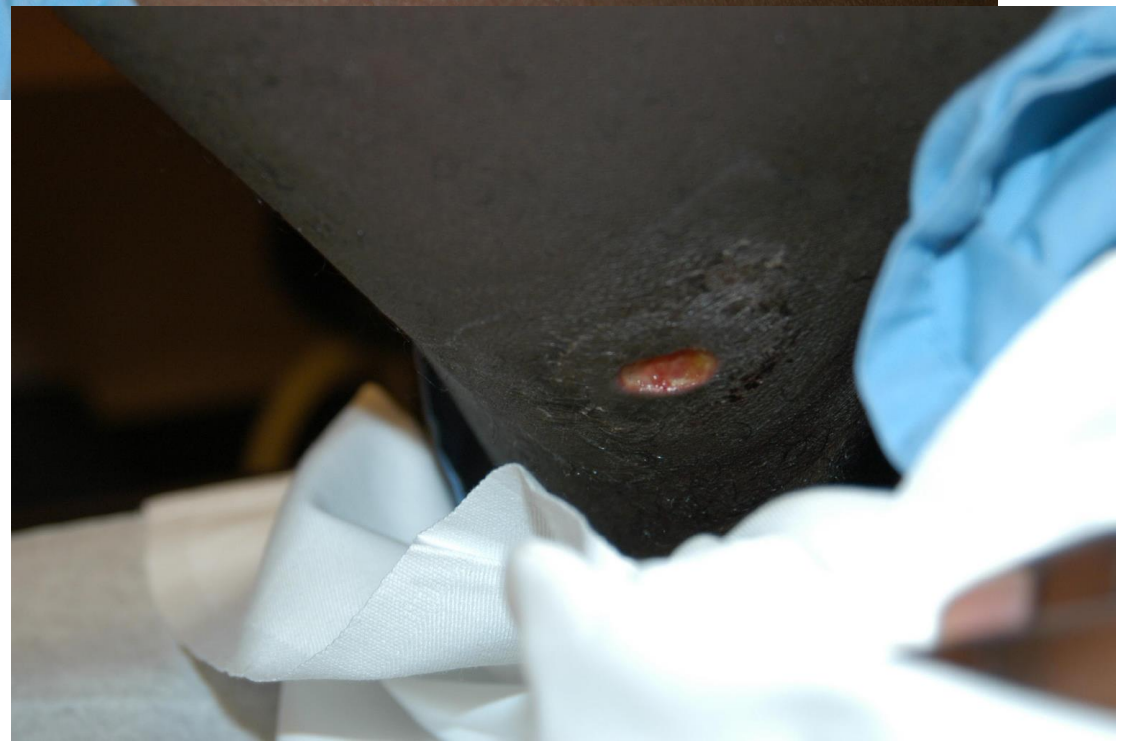
Take home messages - CL

- Seeing increasing numbers in travellers
  - How little exposure do you really need?
  - Need to be aware of risk, prevention and management if occurs
- Ecotourist lodges may actually be built on sandfly homes…
- Early diagnosis, accurate diagnosis important
  - Particularly in Americas with risk of mucocutaneous disease

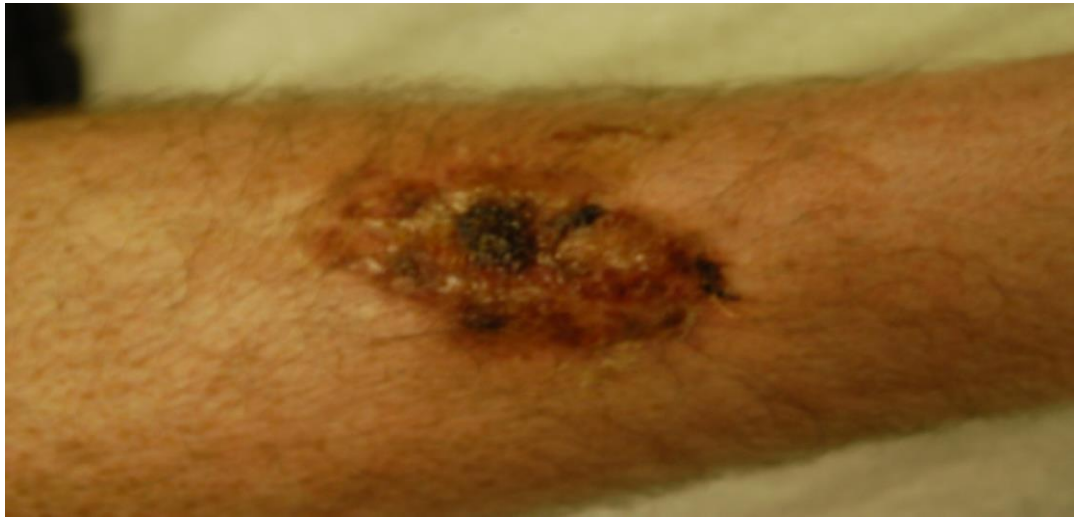
Not everyone with possible exposure has leish…. Important to prove the diagnosis


Is this the same thing?
If not – why not?
cm
1
2
3
DATE
SPEC.


cm
1
2
3
DATE
SPEC.



What is different about these lesions?




After 10 days of Clindamycin

QUESTIONS ?????

Kop Khun Ka

Thank you very much for your welcoming and hospitality