Integrated Skin NTDs: CL and PKDL

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Topics to be covered

- **Skin NTDs**
  - Definition
  - Diseases spectrum

- **Cutaneous leishmaniasis (CL)**
- **Post kala-azar dermal leishmaniasis (PKDL)**
  - **Pathogenesis**
  - **Clinical features**
  - **Diagnosis**
  - **Differential diagnosis**
  - **Management**

Skin NTDs

- NTD: **diverse group of conditions that are mainly prevalent in tropical areas where they affect mostly more than 1 billion people who live mostly in poor communities.**

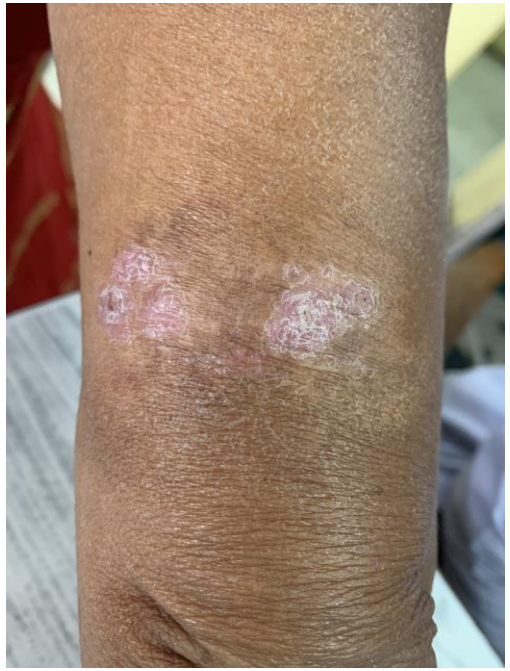
- Diseases of tropics ; poor populations

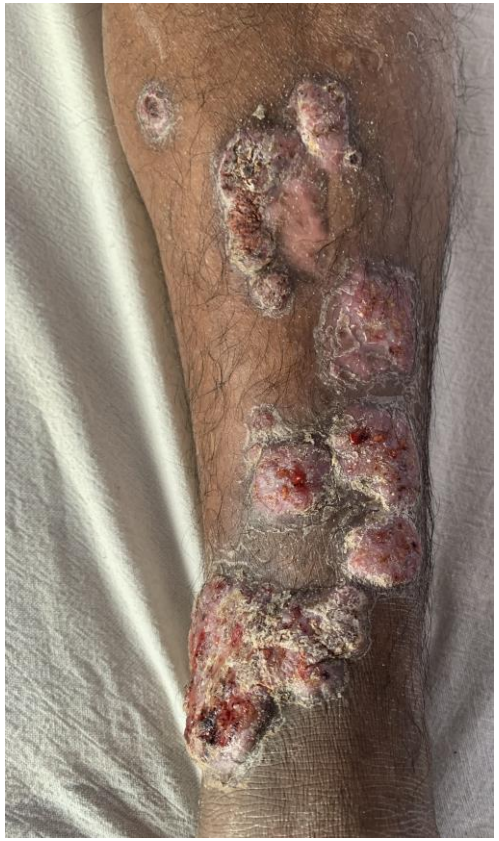
- **Neglected:**
  - research,
  - funding and
  - government support

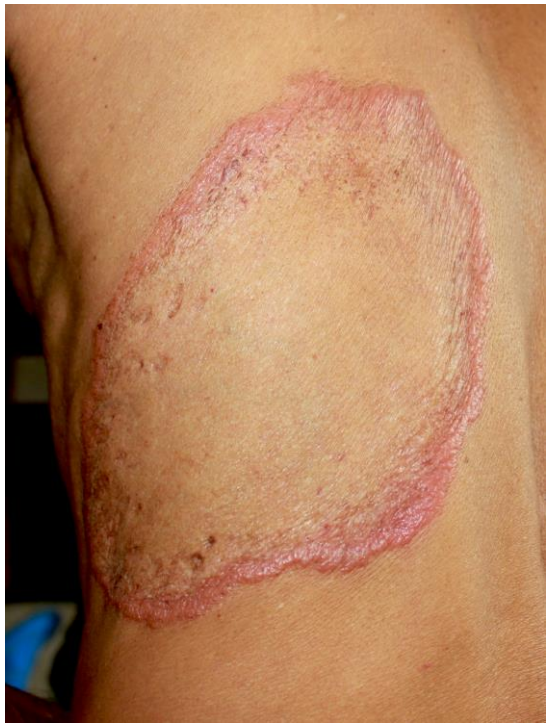
List of skin NTDs

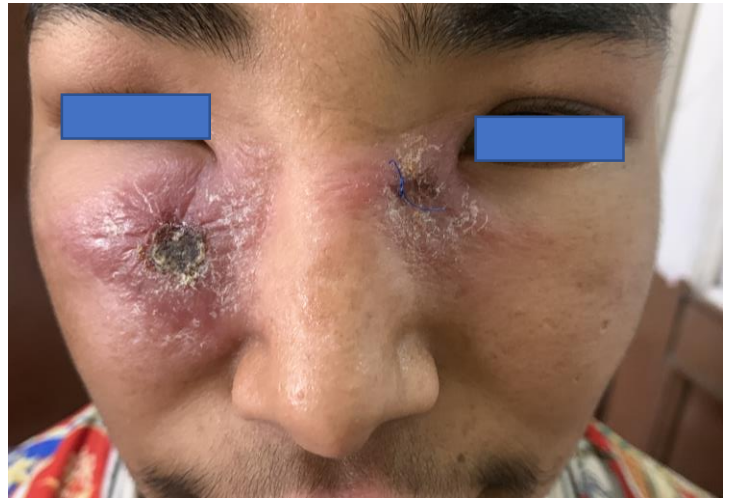
- **Leprosy**
- **Leishmaniasis**
- **Mycetoma**
- **Scabies**
- **Sporotrichosis**
- **Lymphatic filariasis**
- **Chromoblastomycosis**

- Onchocerciasis
- Buruli ulcer
- Tungiasis
- Yaws
- Podoconiosis
- Others









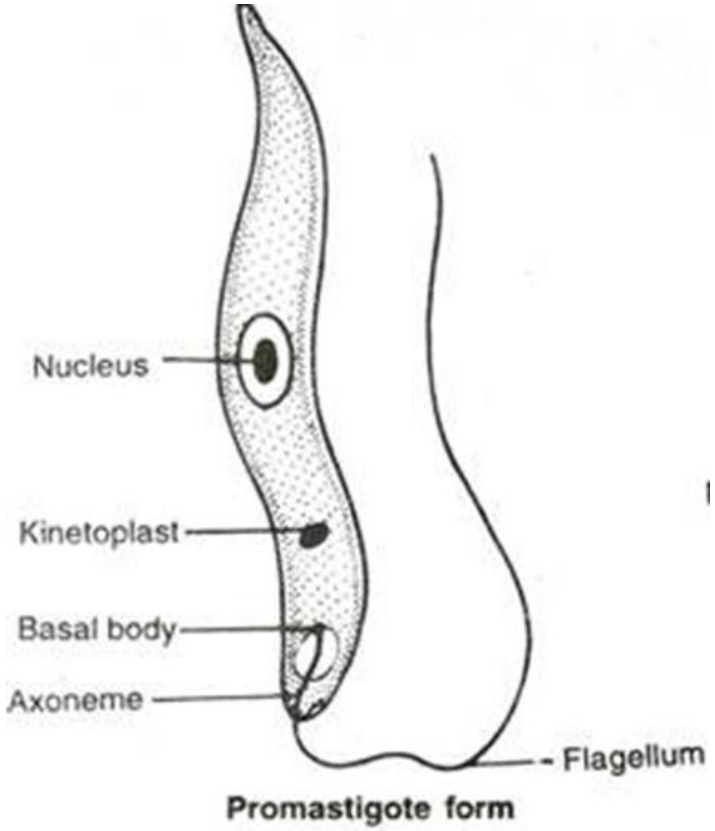
Leishmaniasis

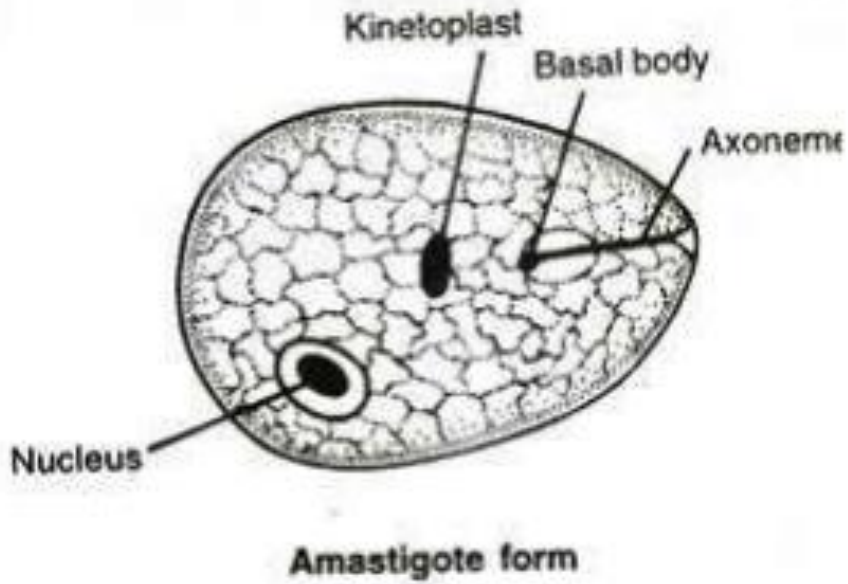
- A vector borne disease caused by several species of **Leishmania,** transmitted by bite of female phlebotomus **sandfly**.

  - Genus:- Leishmania
  - Phylum:- Sarcomastigophora
  - Order:- Kinetoplastida
  - Family:- Trypanosomatidae

Leishmania

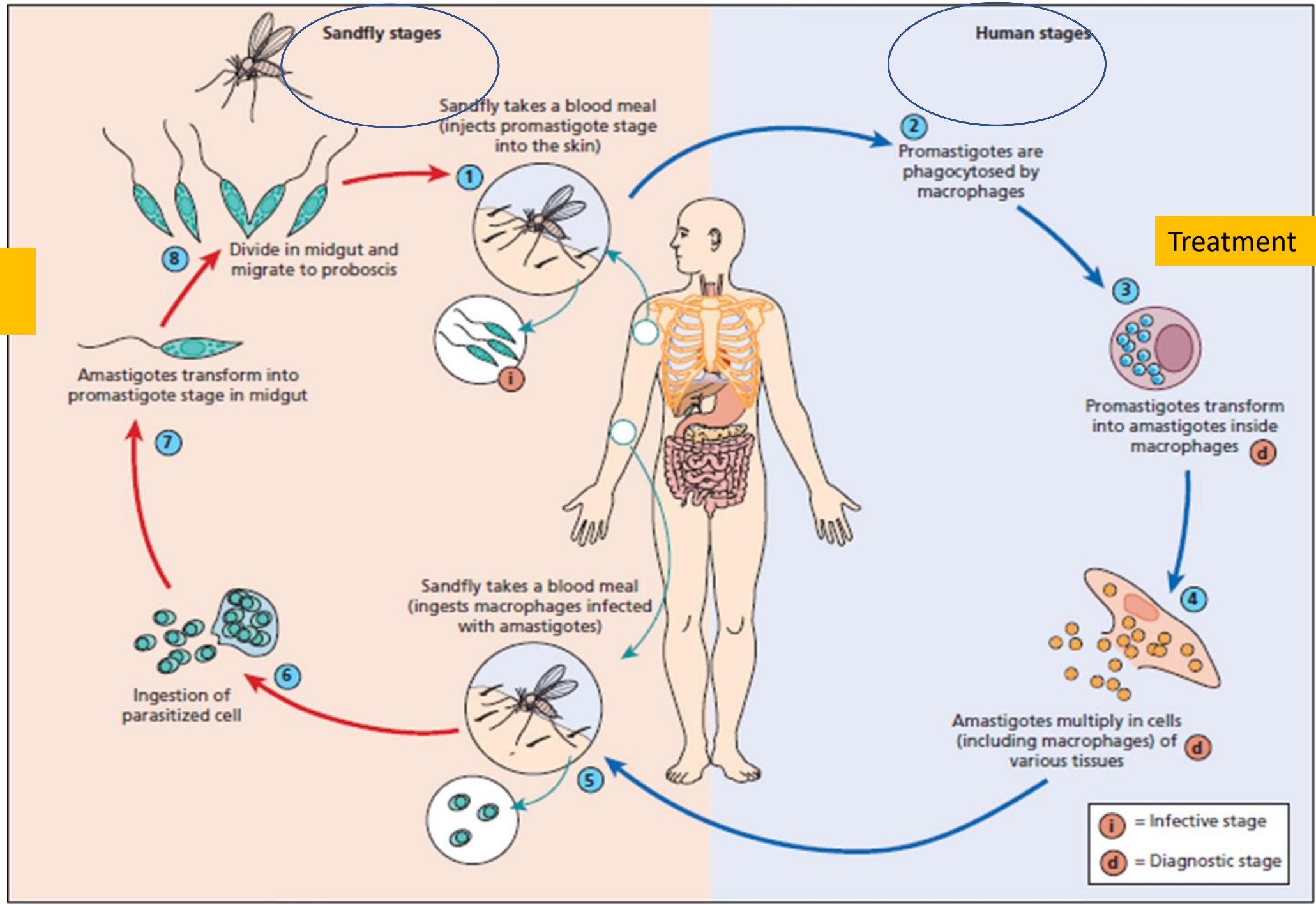
Dimorphic protozoa



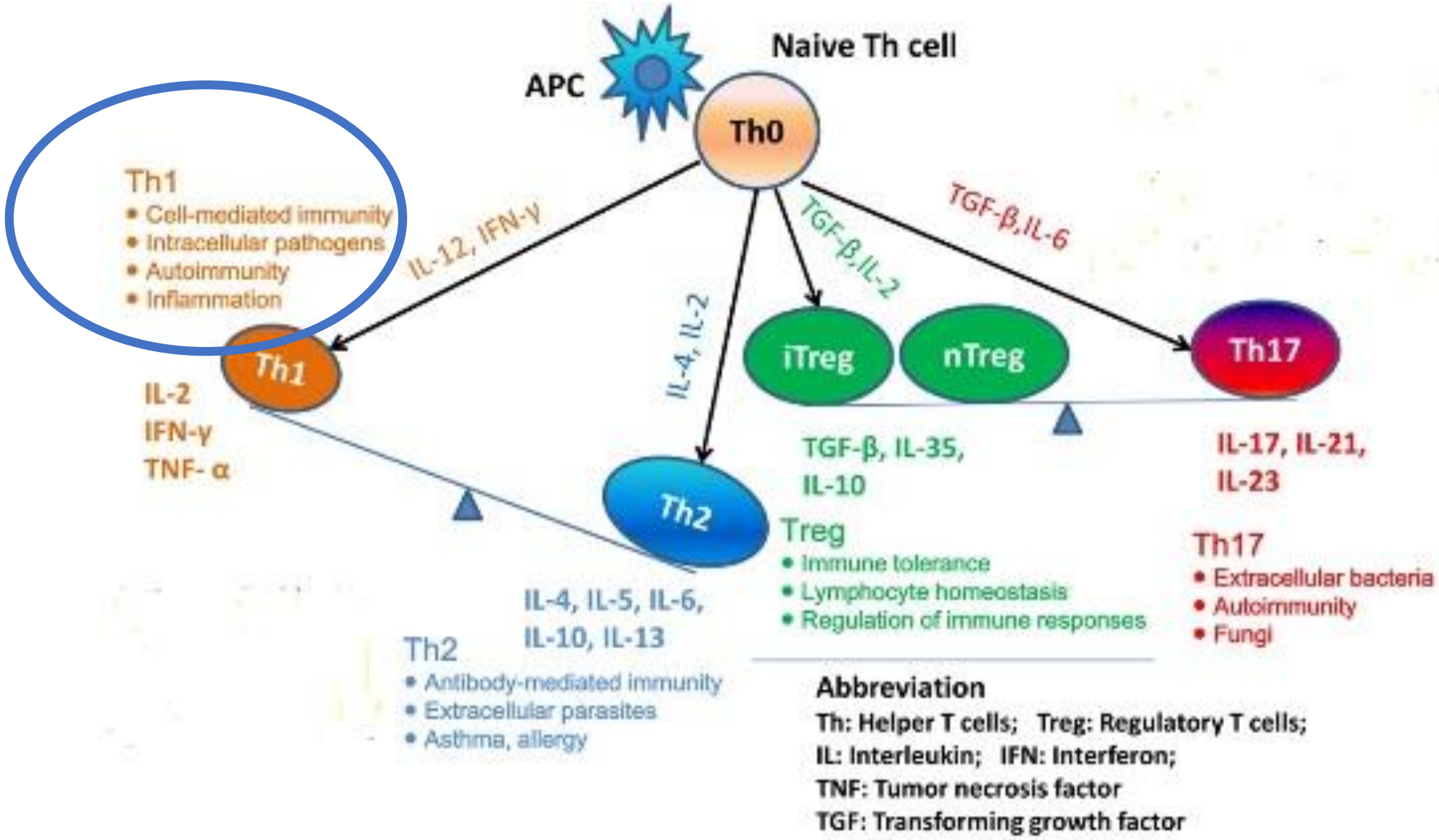


Life cycle

Preventive measures



Immune response



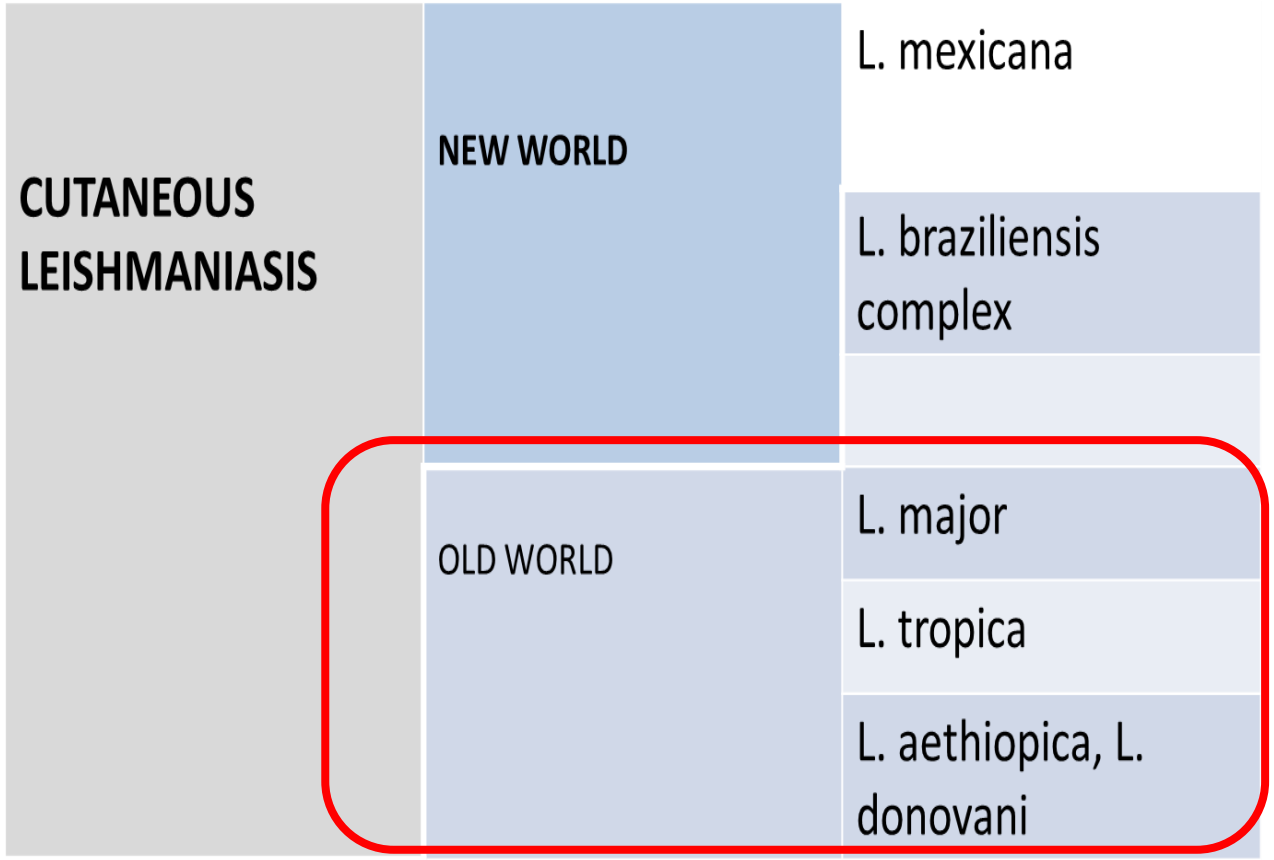
Classification

- **Cutaneous**
  - **Most common form** of the disease, usually producing ulcers on the exposed part of the body
- **Mucocutaneous**
  - Disabling form of leishmaniasis which can lead to partial or total destruction of the mucous membranes of the nose, mouth and throat cavities and surrounding tissues
- **Visceral** >>>>>PKDL
  - Most serious form, also known as Kalazar
  - PKDL-complication of visceral leishmaniasis (VL) in areas where Leishmania donovani is endemic

Cutaneous Leishmaniasis (CL)

- **First CL case recorded?**

- 1885 BC
- “Nile Pimple” in Pharaoh’s Papyrology



Types-CL

Duration

- Acute : heals with in 1 year
- Chronic : disease lasting longer than 1 year

Species

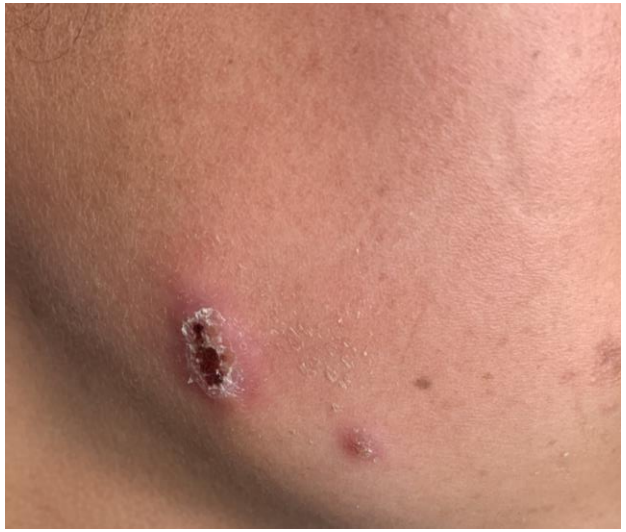
- Old world (urban/ dry and moist/ rural)
- New world

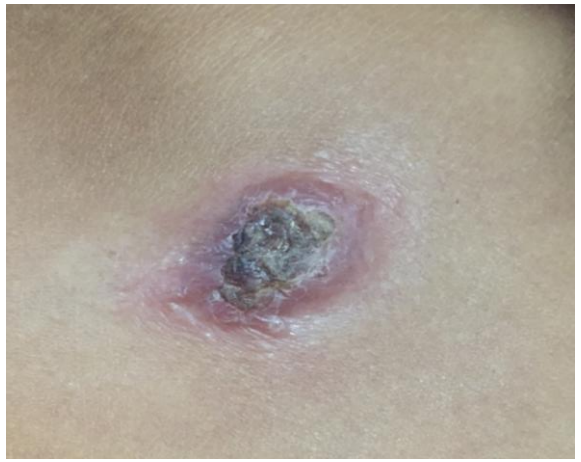
Lesion

- Localised CL
- Diffuse CL

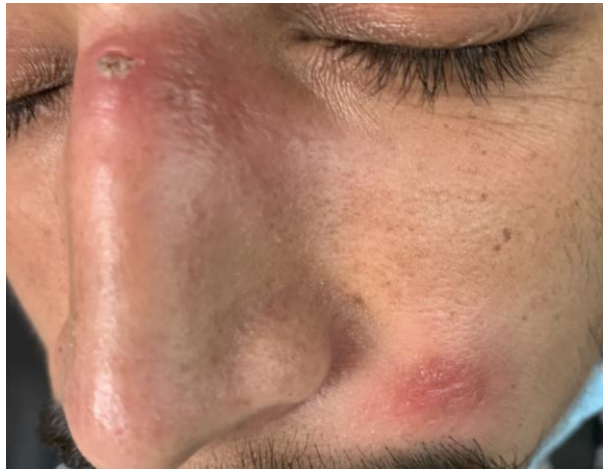
Clinical features

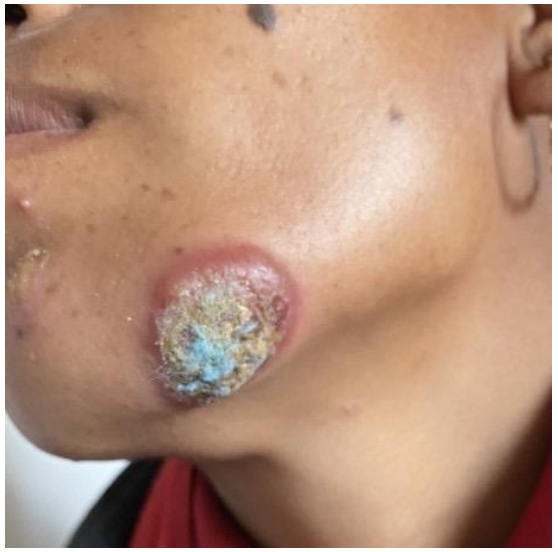
- **Indolent,** slowly increasing
- “Volcano-like” nodular plaque
- **Healing with scarring**

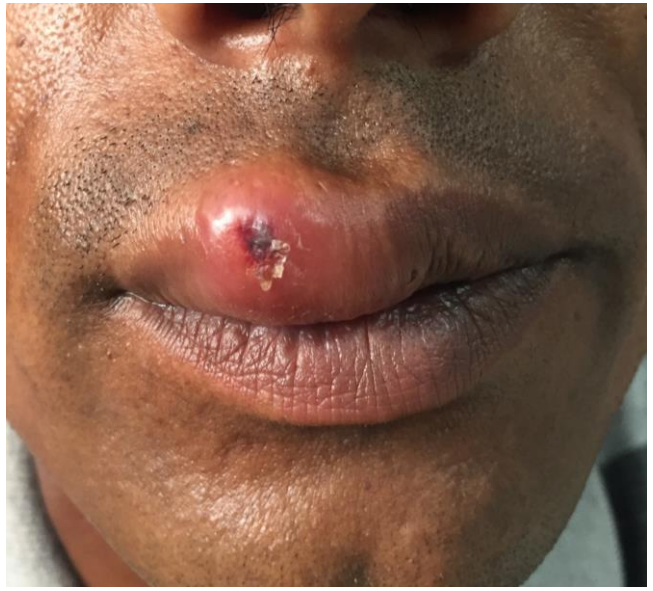




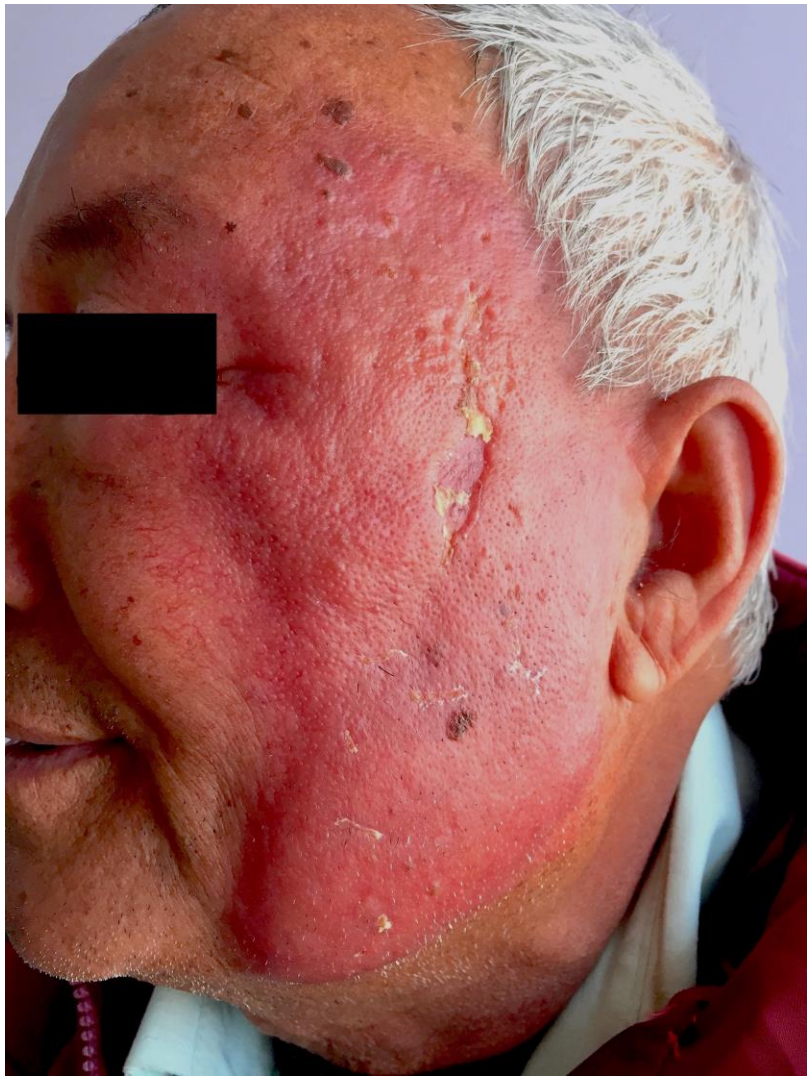
Cutaneous leishmaniasis?

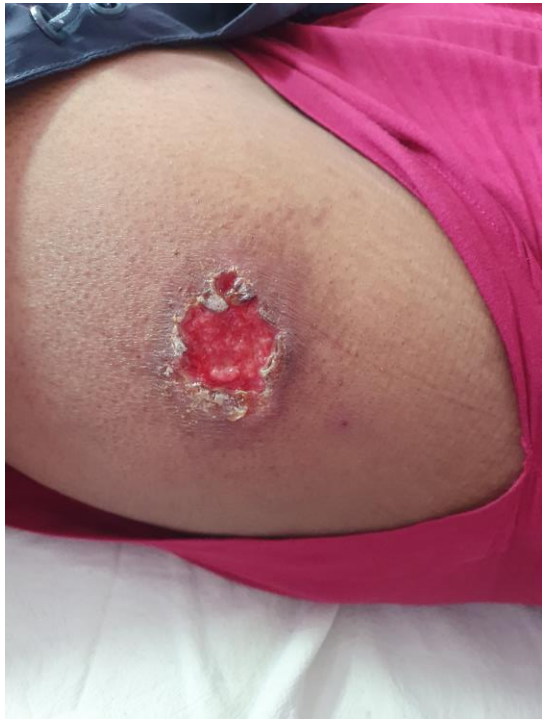


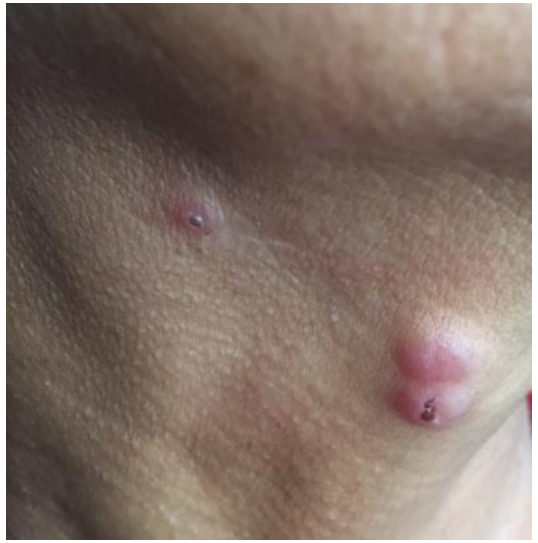


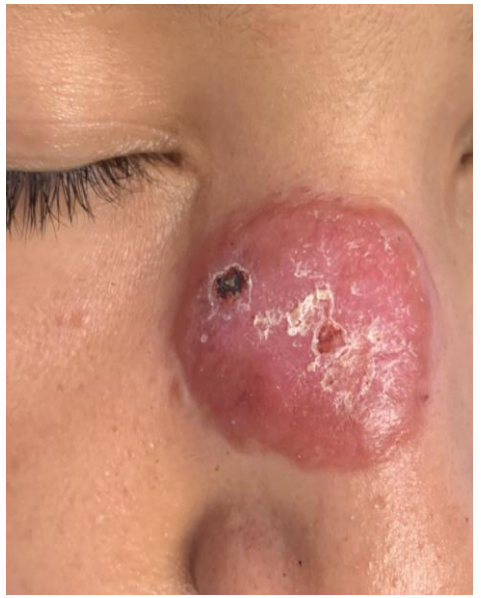


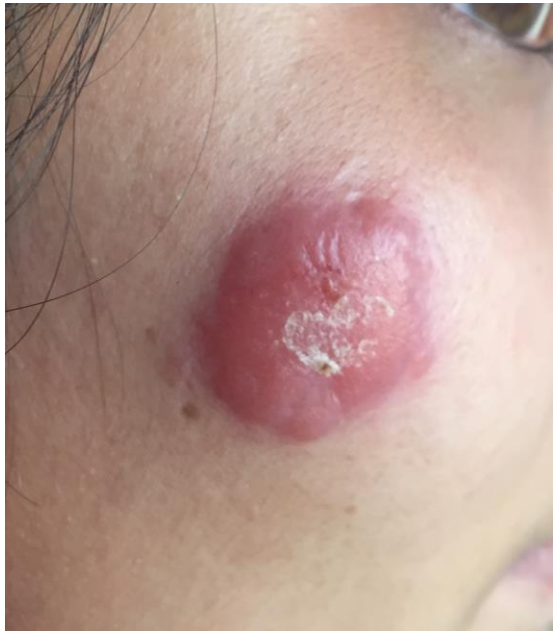
Atypical presentation?

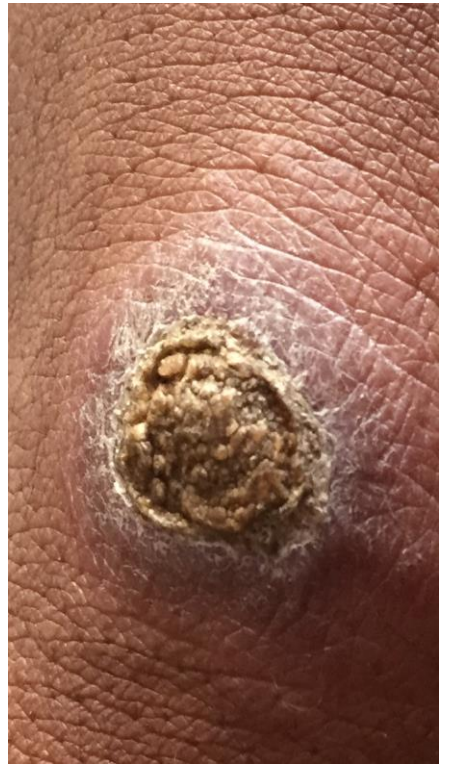


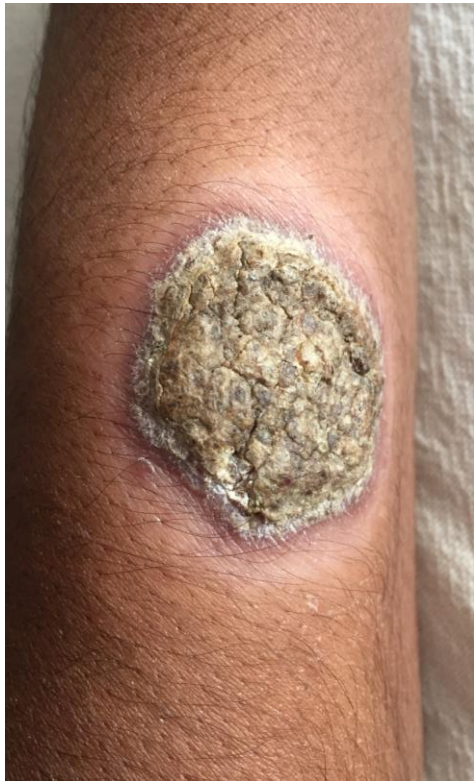












Diffuse CL

- Old World: L. aethiopica
- New world: l.Mexicana

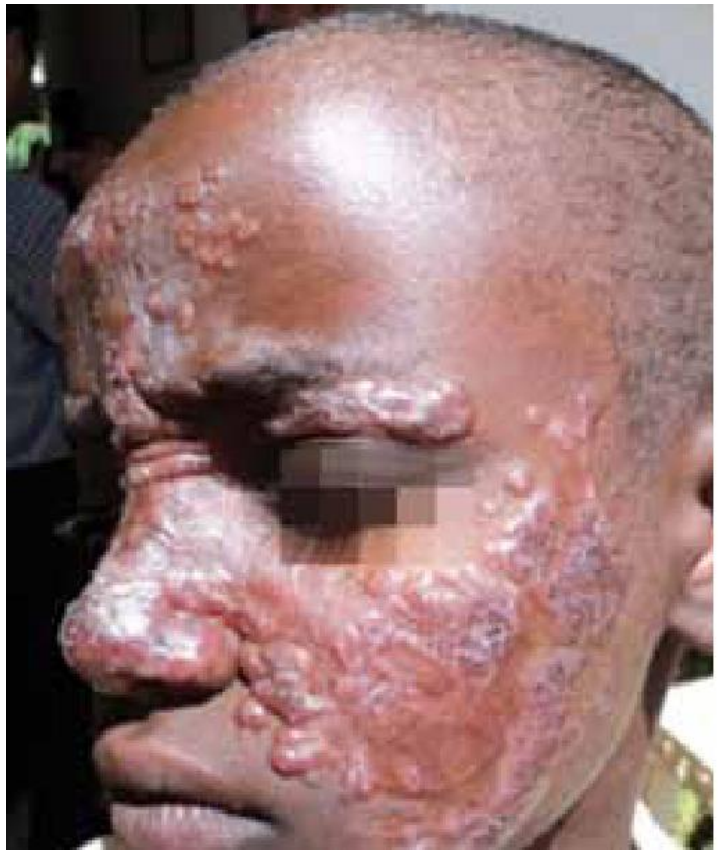
- Multiple nodules: shiny, slightly erythematous

- **Does not ulcerate**

- **Superabundance** of parasites in the lesions

- Treatment: **gradual** improvement

- **Relapse is the rule**



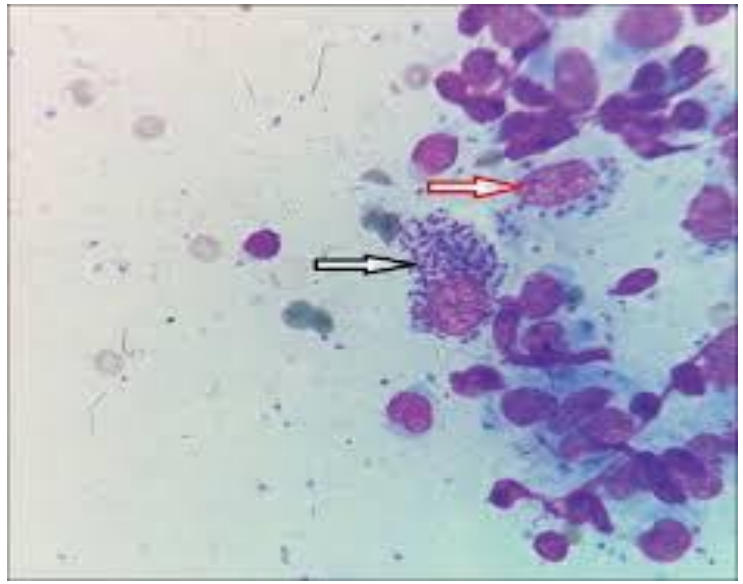
Differentials?

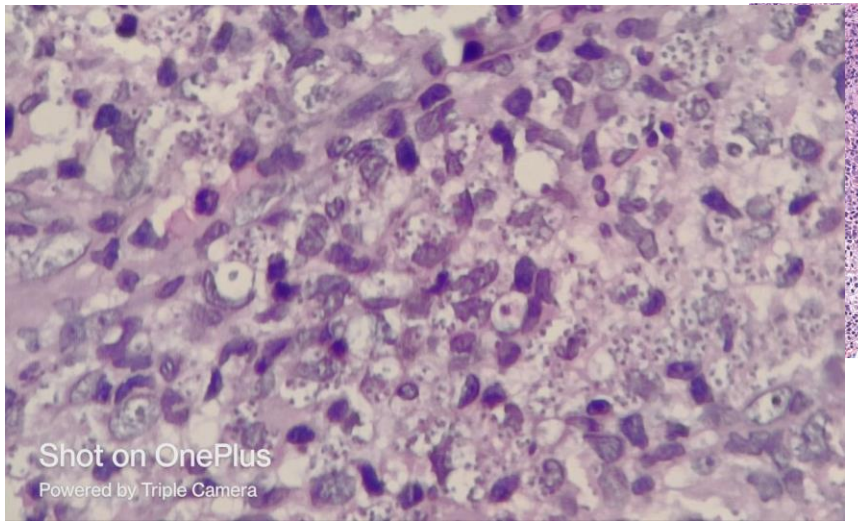
- Granulomatous conditions
  - Site
  - Morphological
- Bacterial infections
- Eczemas
- Leprosy
- Sarcoidosis
- Skin neoplasm
- Cutaneous TB

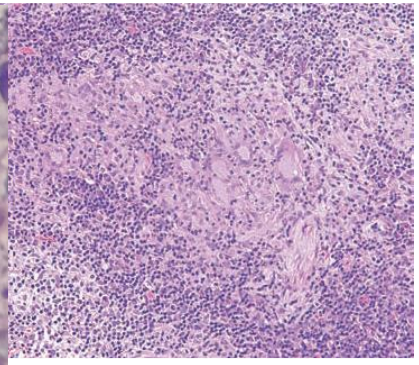
Diagnosis

Parasitological

- Demonstration of **amastigote** in Giemsa-stained smears /tissue from infected skin by direct microscopy
- Tissue samples can be obtained: Aspiration, Scrapings, Slit skin, or biopsy



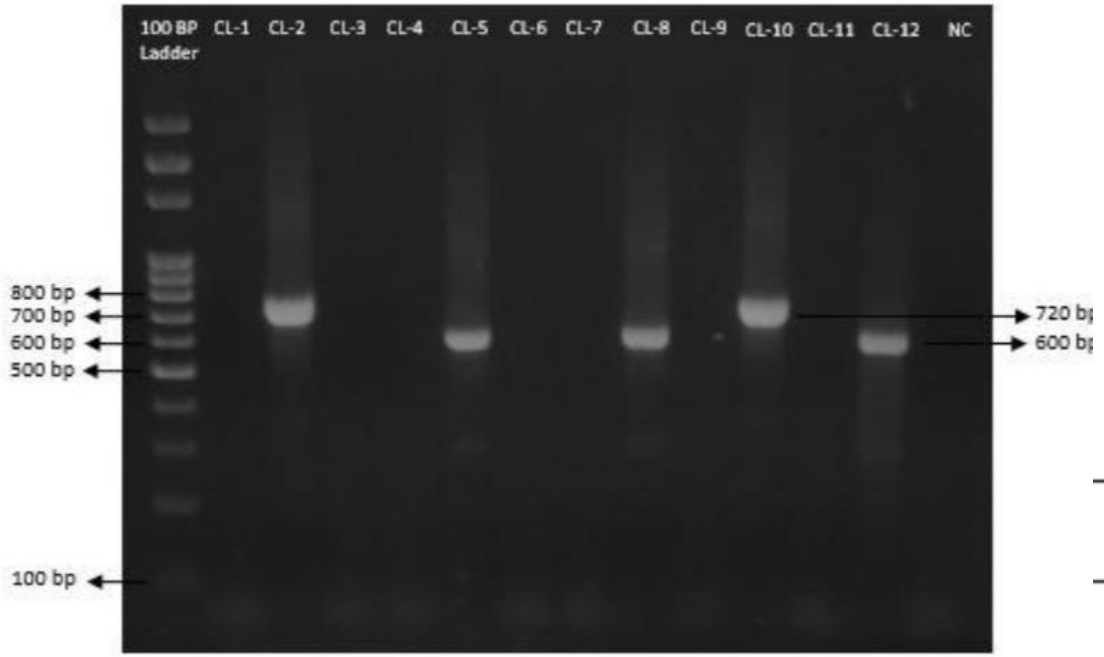


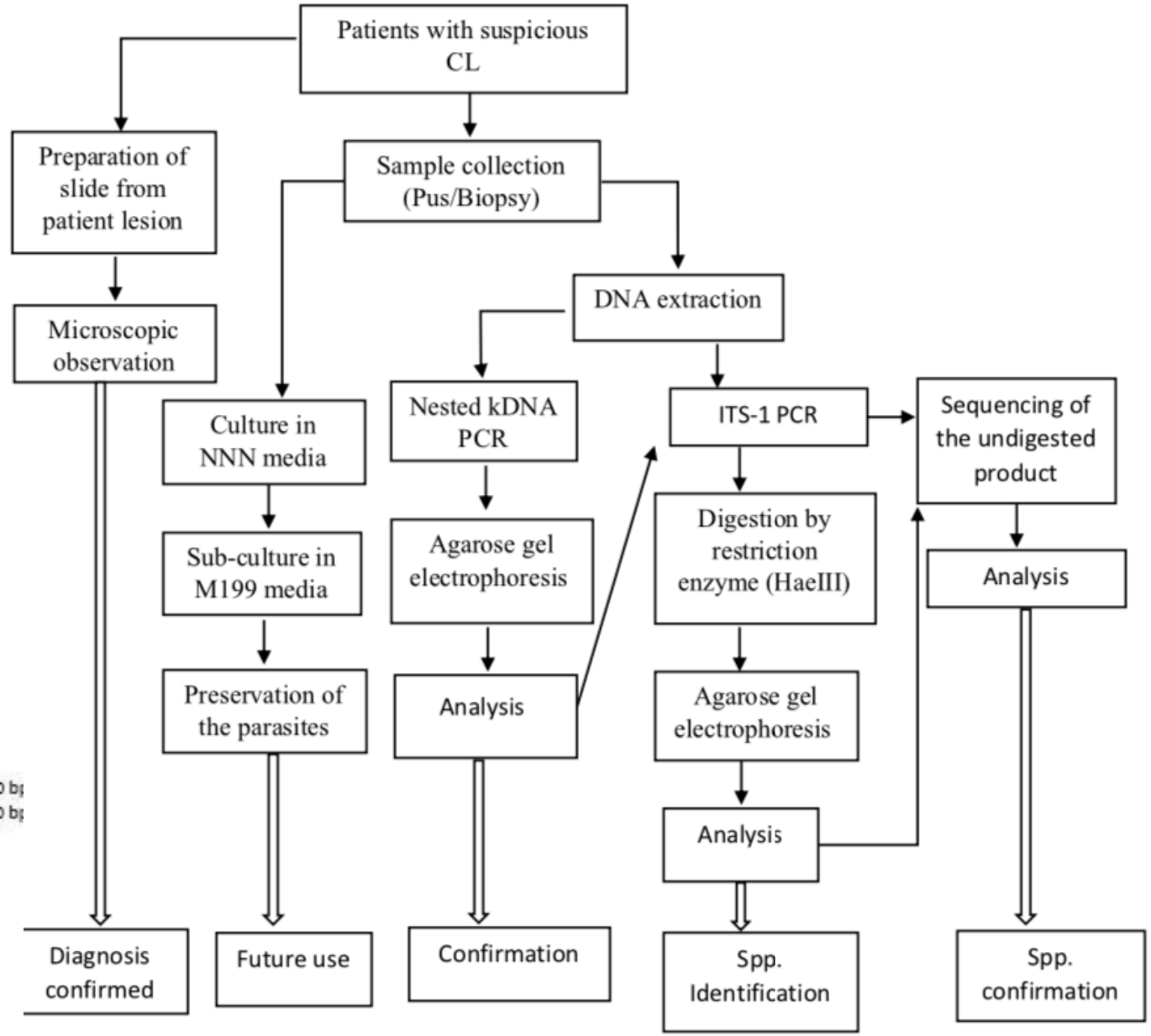


Histology

- Hallmark of the disease (70%): numerous amastigotes within histiocytes (**Leishman-Donovan bodies**) and extracellularly
- Dense and diffuse mixed inflammatory cell infiltrate of histiocytes, multinucleated giant cells, lymphocytes, and **plasma cells**
- Sparing of the papillary dermis (grenz zone)

PCR in Leishmaniasis





Leishmania donovani persistence and circulation causing cutaneous leishmaniasis in unusual-foci of Nepal

Tinmaya Rai, Srijan Shrestha, Sabita Prajapati, Anup Bastola, Niraj Parajuli, Pragya Gautam Ghimire, Parmananda Bhandari, Kishor Pandey, Manju Jain, Greg Matlashewski, Rachel Bras-Goncalves & Krishna Das Manandhar — Show fewer authors

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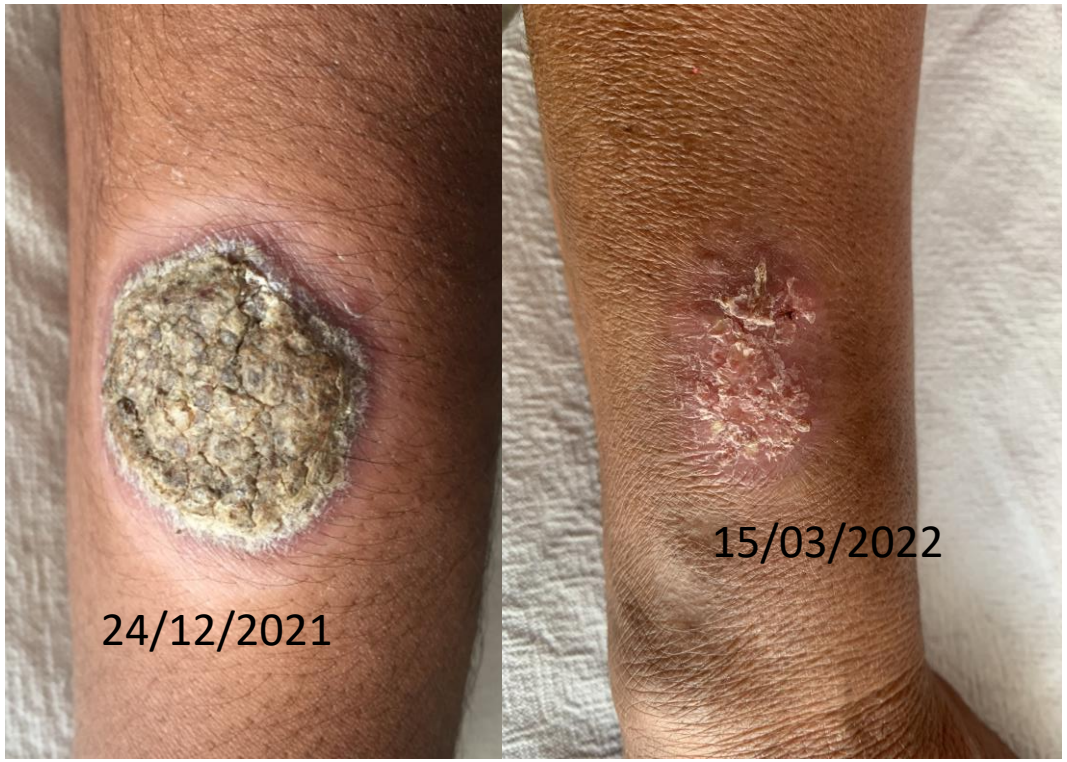
Cite this article

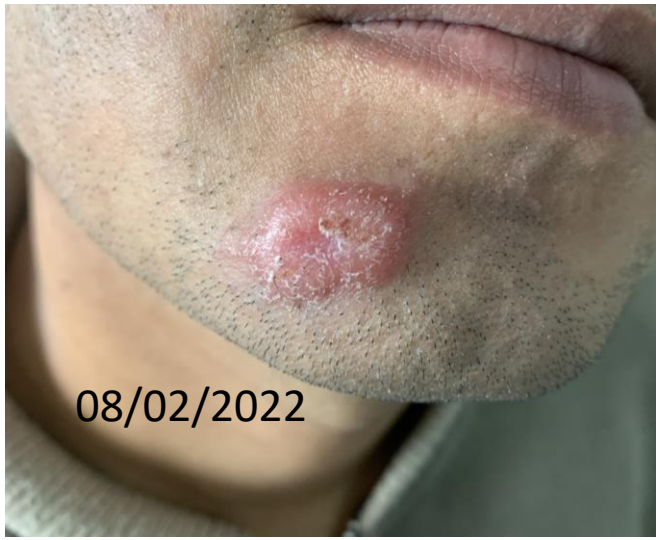
Total: 40 patients
PCR: 22 in total
L. donovani- 13
L. major- 9
ITS1 PCR: 12/22 (confirmation of L.donovani- 7/13
L. majora- 5/9)

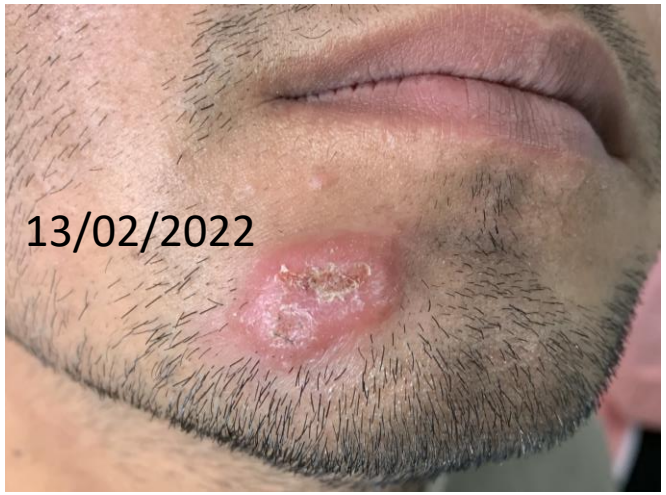
dramatically in recent years in Nepal. The study offers molecular identification of the *Leishmania* species using 40 patient's aspiration biopsy samples, targeting markers kinetoplast minicircle DNA (kDNA) and internal transcribed spacer-1 (ITS1). Among molecularly diagnosed 22 cutaneous leishmaniasis cases, *L. donovani* complex was identified in 13 instances and *L. major* in 9 cases. The ITS1 PCR was positive in 12 of the positive nested-kDNA PCR cases (12/22), confirming *L. donovani* complex in seven of the cases and *L. major* in five of the cases. In addition, the study conclude that concurrent occurrence of atypical cutaneous infections caused by *L. donovani* parasite in 59.1% of cases and typical cutaneous infections caused by *L. major* parasite in 40.9% of cases. A Phylogentic analaysis showed that the detected *L. donovani* species present null genetic distances from seven references of *L. donovani*, but slight differences between ITS1 sequences and not grouped into a significant monophyletic cluster.

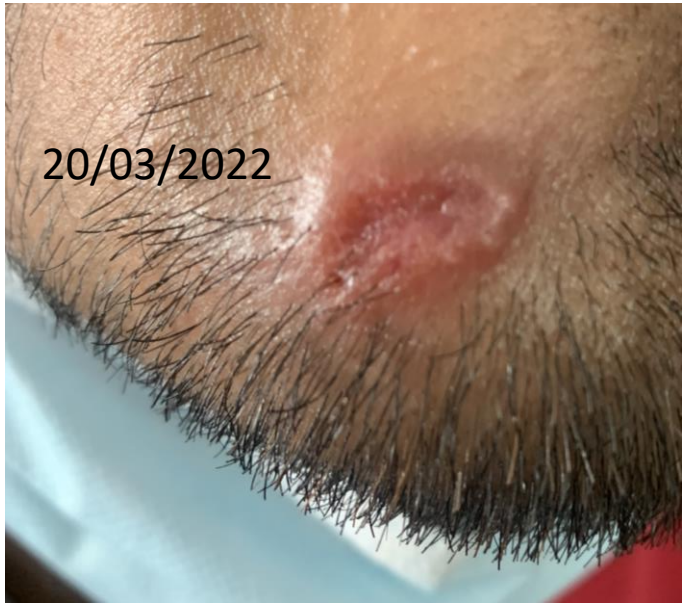
Treatment (CL)

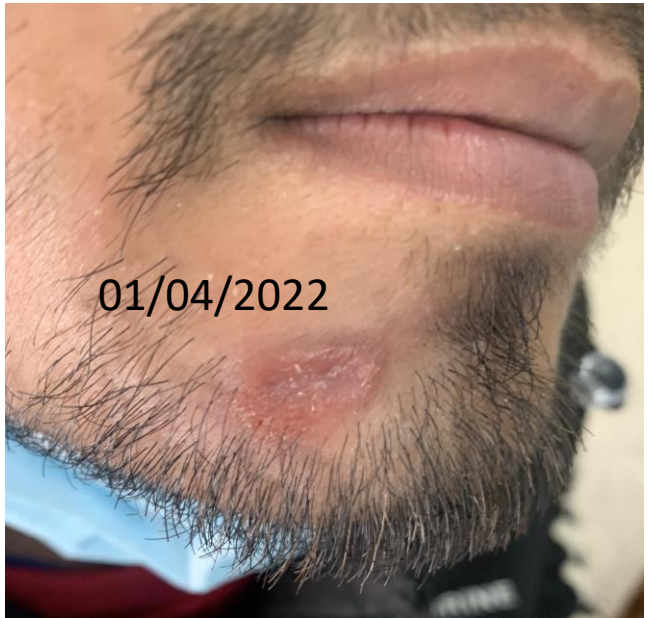
- Depends on size, site, number of lesions and species involved





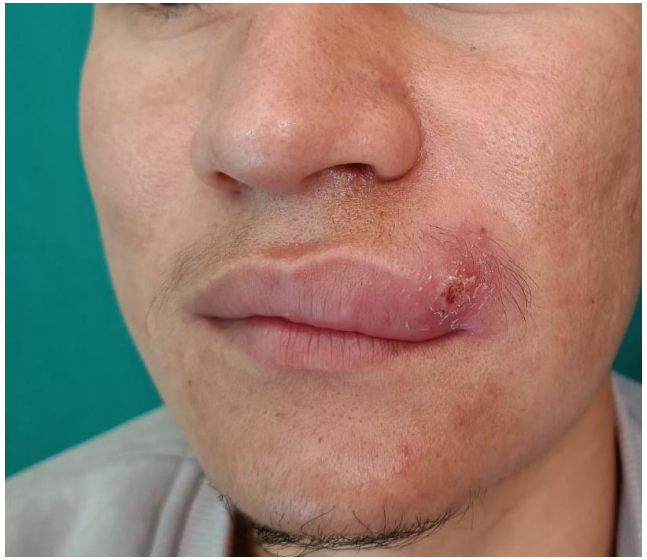


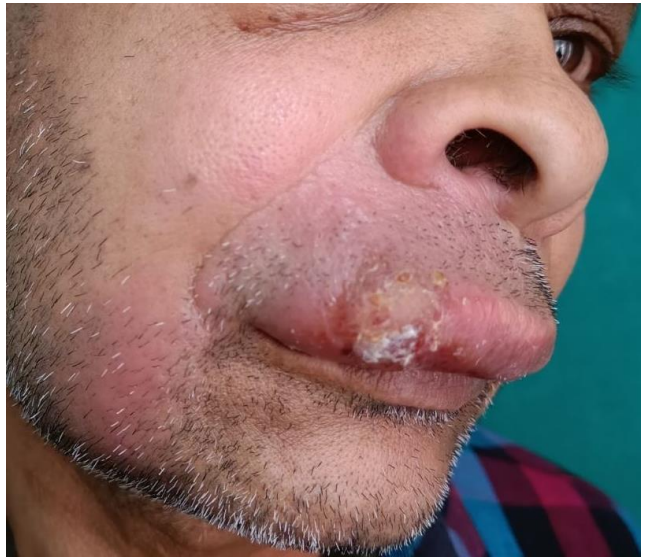


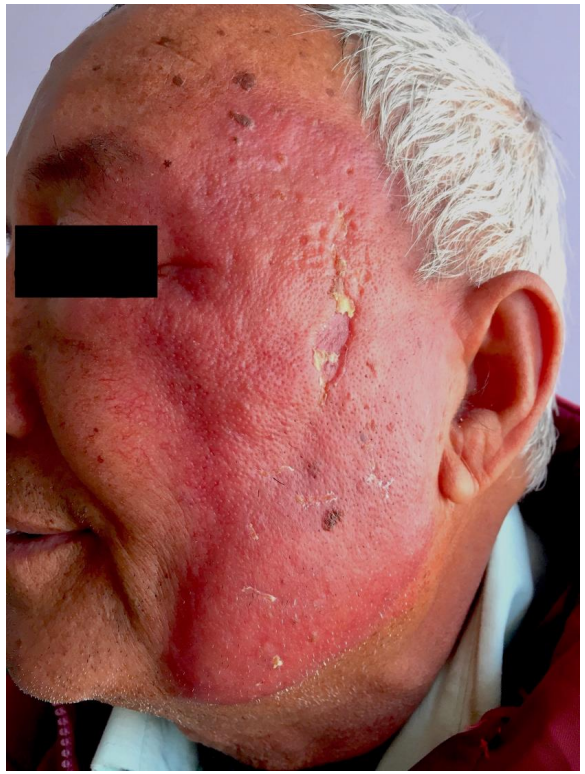


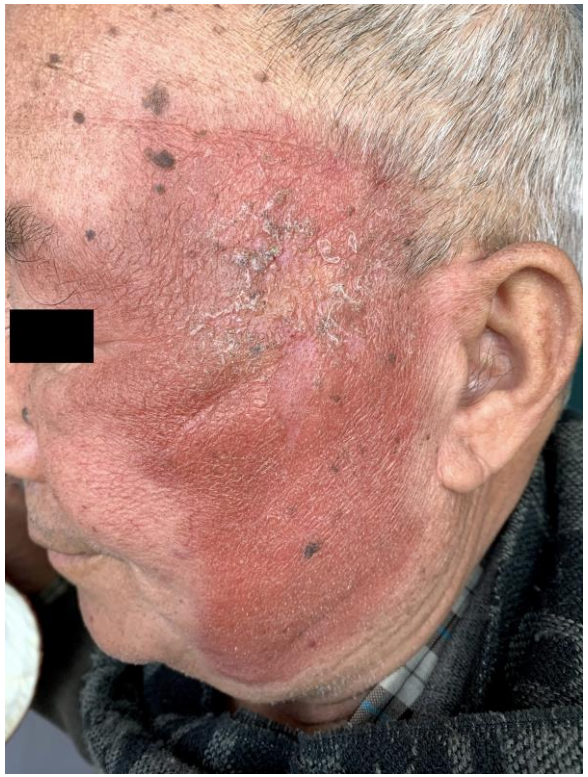
Treatment

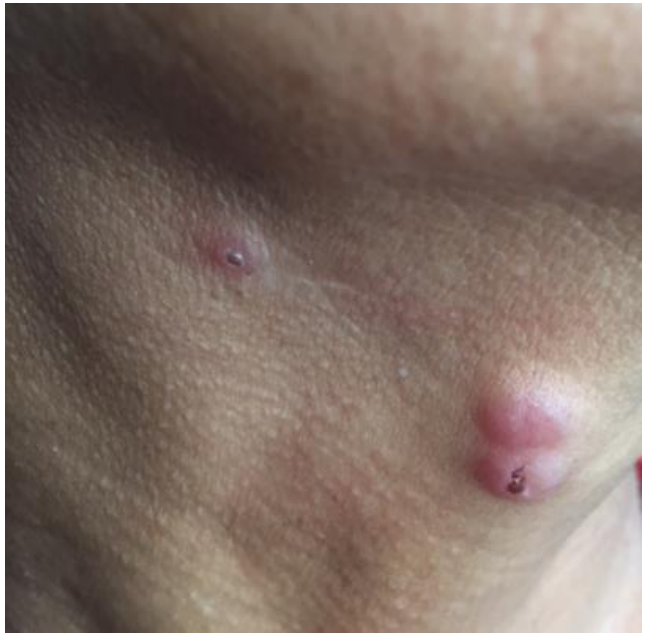
rk 39 (+ve)
Cervical lymph node enlargement











Type	Simple CL	Complex CL
Causative species	Unlikely to cause MCL	Species likely to be associated with MCL
Mucosal Involvement	No	Yes
Regional lymphadenopathy	Small	Large
Number of skin lesions	Only a single or few	More than 4 skin lesion
Size of lesion	Less than 1 cm diameter	Single lesion 5cm or more in diameter
Location	Non-exposed parts	Face (including ears, eyelids or lips), fingers, toes or other joints or genitalias
Host immunity	Immunocompetent	Immunocompromised
Lesion resolving without prior therapy	Yes	Clinical failure of local treatment
Atypical forms	No	Diffuse CL, disseminated Cl and Leishmaniasis recidivans

Treatment

- **Local therapy**: Heat therapy
  Cryotherapy
  Topical treatment like azole antifungals and paromomycin
  Photodynamic therapy and laser
  Intralesional injection of pentavalent antimony

- **Systemic:** Pentavalent antimony derivates: Meglumine antimoniate
  Sodium Stilbogluconate

  Oral Miltefosine (2.5mg/kg/day x 28 days):
  Injection Amphotericin B
  Oral azoles: varying efficacy

Miltefosine

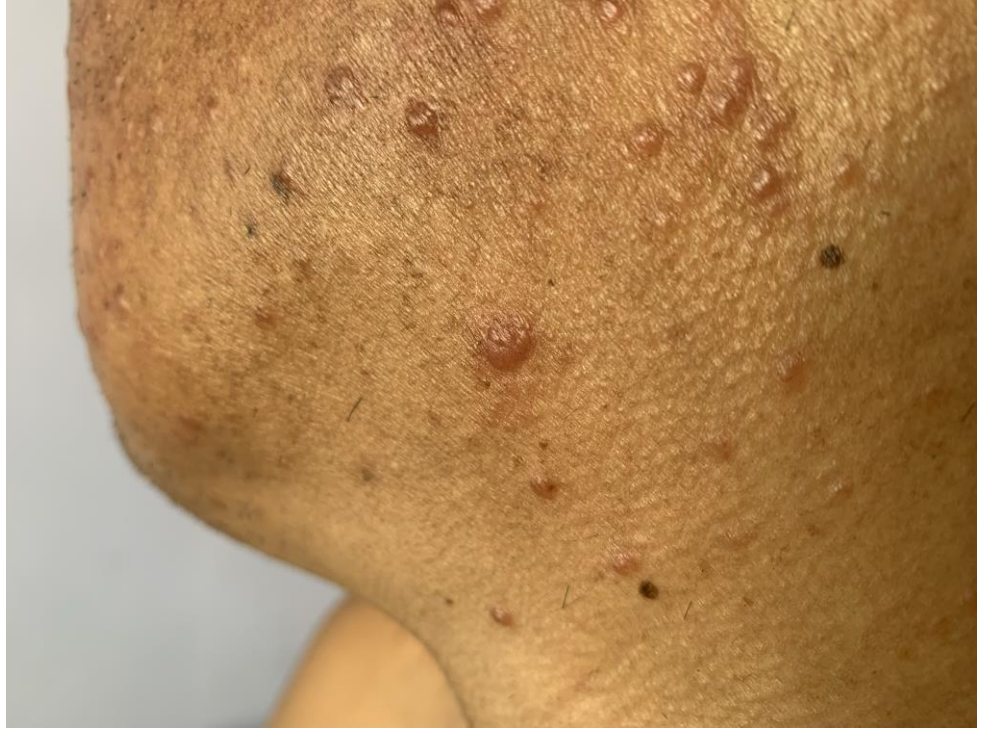
Drug category	Morning	Evening
More than 12 years of age More than 50 kg body weight	100mg	50mg
More than 12 years of age More than 25- 50 kgs	50mg	50mg
Upto 12 years Less than 25 kgs	50mg	0
Children (2-11 years)	2.5mg/kg/day	@8-day treatment to be completed by 35 days.

Side-effects: N/V, diarrhea, abdominal pain, renal and liver

Contraindications: Pregnancy, Liver failure, Renal failure

Monitoring: **CBC, Pregnancy tests, Urine**: pretreatment
CBC: on completion

PKDL



- Neglected complication of VL
- Mostly seen in Sudan and India
- Major reservoirs of the infection **L. donovani**
- 2 types of morphological lesions are seen
  - **Early** : hypopigmented macule on face, arms and upper part of trunk
  - **Late** : papular warty nodular lesions

PKDL

	Sudan	India
Can occur in absence of VL	Yes	Yes
May occur while on treatment for VL	Yes	No
Site	Face>trunk>arm>legs	same
Rash	Papular	Macular
Lymphadenopathy	Frequent	Rare
Frequency following VL(%)	50-60	10-20
Interval between VL and PKDL	0-6 months	2-3 years or more
Age	Children	Adults
Mucosal involvement	Yes	Yes
Self cure	Probably	Yes
Treatment policy	Chronic>6month Grade 2 and 3	All
Marker for cure	Clinical	Clinical

Summary of epidemiological studies published from 2000 to 2017 on prevalence, incidence, and interval between onset of PKDL and VL treatment in Nepal.

Place of study	Period of study	Type of study	Case findings	PKDL Rate	interval after VL
Endemic districts	2000- 2009	retrospective	Active	Mean 2.4% <2 years: 1.4% <8 years: 3.6%	23 months (IQR 15-41)
Dharan	1998- 2000	Hospital- based case series (n=22)	Passive		Mean: 26.9+/- 11.9 Range: 6-60 months

https://doi. Uranw S, Ostyn B, Rijal A, Devkota S, Khanal B, et al. (2011) Post-kala-azar dermal leishmaniasis in Nepal: a retrospective cohort study (2000±2010). PLoS Negl Trop Dis 5: e1433. org/10.1371/journal.pntd.0001433 PMID: 22206030

Garg VK, Agrawal S, Rani S, Joshi A, Agarwalla A, et al. (2001) Post-kala-azar dermal leishmaniasis in Nepal. Int J Dermatol 40: 179±184. PMID: 11422520

Prevalence of post kala-azar dermal leishmaniasis (PKDL) and treatment seeking behavior of PKDL patients in Nepal

Anand Ballabh Joshi et al. PLoS Negl Trop Dis. 2023.

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2023 Feb 9;17(2):e0011138.
doi: 10.1371/journal.pntd.0011138.
eCollection 2023 Feb.

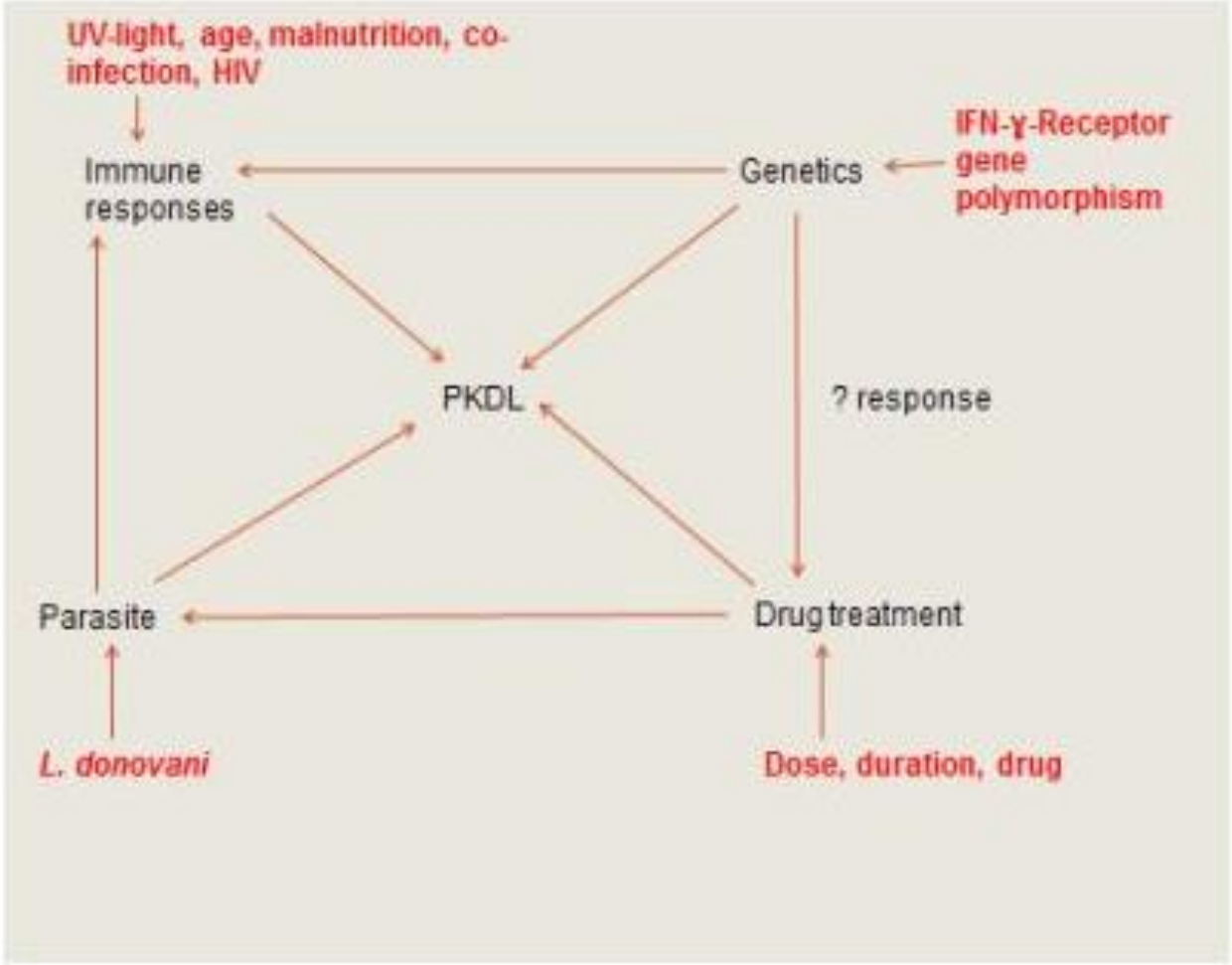
Authors

Anand Ballabh Joshi [1], Megha Raj Banjara [2 3], Murari Lal Das [1], Pragyan Ghale [1], Krishna Raj Pant [1], Niraj Parajuli [4], Uttam Raj Pyakurel [5], Gokarna Raj Dahal [5], Chuman Lal Das [5], Axel Kroeger [6], Abraham Aseffa [3]

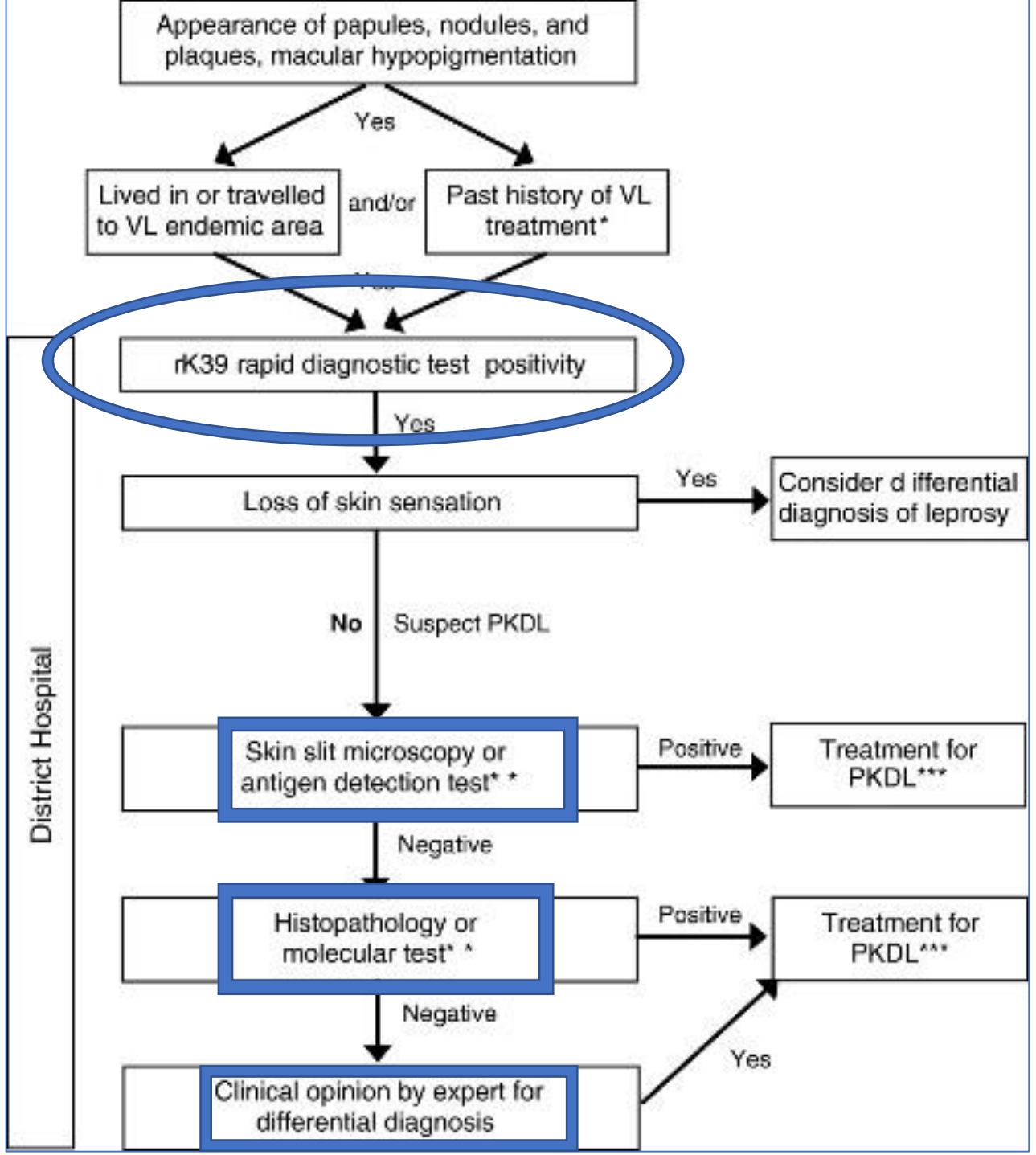
Methodology/principal findings: Household surveys were conducted in 98 VL endemic villages of five districts that reported the highest number of VL cases within 2018-2021. A total of 6,821 households with 40373 individuals were screened for PKDL. Cases with skin lesions were referred to hospitals and examined by dermatologists. Suspected PKDL cases were tested with rK39 and smear microscopy from skin lesions. An integrated diagnostic approach was implemented in two hospitals with a focus on management of leprosy cases where cases with non-leprosy skin lesions were tested for PKDL with rK39. Confirmed PKDL patients were interviewed to assess knowledge and stigma associated with PKDL using explanatory model interview catalogue (EMIC) with maximum score of 36. Among 147 cases with skin lesions in the survey, 9 (6.12%) were confirmed as PKDL by dermatologists at the hospital. The prevalence of PKDL was 2.23 per 10,000 population. Among these 9 PKDL cases, 5 had a past history of VL and 4 did not. PKDL cases without a past history of VL were detected among the "new foci", Surkhet but none in Palpa. None of the cases negative for leprosy were positive for PKDL. There was very limited knowledge of PKDL and VL among PKDL cases. PKDL patients suffered to some degree from social and psychological stigma (mean ± s.d. score = 17.89 ± 12.84).

Pathogenesis (PKDL)…

- **Reinfection or relapse**, which includes the pentavalent antimonial drugs: SAG
- **Genetic** susceptibility of the host: IF-gamma receptor polymorphism
- **UV-induced skin damage**: LG-C
- **Organ-specific failure of memory T cell**: necessary treatment in Indian type
- **Re-infection or persistence** of the parasite: Like in TB



Diagnostic algorithm



Report of the Post Kala-Azar Dermal Leishmaniasis (PKDL) consortium meeting, New Delhi, India, 27–29 June 2012

Biomarkers

- Parasitological
- Serological,
- Immunological, and
- Pathological or
- Repeated clinical assessments

Diagnosis

- Clinical: history of VL (incase of PKDL)
  typical skin lesions
  evidence of past VL

Exclusion of skin diseases including leprosy

Treatment (national)

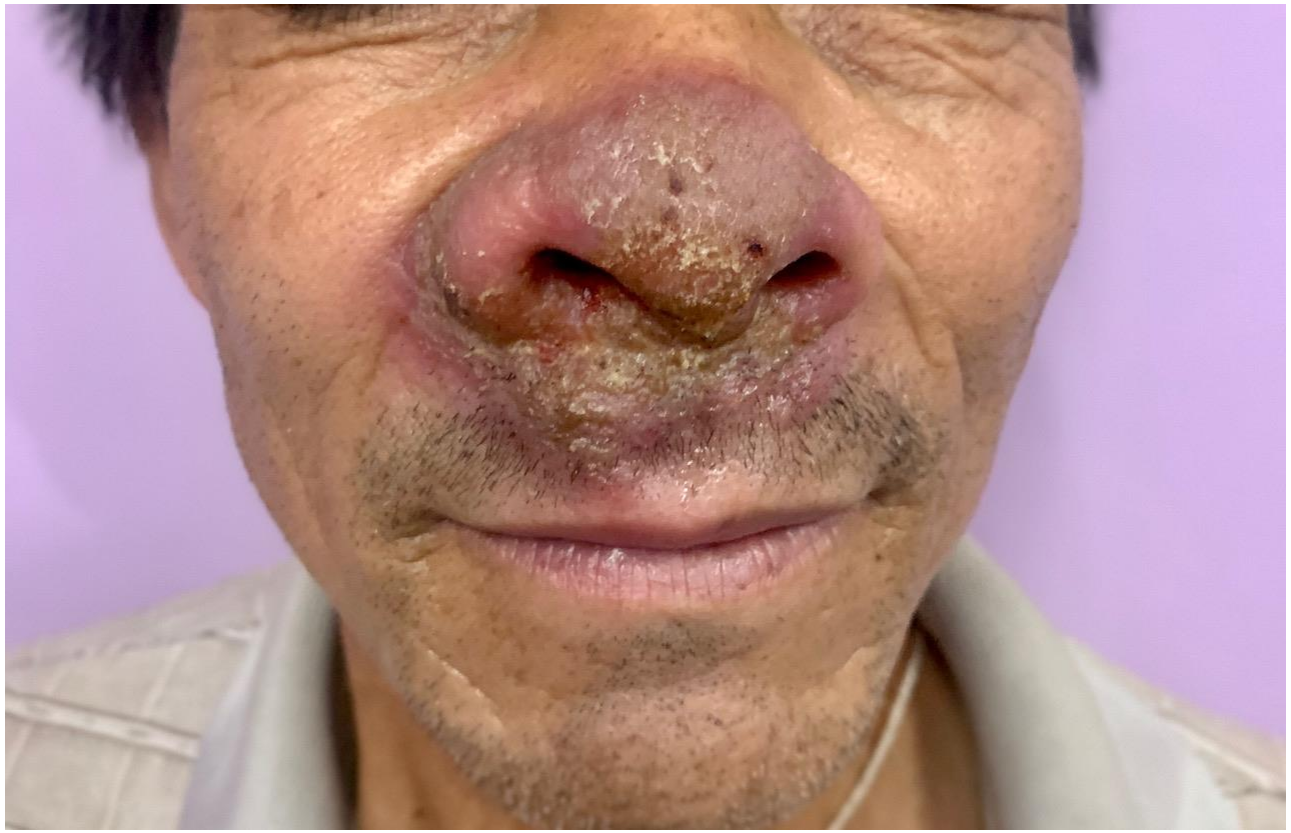
Drug	Dose	Schedule
Miltefosine	>25 kgs: 100mg/day Less than 25 kgs: 50mg/day	Daily for 12 weeks
Amphotericin B	1mg/kg IV infusion	60-80 doses over 4-5 months with 20 doses followed by 20 days interval
Liposomal Amphotericin B	5mg/kg/day by infusion two times per week	Duration of 3 weeks for a total of 30mg/kg *

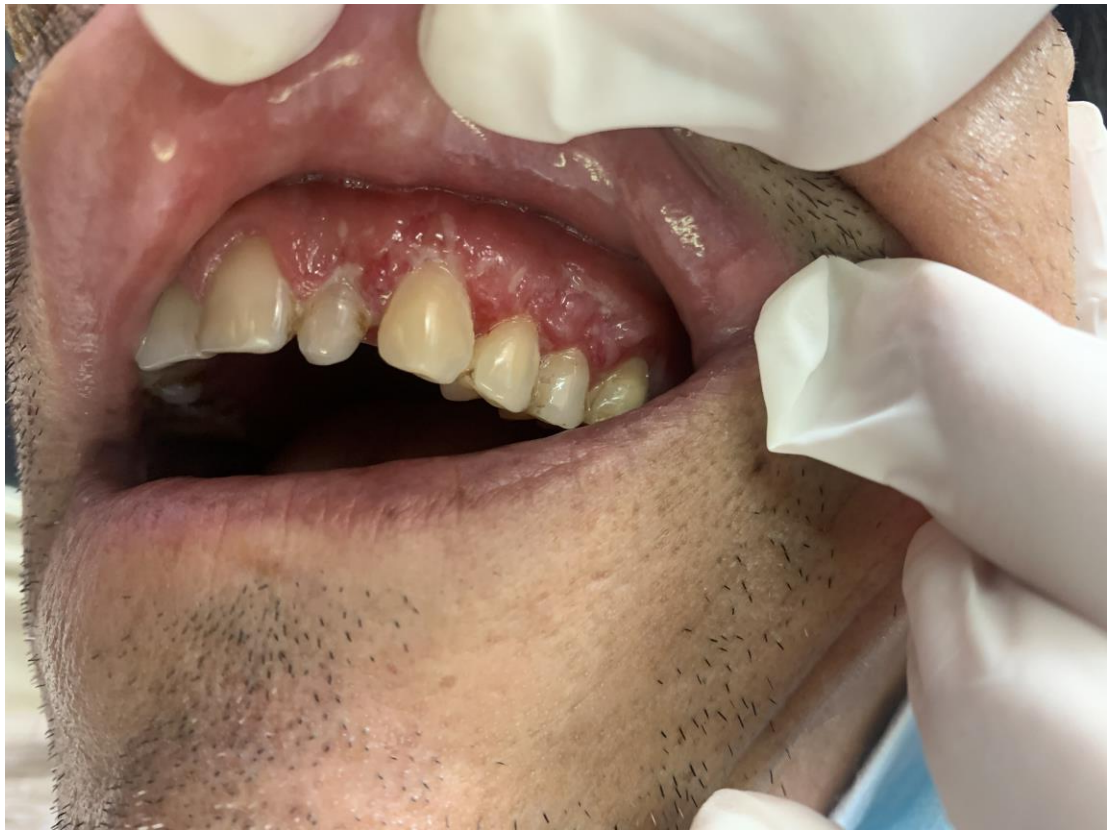
Treatment outcome (PKDL)

- **Initial cure**: clinical improvement at the end of treatment-defined as a considerable reduction in the number and the size of skin lesions

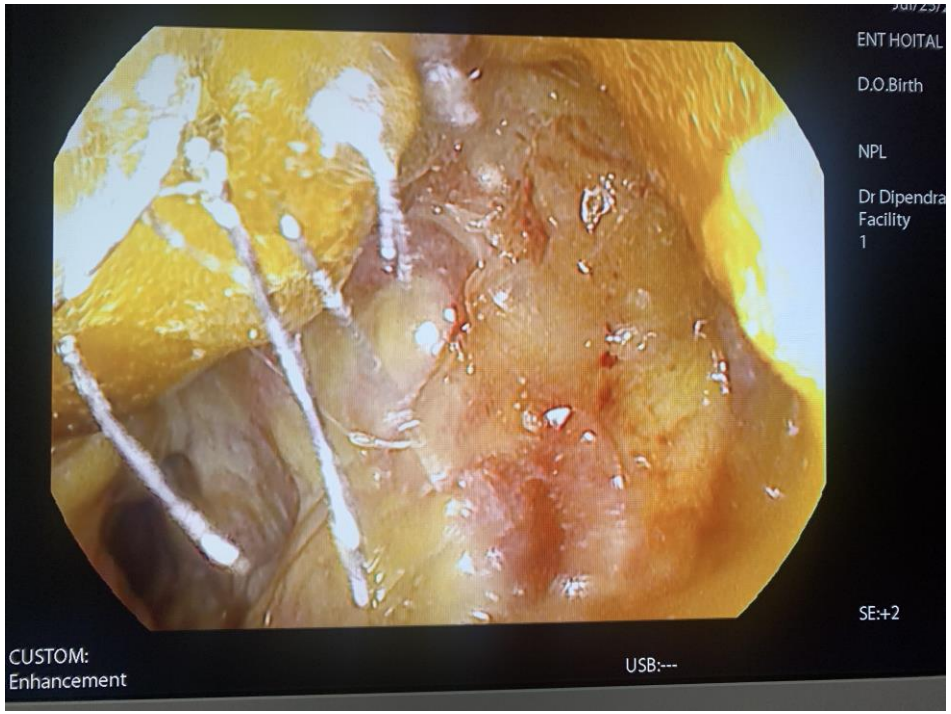
- **Final cure**: clinical cure 12 months after the end of treatment- defined as a complete resolution of macules, papules, plaques and nodules, no new lesions and near total new re-pigmentation

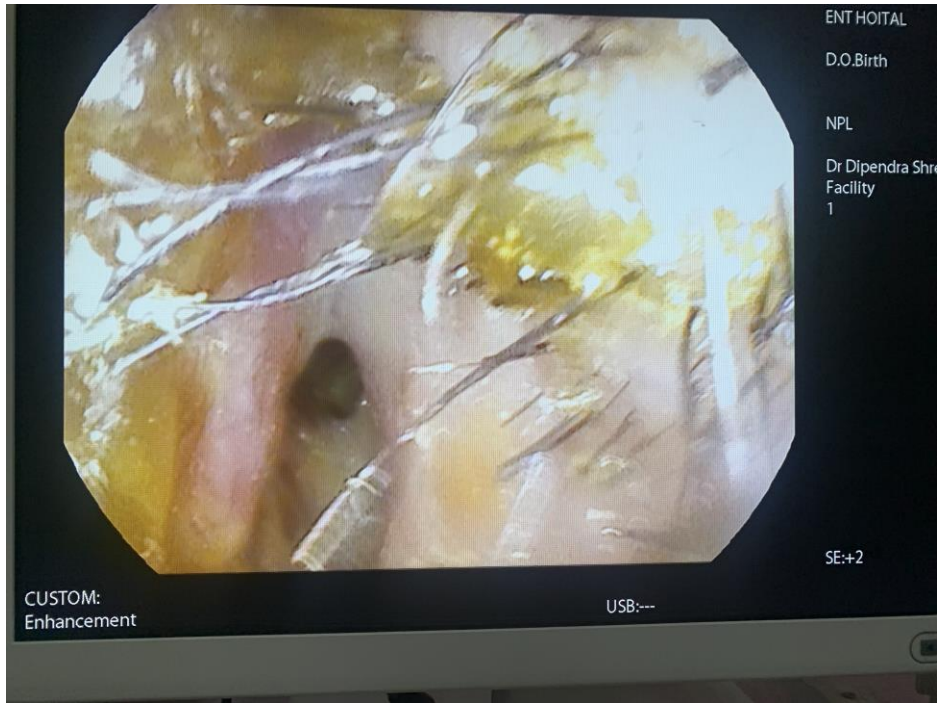
MCL in Nepal

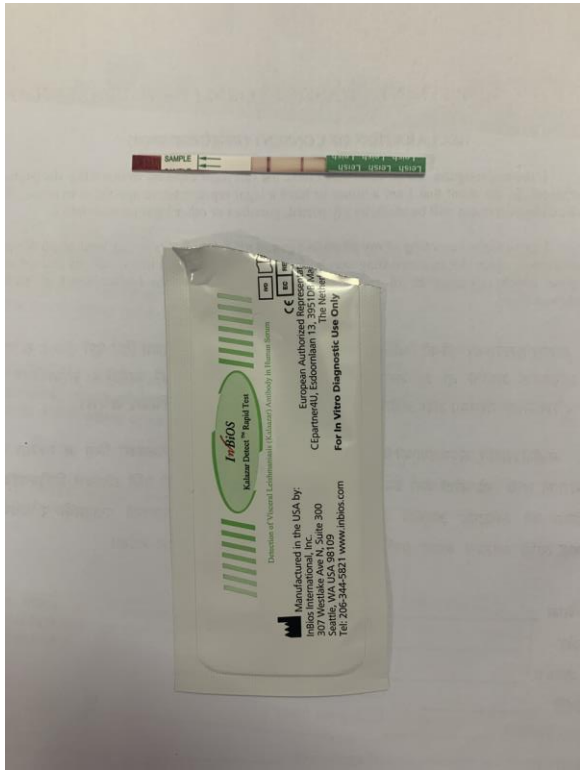




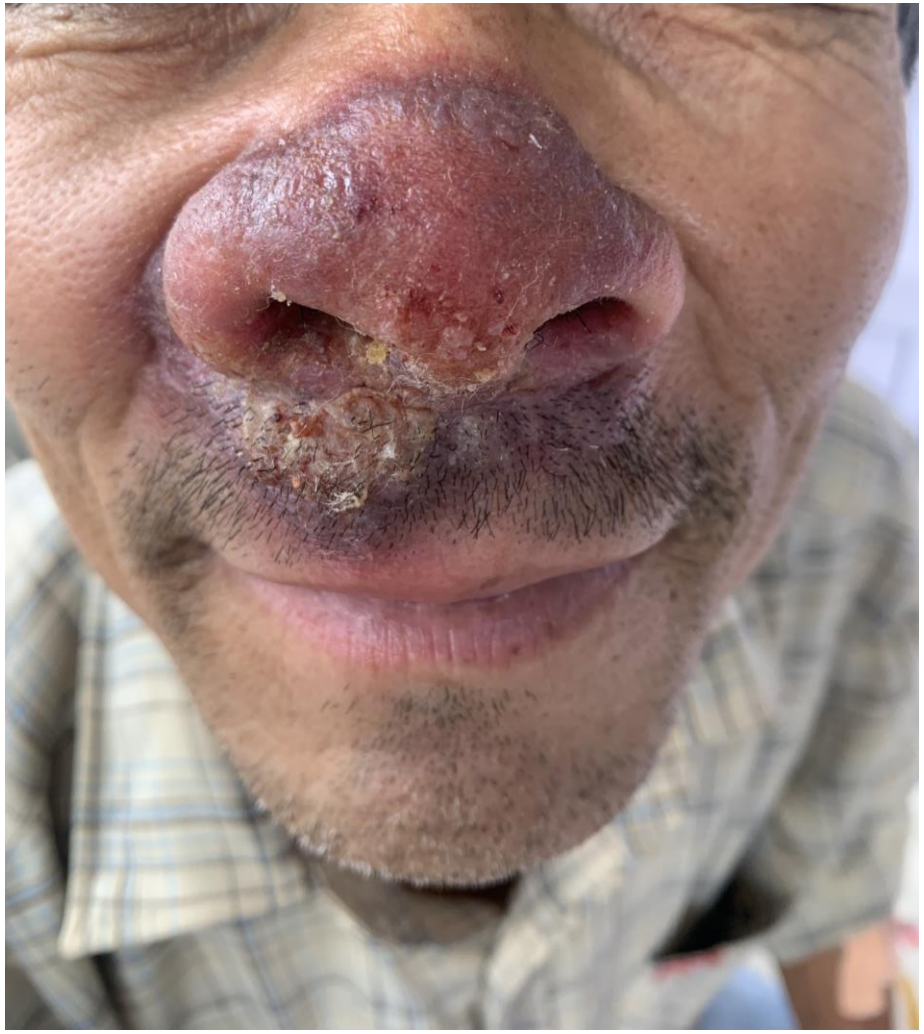
NPL (Normal vs disease)

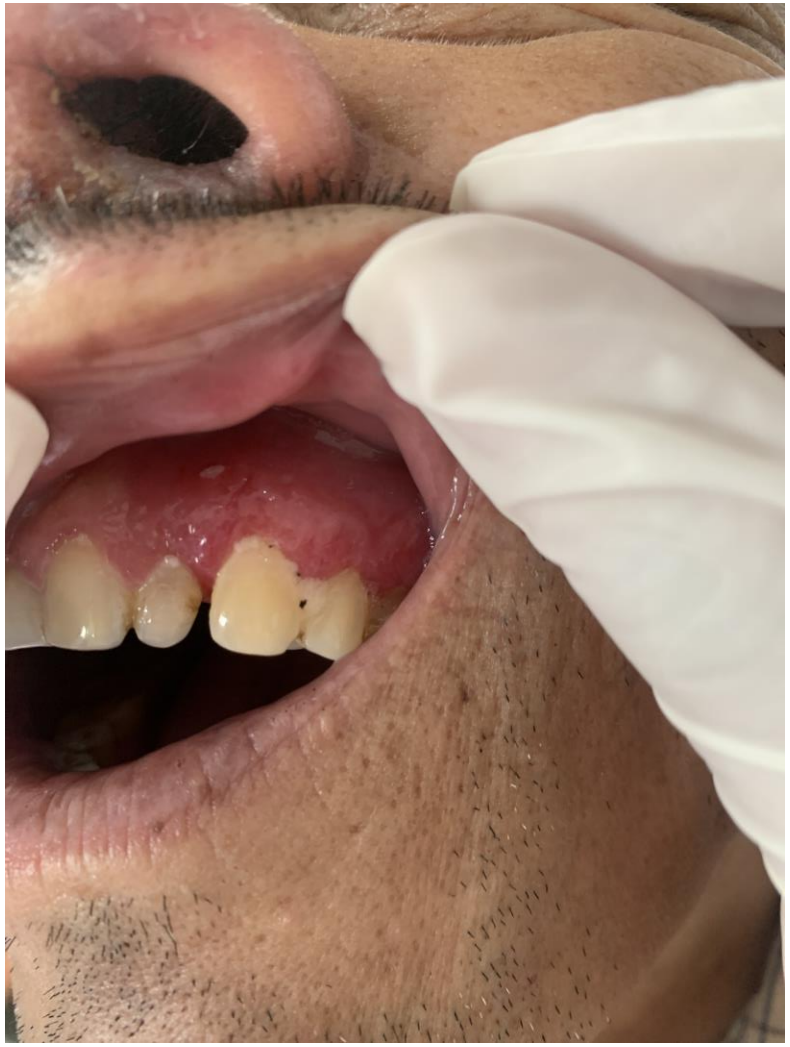




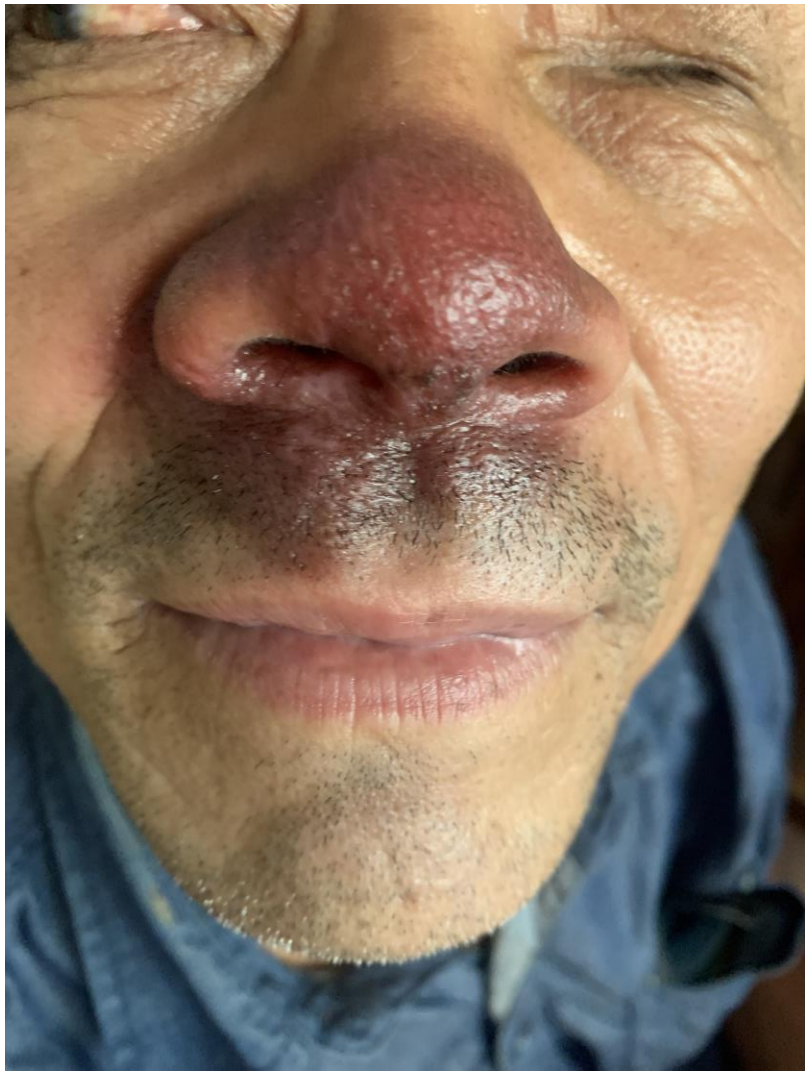


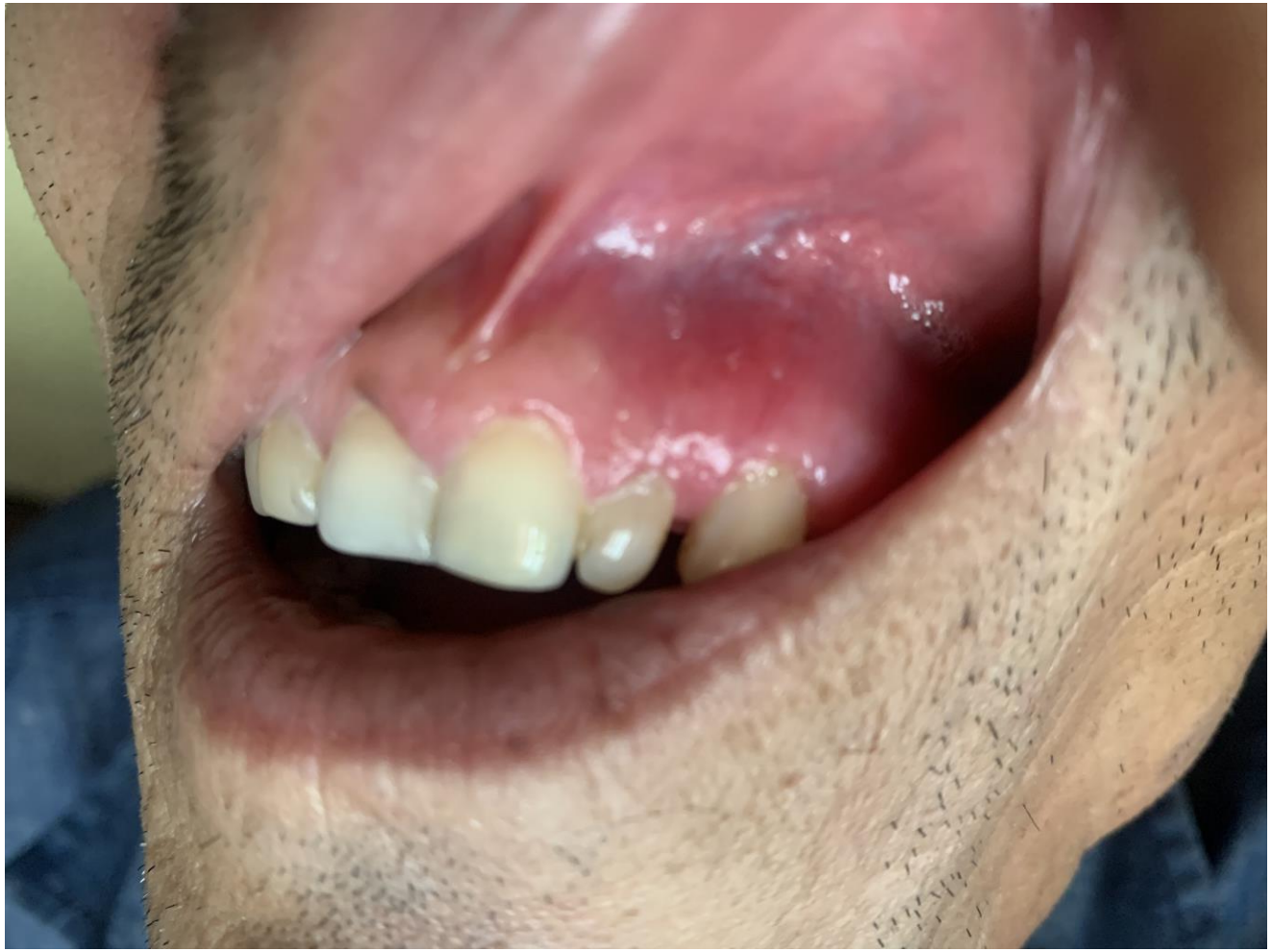
Post- treatment (1week)





Post-treatment (1 month)





Take home message

- CL is increasing, so is other forms.
- CL might have been underdiagnosed or even misdiagnosed.
- Prevalence of CL seems to be higher as compared to cutaneous TB, so be cautious in labelling patient as cutaneous TB.
- Few pointers:
  - Non-painful swelling
  - Not improving on regular treatment
  - Swelling with the typical features
  - Crusting over the lesions
  - Lymphnode enlargement
  - Swelling decreasing on intervention

First Global Skin NTDs Meeting in Geneva

Mini Skin NTDs meeting during the NNN conference in Tanzania

Thank you