# Cutaneous Leishmaniasis: An Evolving Disease with Ancient Roots

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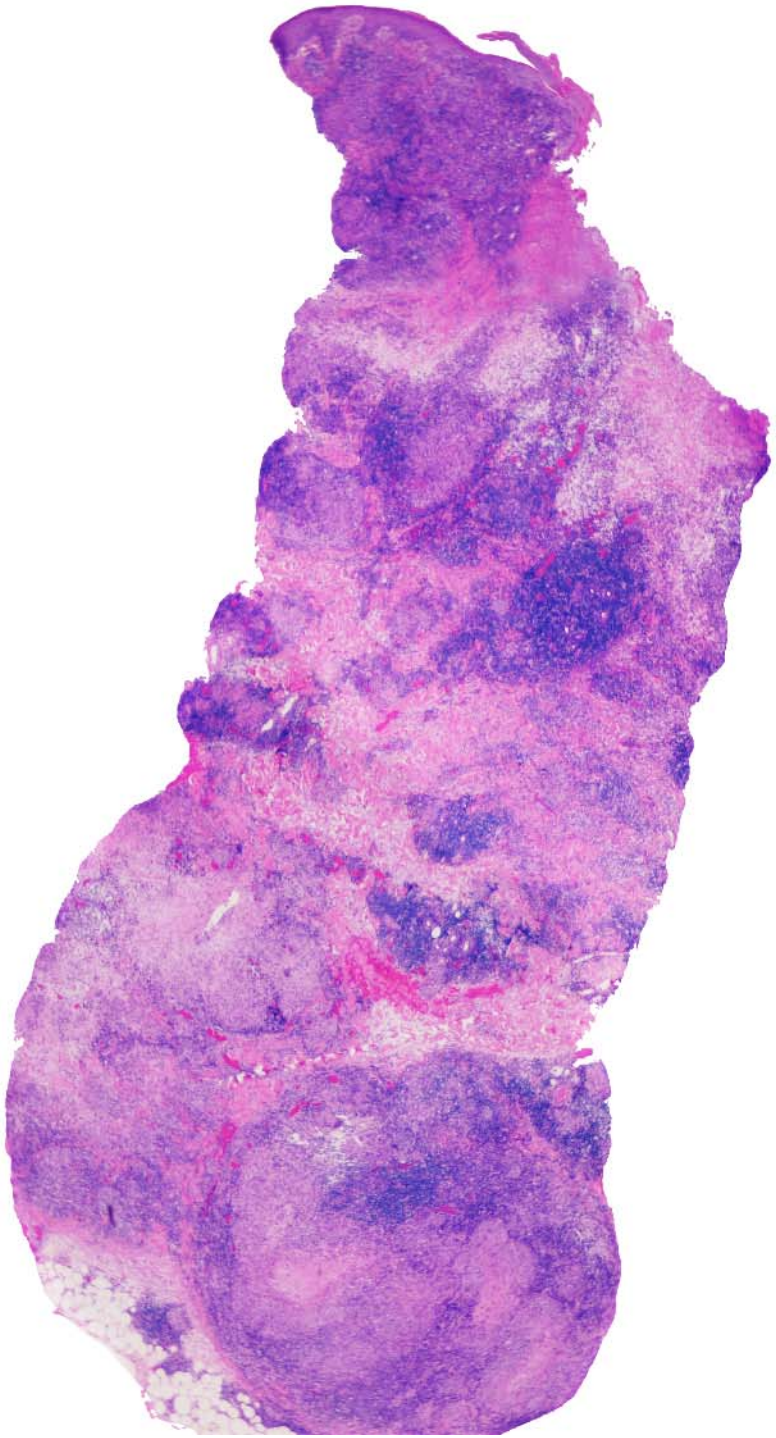
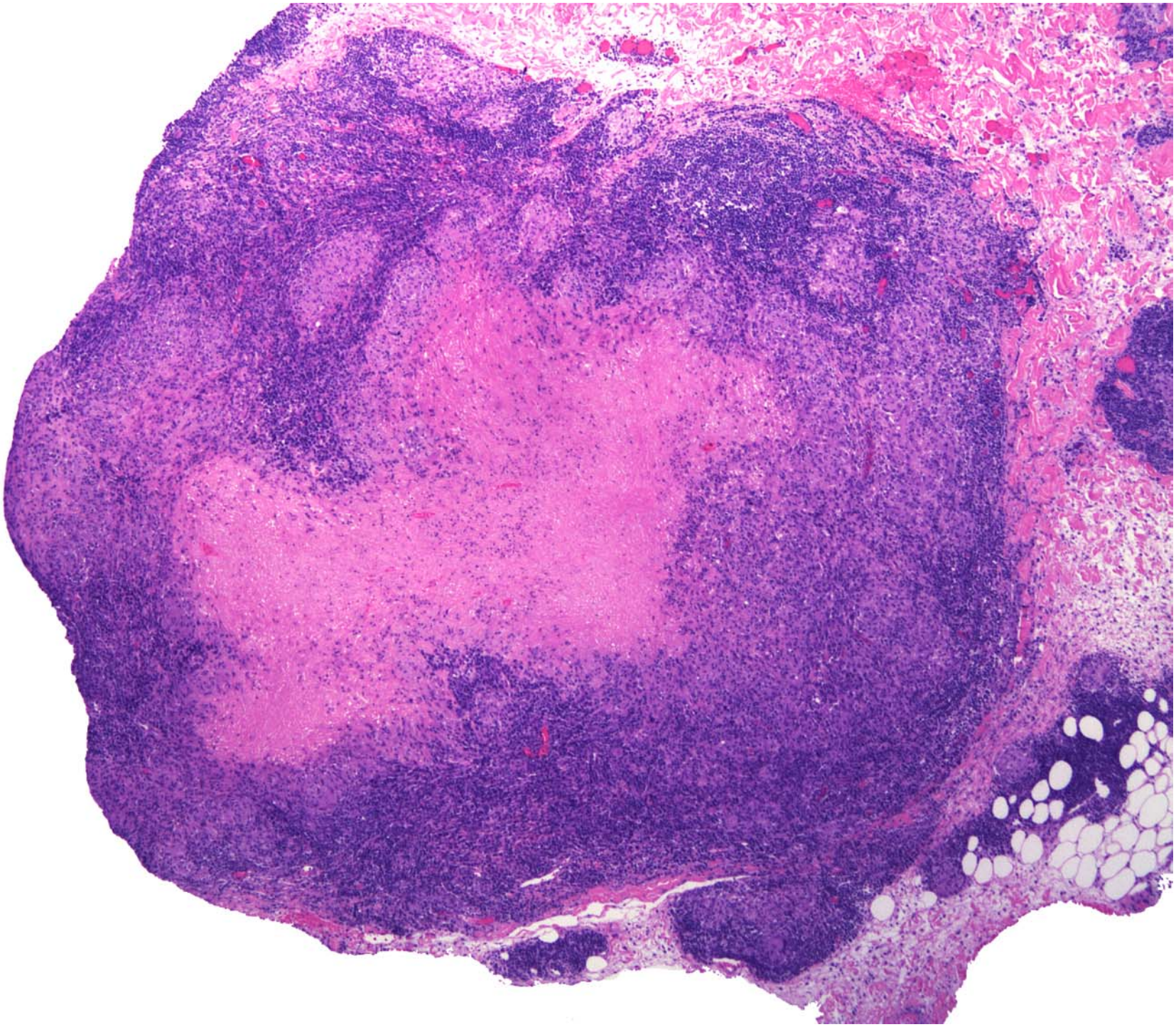
# Road Map

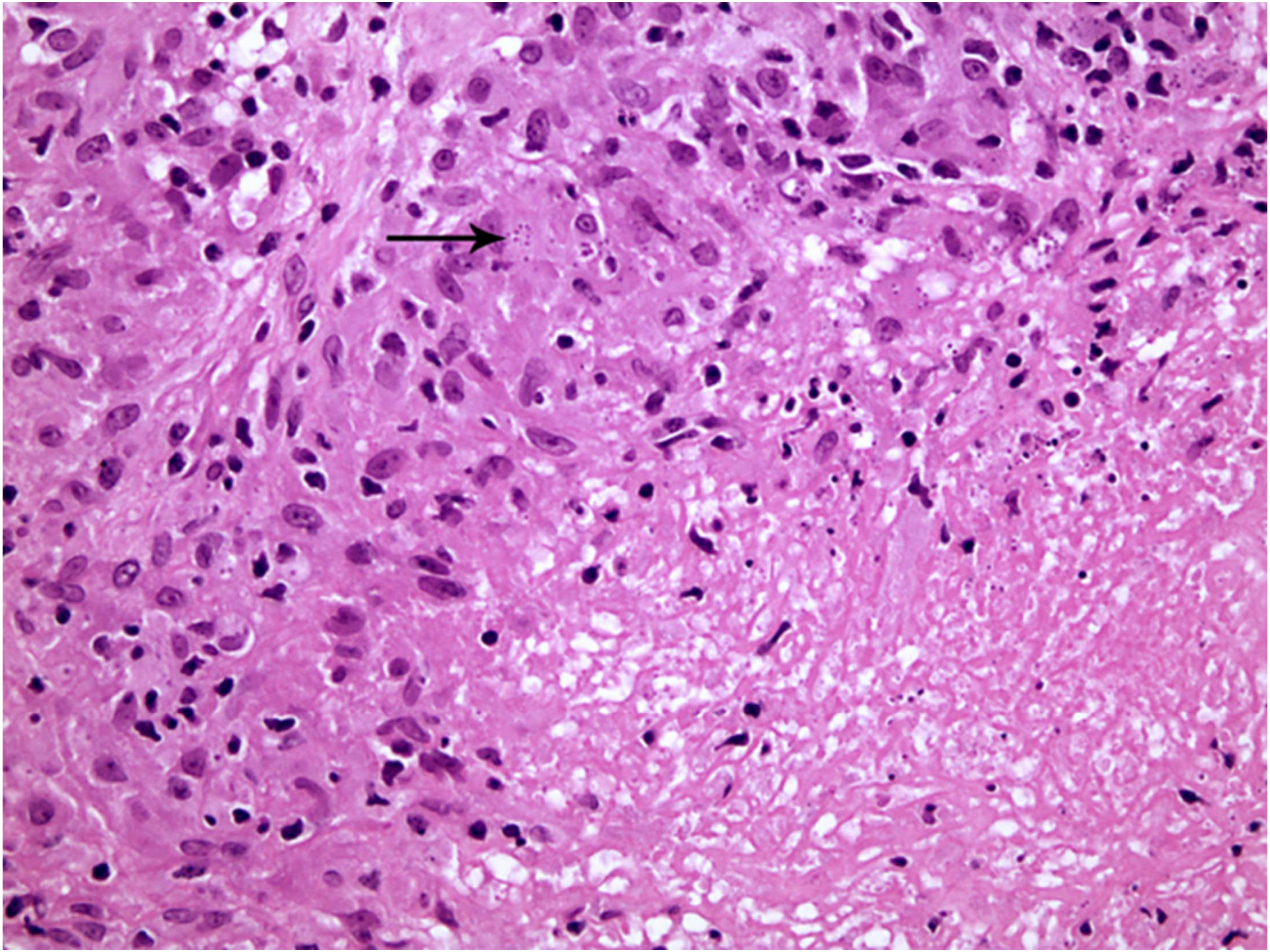
- Case presentation
- Introduction
- Presentation
- Ongoing epidemic
- Diagnosis
- Mimickers

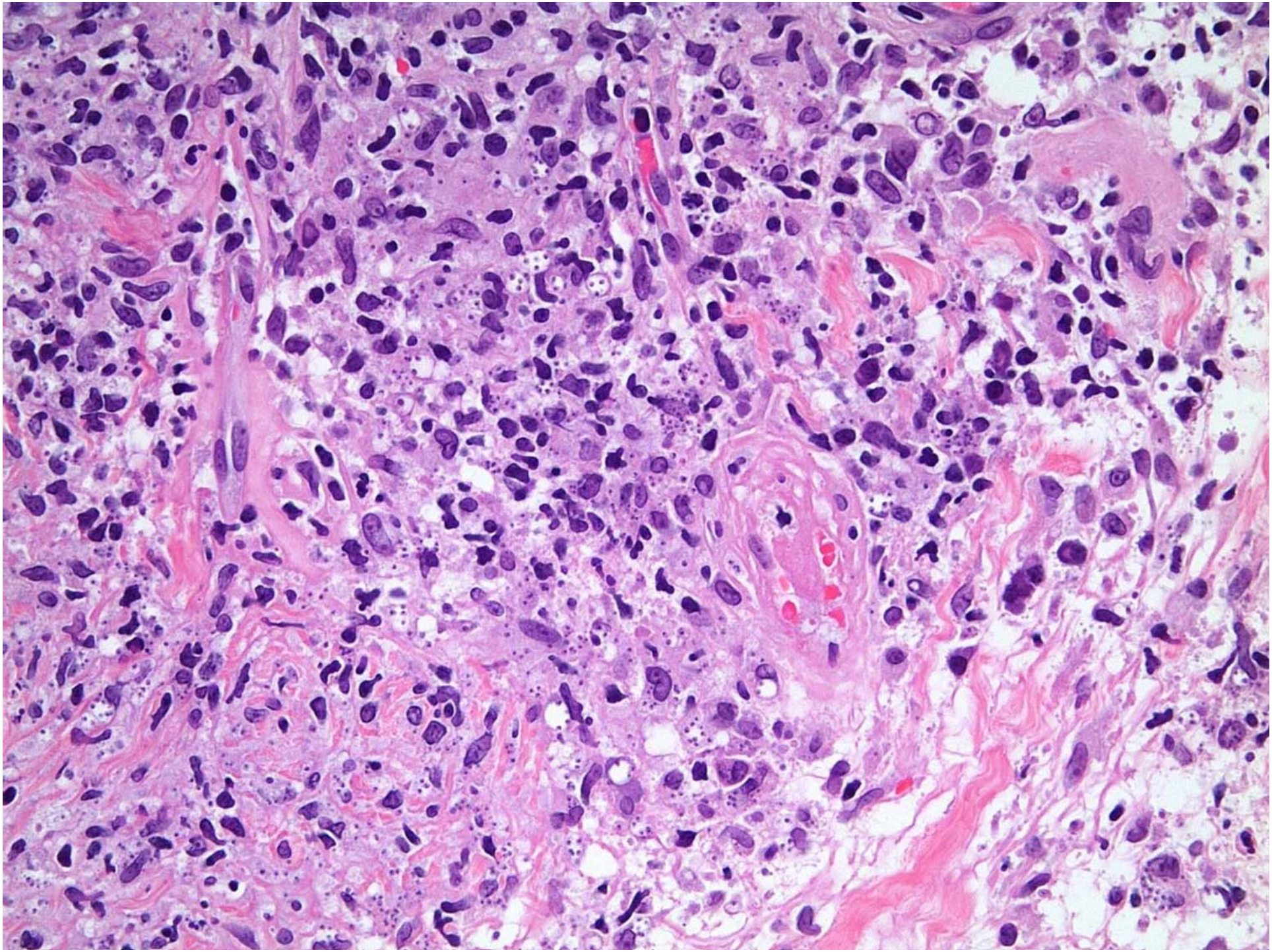
# Case Presentation

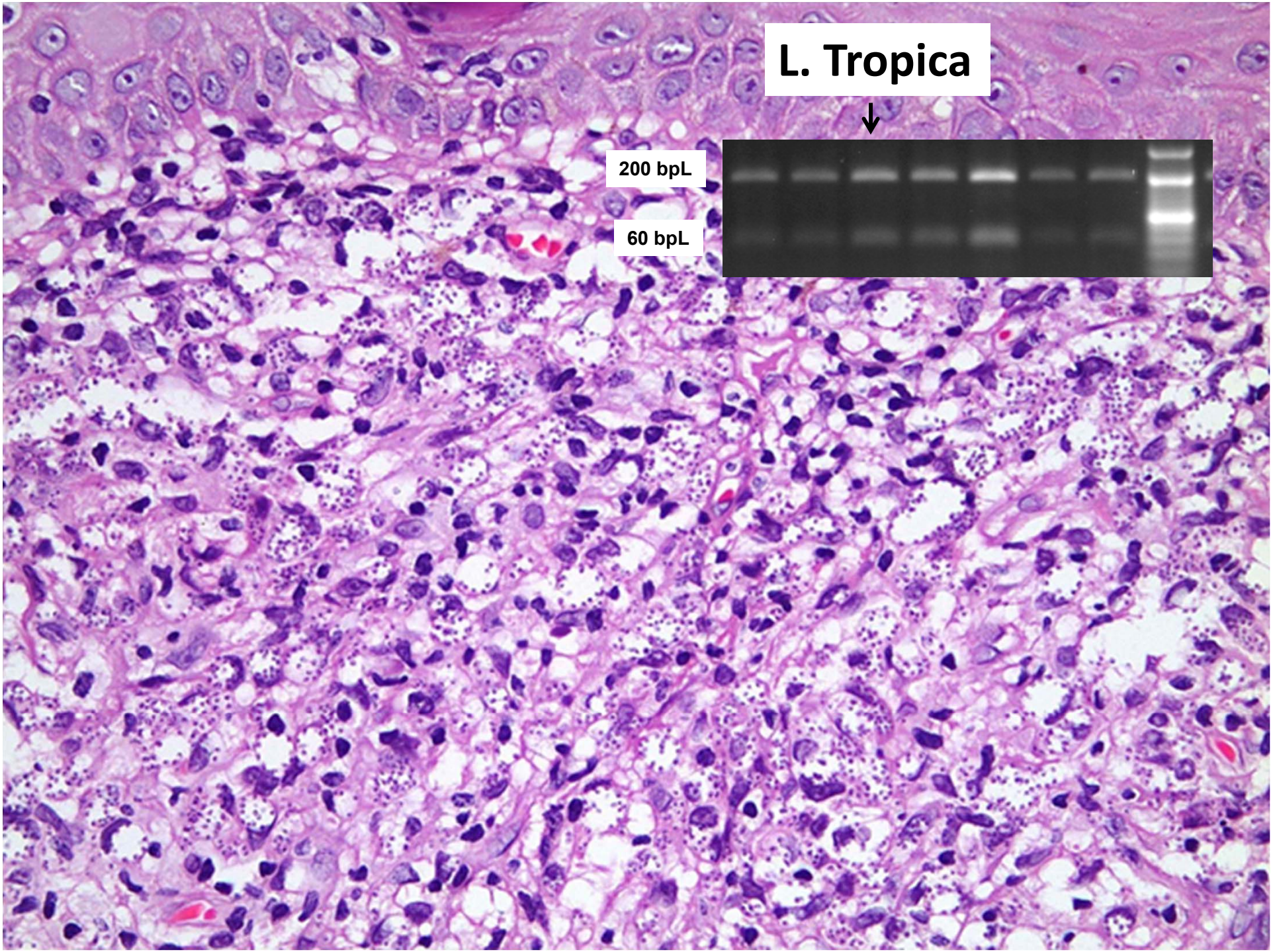
- 70-year-old woman with a painless ulcerated plaque on the left hand for 3 months.
- R/O squamous cell carcinoma versus infection





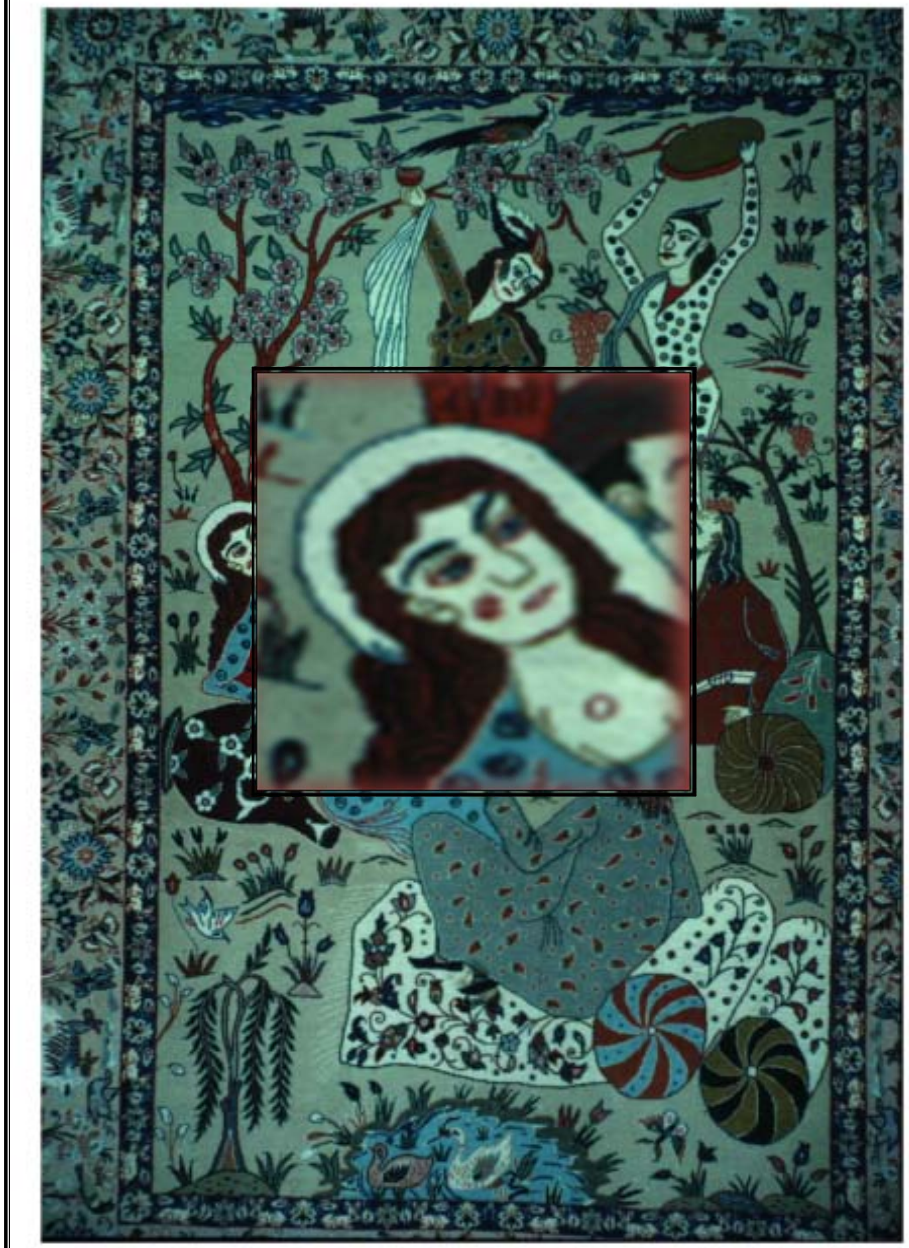





L. Tropica
200 bpL
60 bpL

# Introduction

# Persian Carpet



# Rose of Jericho “Maryam's flower”

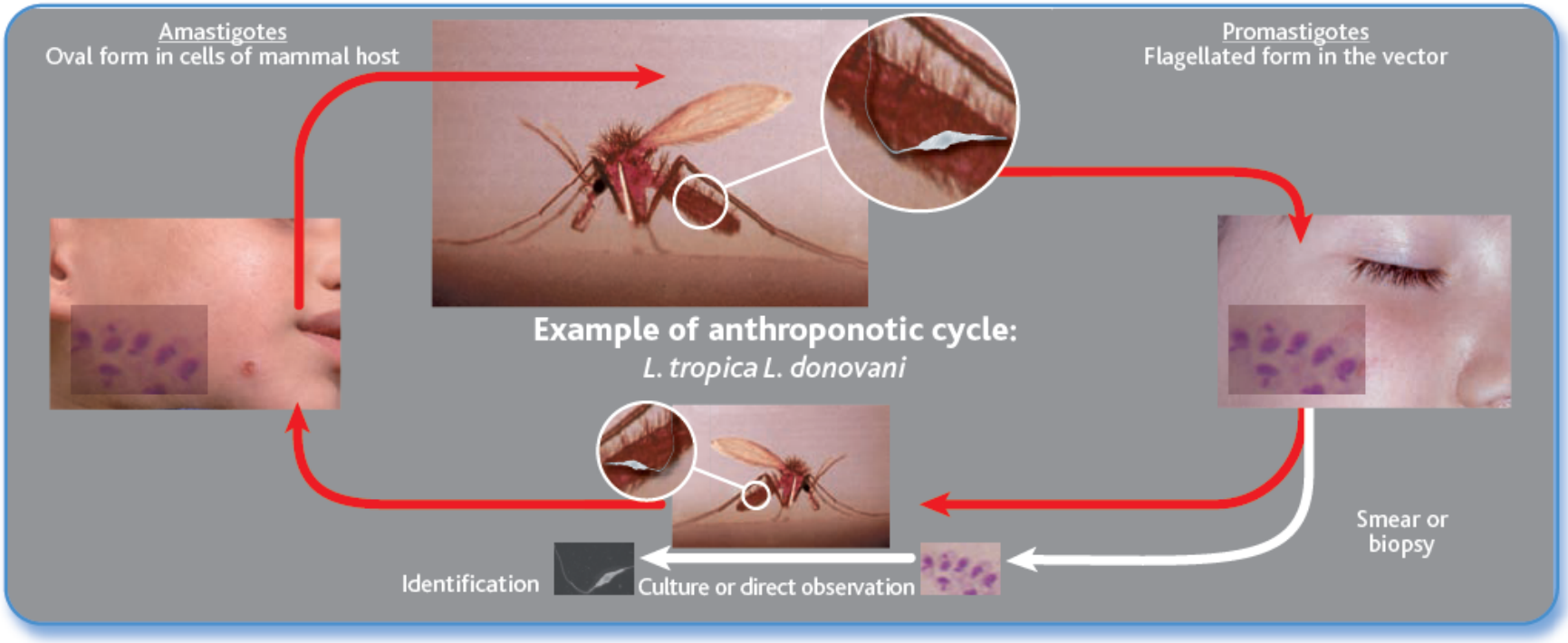
# Introduction

- Frequent disease: New and Old World
- Global Prevalence: 10 million cases
- Annual incidence: 1.5-2 million (high proportion in children)
- Annual mortality: 70,000
- Disease burden disability-adjusted life years (DALY): 2.4 million
- Endemic tropical disease
- World health organization (WHO) priority disease

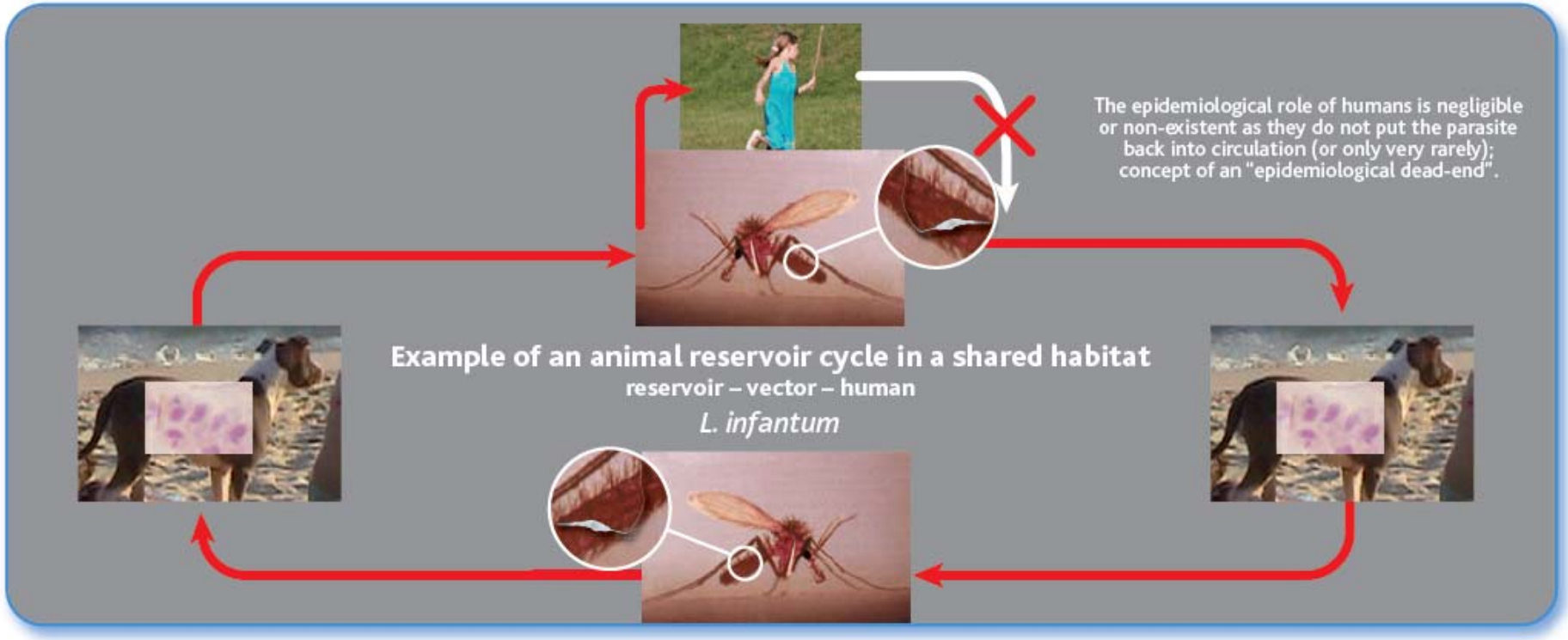
# Parasitology

- L. is transmitted by the bite of female sandflies:
  - Phlebotomus in the old world
  - Lutzomyia in the New World
- Leishmaniasis has both zoonotic and anthroponotic forms

# Anthroponotic Cycle



# Zoonotic Cycle



# Clinical Presentation

# Clinical Presentation

1. Parasitic factors:
   - L. donovani & amazonensis: visceral form
   - L. braziliensis: mucosal form.
2. Host factors:
   - Disease extension
   - Disease evolution

# Clinical Presentation

1. Localized Cutaneous Leishmaniasis
2. Multilesional forms:
   - Post kala-azar dermal leishmaniasis
   - Diffuse cutaneous leishmaniasis
   - Disseminated cutaneous leishmaniasis
3. Rare cutaneous forms (still evolving)

# Localized Cutaneous Leishmaniasis

- Well circumscribed Papule (1w)

↓

- Nodule/plaque (3m)

↓

- Ulcerated/verrucous (5m)

↓

scarring (8m)

# Tunisia

ZLC (2- 8 m)

Curtsey of Dr. Mourad MOKNI

Papule/June

Nodule/Sept

Ulcer/Oct

Scar/jan

# Types of CL (Iran)

## Anthroponotic CL (ACL)

- Urban type
- Dry lesions
- Chronic
- Longer incubation period (2-8 months)
- Longer duration of self healing (up to 2 years)
- A few lesions usually
- Caused by *L. tropica*

## Zoonotic CL (ZCL)

- Rural type
- Wet lesions
- Acute
- Shorter incubation period (2 weeks to 2 months)
- Shorter duration of self healing (up to 1 year)
- Could be numerous lesions
- Caused by *L. major*, *L. aethiopica* & rarely *by L. infantum*

Curtsey of Dr. Ali Khamesipour

Chronic cutaneous leishmaniasis, a great mimicker with various clinical presentations: 12 years experience from Aleppo

Papulonodular form (a-d)

Plaque Form(e-i)

Gyrate From (j)


*J Eur Acad Dermatol Venereol. 2012 Oct;26(10):1224-9*

Tumoral form(e-a)

Verrucous form (b-c)

Ulcerative form (d–f )

Erysipeloid form (g-h)

# Histopathology

**Ridely's classification**

I. Normal skin/Collagen deg.

↓

II. Pan-necrosis

↓

III. Mixed inflammatory inf.

↓

IV. Scattered giant cells

↓

V. Granulomas

*Trans R Soc Trop Med Hyg. 1980;74(4):508-14.*

J Cutan Pathol 2011
doi: 10.1111/j.1600-0560.2011.01844.x
John Wiley & Sons. Printed in Singapore



Journal of
Cutaneous Pathology

# Cutaneous leishmaniasis mimicking inflammatory and neoplastic processes: a clinical, histopathological and molecular study of 57 cases

**Background:** Cutaneous leishmaniasis displays considerable variation in its histopathological and clinical presentation. Clinically, it progresses from a papule into a painless ulcerated and crusted nodule/papule. Microscopically, it progresses from sheets of amastigote-filled histiocytes to granulomatous inflammation.
**Methods:** The study was conducted on 145 skin biopsies from untreated patients with histopathological and/or clinical suspicion of cutaneous leishmaniasis in Lebanon, Syria and Saudi Arabia (1992–2010). The pre-biopsy clinical diagnosis and demographic data were collected. Biopsies were evaluated for the major microscopic pattern, and the parasitic index (PI) was also determined. Diagnosis was confirmed by polymerase chain reaction (PCR) followed by molecular sub-speciation.
**Results:** Of the 145 patients, 125 were confirmed as cutaneous leishmaniasis by PCR. Eighteen cases presented with a pre-biopsy clinical diagnosis other than cutaneous leishmaniasis that ranged from dermatitis to neoplasm. Of the 125 cases, 57 showed a major histopathological pattern other than cutaneous leishmaniasis. Identification of amastigotes was equivocal (PI $\leq$1) in 38 of the 57 cases. Of interest, all the 18 cases with a pre-biopsy clinical diagnosis other than cutaneous leishmaniasis also showed atypical histopathology for cutaneous leishmaniasis.
**Conclusions:** The manifestations of cutaneous leishmaniasis are broad and may mimic other inflammatory and neoplastic diseases. Pathologists and dermatologists should be aware of such pitfalls and can utilize PCR to confirm the diagnosis of leishmaniasis.

*Keywords:* cutaneous leishmaniasis, mimic, molecular sub-speciation, simulant

Saab J, Fedda F, Khattab R, Yahya L, Loya A, Satti M, A-G Kibbi, Houreih MA, Raslan W, El-Sabban M, Khalifeh I. Cutaneous leishmaniasis mimicking inflammatory and neoplastic processes: a clinical, histopathological and molecular study of 57 cases.
J Cutan Pathol 2011. © 2011 John Wiley & Sons A/S.

**Jad Saab[1], Faysal Fedda[1], Ruba Khattab[1], Lamis Yahya[2], Asif Loya[3], Mohamed Satti[4], Abdul-Ghani Kibbi[5], Mohammad Adib Houreih[6], Wasim Raslan[7], Marwan El-Sabban[2] and Ibrahim Khalifeh[1]**

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[5]Department of Dermatology, American University of Beirut Medical Center, Beirut, Lebanon.
[6]Department of Pathology, Tishreen University, Lattakia, Syrian Arab Republic. and
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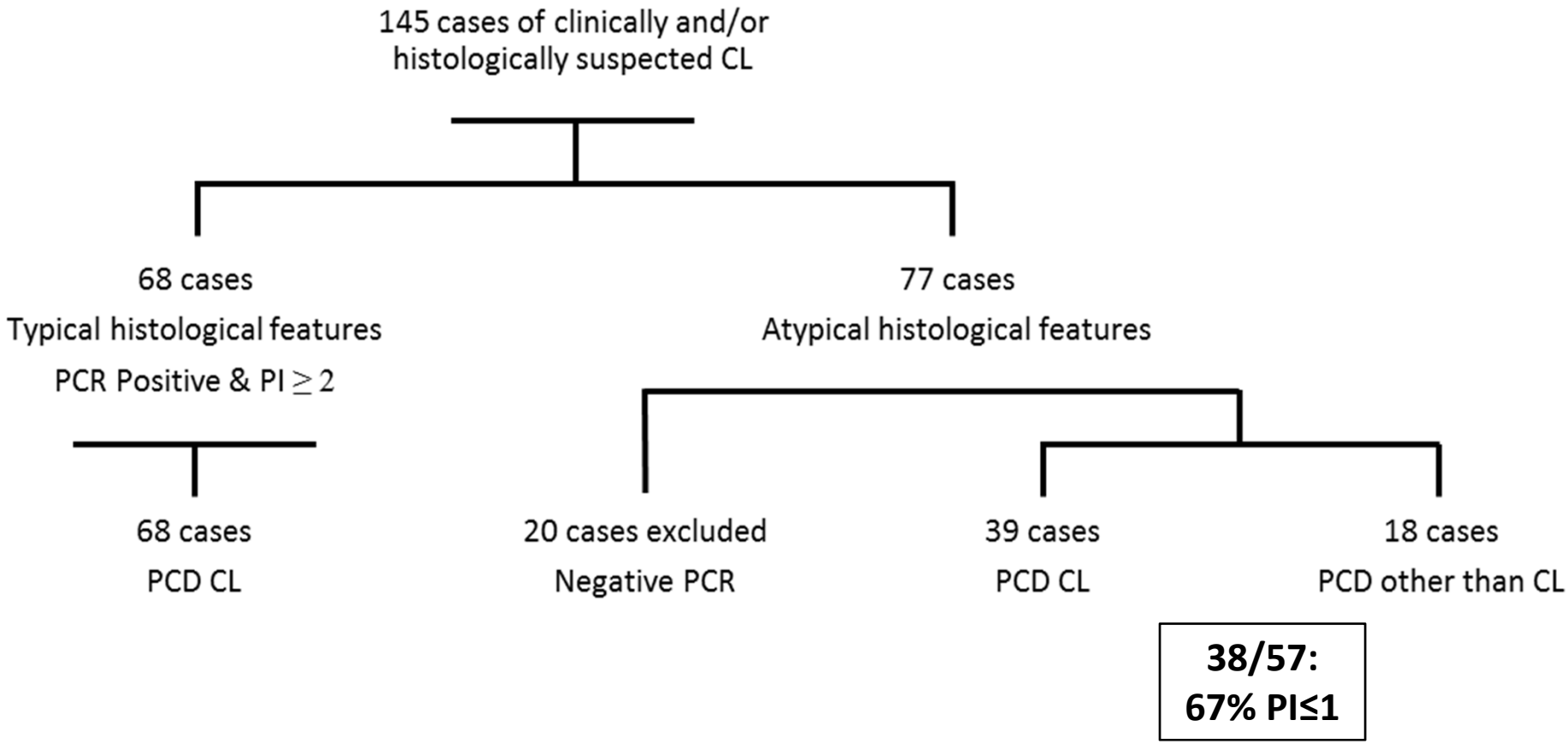
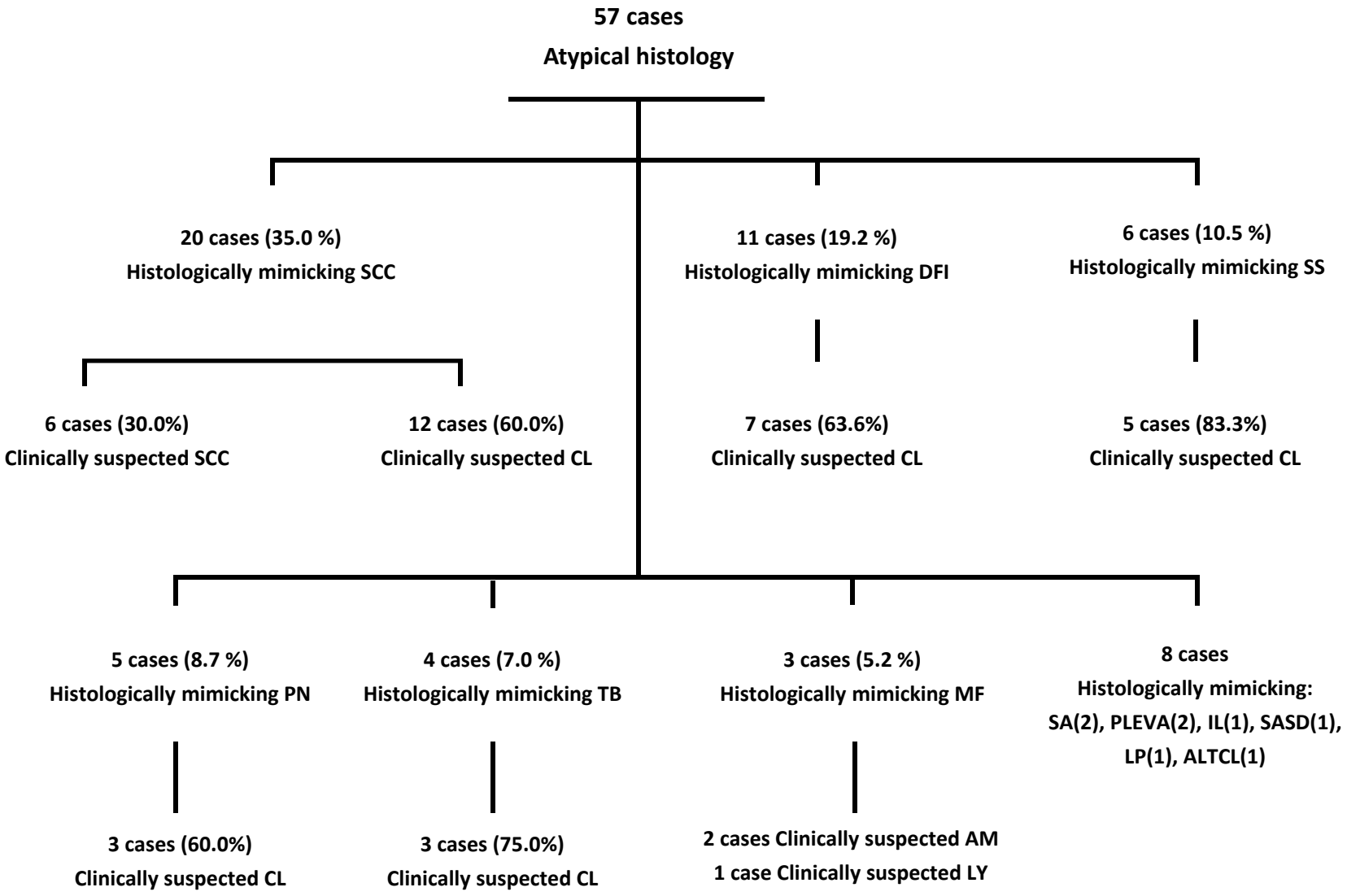
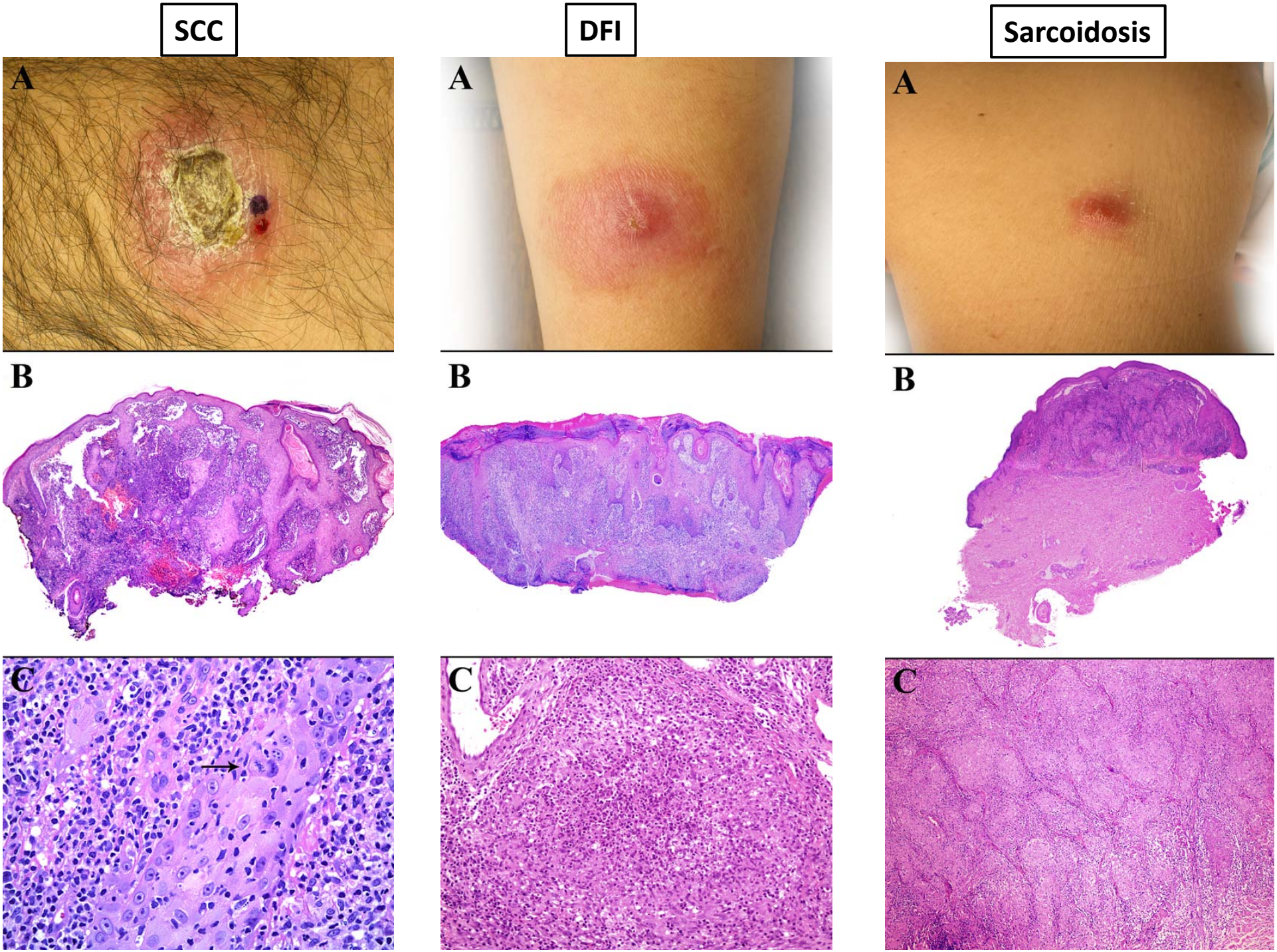
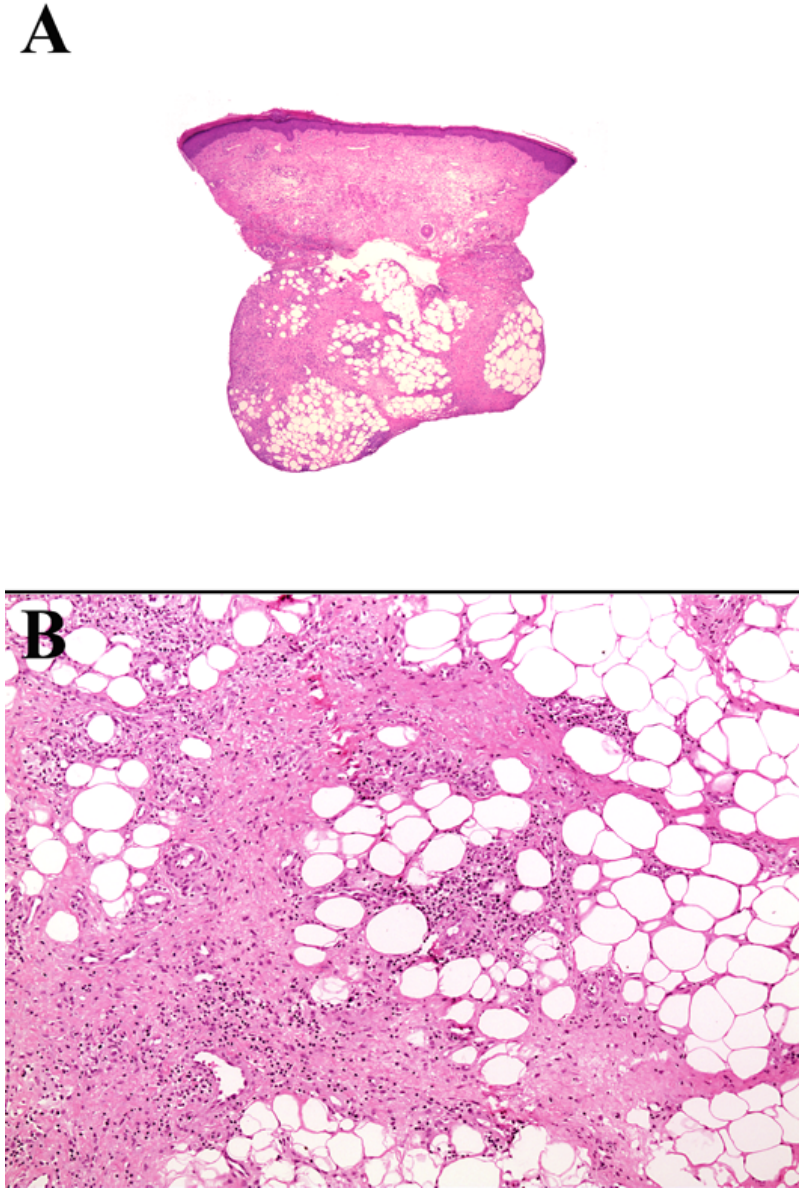

145 cases of clinically and/or histologically suspected CL
68 cases
Typical histological features
PCR Positive & PI ≥ 2
77 cases
Atypical histological features
68 cases
PCD CL
20 cases excluded
Negative PCR
39 cases
PCD CL
18 cases
PCD other than CL
38/57:
67% PI≤1



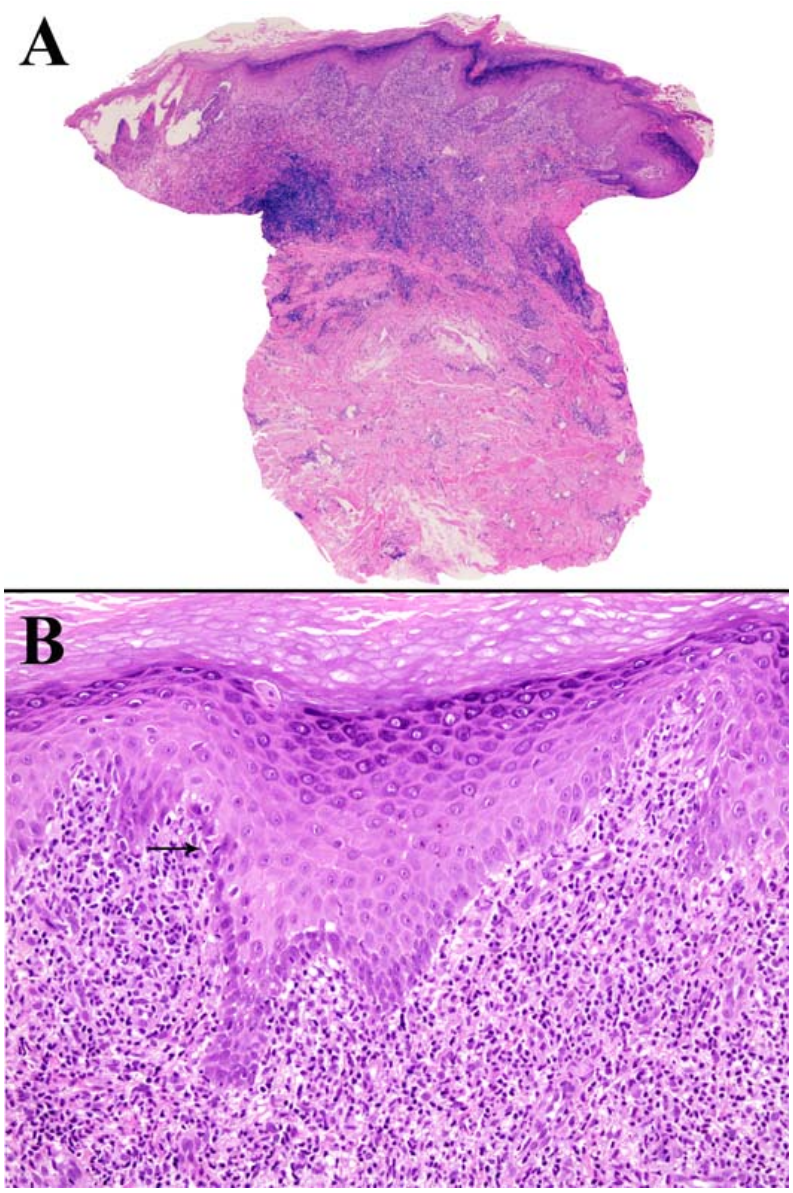

**ALTCL**: anaplastic large T cell lymphoma; **DFI**: deep fungal infection; **IL**: indeterminate leprosy; **LP**: lichen planus; **MF:** mycosis fungoides; **PLEVA**: pityriasis lichenoides; **PN**: panniculitis; **SCC**: squamous cell carcinoma; **SS**: secondary syphilis; **TB**: tuberculosis.


SCC
DFI
Sarcoidosis
A
A
A
B
B
B
C
C
C

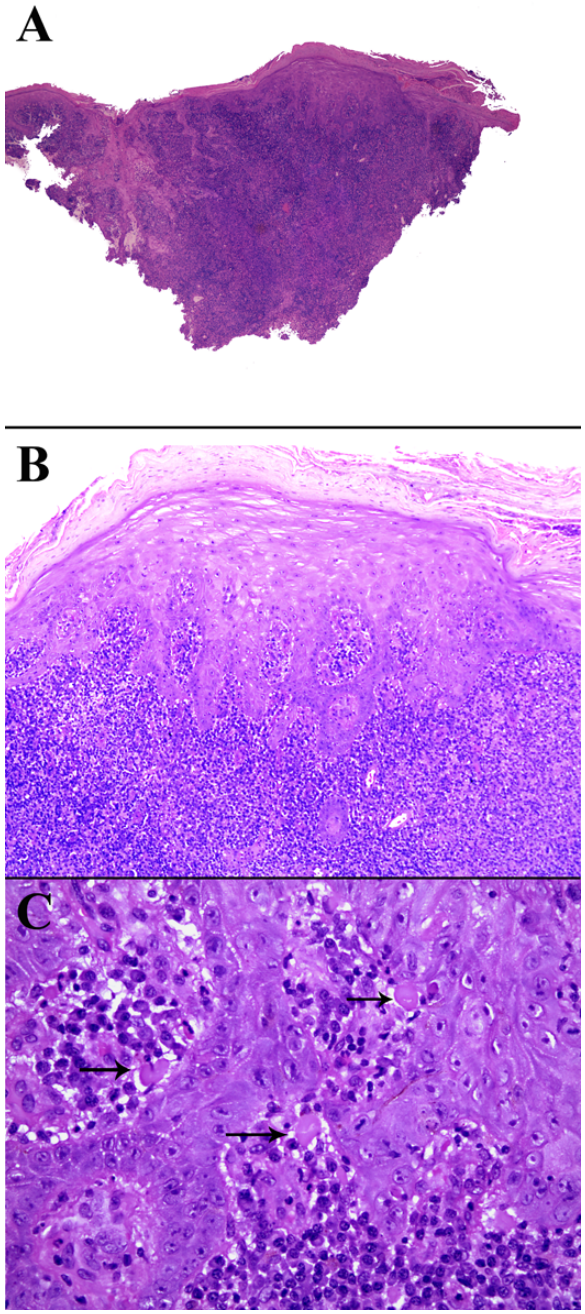
Panniculitis



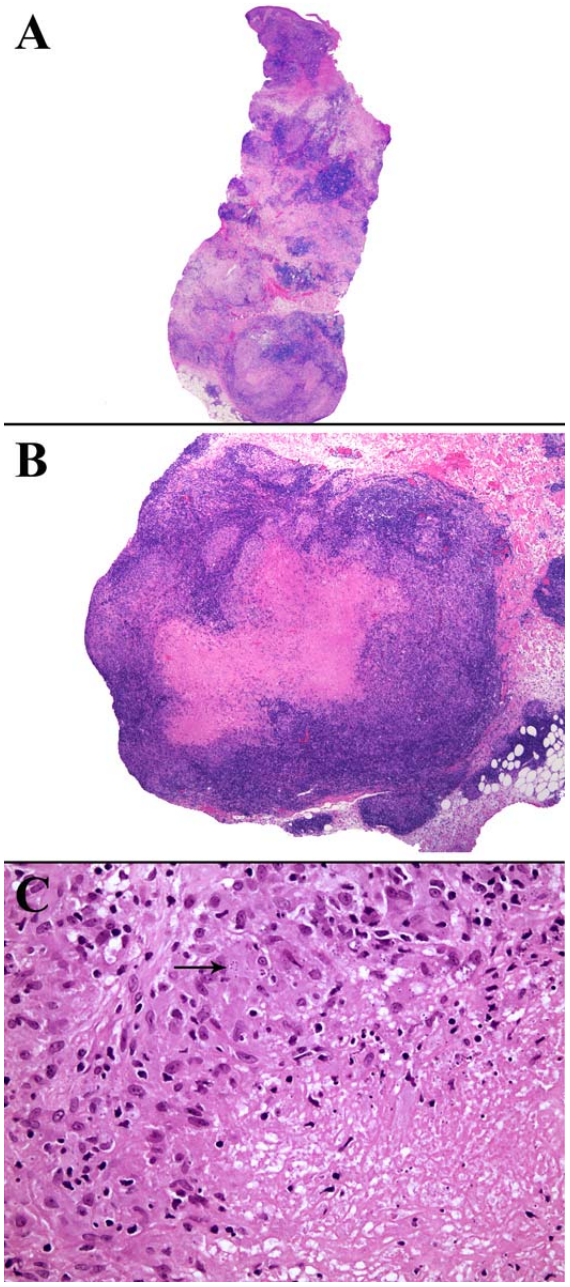

Lichen Planus



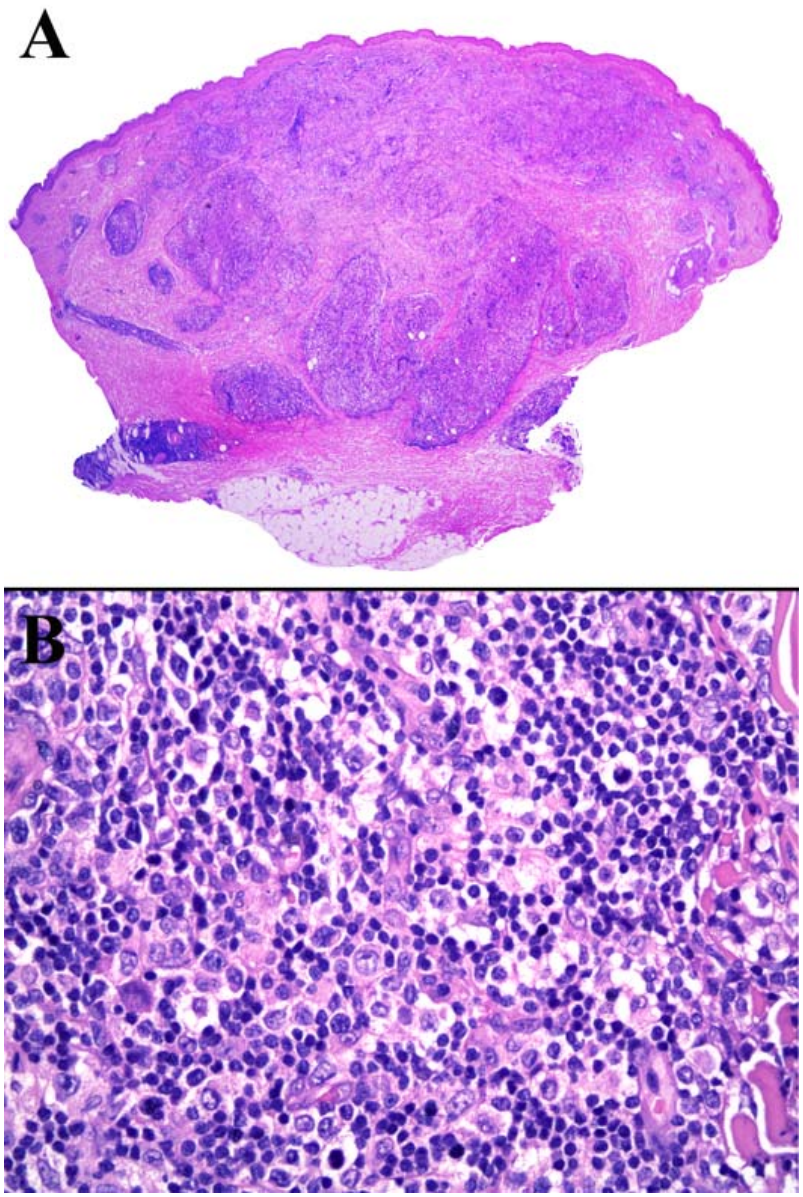
Secondary Syphilis



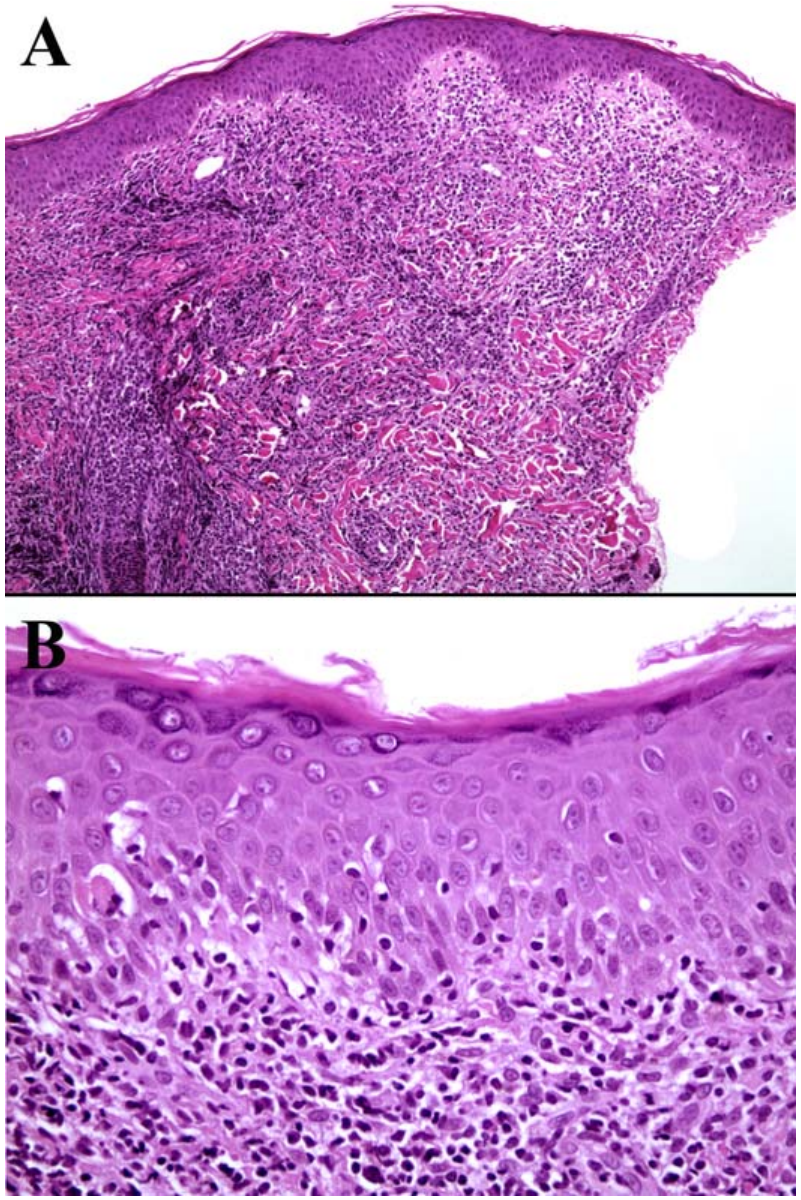

TB



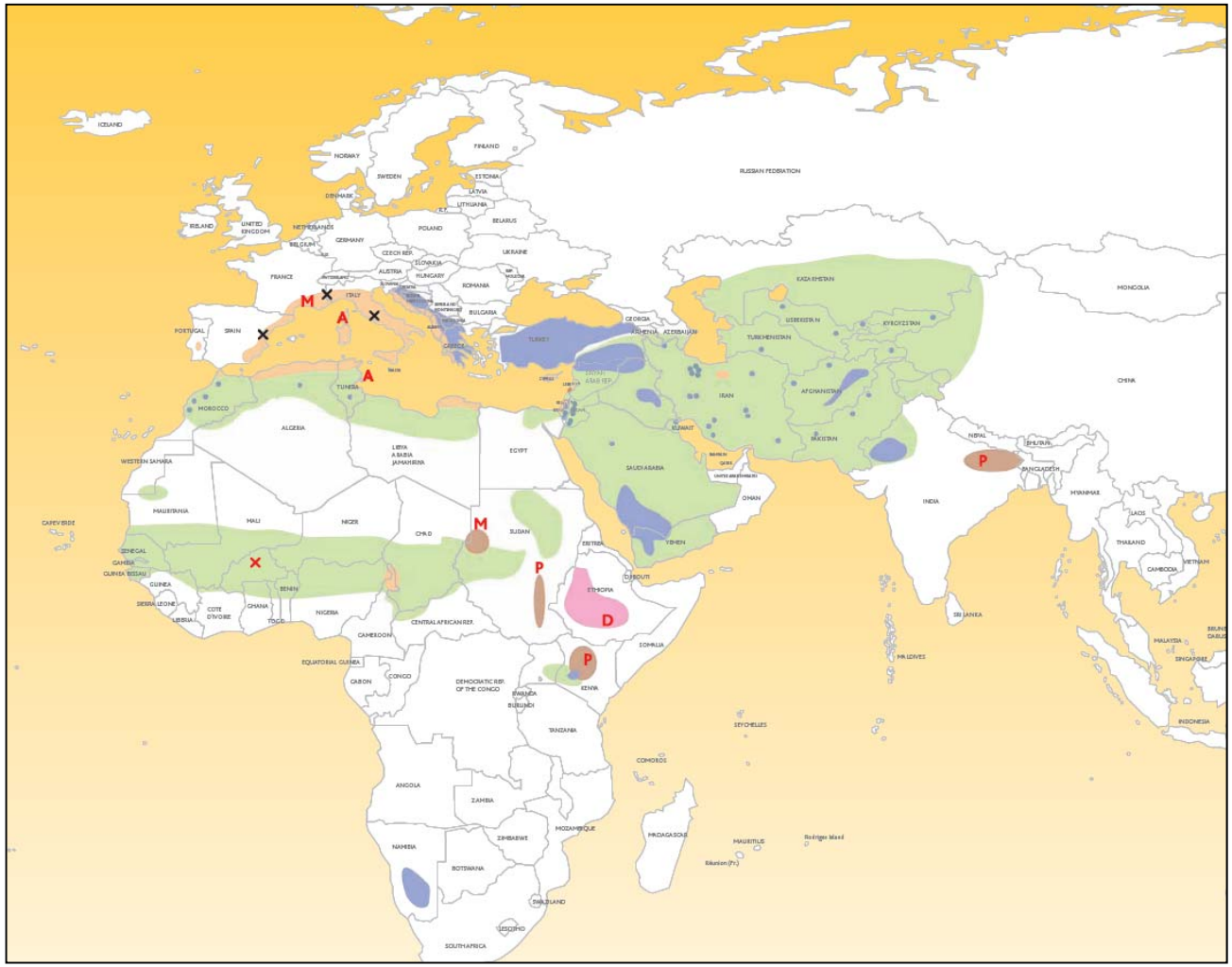
ACTL




MF



# Geography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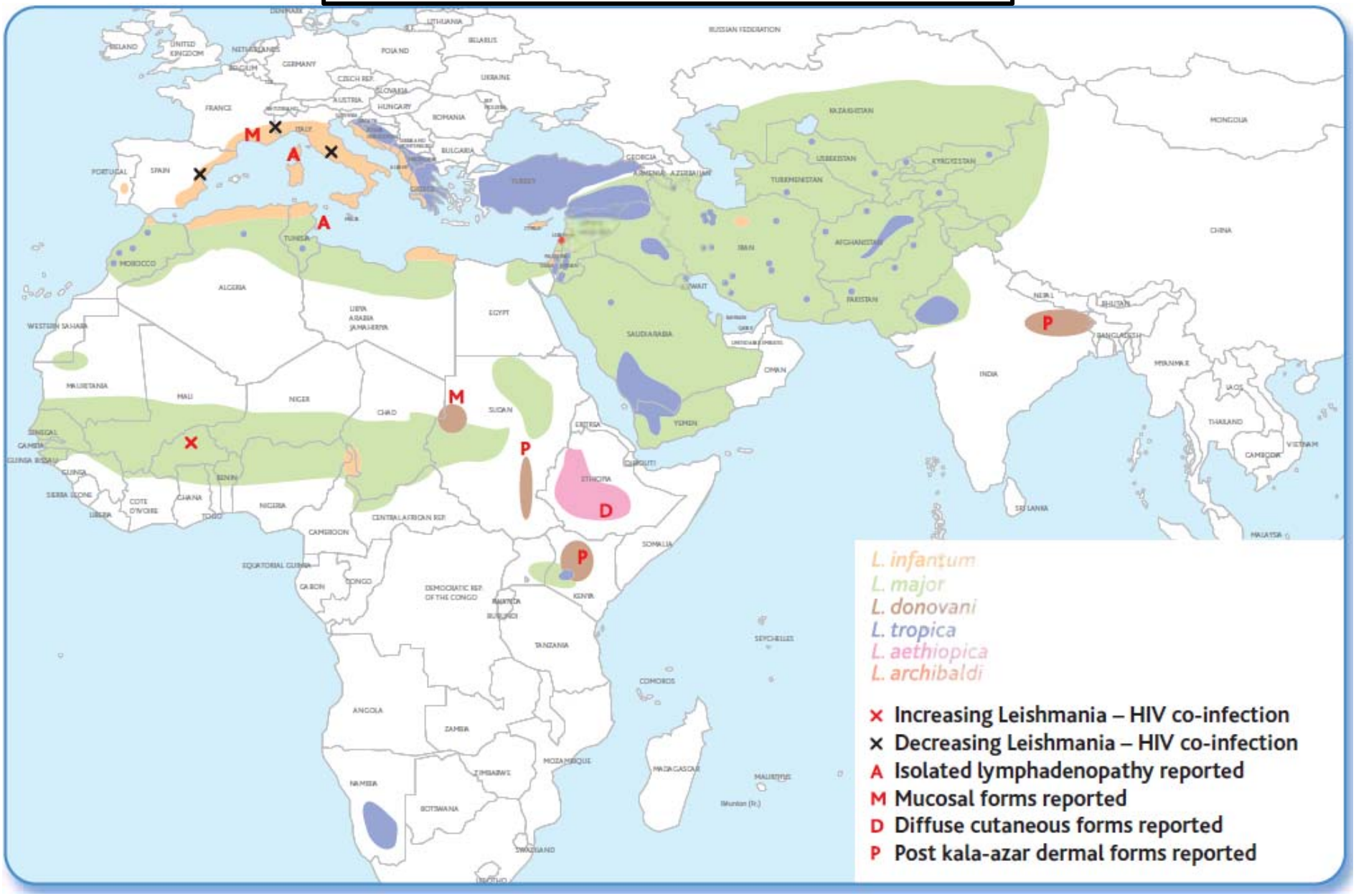
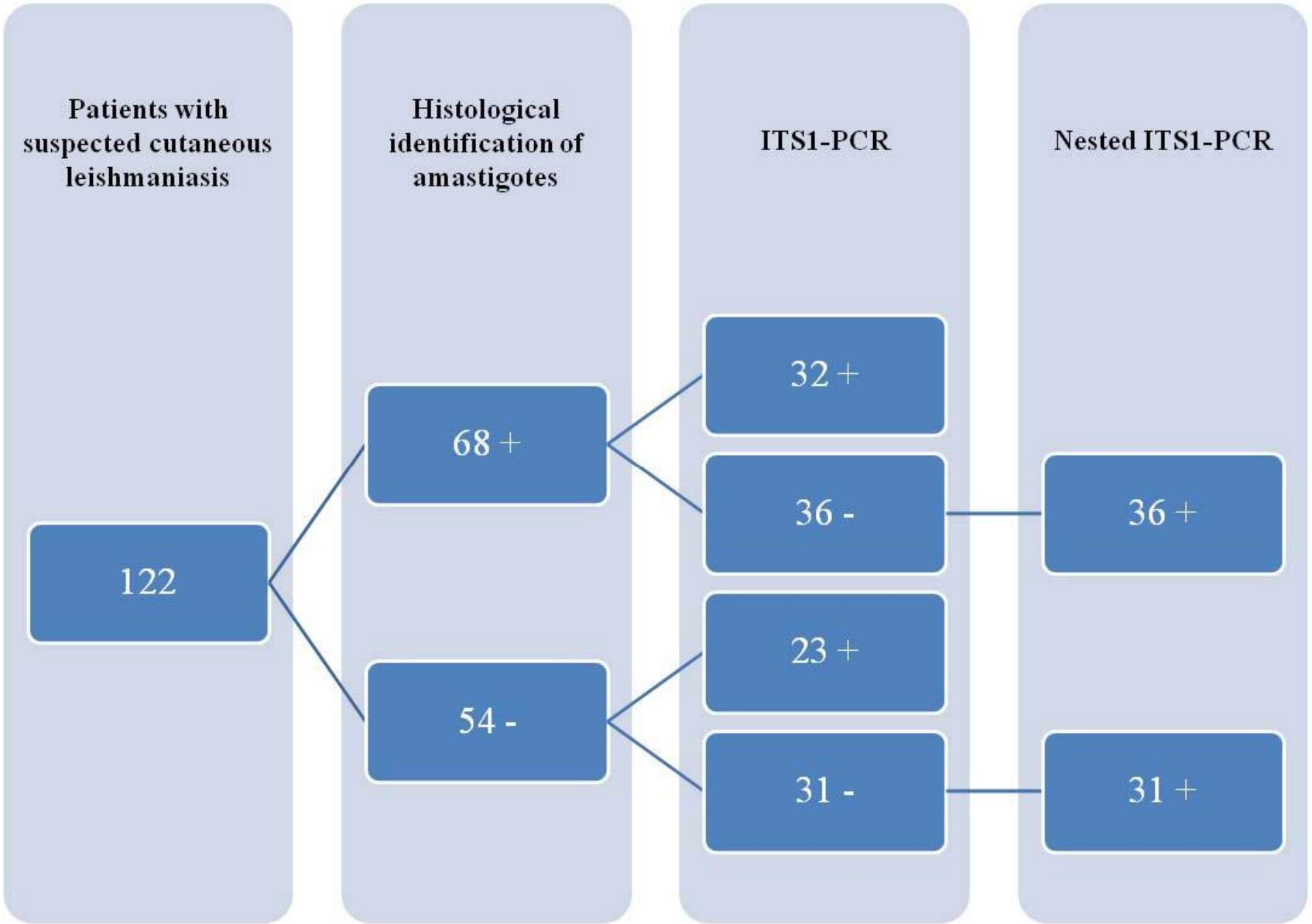
NORWAY
SWEDEN
FINLAND
RUSSIAN FEDERATION
ESTONIA
LATVIA
LITHUANIA
BELARUS
IRELAND
UNITED KINGDOM
NETHERLANDS
BELGIUM
GERMANY
POLAND
CZECH REP.
SLOVAKIA
UKRAINE
FRANCE
AUSTRIA
HUNGARY
ROMANIA
MOLDOVA
ITALY
SWITZERLAND
SLOVENIA
BOSNIA & HERZEGOVINA
BULGARIA
PORTUGAL
SPAIN
GEORGIA
ARMENIA
AZERBAIJAN
TURKEY
KAZAKHSTAN
MONGOLIA
UZBEKISTAN
KYRGYZSTAN
TURKMENISTAN
CHINA
AFGHANISTAN
IRAN
TUNISIA
MOROCCO
ALGERIA
CYPRUS
SYRIAN ARAB REP.
LEBANON
ISRAEL
JORDAN
KUWAIT
SAUDI ARABIA
BAHRAIN
QATAR
UNITED ARAB EMIRATES
OMAN
YEMEN
NEPAL
BHUTAN
BANGLADESH
INDIA
MYANMAR
LAOS
THAILAND
CAMBODIA
VIETNAM
WESTERN SAHARA
EGYPT
LIBYA
A BAHIA JAMAHIRIYA
MAURITANIA
MALI
NIGER
CHAD
SUDAN
ERITREA
DJIBOUTI
ETHIOPIA
CAPE VERDE
SENEGAL
GAMBIA
GUINEA BISSAU
GUINEA
BENIN
SIERRA LEONE
LIBERIA
COTE D'IVOIRE
GHANA
TOGO
NIGERIA
CENTRAL AFRICAN REP.
CAMEROON
EQUATORIAL GUINEA
GABON
CONGO
DEMOCRATIC REP. OF THE CONGO
RWANDA
BURUNDI
KENYA
SOMALIA
TANZANIA
SRI LANKA
MALAYSIA
SINGAPORE
BRUNEI DARUSSALAM
INDONESIA
MALDIVES
SEYCHELLES
COMOROS
ANGOLA
ZAMBIA
ZIMBABWE
MOZAMBIQUE
MADAGASCAR
MAURITIUS
Rodrigues Island
Réunion (Fr.)
NAMIBIA
BOTSWANA
SWAZILAND
LESOTHO
SOUTH AFRICA
M
A
P
D

Geographic distribution of the primary cutaneous leishmaniasis species Old World

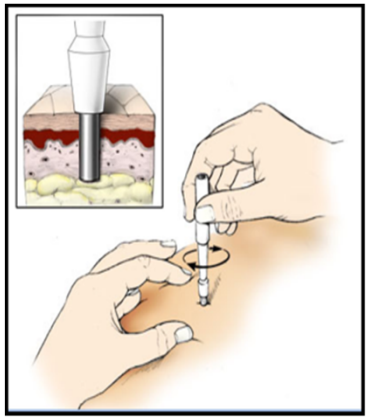
*Magill, A.J.; Dermatol Clin. 1995 Jul;13(3):505-23*



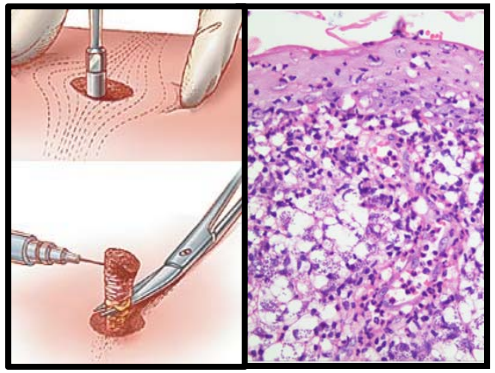
# Diagnosis


Patients with suspected cutaneous leishmaniasis
Histological identification of amastigotes
ITS1-PCR
Nested ITS1-PCR
122
68 +
54 -
32 +
36 -
23 +
31 -
36 +
31 +

# Triage

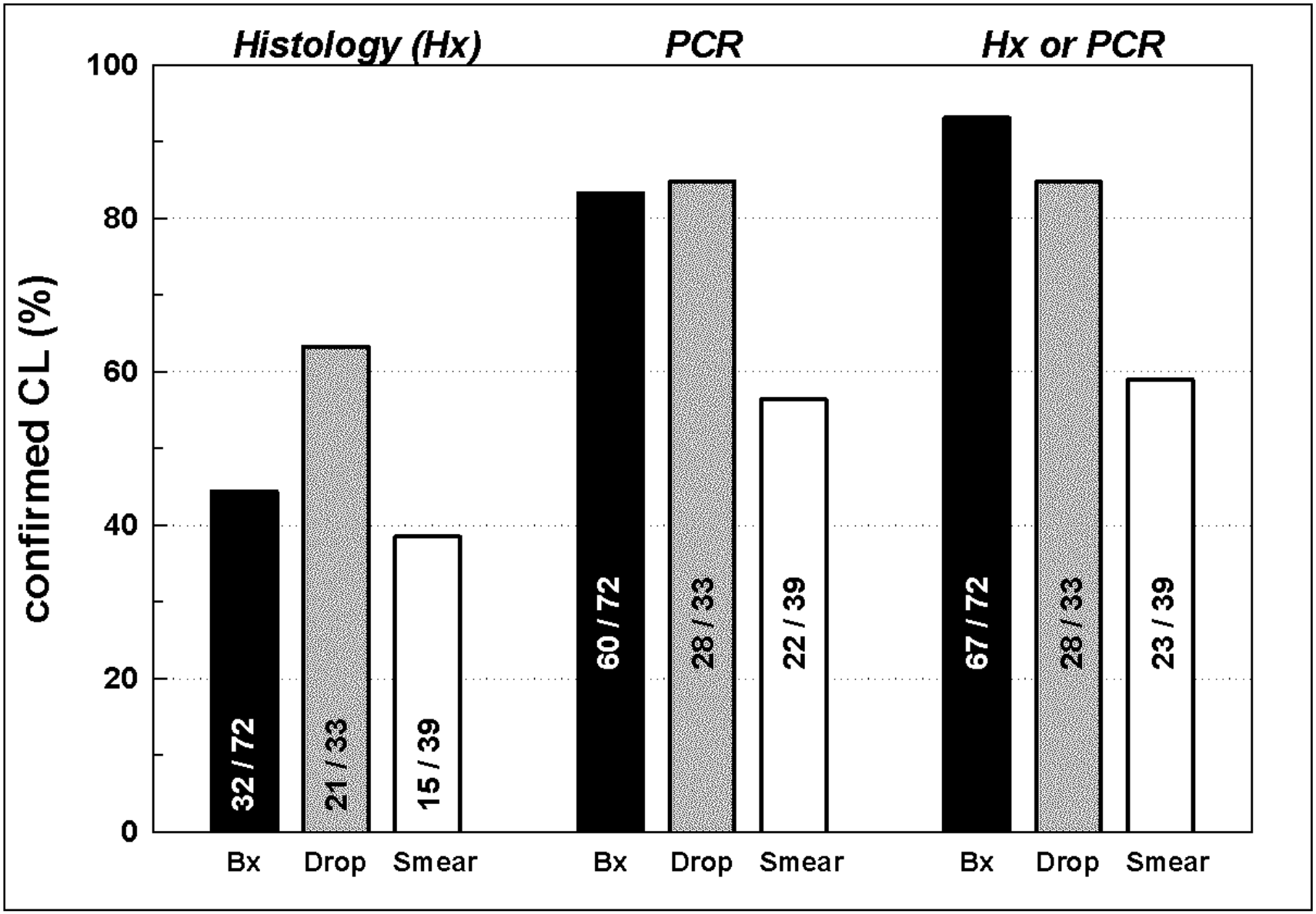


Patient's Form

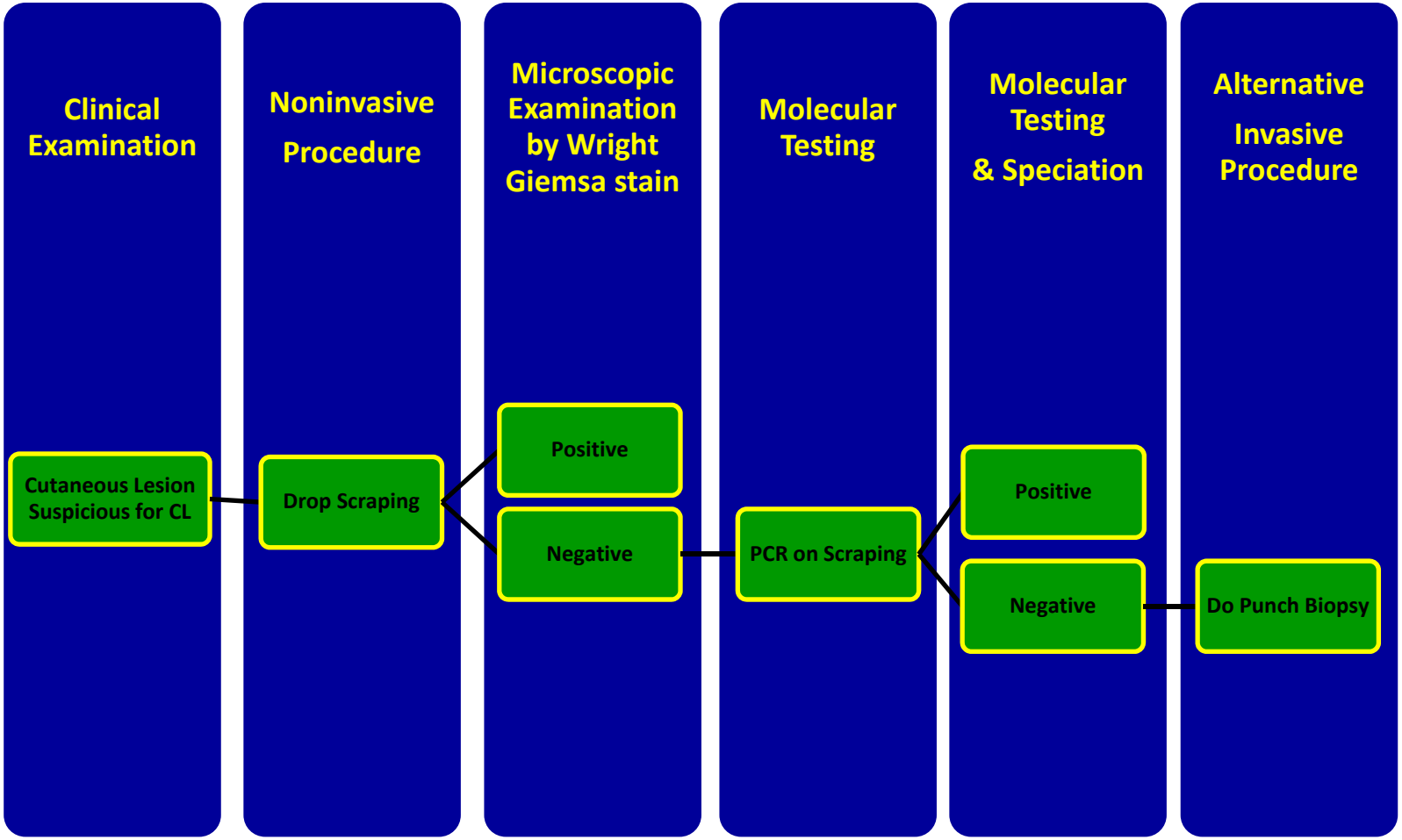


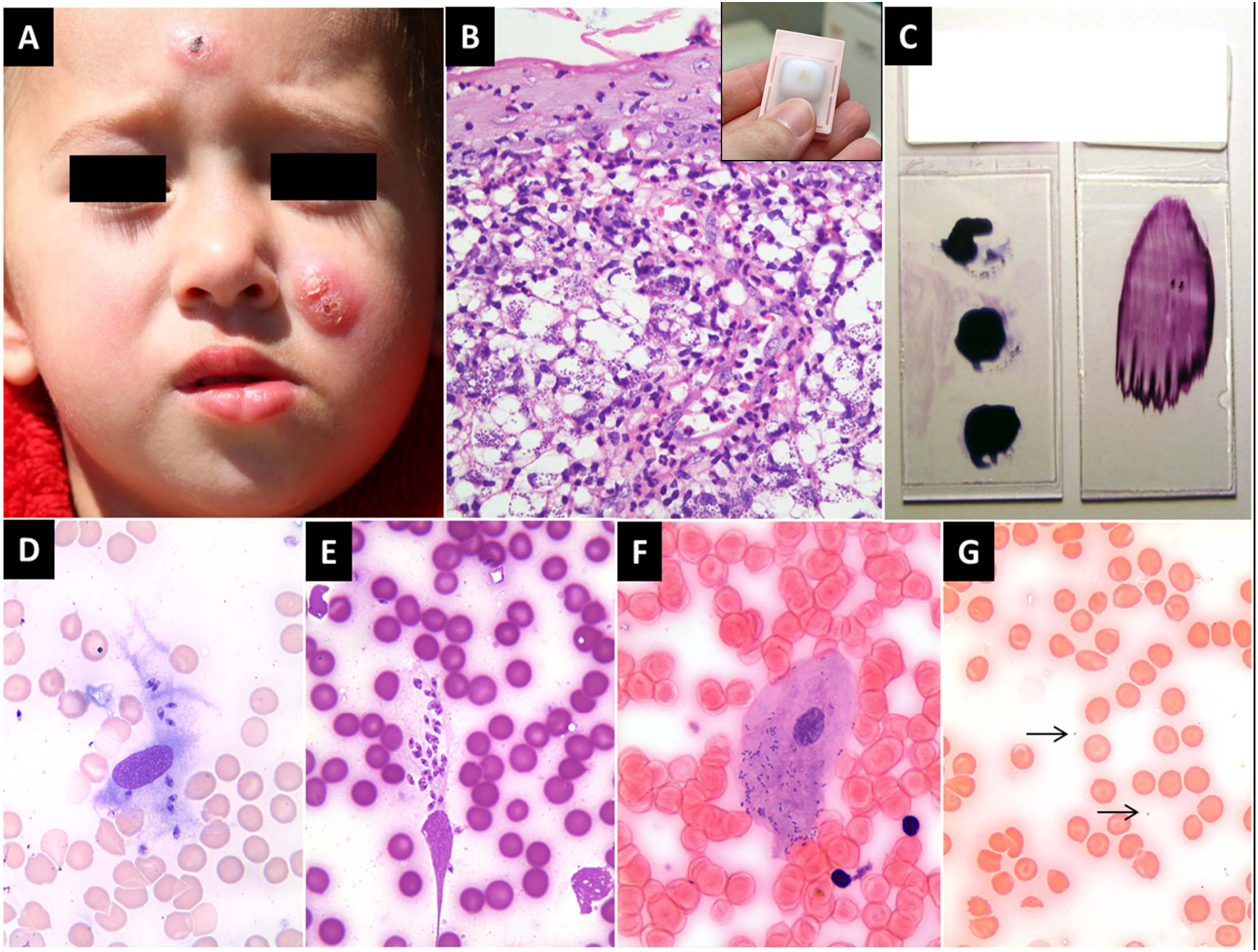
PCR

# The Diagnostic Sensitivity By Microscopy & PCR testing



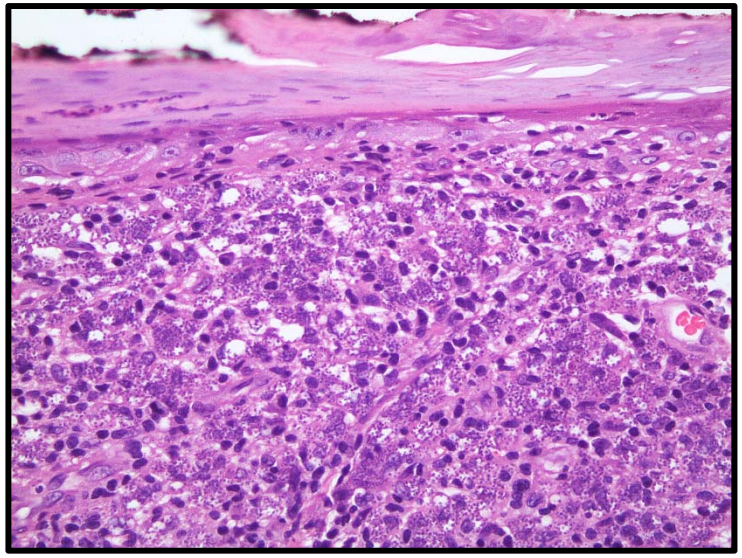
# Optimized Rapid Method for Diagnosis

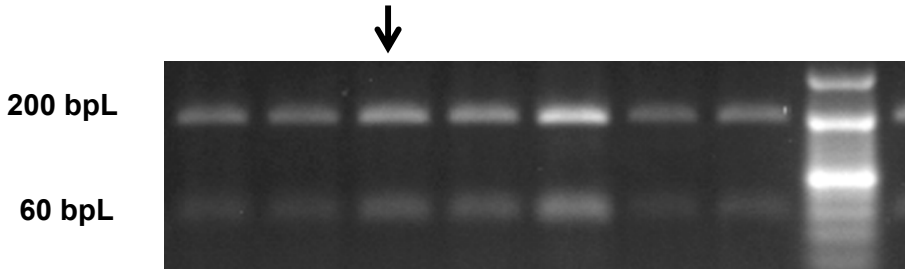



A
B
C
D
E
F
G

# Ongoing Epidemic of CL among Syrian Refugees in Lebanon

*http://wwwnc.cdc.gov/eid/article/20/10/14-288_article*

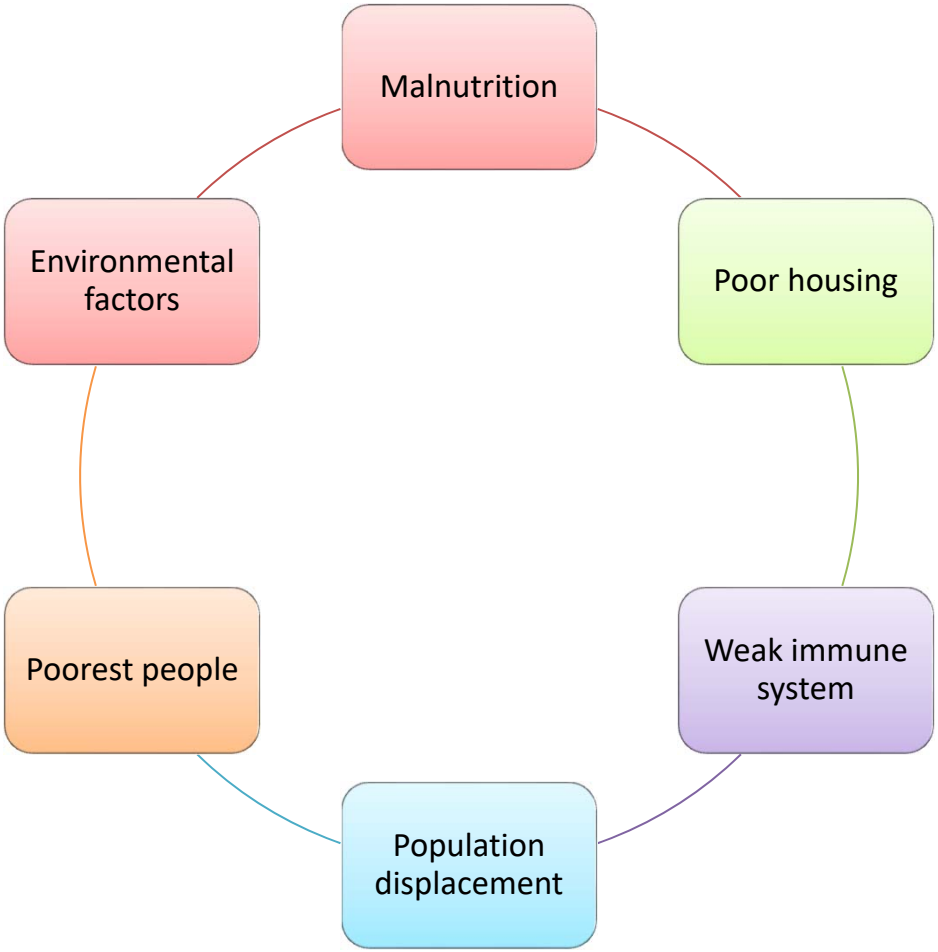





## Z.A.

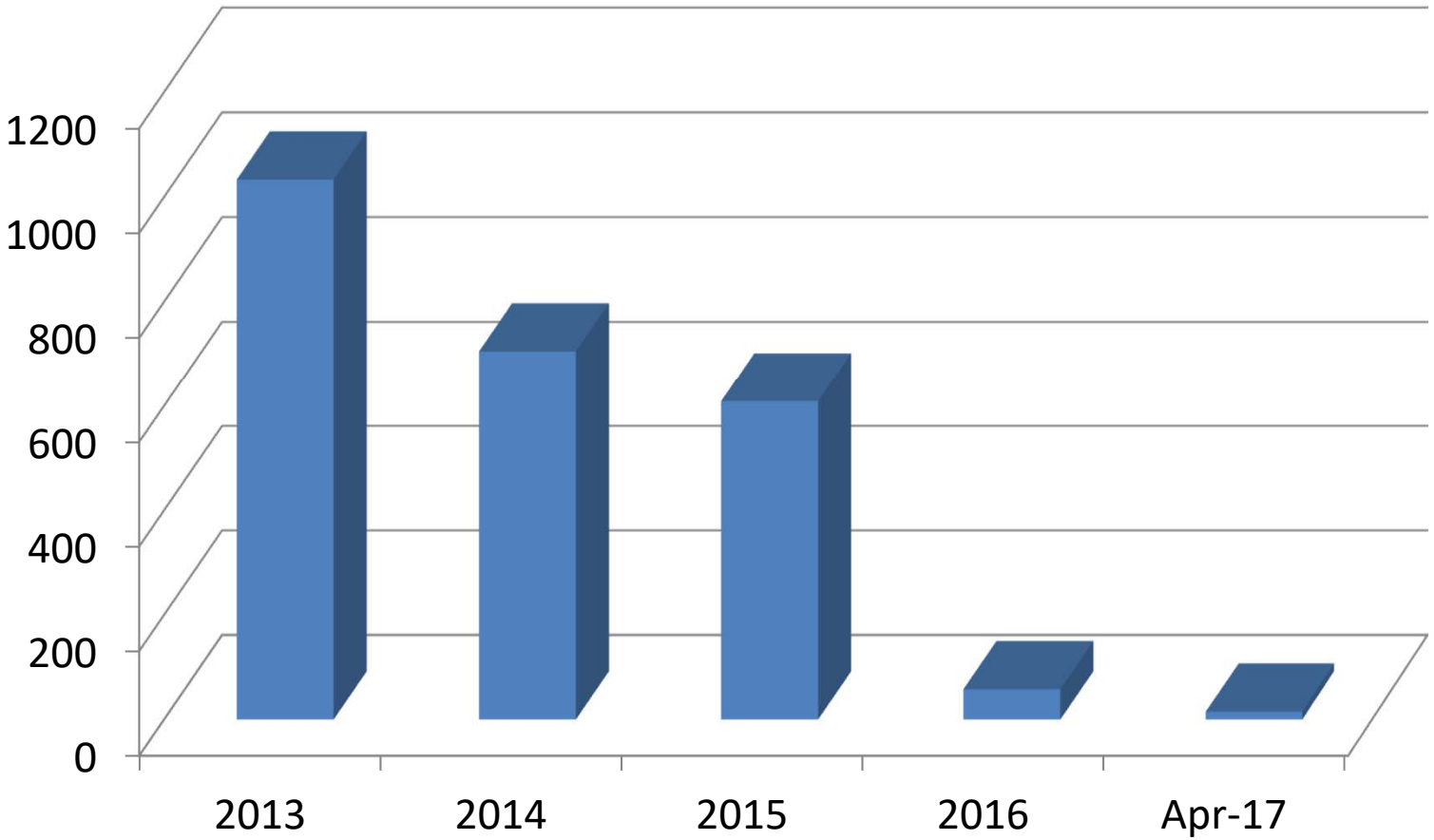
- 6 YO
- Coming from Idlieb
- Been in Lebanon for 3 months
- Has lesion for 6 months
- L. Tropica

# Risk Factors of CL

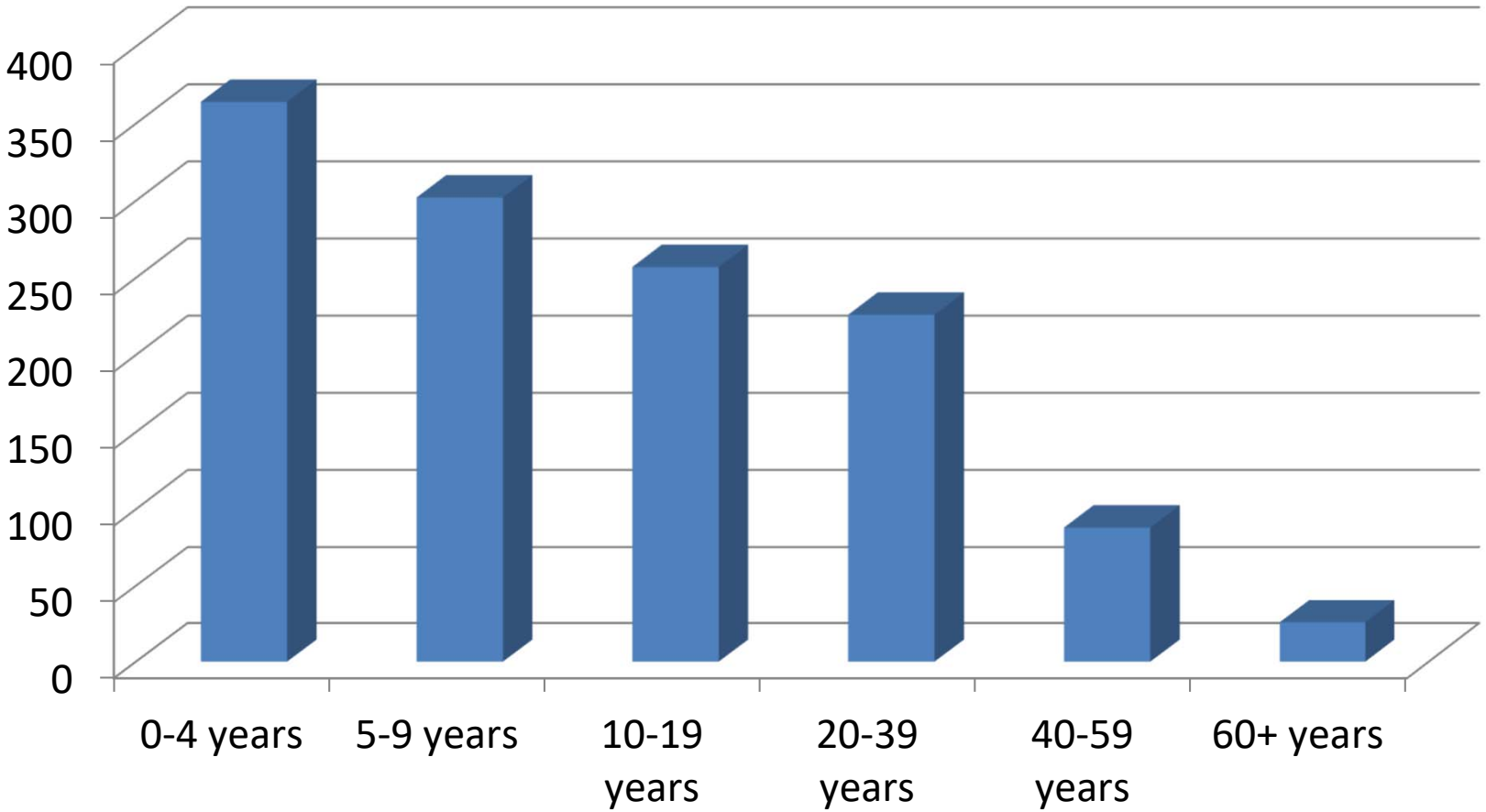



*Tropical medecine and Hygiene,Desjeux et al,2001,239-243*

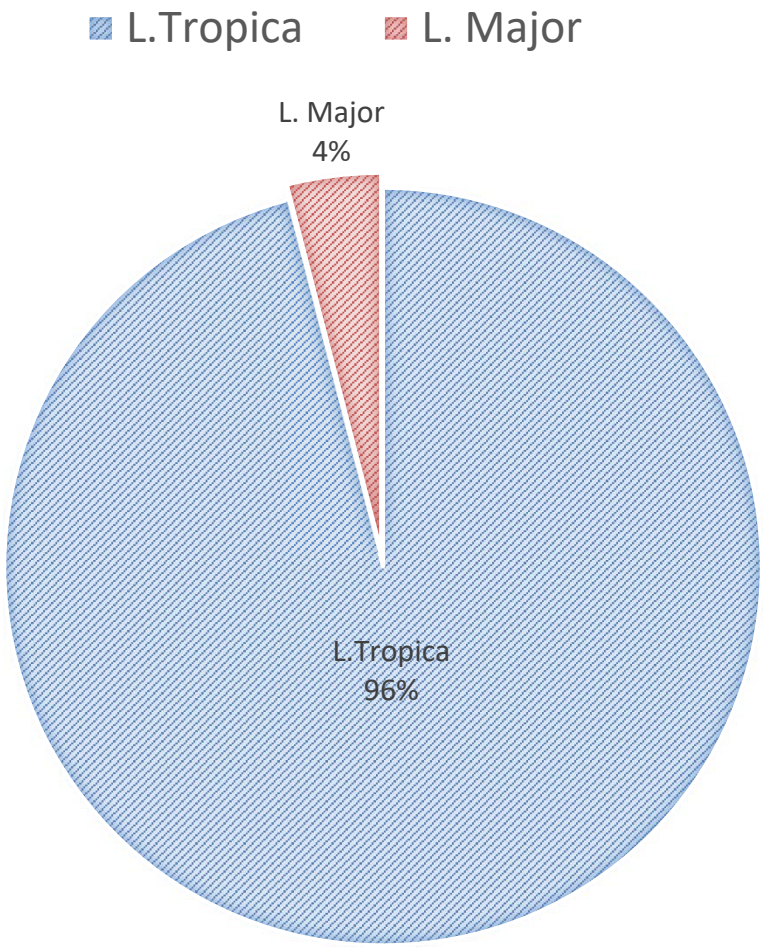
# Number of Patients Treated (n=2420)

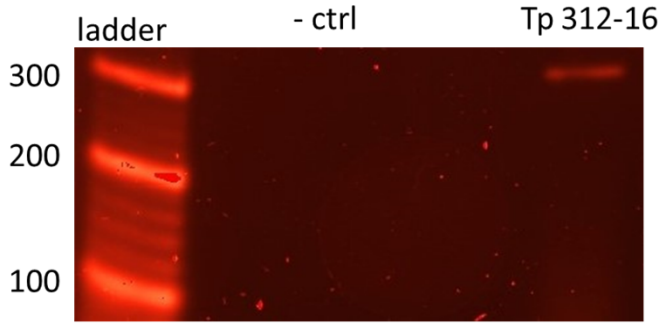


# Age Distribution (n=2420)

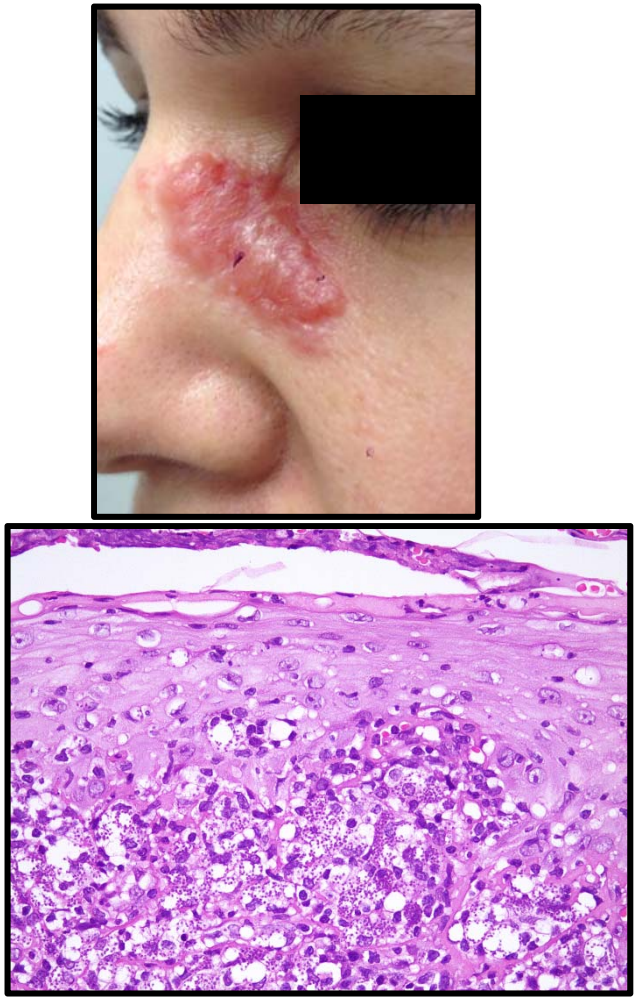


# Leishmania Species

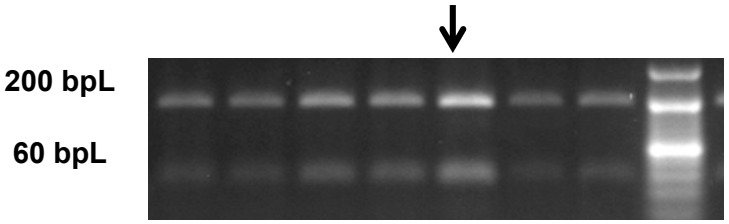


# Lebanese Patients



- Lebanese: 5
- History of travel to Syria: 3/5.
- All L. Tropica



# Potential Vectors in Lebanon

**Vectors of Cutaneous Leishmaniasis**

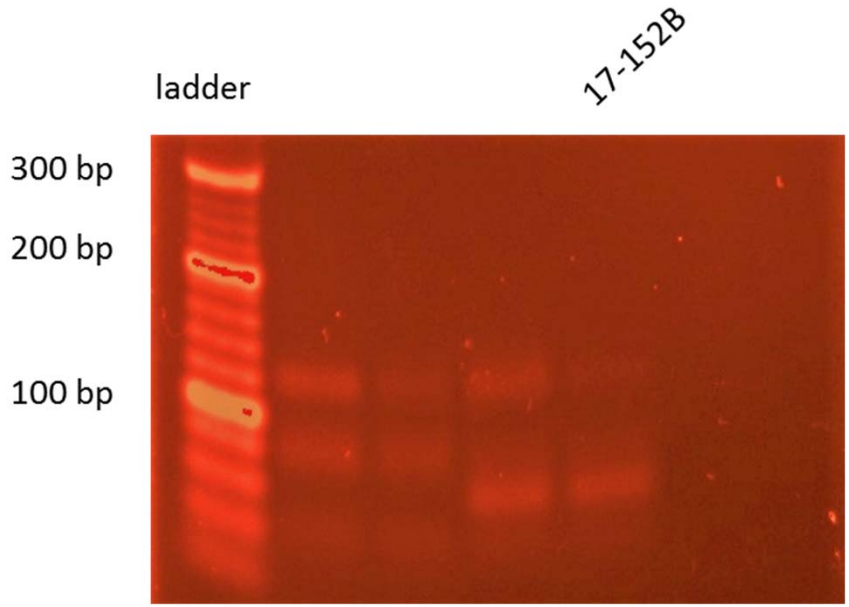
- Vectors of ZCL (*L. major*)
  - P. papatasi
- Vectors of ACL (*L. tropica*)
  - P. sergenti

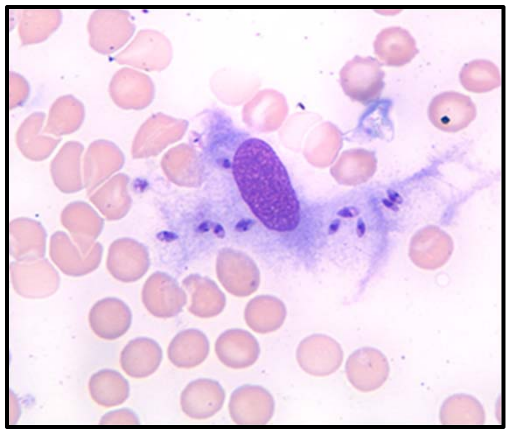
**Vectors of Visceral Leishmaniasis**

- *P. syriacus*
- *P. tobbi*
- *P. jacusieli*
- *P. simici*

# Viseral Leishmania

- 6 patients
- All Syrian
- All L. Infantum
- 5/6 died of disease
- All have infected family members



# Extensive Disease

# The Epidemic of Cutaneous Leishmaniasis among Syrian Refugees in Lebanon

- Extensive disease (1 or more of the following):
  - Disfiguring
  - Threatening the function of vital sensory organs
  - Lesion present for >12 months
  - Lesions >3cm
  - More than 5 lesions
  - Special forms of CL (i.e. sporotrichoid).

# Incidence and Determinants of Extensive Disease

- Extensive disease: 59% of patients
  - 49% lesions >3cm in size
  - 37.3% disfiguring disease
  - 27.3% disease comprising vital sensory organs
  - 20% ≥5 lesions
  - 9%special forms of CL
  - 9% with chronic disease.

# Lesions >3cm in size (49%)

# Disfiguring (37.3%)

# Disfiguring (37.3%)

# Comprising Vital Sensory Organs (27.3%)

# Five lesions or more (n=22)

# Special Forms of CL (9%)



# Incidence and Determinants of Extensive Disease

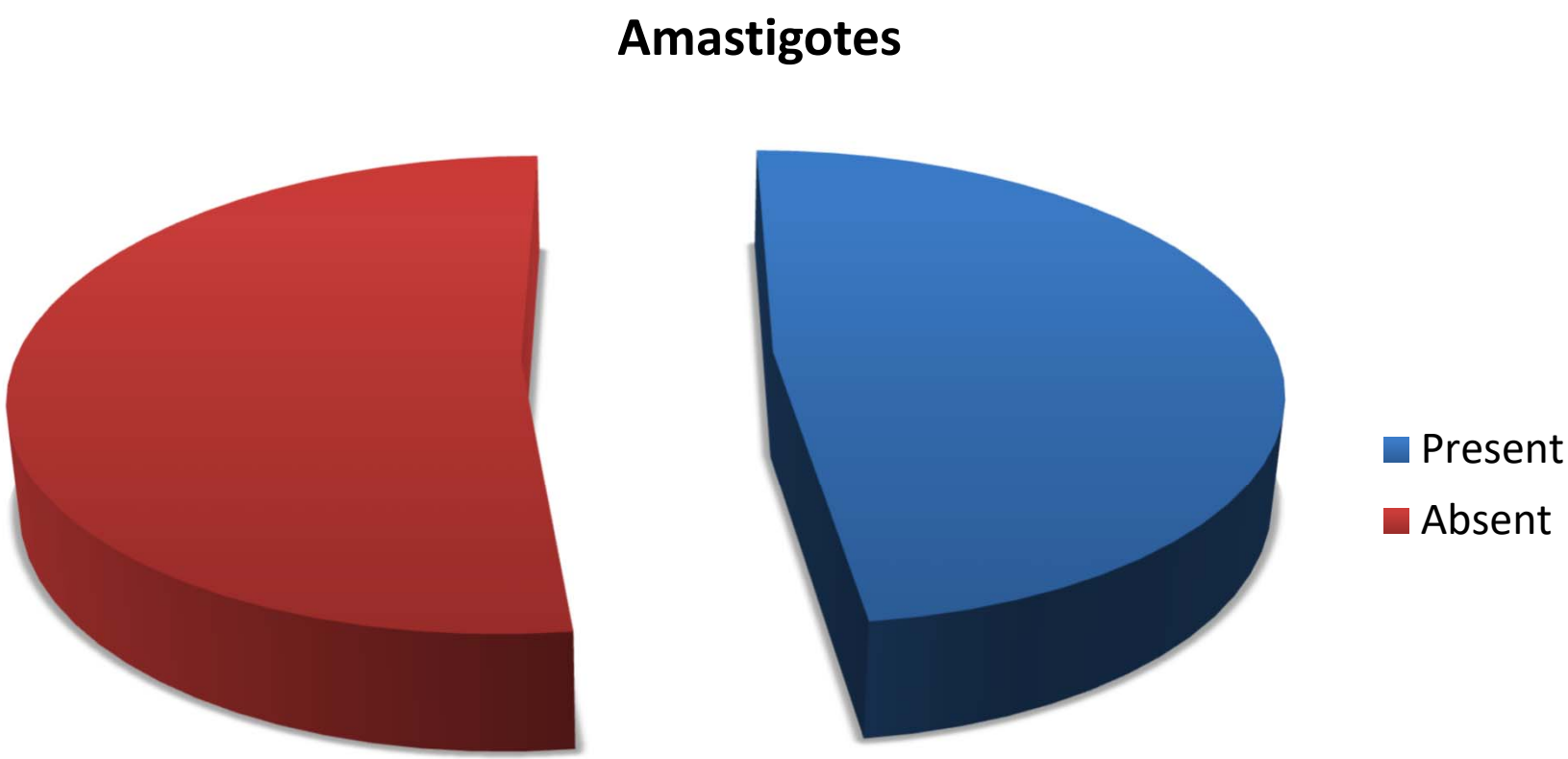
- Parasitic index, molecular type and geographic location were similar for extensive versus non-extensive disease groups.
- Extensive disease was more prevalent:

  - Among children (median 9 vs. 21 years; p=0.002)

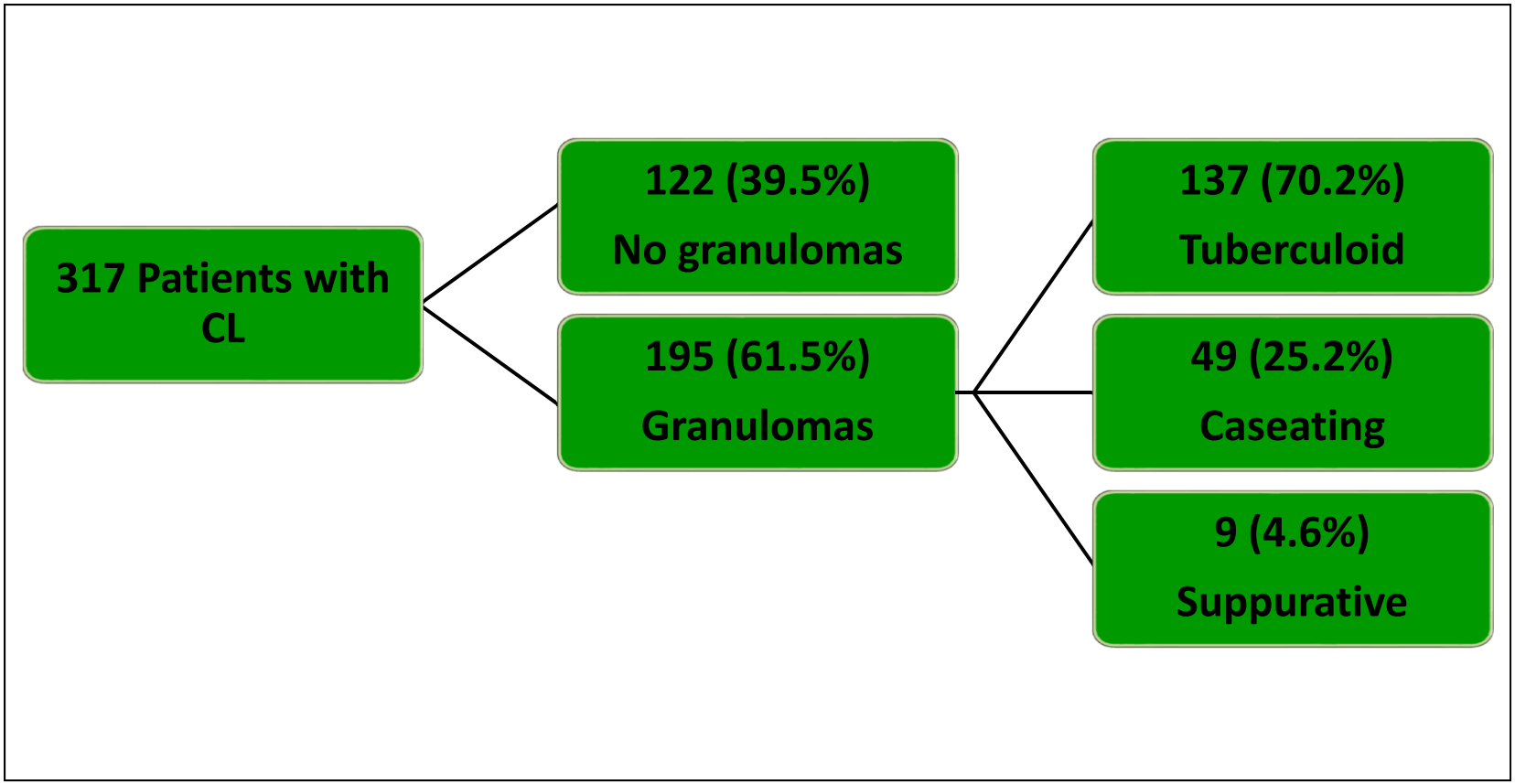
  - On the face and lower extremities (p=0.002).

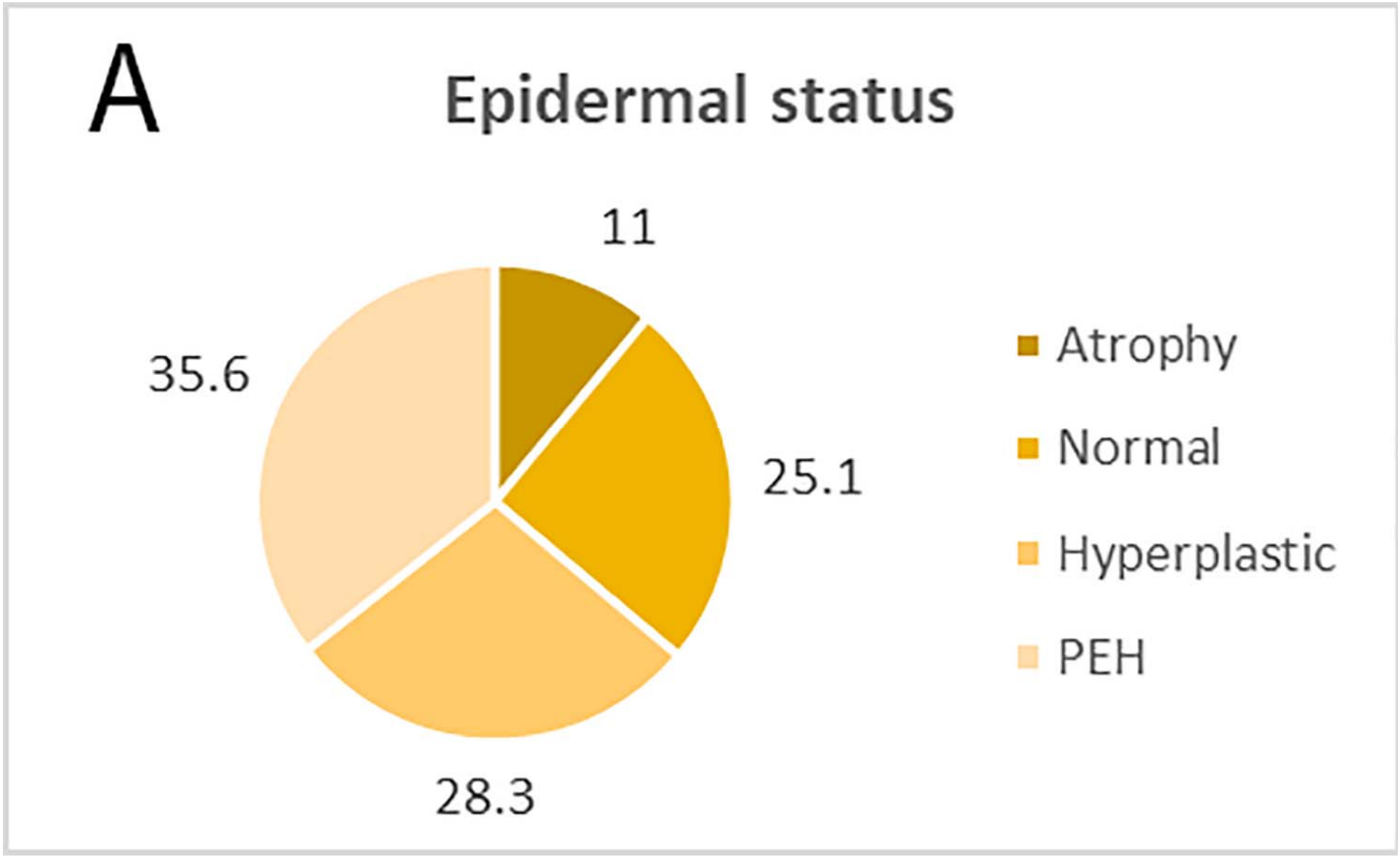
  - Both age and anatomic location were predictors of extensive disease by multivariate logistic regression.

# Infections Mimicking CL

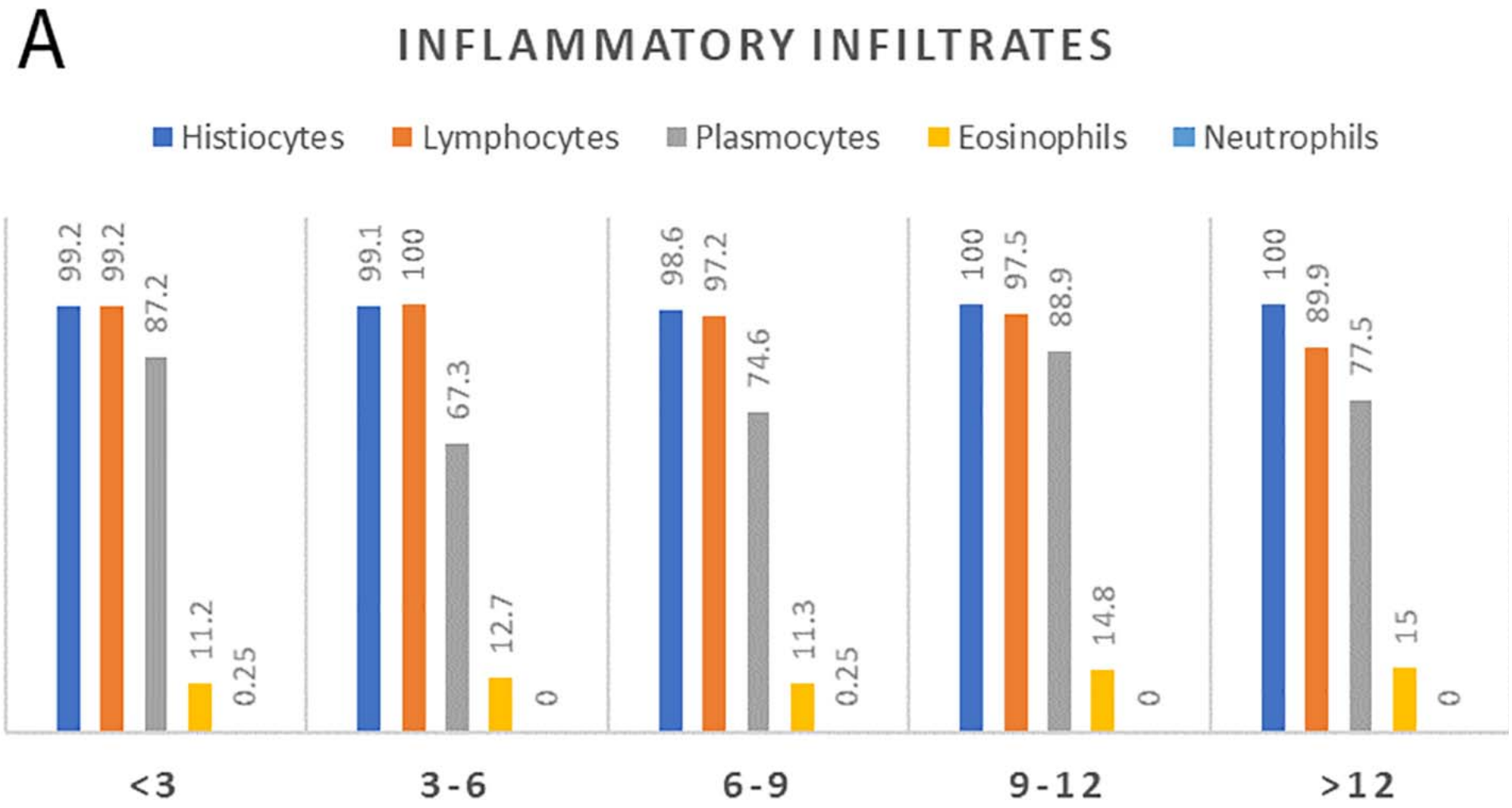

Amastigotes
Present
Absent

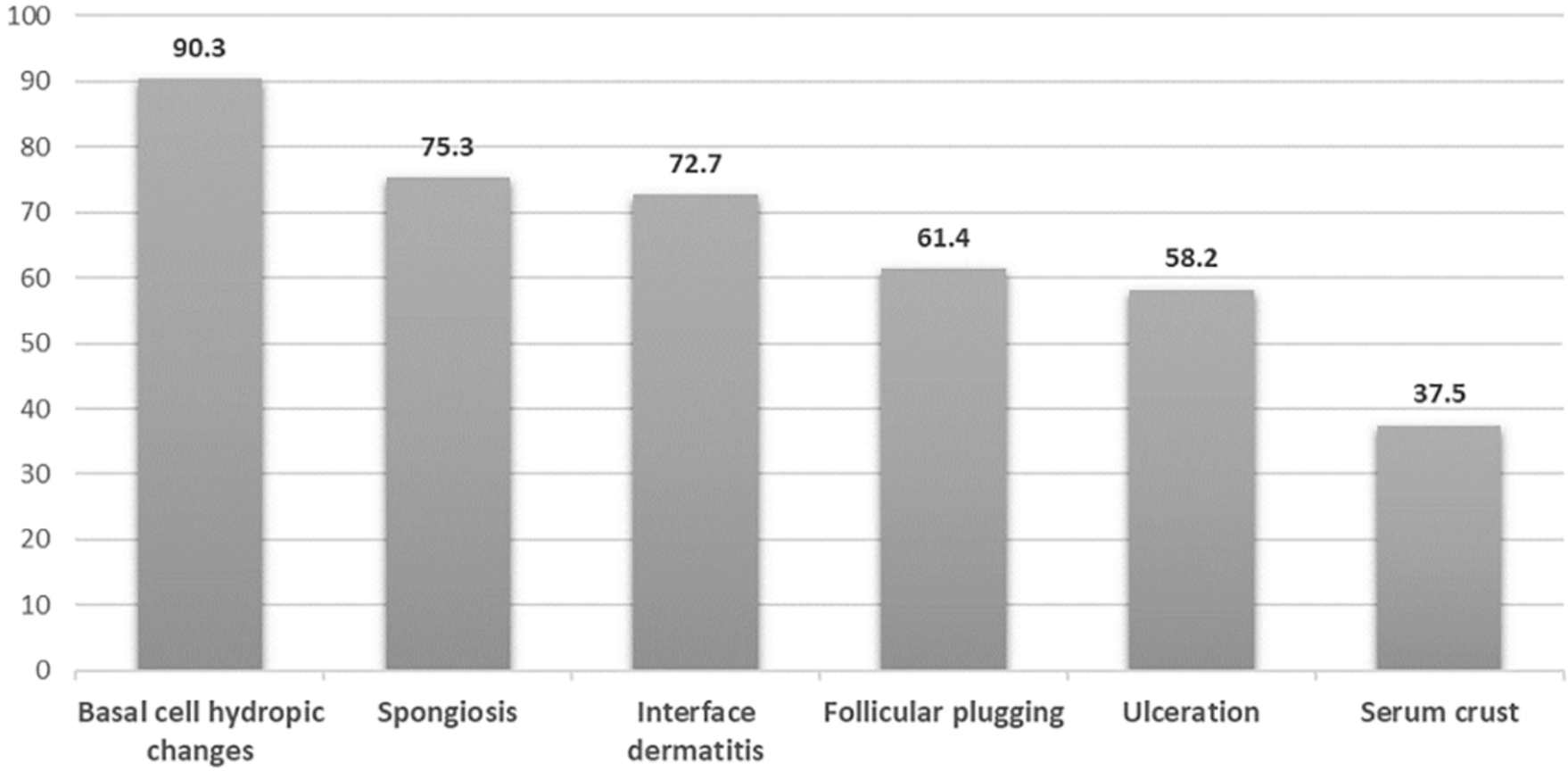
# 15.5 % (49/317) Presented with Caseating Granulomas

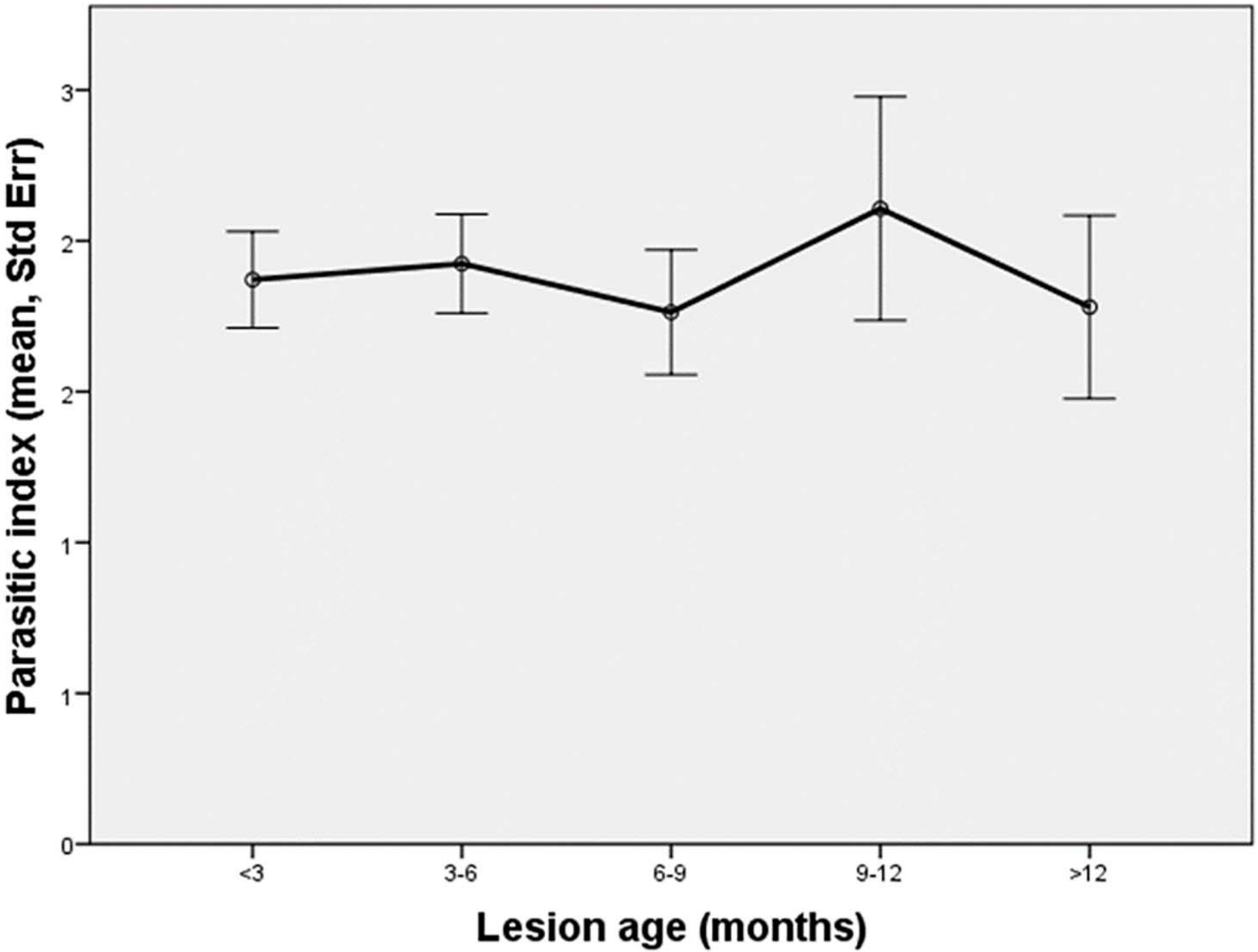


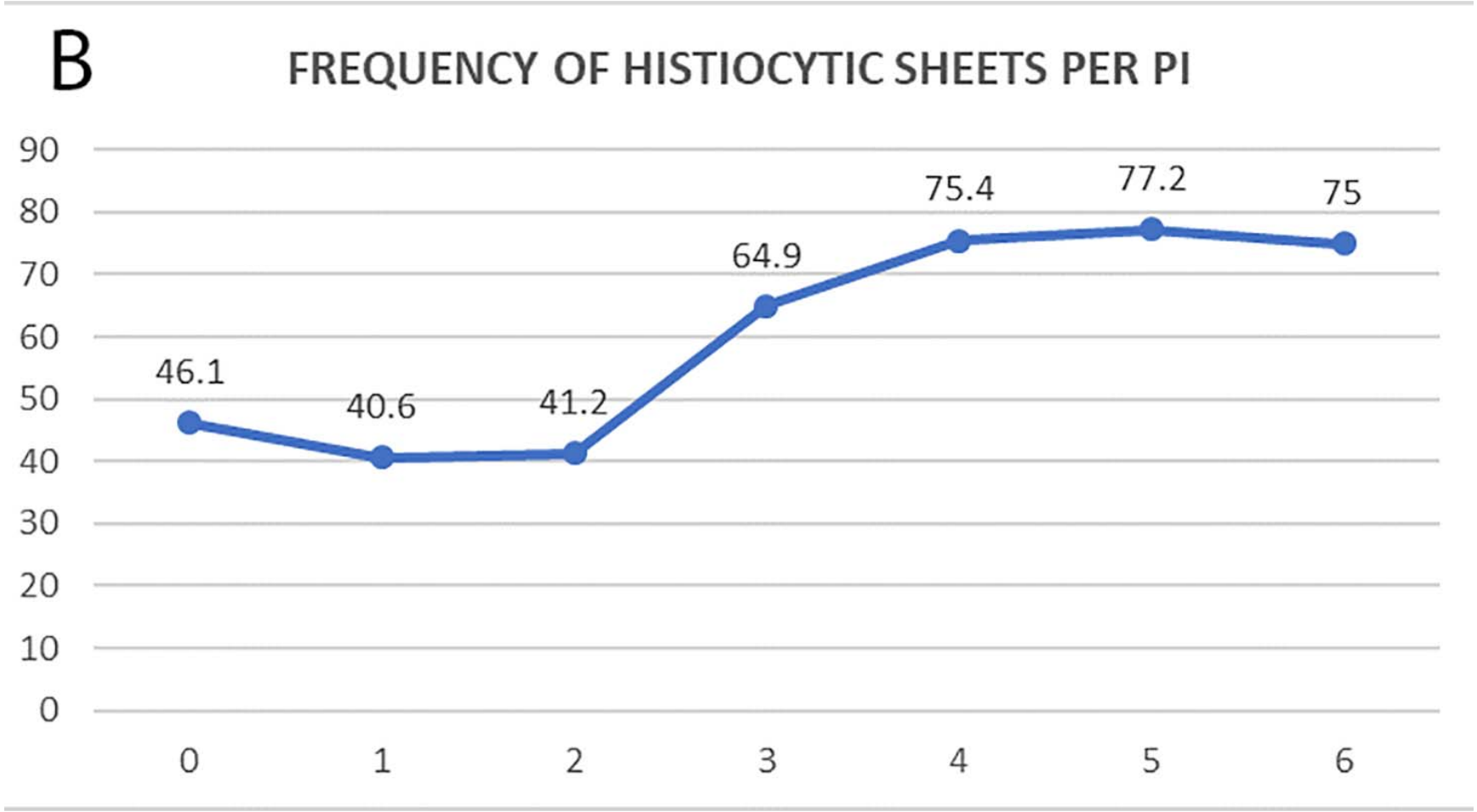

A
Epidermal status
11
25.1
28.3
35.6
Atrophy
Normal
Hyperplastic
PEH

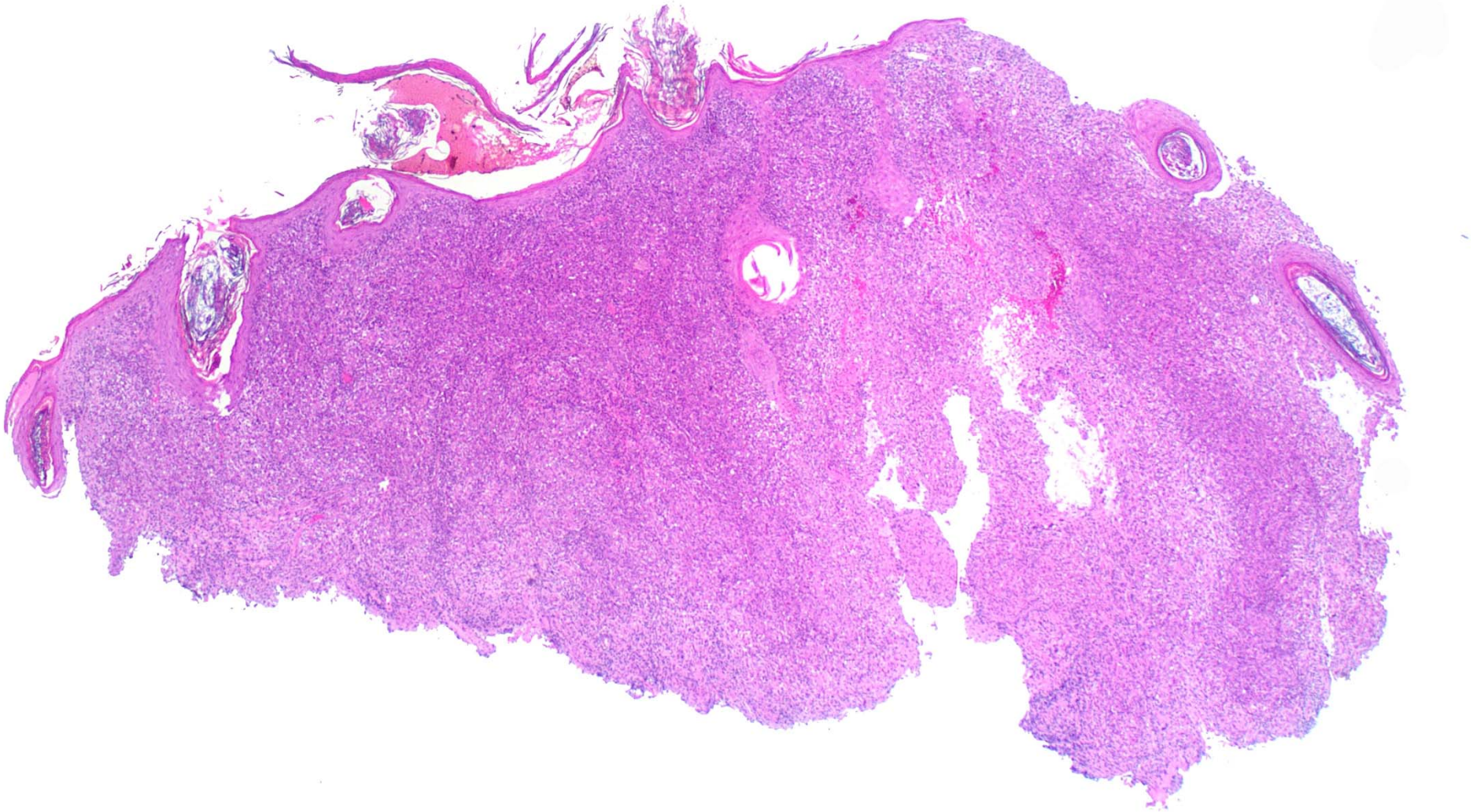
A

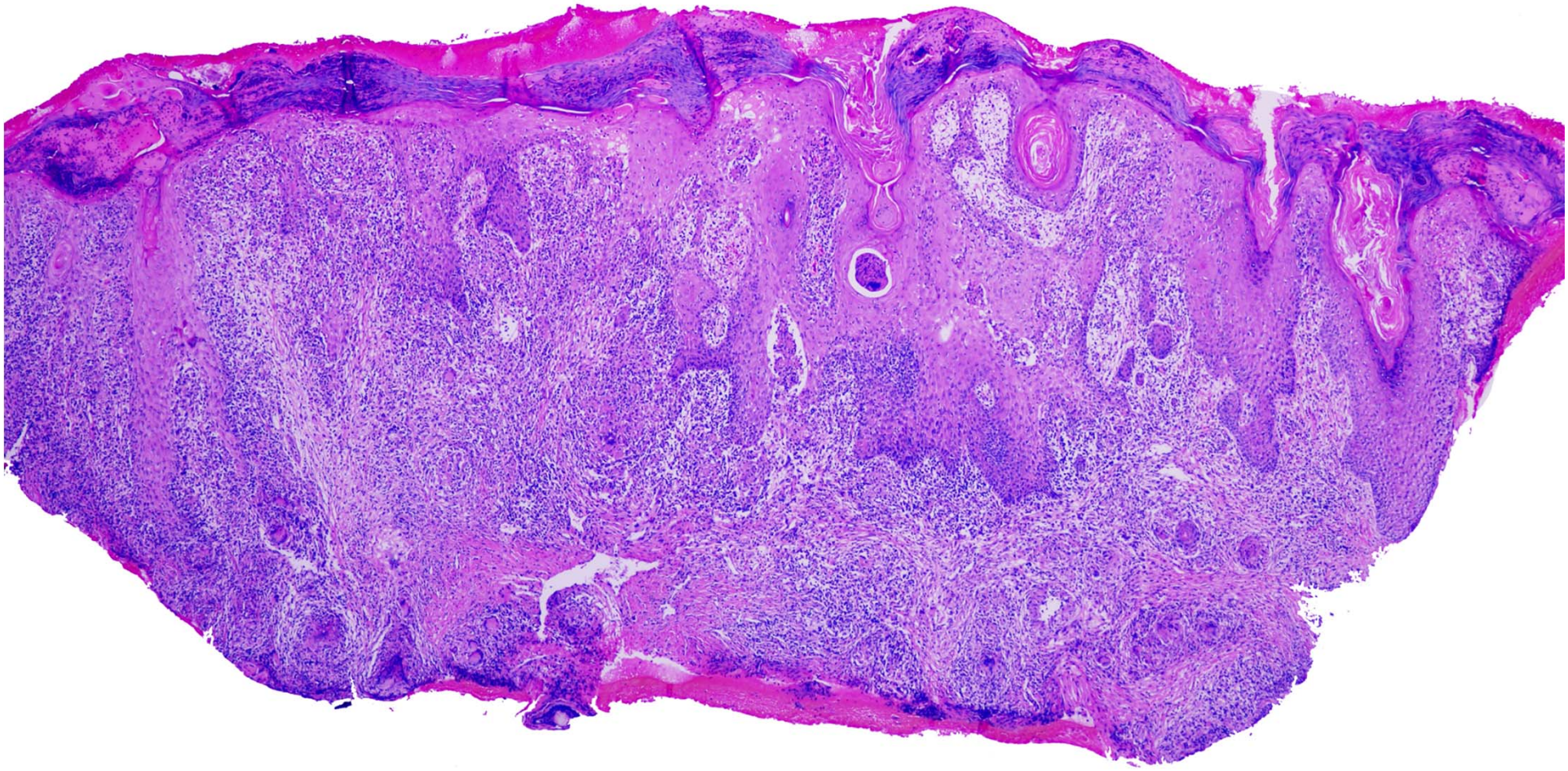

INFLAMMATORY INFILTRATES
Histiocytes
Lymphocytes
Plasmocytes
Eosinophils
Neutrophils
99.2
99.2
87.2
11.2
0.25
99.1
100
67.3
12.7
0
98.6
97.2
74.6
11.3
0.25
100
97.5
88.9
14.8
0
100
89.9
77.5
15
0
<3
3-6
6-9
9-12
>12

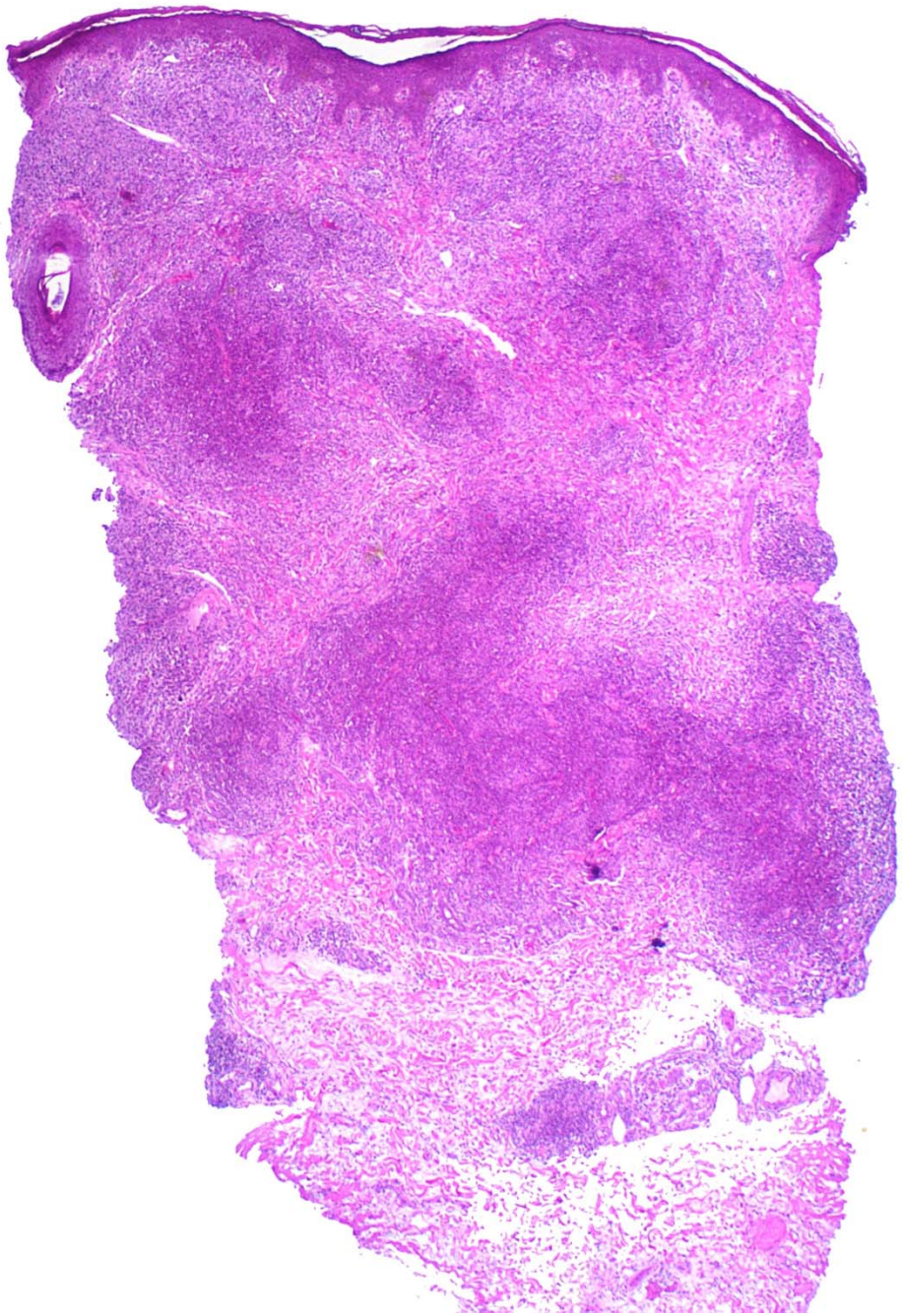

100
90
80
70
60
50
40
30
20
10
0
90.3
75.3
72.7
61.4
58.2
37.5
Basal cell hydropic changes
Spongiosis
Interface dermatitis
Follicular plugging
Ulceration
Serum crust

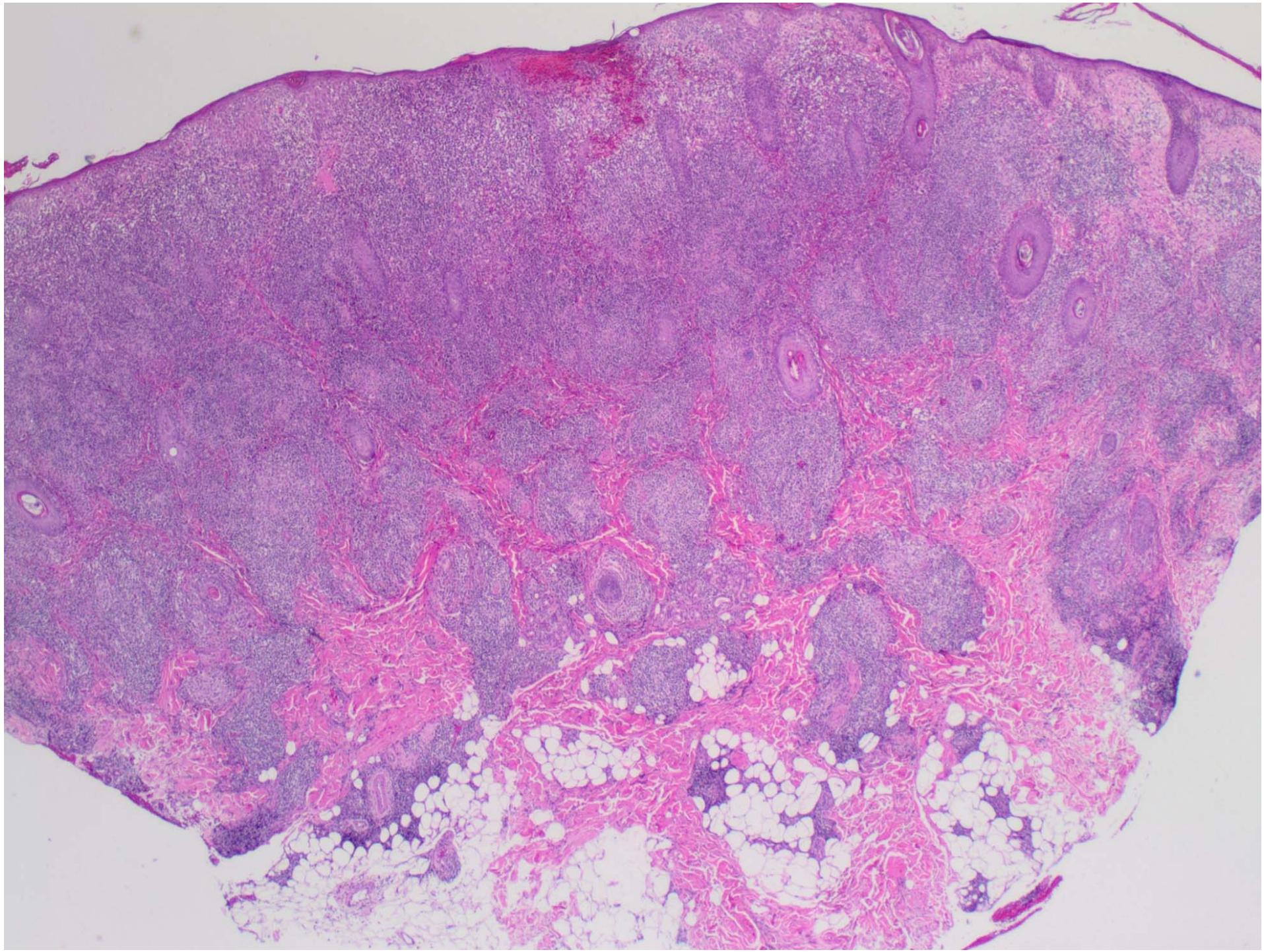

Parasitic index (mean, Std Err)
3
2
2
1
1
0
<3
3-6
6-9
9-12
>12
Lesion age (months)

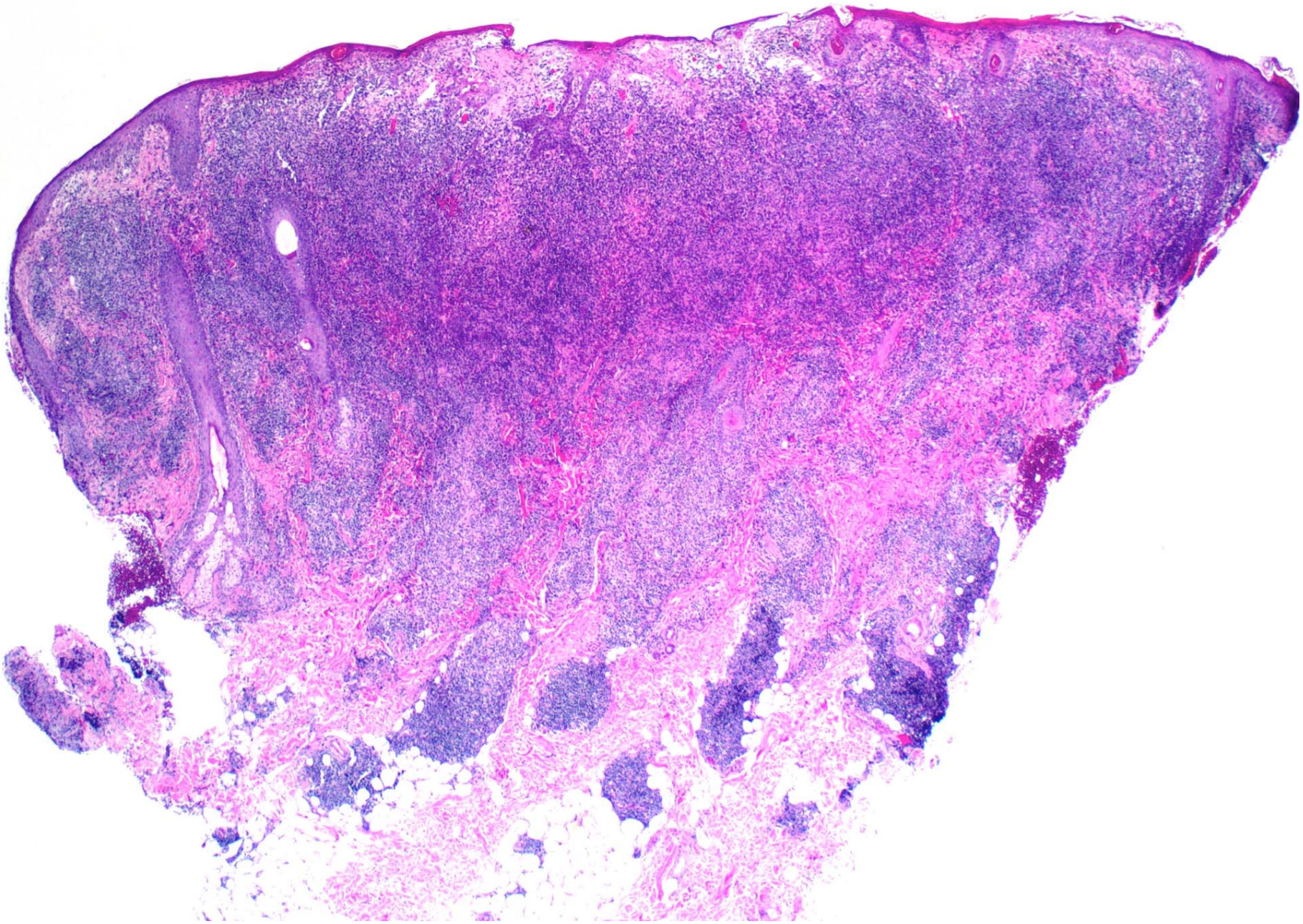

B
FREQUENCY OF HISTIOCYTIC SHEETS PER PI
90
80
70
60
50
40
30
20
10
0
46.1
40.6
41.2
64.9
75.4
77.2
75
0
1
2
3
4
5
6

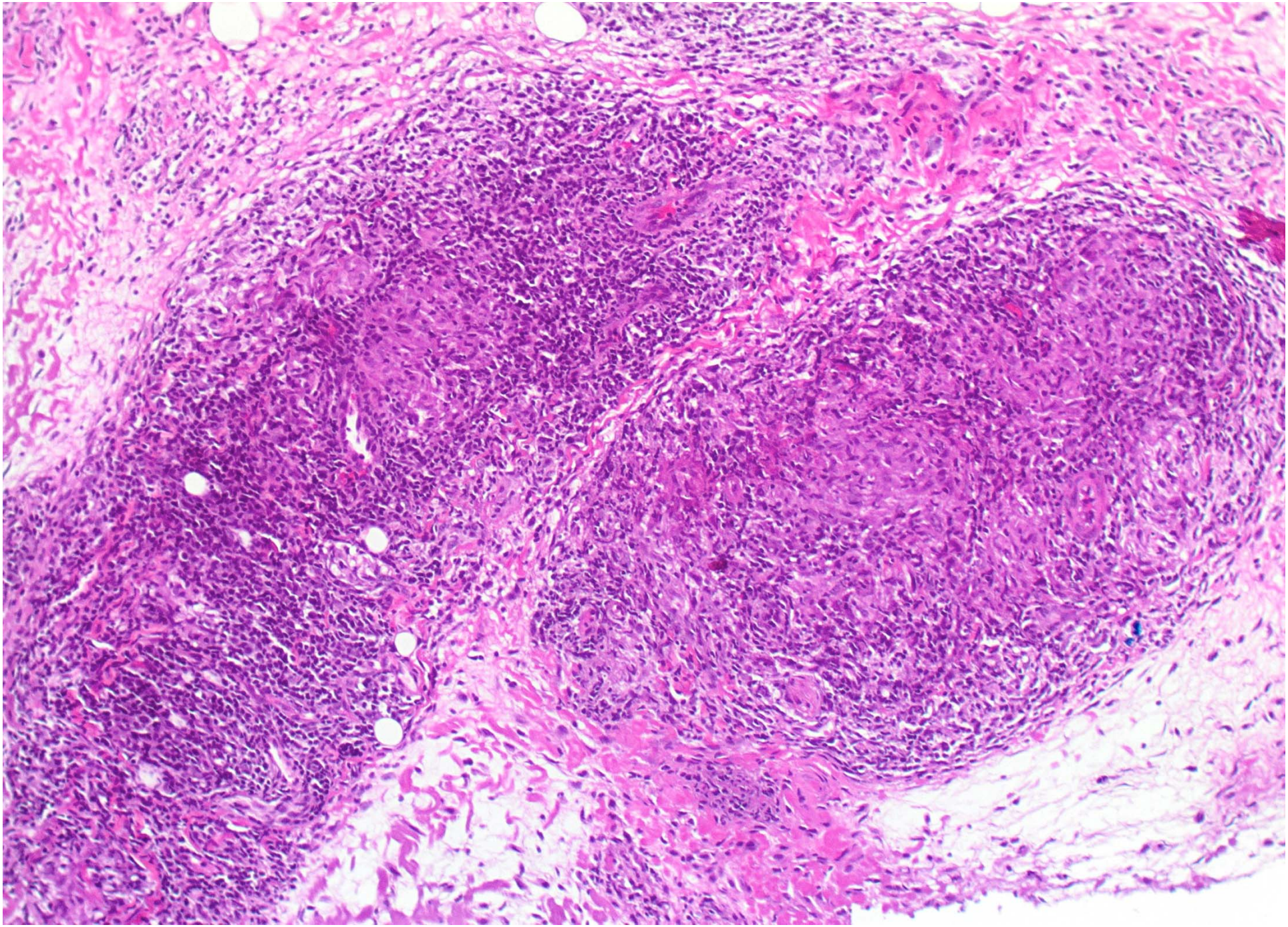


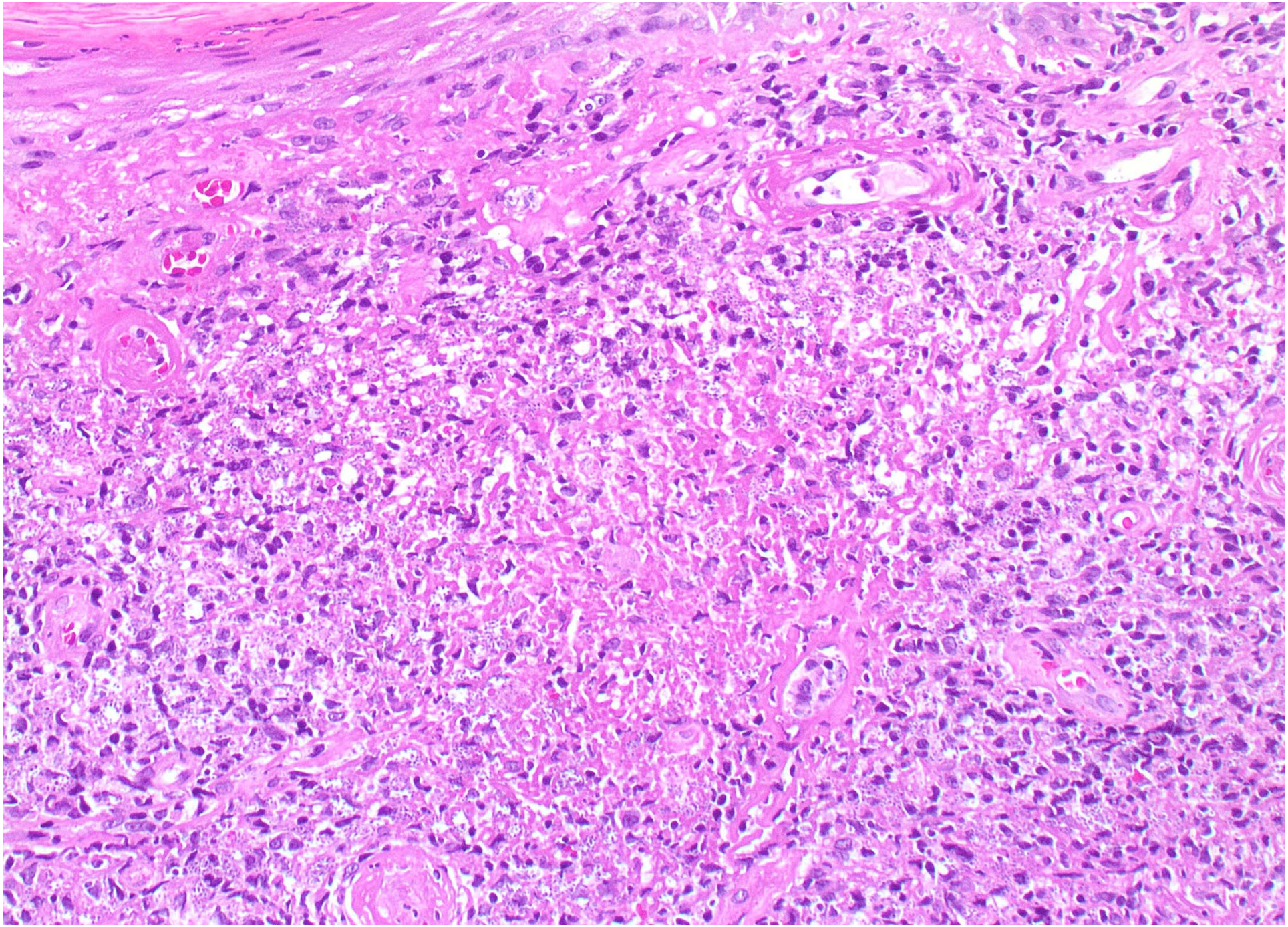


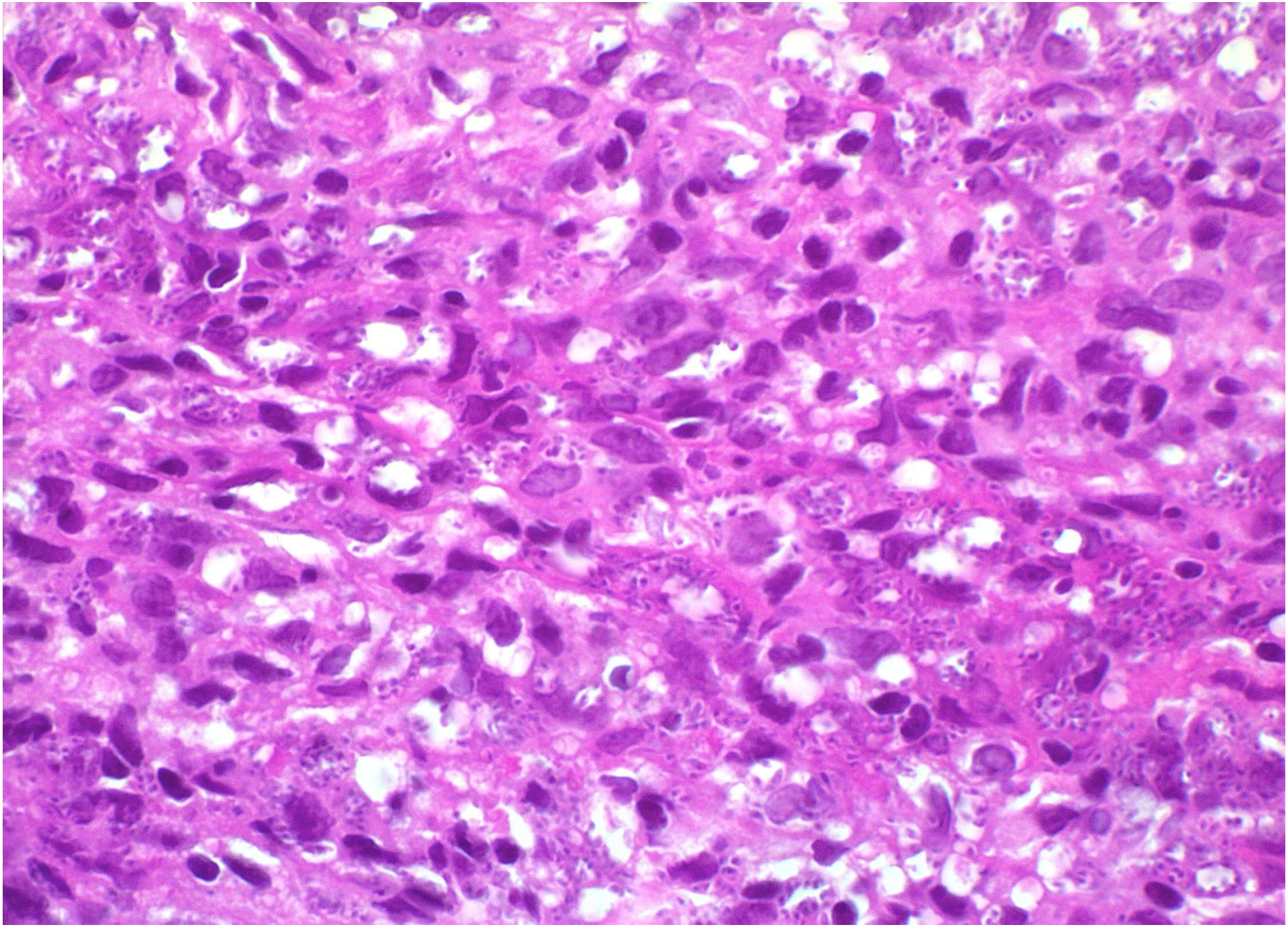


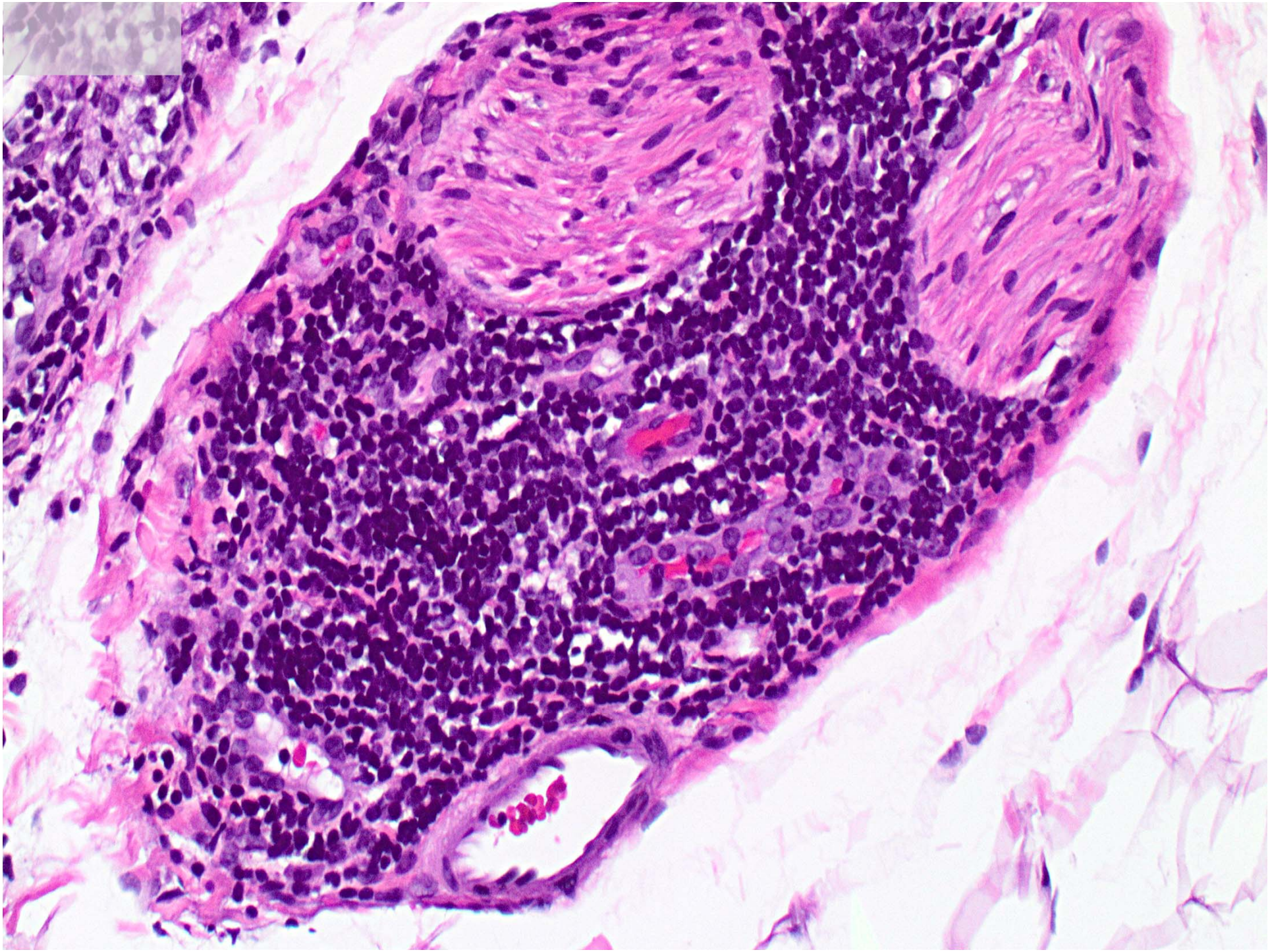


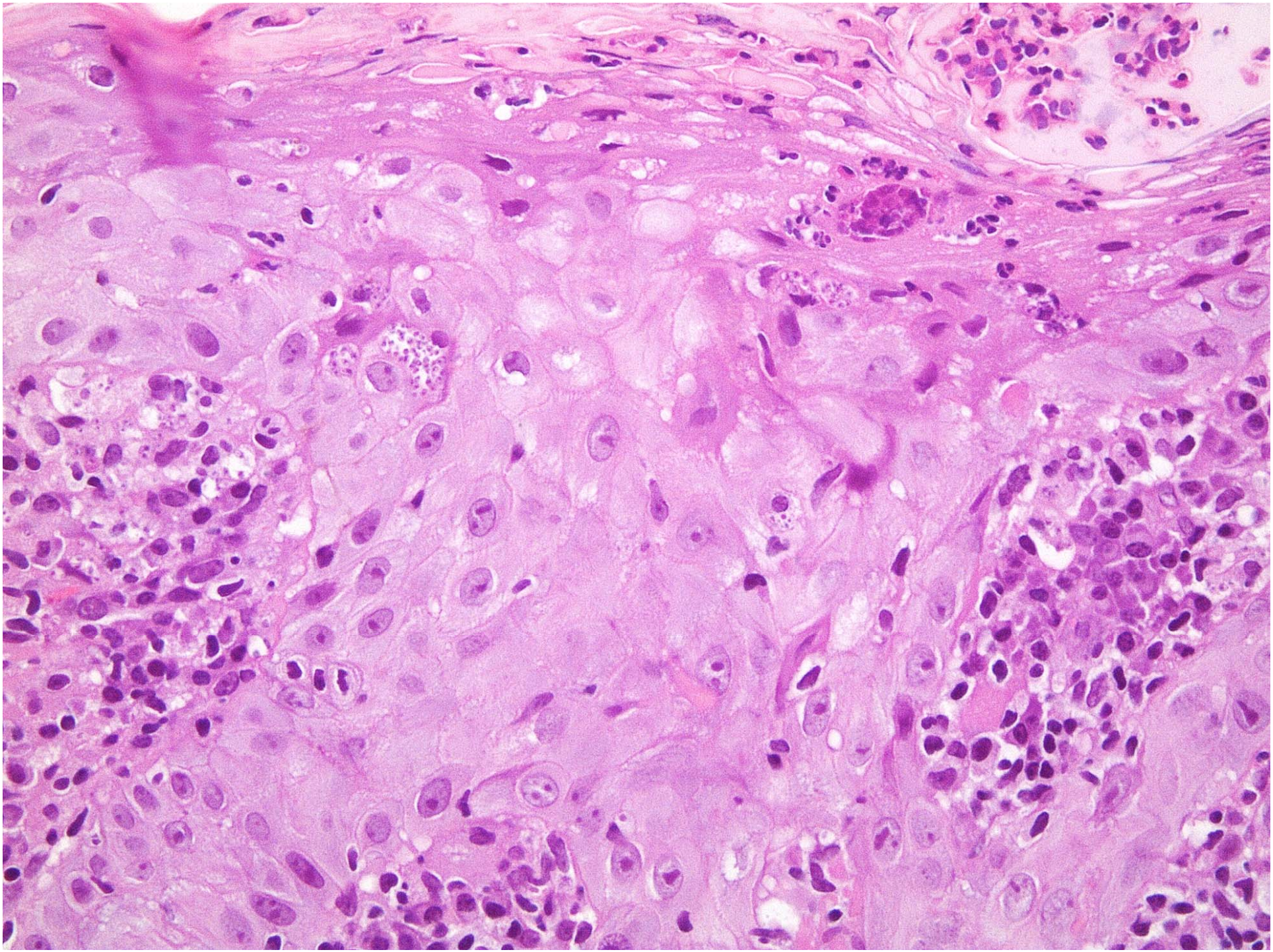


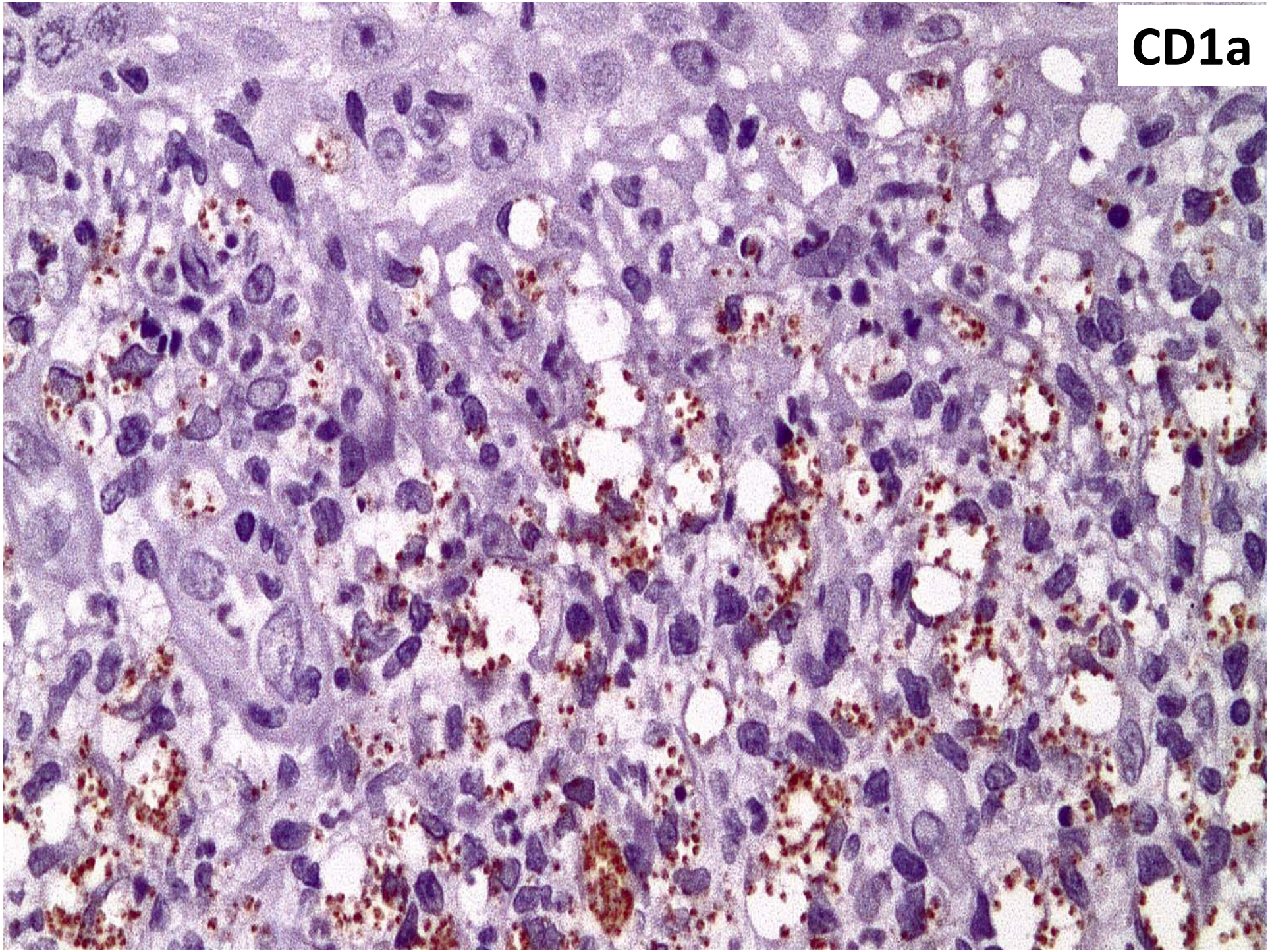








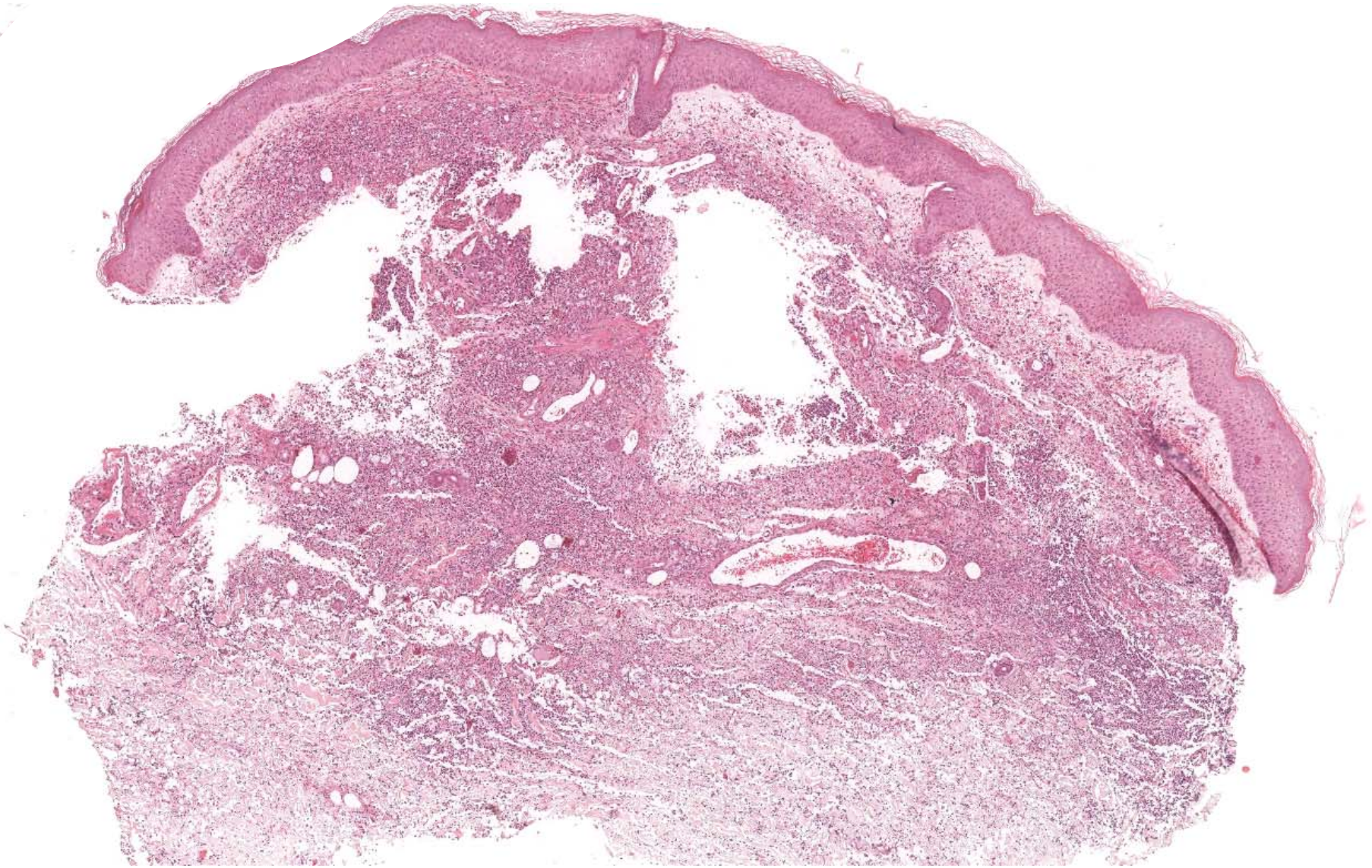


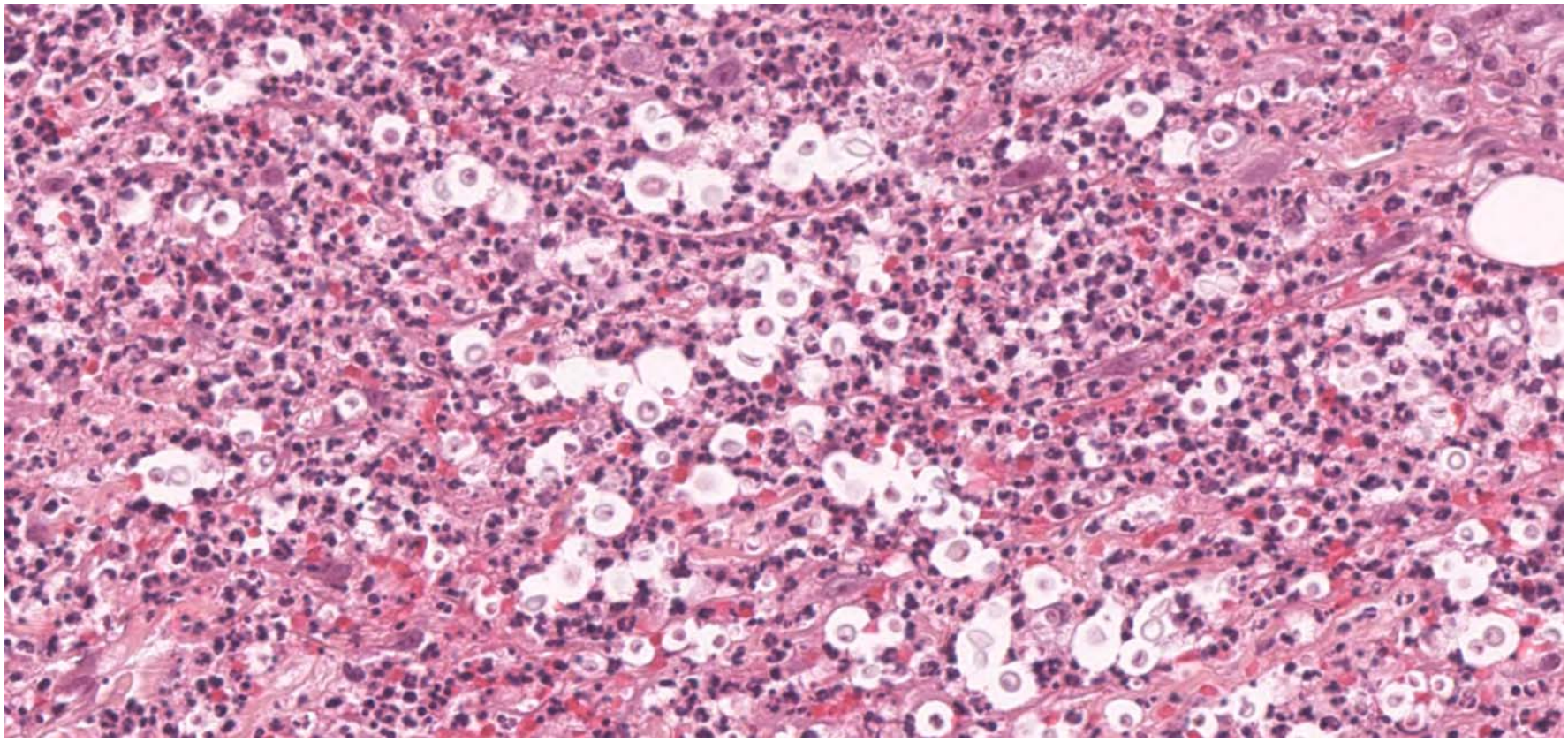

CD1a

## Infections Mimicking Cutaneous Leishmaniasis

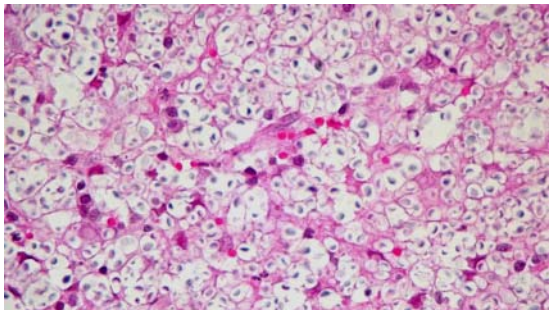
- Cryptococcosis
- North American Blastomycosis
- Phaeohypomycosis
- Chromomycosis
- Coccidioidomycosis
- Toxoplasma gondii
- Histoplasmosis

# Cryptococcosis



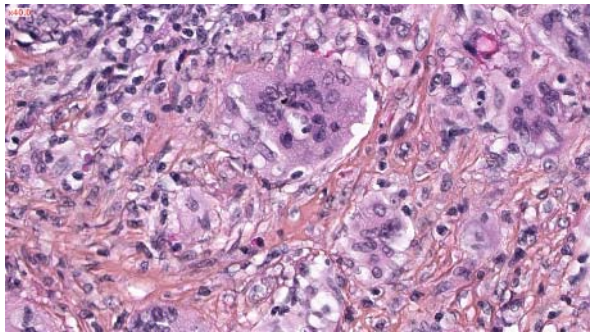


## Gelatinous Pattern



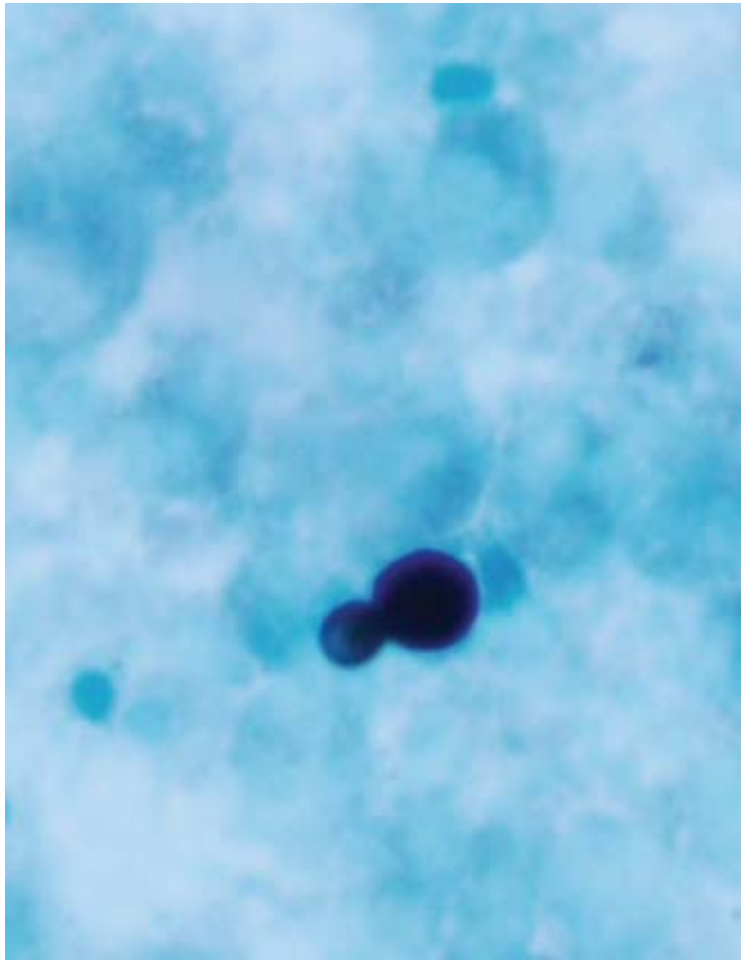
- Numerous large organism
- Plump capsule
- Abscess like reaction with edema

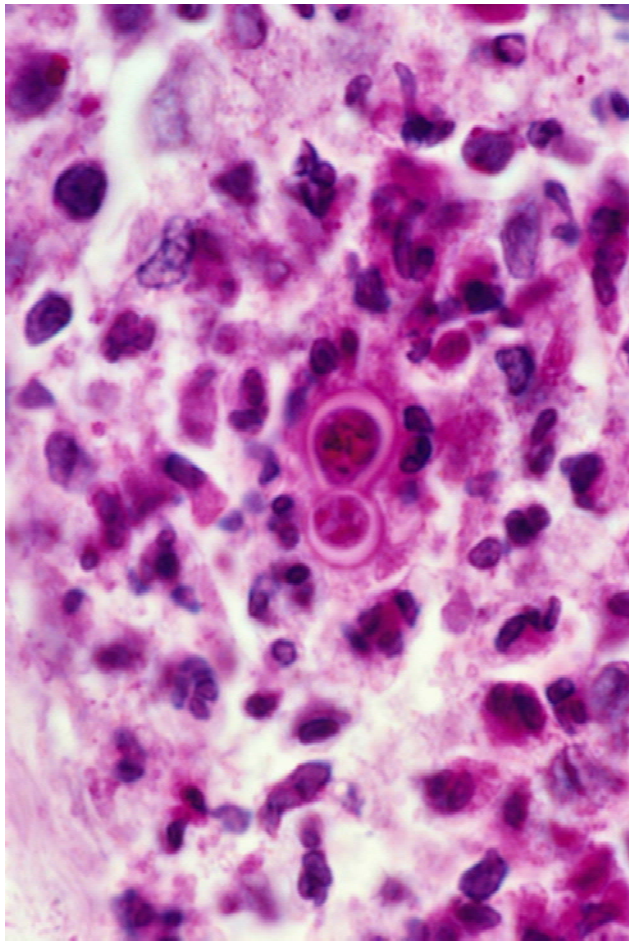
## Granulomatous Pattern



- PEH
- Granulomas
- Small and few organisms

# North American Blastomycosis

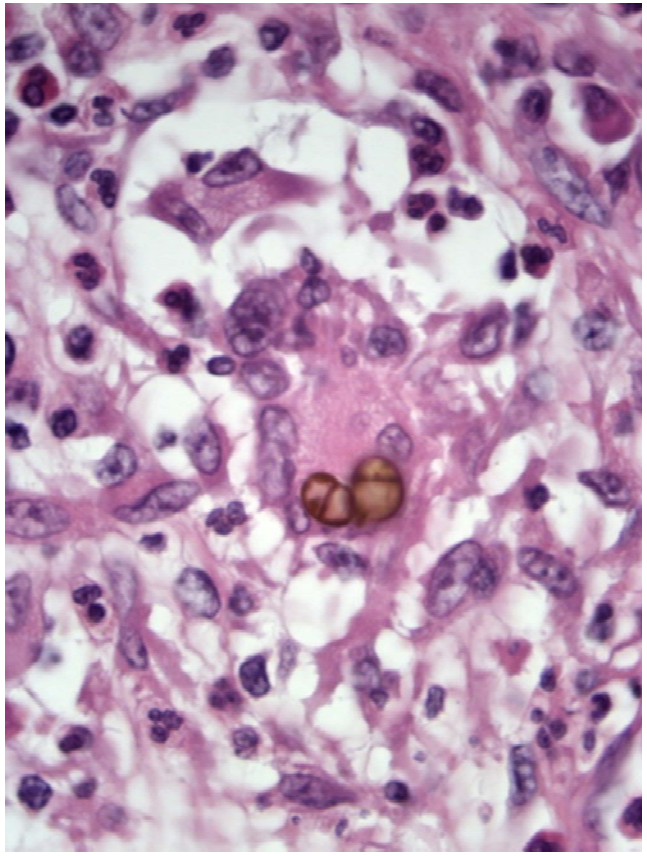




# Pigmented dermal Fungi

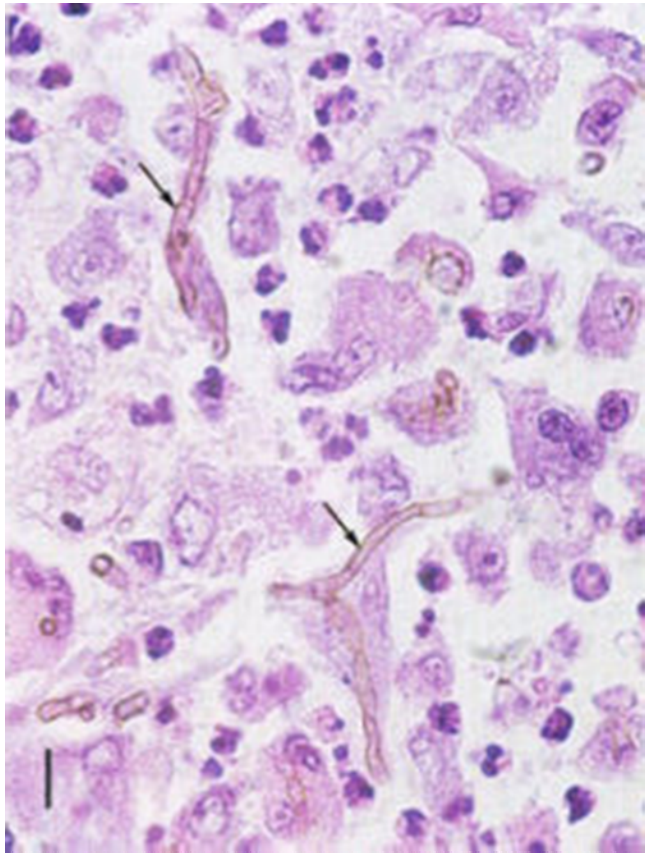
## Chromomycosis

**medlar bodies**

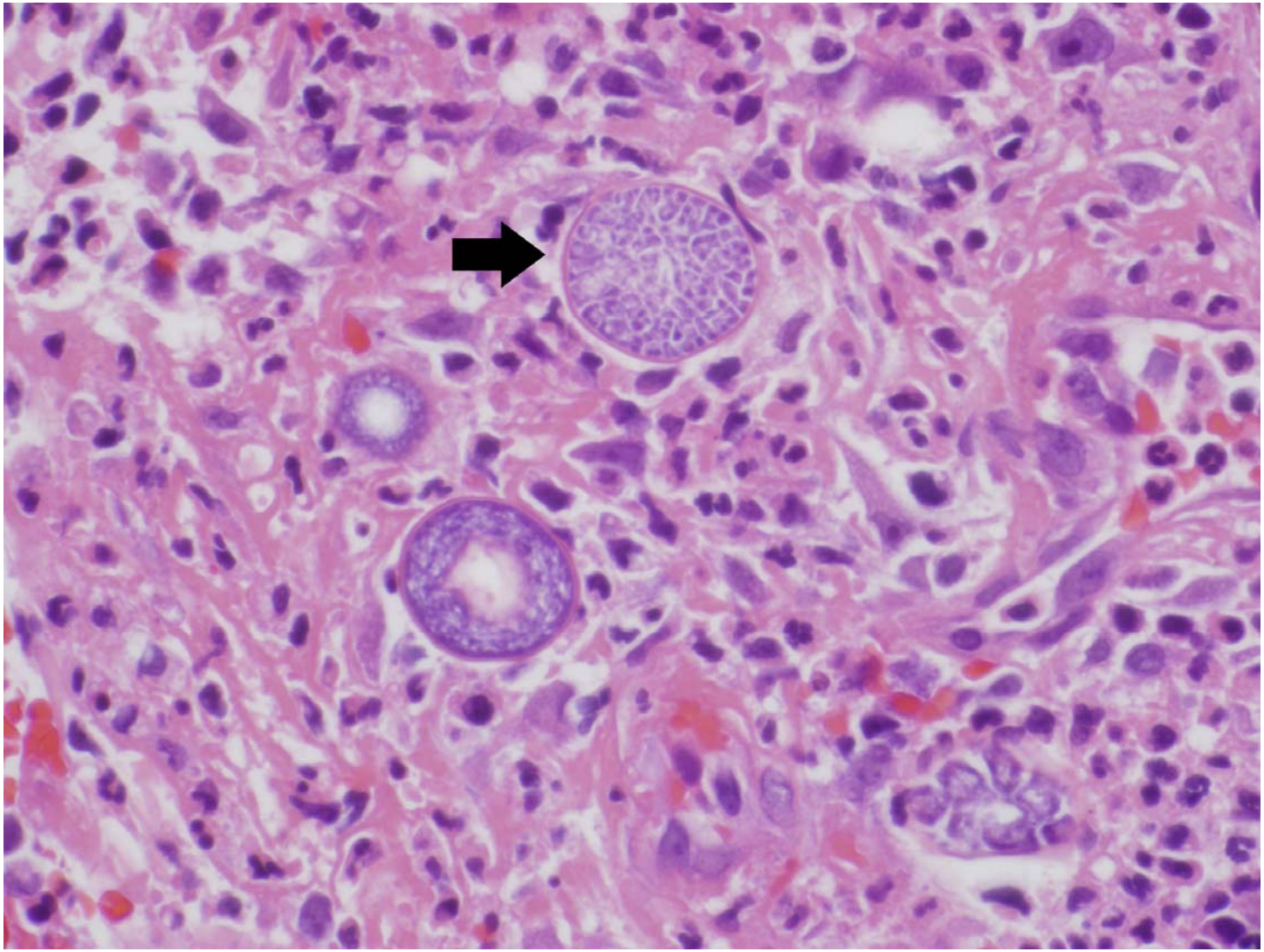


## Phaeohypomycosis

**Brown Hyphae**



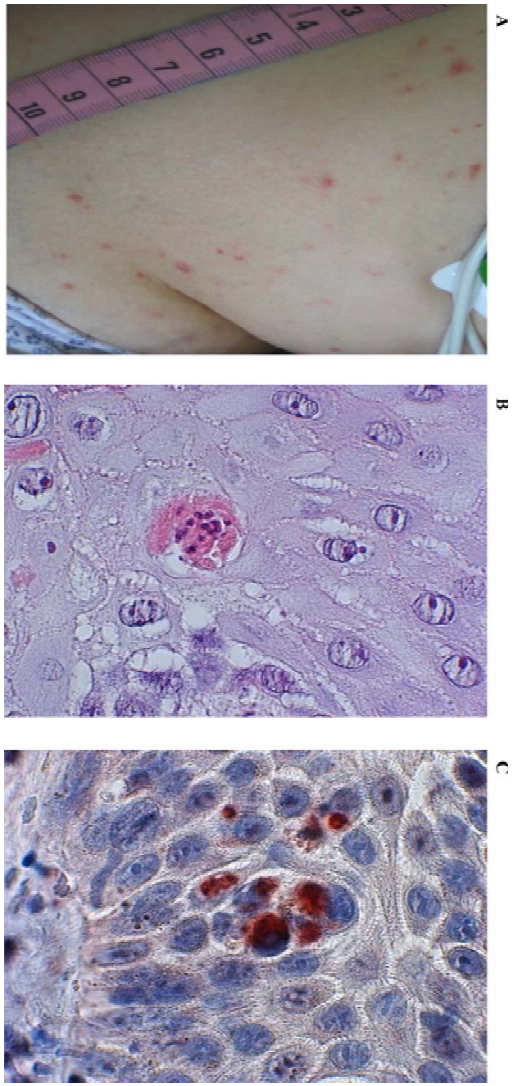
# Coccidioidomycosis



# Toxoplasma Gondii

- Dermatological manifestations: rare.
- Congenital toxoplasmosis: Hemorrhagic and necrotic Papules.
- Acute acquired toxoplasmosis:

  Telangiectatic macules.

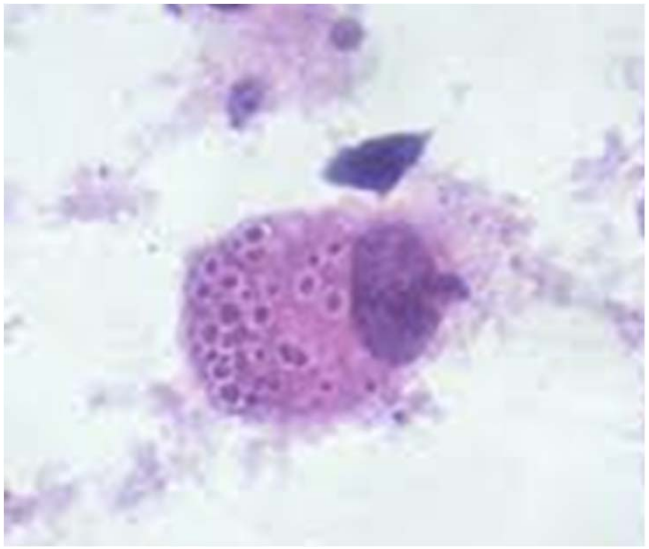


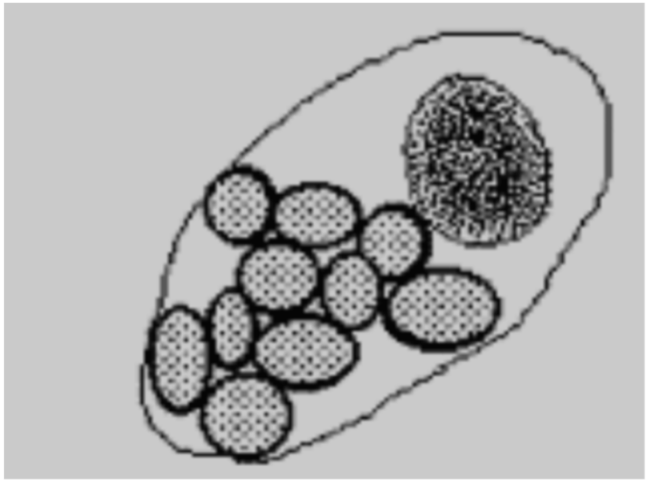
*https://jcm.asm.org/content/51/4/1341*

## Histoplasmosis

3-4 µm

PAS/GMS

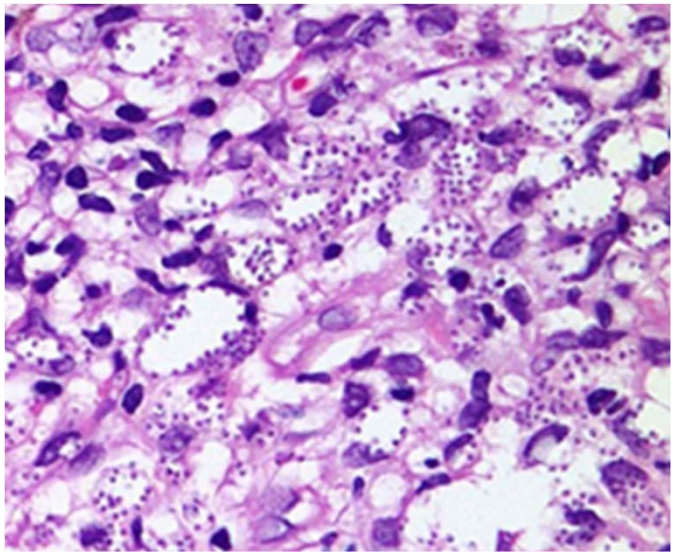


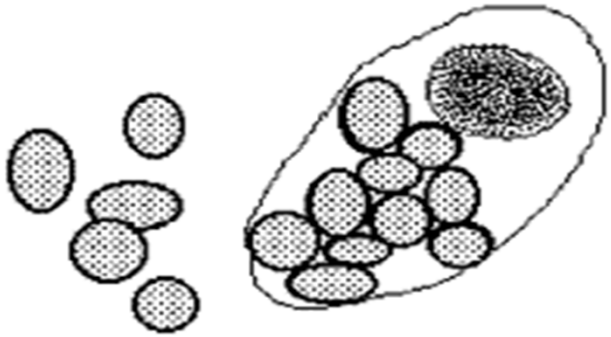


## Leishmania

3-4 µm

H&E





## Histoplasmosis

## Leishmania

Clinically

- Lung
- Wide range of clinical presentation

- Skin
- Wide range of clinical presentation

# Acknowledgment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