Clinical History

A 25 - year-old woman was admitted to IM unit because of fever, skin lesions and deteroration of general condition

Personal Clinical History

She was from Brazil and had been in Spain looking for work for 6 months before the visit.

She works as a waitress, is single and lives with her sister.

She has one son, who lives in Brazil

She has no previous relevant clinical nor family history

No current treatment, no allergies and no previous admissions

Current disease

She went to the Emergency Room with 39 degrees fever, and had been feeling poorly for 3 days.

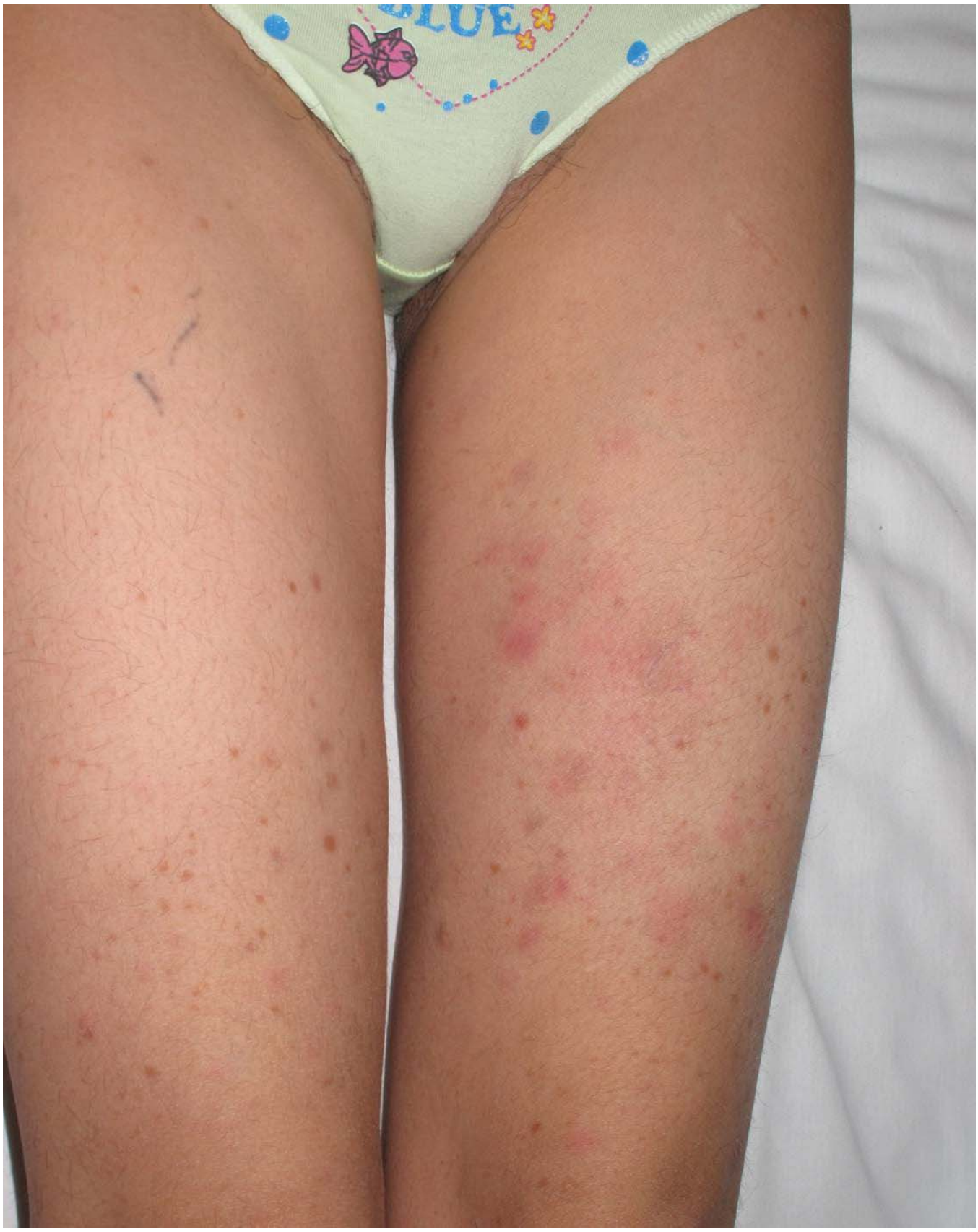
She said she had been suffering from nasal congestion, bilateral rhinorrhea and frontal headaches and pain in both sinus areas with photophobia and a yellow secretion from both eyes in the last month.

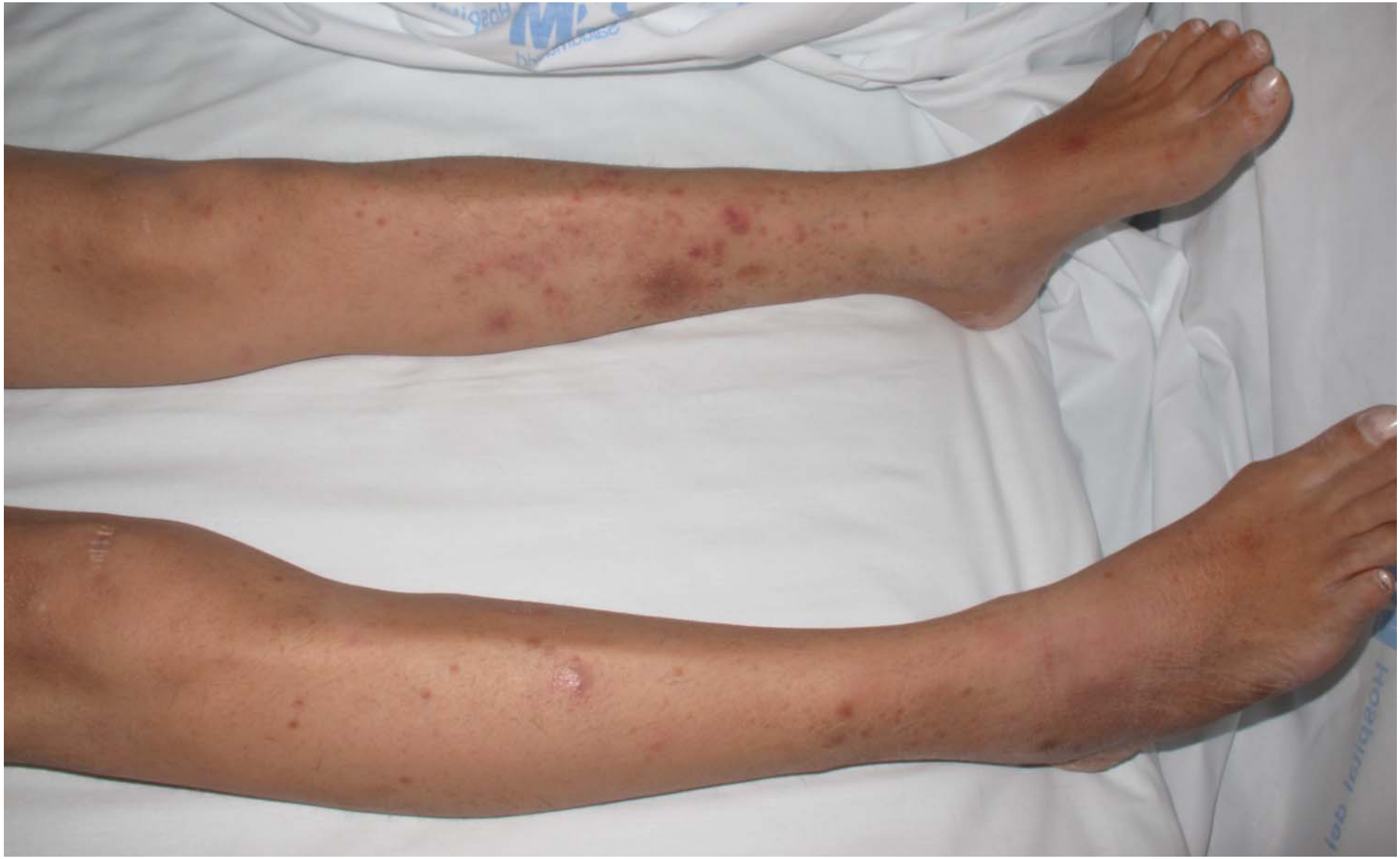
She had taken ibuprofen and paracetamol without significant effect

She also said she had had reduced apetite and had lost 10 kg and noticed the appearance of painful skin lesions in 4 limbs, erythematous and not itching, coming and going in days and leaving a dark color scar, lasting 3-4 days each outbreak, and new ones appearing.

No urinary symptoms, cough, joint pain,and no other symptoms

No noticed insect bites . No drugs. No contact with animals and no sexual relations in the last few months





Clinical Exam

Blood Pressure: SBP 110 mm Hg. DBP 65 mm Hg. Temp. **39º** very thin, weight 38 Kg Height 1.61 m BMI 15. Normal skin color. Normal mental status

Head: hyperemic pharynx , no lesions in the eyes, but conjunctival injection , with a yellow exudate . **Neck**: no goiter , normal jugular venous pressure, small bilateral lymphadenopathy in several areas; cervical, submaxilar, supraclavicular. They were mobile and not painful. Pain in paranasal region when pressed, and she had a red nose with rhinorrhea

Heart: regular rhythm 100 bpm with no murmurs **Lung** Auscultation: normal

Abdomen: not painful and with no abnormal findings. Multiple bilateral lymph nodes in the groin of 1 cm maximum in size

Limbs with several erythematous lesions with nodules, painful in some areas in arms and legs. There were some brown colored papules in fingers, with necrosis in some of them. Others were purpuric papules, as well as two areas with necrotic aspect of approximately 5mm in size. No mucosal alterations and no alteration in soles and palms. No edema and no arthritis

Neurological examination: normal

Other tests

Blood analysis:

Coulter **Hb 10.8 g/dl**. MCV 77.1 fl. **Leuko 19,900** /mm^3.

Sedimentation rate **120** mm Coagulation: **INR 1.3**. Fibrinogen **909** ng/dl (nr 200 a 400 mg/dL)

Biochemical: Glucose 106.0 mg/dl. ALT 19.0 U/l. AST 20.0 U/l. Total Bilirrubin 0.49 mg/dl. GGT 54.0 U/l. Alk Phos 126.0 U/l.(nr 44 a 147 UI/L) LDH 147.0 U/l.(nr 100 y 220 U/l), Creatinine 0.57 mg/dl. Urea 15.0 mg/dl. Na 133.0 mEq/l. K 3.84 mEq/l. PCR 26.43 . Vitamin B12 and Folic Acid normal, iron 22, haptoglobulin **521** (n.r 41 a 165 mg/dL) , ferritin **337** (nr 12-150 ng/mL), transferrin 151. Ig G **1780** (nr 560 a 1800 mg/dL)

Urine and smear: Normal. And a negative pregnancy test

Microbiology Blood Cultures (3) Negative

Thorax and abdomen X ray: Normal.

Paranasal sinus X ray: Normal

Evaluated (ER) by Dermatologist and Otolaryngologist without a clear diagnosis

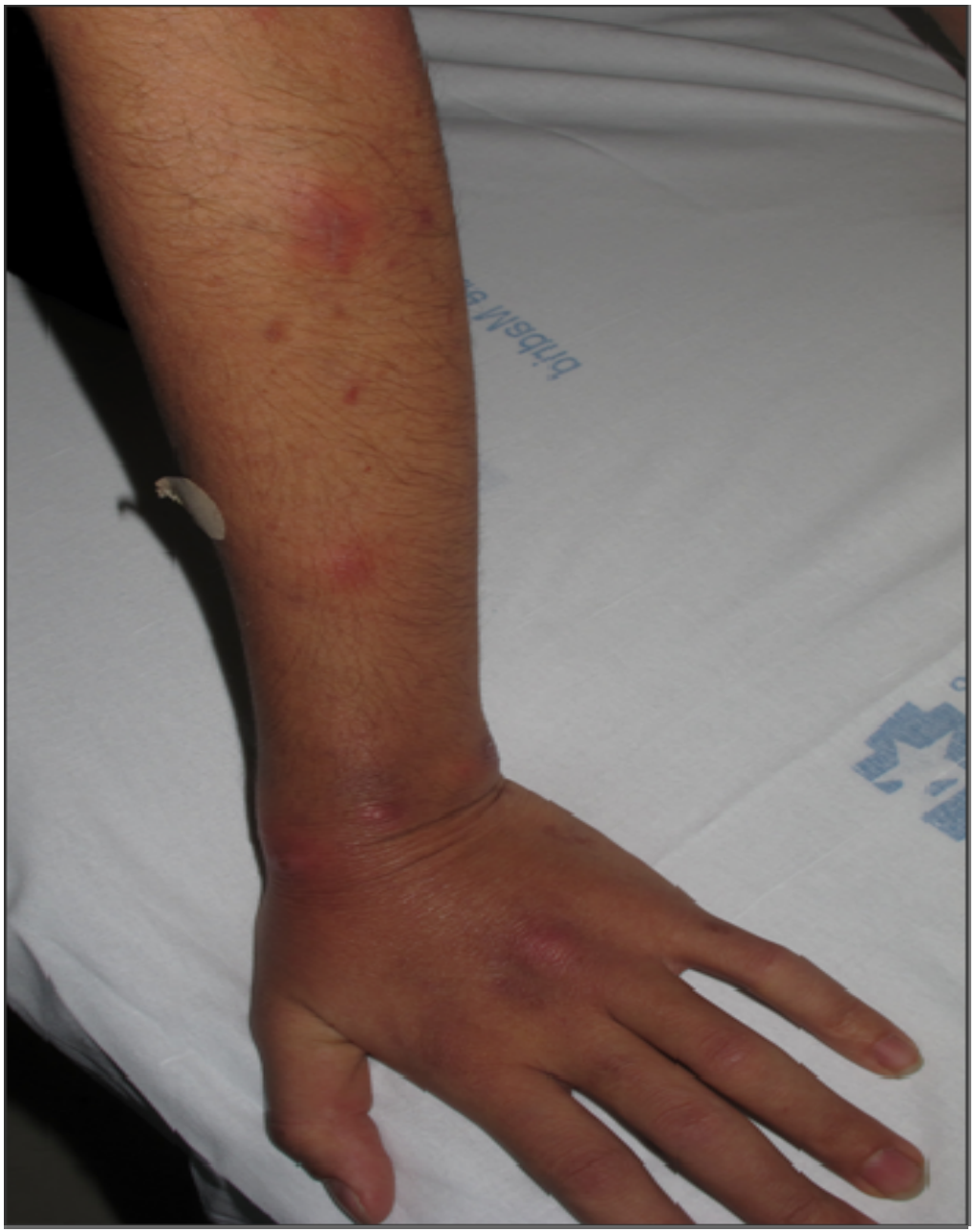
Initial assessment and plan

We have…

A Young female patient admitted to Internal Medicine Department because of high temperature and deterioration of general condition, with nasal congestion and different kinds of skin lesions in limbs.

……and

She presented new skin lesions within 48 hours of admission, and still had high fever (39º) and mild ankle inflamation and edema, painful when moved.



(admitted in I.M. ward)

Posible Diagnosis of :

Acute febrile neutrophilic dermatosis Sweet's Syndrome ?

Granulomatosis with polyangiitis (Wegener's)

Erythema nodosum

Skin Tuberculosis

Other systemic vasculitis……

Treated initially with doxycycline and amoxycllin/clavulinic acid without benefit..

Differential Diagnosis

method ("Shirley Rigby")

V	vascular…eg vasculitis
I	Infective…eg syphilis,
T	trauma.. (No in this case)
A	autoimmune.. SLEM..
M	metabolic/endocrine
I	idiopathic or iatrogenic
N	neoplasia…

Any other test?

What do you think……

Questions and opinions…

Complementary tests

Blood test

Hb: 9,7 g/dL, leuco: 12600(Neu:9300)

Platelets: 303,000 Normal biochemistry

PCR: 13,5 INR: 1.23, **Fibrinogen: 838**

Inmunological Study

autoinmunity: NEGATIVE

inmunoglobulins : Ig G: **2.090** (nr 560 a 1800 mg/dL)

Microbiology

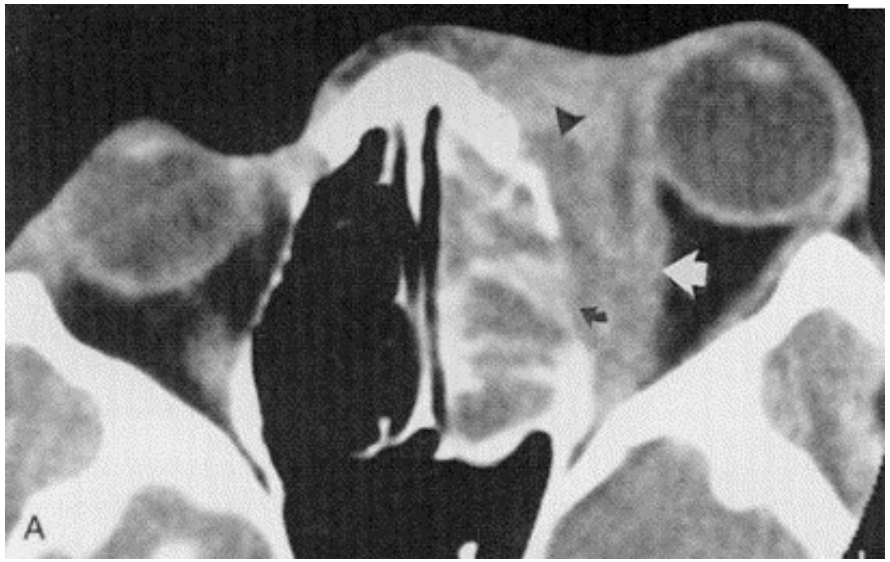
Virus: AIDS , hepatitis B, hepatitis C,CMV,E-B, Parvovirus B19, NEGATIVE

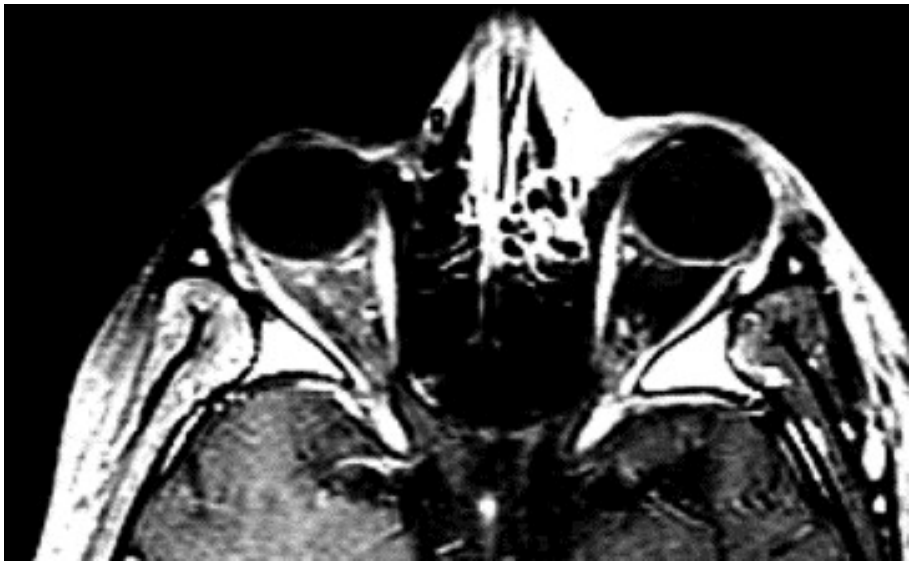
Toxoplasma , Coxiella, Treponemic Screening Borrelia , Rickettsia, Brucella, Leishmania --→ NEGATIVE

Other Tests

CT scan paranasal synus

Occupation by mucosal edema in ethmoid cells, frontal sinuses and moderately in **maxillary sinuses bilaterally suggesting inflammatory disease.**



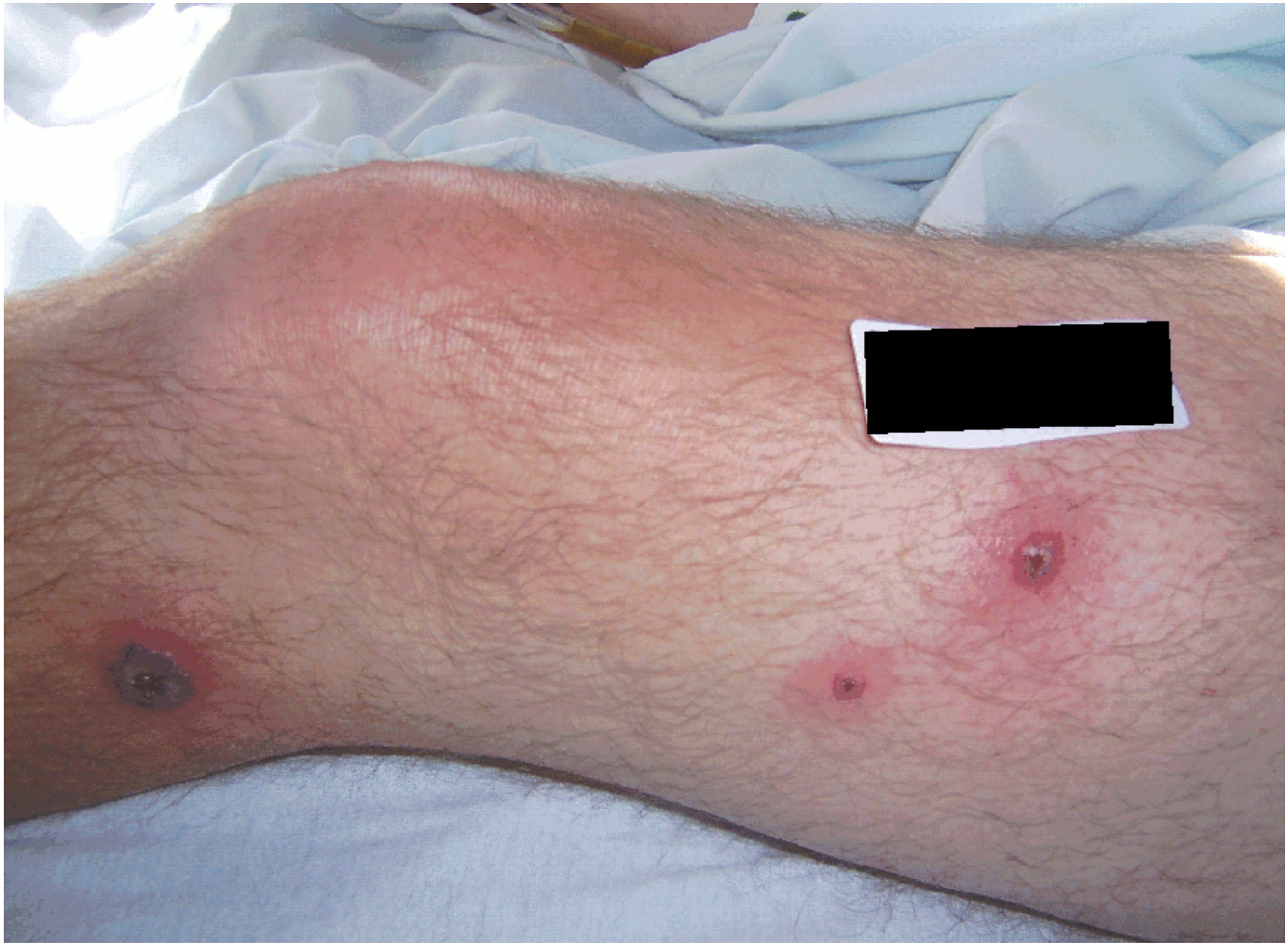


Acute febrile neutrophilic dermatosis
Sweet's syndrome

A skin disease characterized by the sudden onset of fever, lukocytosis and tender,erythematous well-demarcated papules and plaques

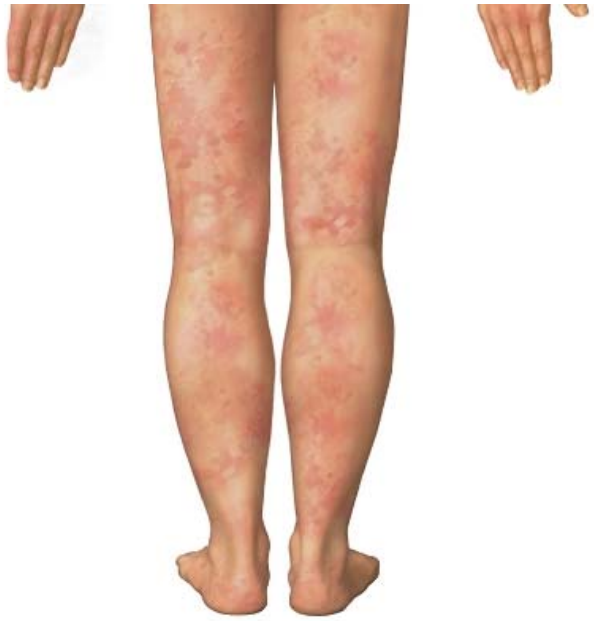
There are dense infiltrates by neutrophil granulocytes on histological examination.

Often associated with hematologic and inmmunological disease (leukemia, rheumatoid arthritis, inflammatory bowel disease .



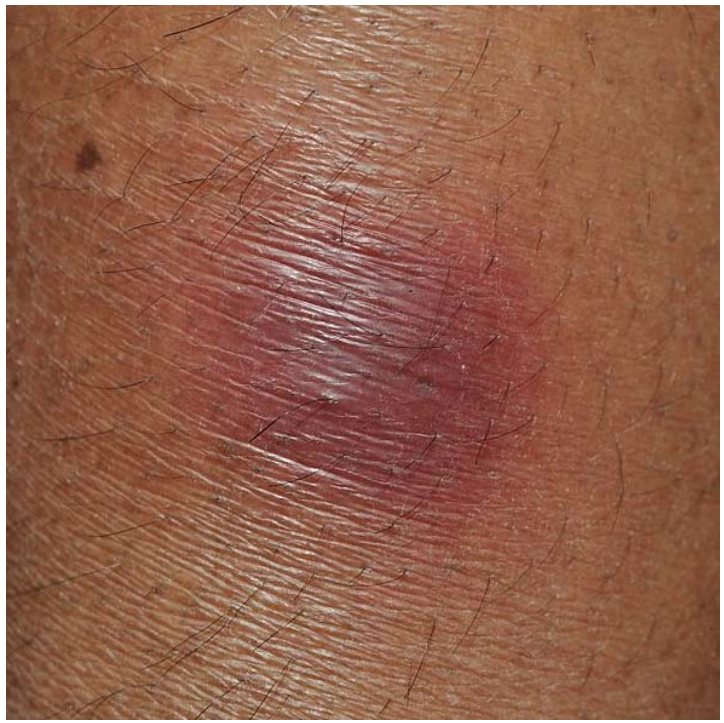
Erythema nodosum

may be associated with a wide variety of diseases including:



Sarcoidosis
Many Kind of Infections:

- **Virus: E-B, hepatitis C,**
- **mycobacterias**
- **treponemas**
- **fungi**
- **Streptococci**
- **Mycoplasma**
- **yersinia**



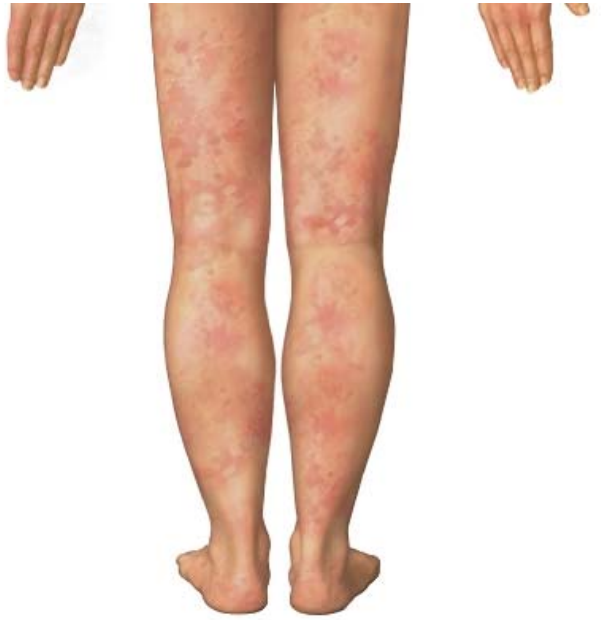
Autoimmune disorders (e.g. SLE, Behcet's..)
Inflammatory bowel disease (e.g. Chron..)

medications (oral contraceptives, sulfas …),

Cancer (eg. Lynfoma..)

Vaccinations, Pregnancy…

Erythema nodosum (*red nodules*)



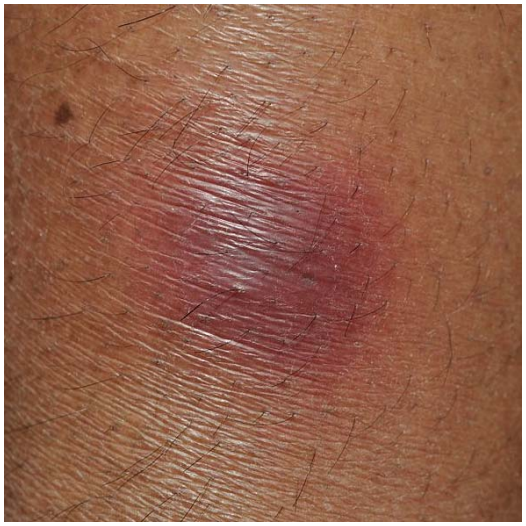
EN is the most common form of panniculitis (inflammation of fat cells under the skin)

EN is an immunologic response to a variety of different causes

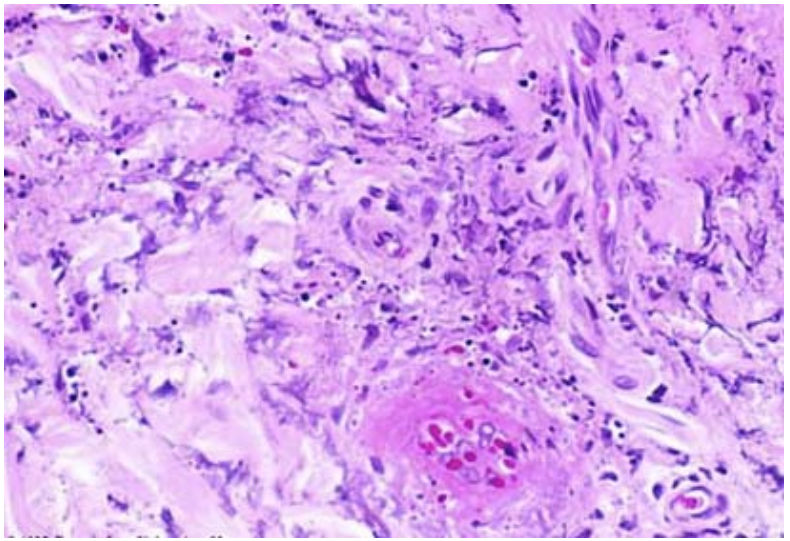
It is characterized by tender red nodules or lumps that are usually seen on limbs

Associated with fever, malaise, and joint pain and inflammation

It resolves itself 3–6 weeks after an event without ulceration or scarring



Biopsy of right forearm lesion

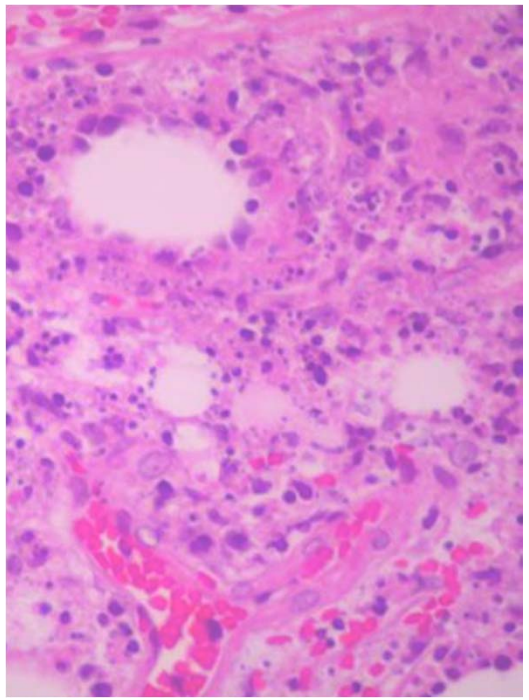


Pathology:

Reticular dermis is observed in a dense **inflammatory infiltrate composed of histiocytes foamy cytoplasm.**

Also are seen groups of neutrophils, low lymphocytes, plasma cells and some multinucleated giant. There is involvement of the adipose tissue and **some images of vasculitis with fibrinoid necrosis.**

Compatible with **Paniculitis**



MICROBIOLOGY

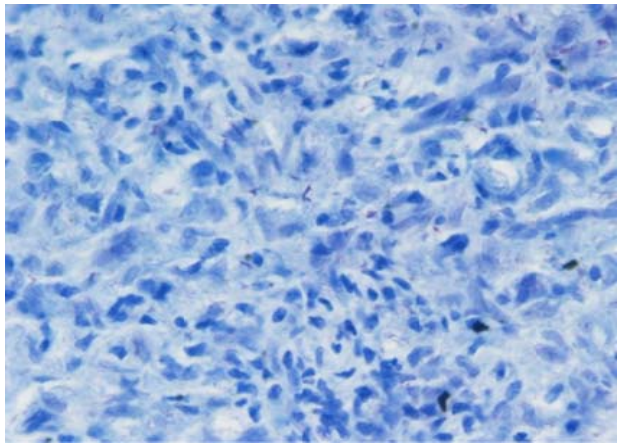
10 M.Leprae / line

Nasal smear +++

Smear right earlobe, right elbow injury and the anterior aspect of the right leg

ALSO POSITIVE 3/3

PCR Mycobacterium : positive confirmed



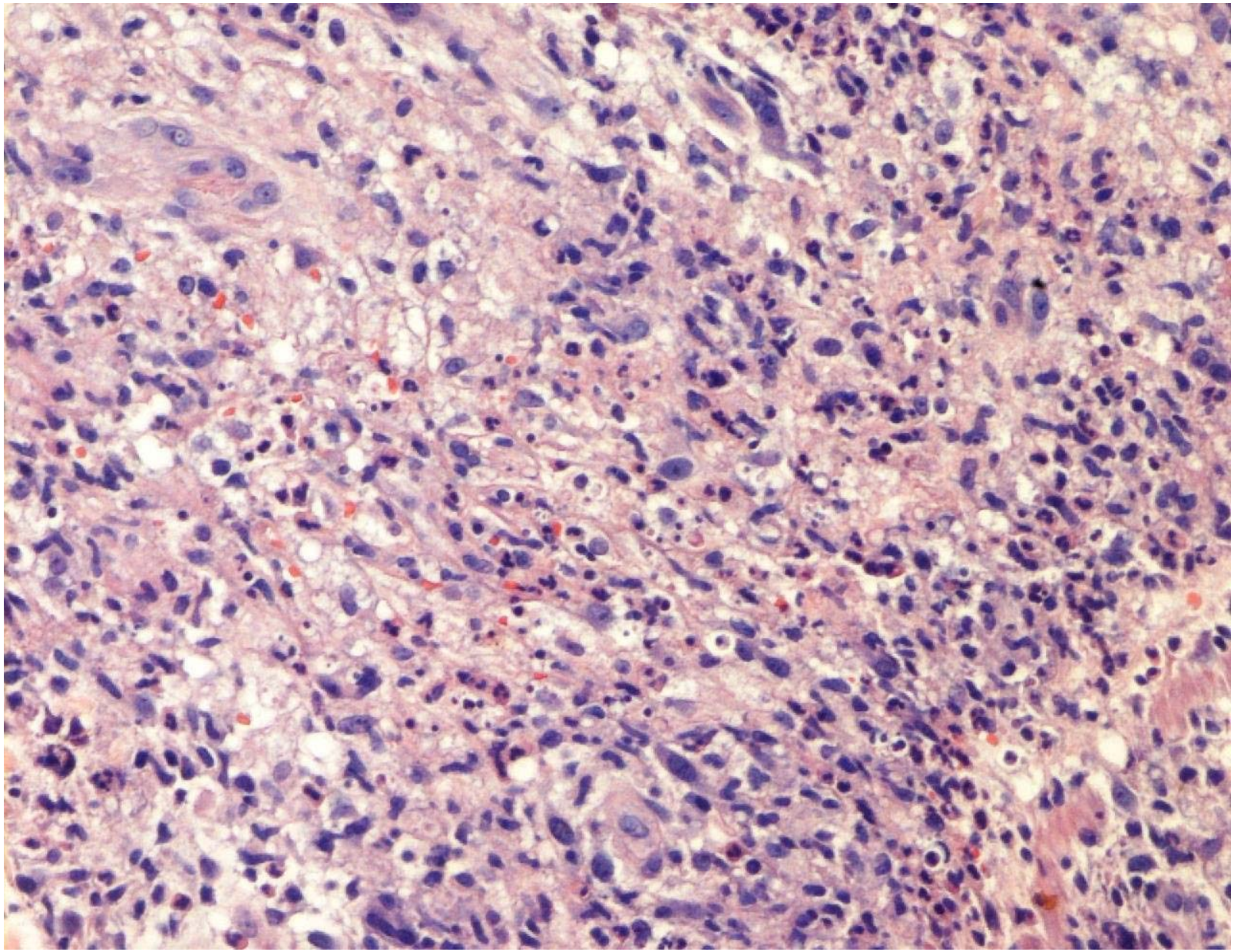
M.Leprae

2 índexes

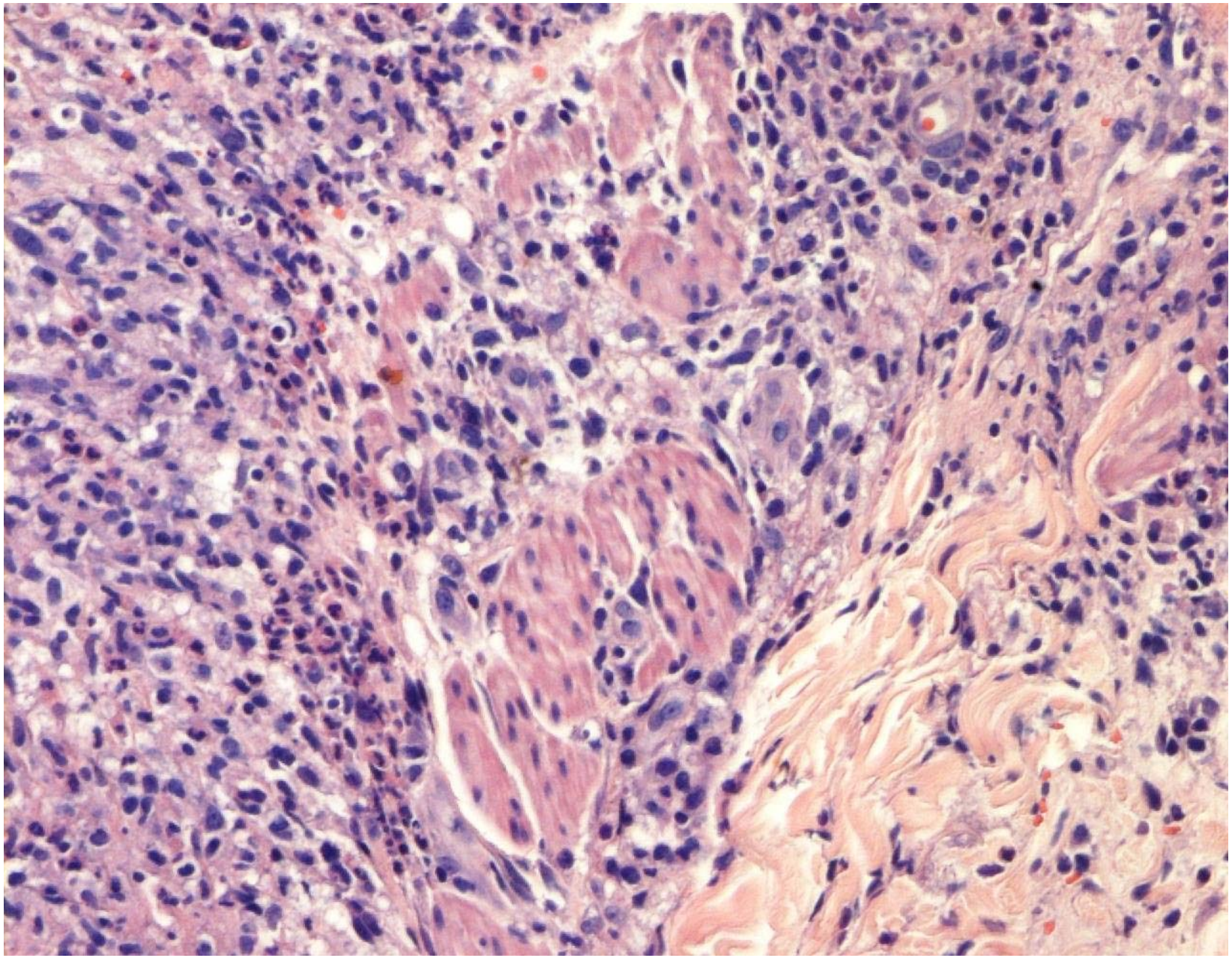
Morfological
nº of Bacillus / line

Bacteriological
Density of de M.Leprae
in dermis

Skin Biopsy "reviewed "



Specific staining



Erythema nodosum leprosum (ENL)

Occurs in patients with BL and LL disease.

It is characterized by sudden eruption of numerous, painful, nodules which can form pustules and may **ulcerate**, discharging yellow pus that contains polymorphs and degenerating acid-fast bacilli, but is sterile on culture.

Final Diagnosis

LEPROMATOUS LEPROSY (LL)

LEPROSUS ERYTHEMA NODOSUM

Evolution and treatment

- Levels tested of G6PDh : normal 0,57(0,44-1,31)

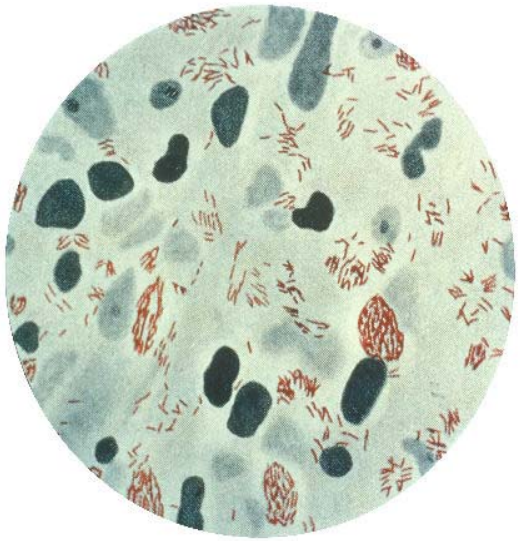
Treatment was initiated according to current guidelines

RIFAMPICINA + DAPSONA + CLOFAZIMINA

and also with prednisone 1mg/kg/day

Rapid and complete response in several months

Discharge and follow-up…



LEPROSY

True or False? About leprosy…

Deformities and other visible manifestations of leprosy can largely be prevented

TRUE

FALSE

True or False? About leprosy…

The clinical manifestations are largely confined to the skin, peripheral nervous system, heart, eyes, and testes

TRUE

FALSE

True or False? About leprosy…

Mycobacterium Leprae is a intracellular Bacillus that may survive outside the body for months

TRUE

FALSE

True or False? About leprosy…

It is one of the few bacterial species that still has not been cultivated on artificial medium or tissue culture

TRUE

FALSE

True or False? About leprosy…

It is the first bacterium to be etiologically associated with human disease

TRUE

FALSE

True or False? About leprosy…

Leprosy is associated with poverty and rural residence and also is often associated with AIDS

TRUE

FALSE

True or False? About leprosy…

Only some individuals appear to be naturally immune to leprosy and do not develop disease manifestations after exposure

TRUE

FALSE

True or False? About leprosy…

The route of transmission of leprosy remains uncertain

TRUE

FALSE

True or False? About leprosy…

Resistance to dapsone and rifampin are common

TRUE

FALSE

True or False? About Reactional states…

The reactions may precipitate presentation for medical attention but usually occurs after treatment

TRUE

FALSE

True or False? About Reactional states…

There is several kind of animal that can trasmit the illness

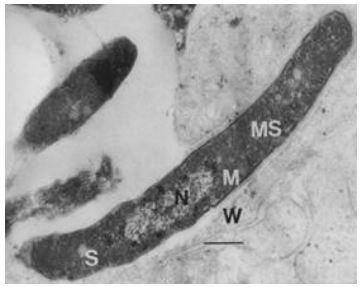
TRUE

FALSE

Only one. Wich one?

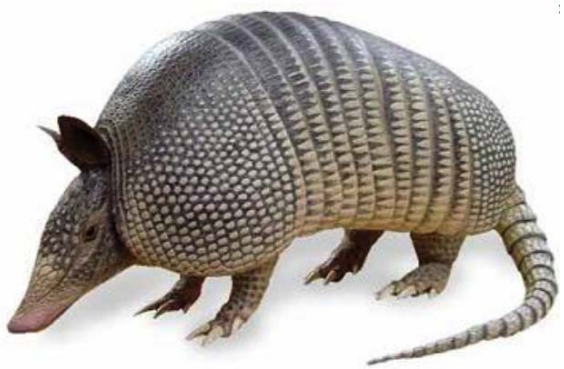
General characteristics

Leprosy (also known Hansen's Disease) is an infectious disease caused by Mycobacterium leprae



Spread by the respiratory route (not fully understood)

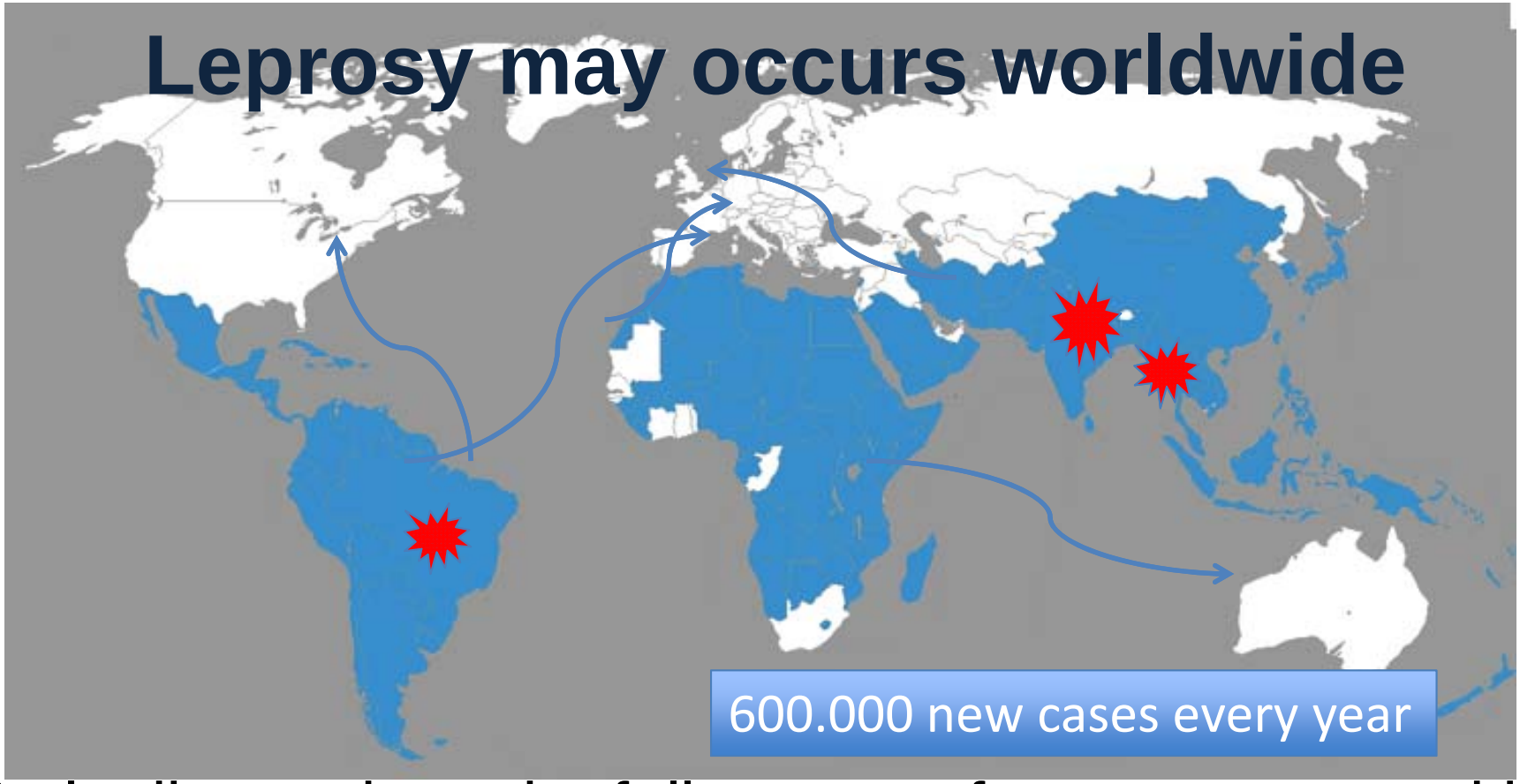
In USA is also a zoonosis, (armadillos)



Involves the skin and peripheral nerves and it is an important global health concern

General characteristics

Greatest burden of disease is in Southeast Asia. India accounts for 50% of new cases of leprosy, with Brazil and Indonesia have high incidence

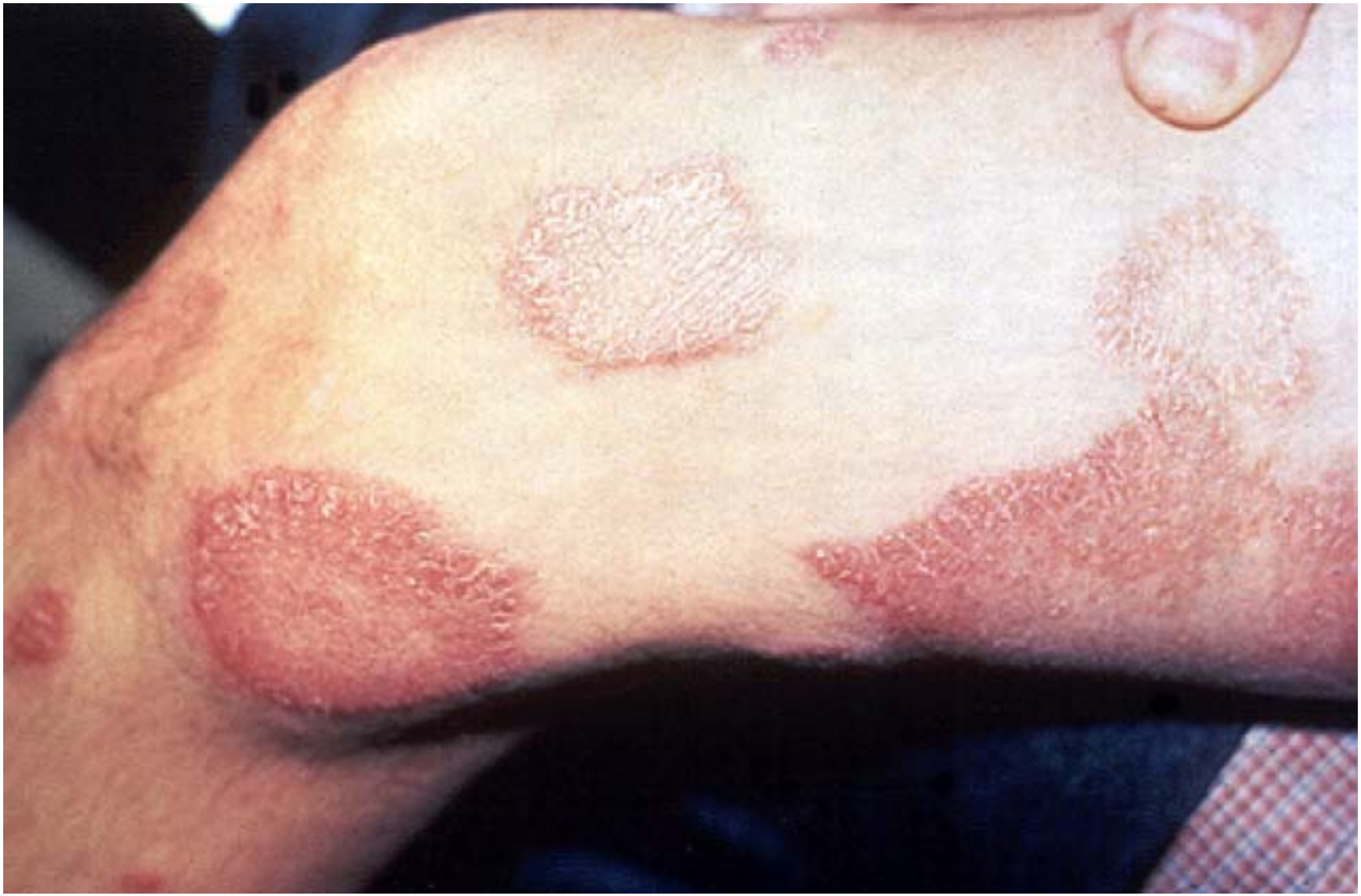


Early diagnosis and a full course of treatment are critical for preventing lifelong neuropathy and disability

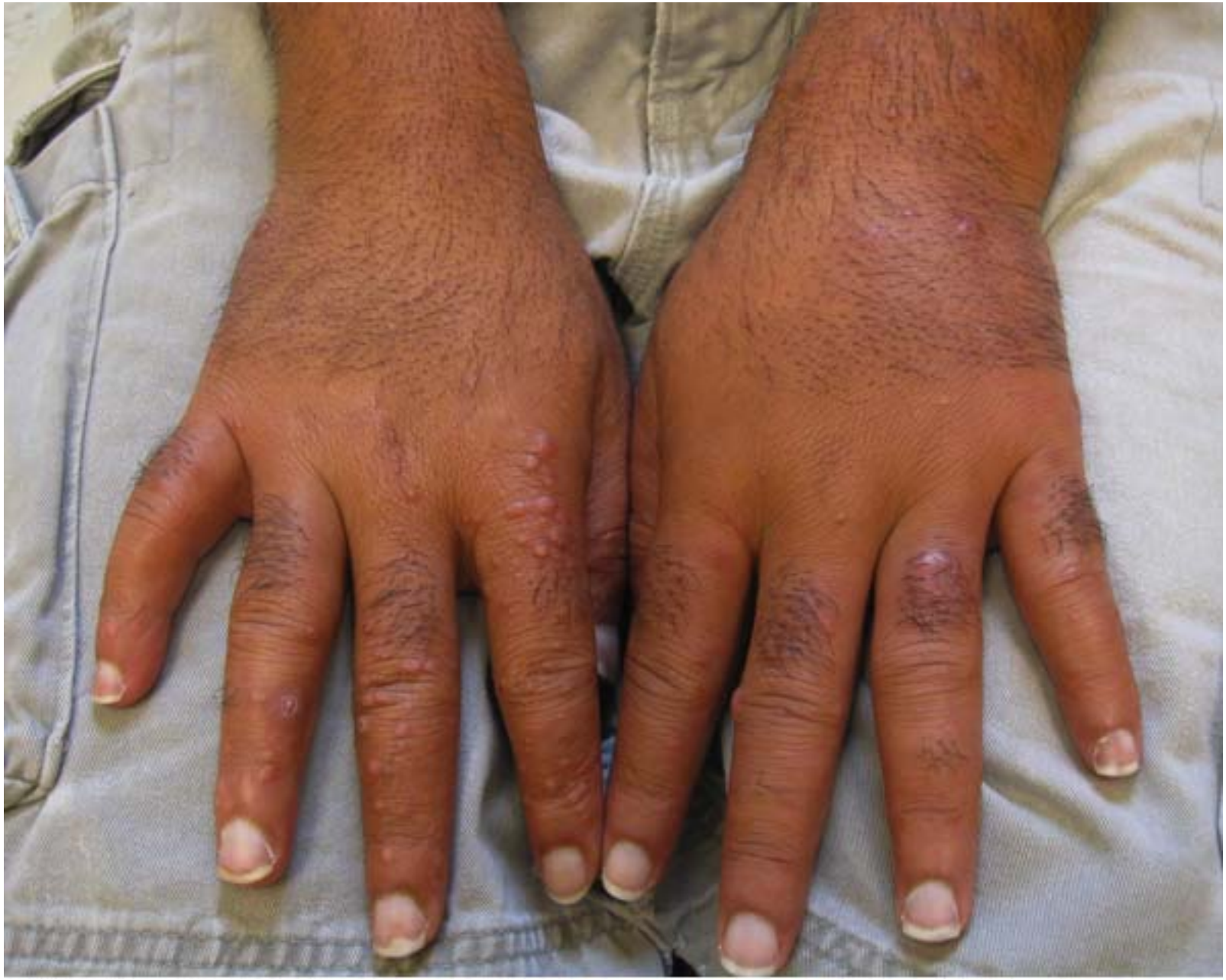
Diagnosis of leprosy should be considered in the setting of the following symptoms:

- Hypopigmented or reddish patch(es) on the skin
- Diminished or loss of sensation within skin patch(es)
- Paresthesias: tingling or numbness in the hands or feet
- Painless wounds or burns on the hands or feet
- Lumps or swelling on the earlobes or face
- Tender, enlarged peripheral nerves

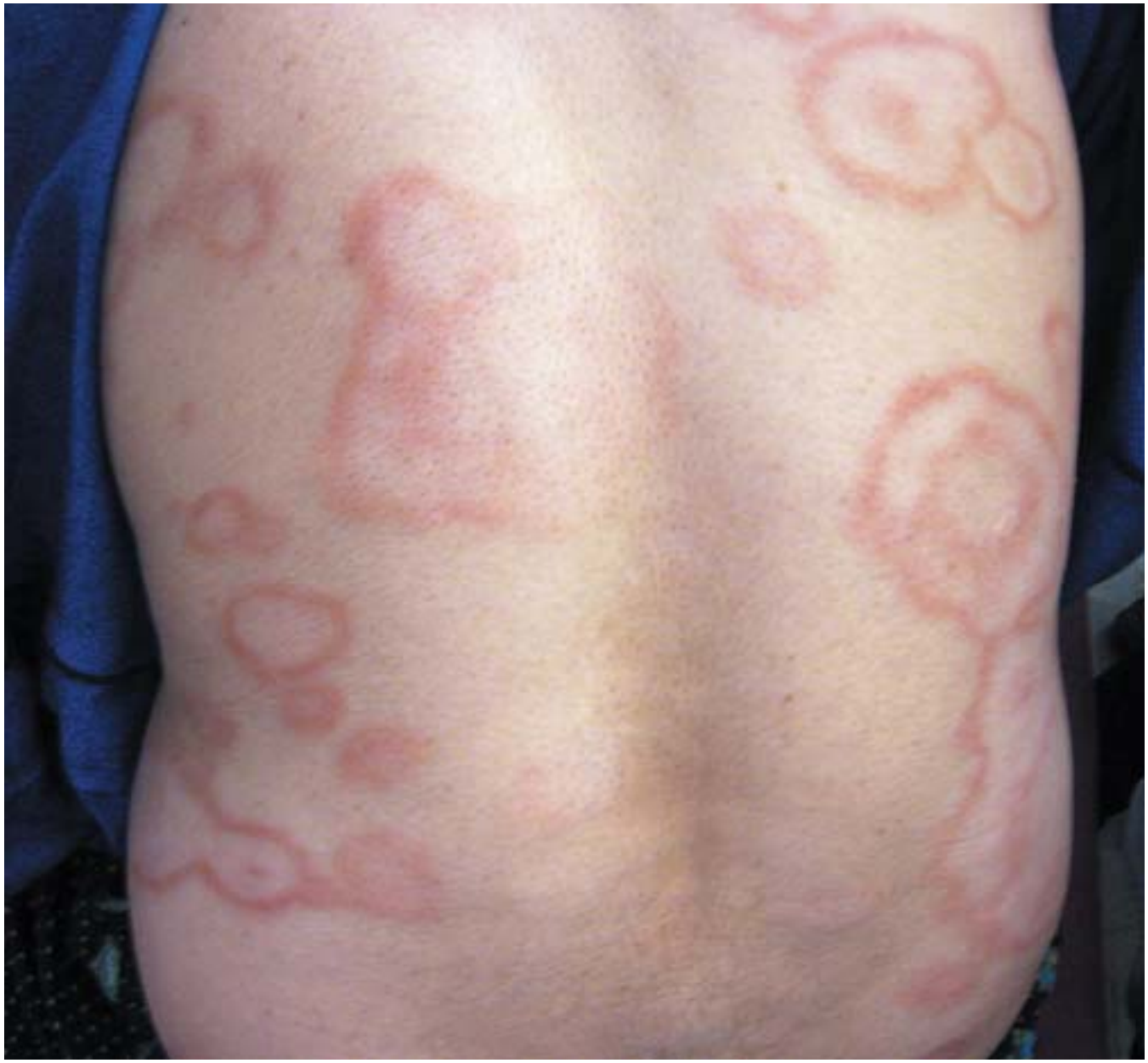
thigh with demarcated cutaneous lesions



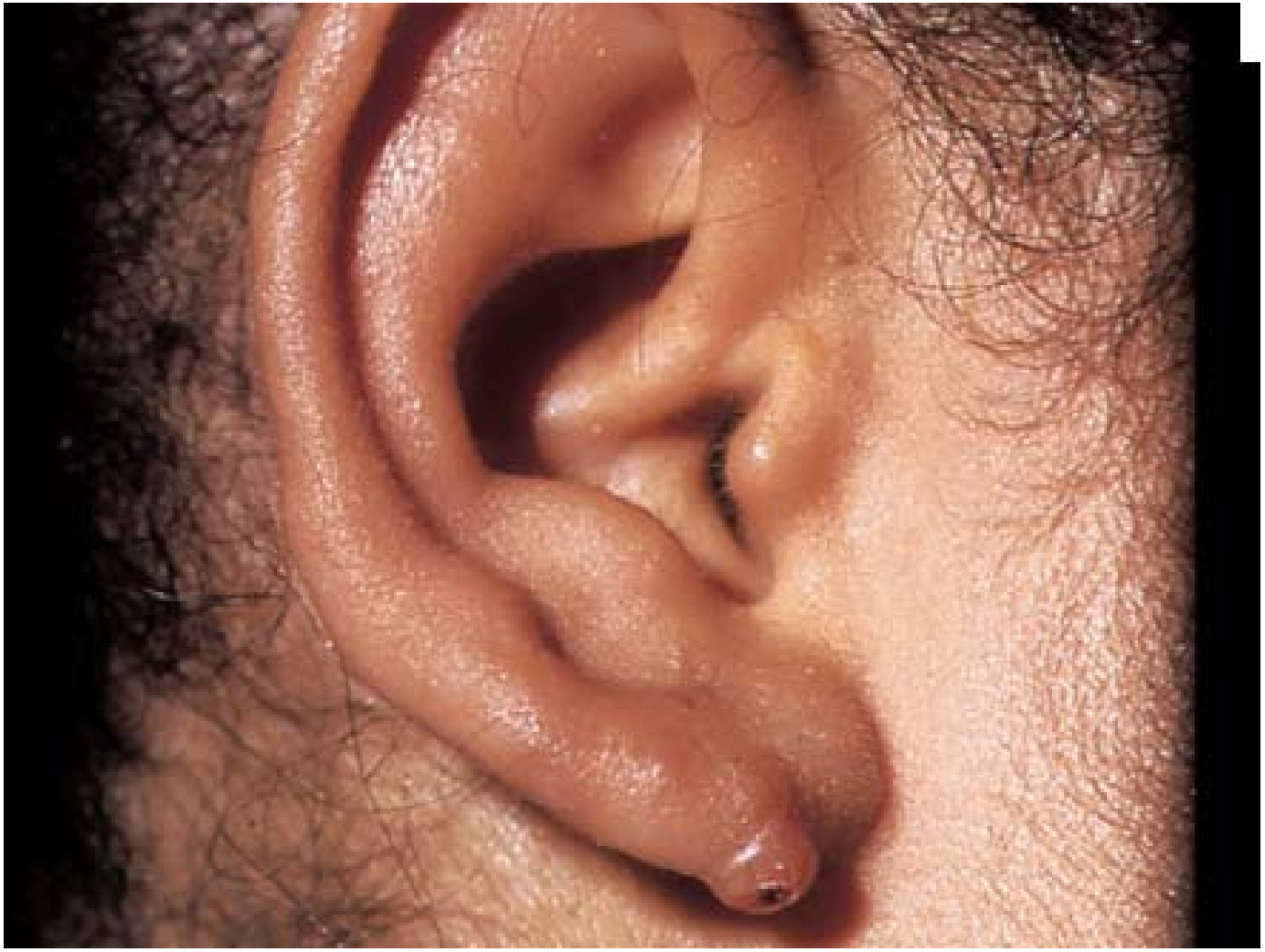
case of leprosy, with nodules developped on normal skin



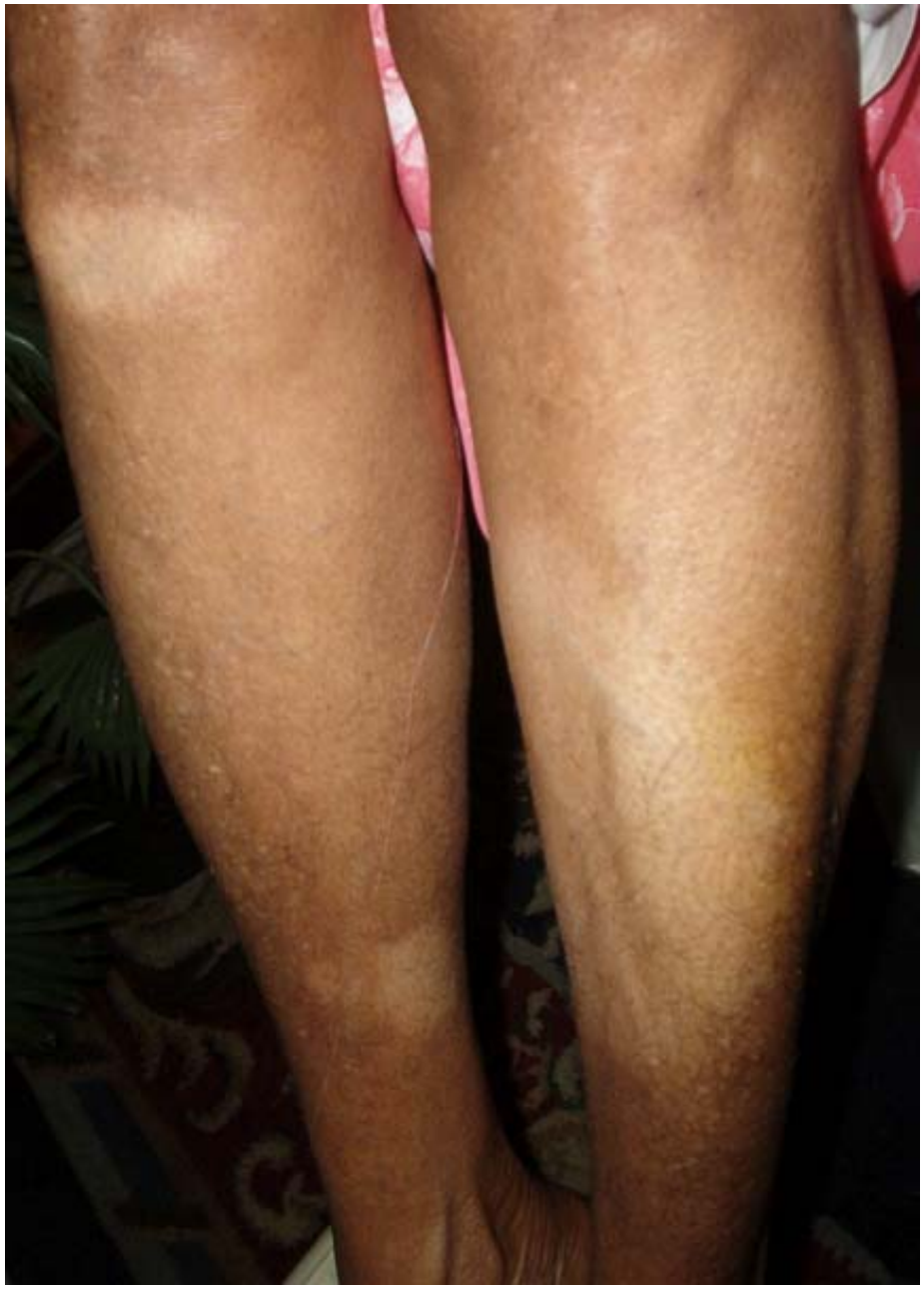
multiple large, annular, hypopigmented, atrophic macules with well-defined, erythematous, raised borders

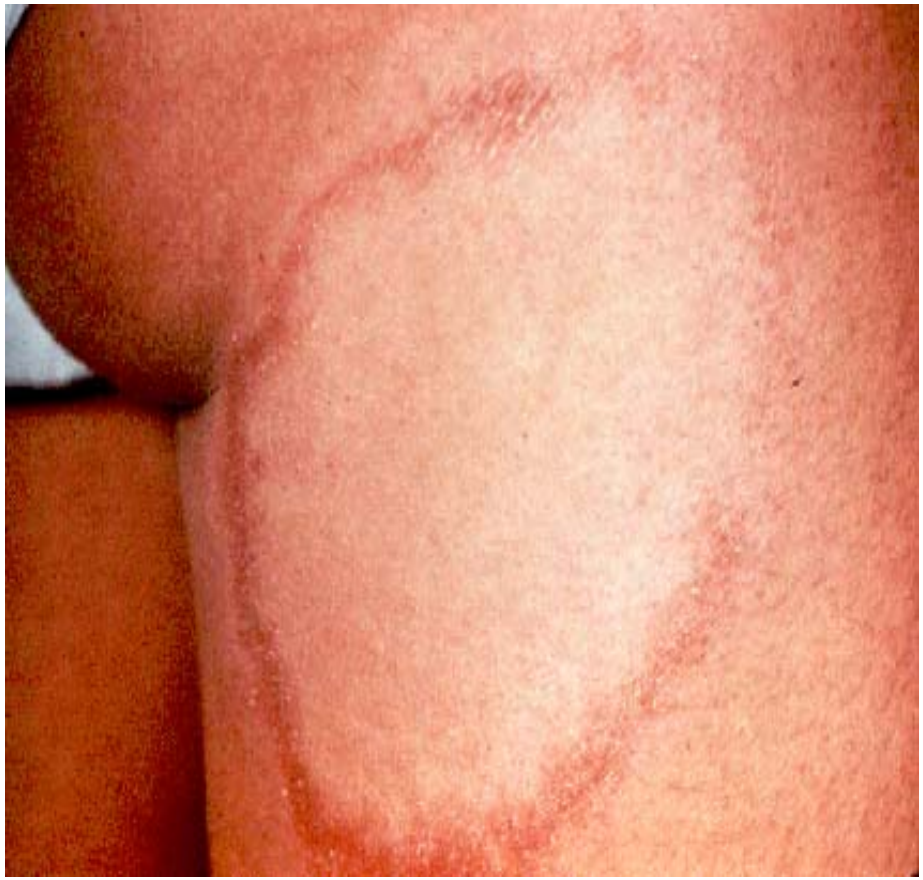


Nodular lesions of the earlobe

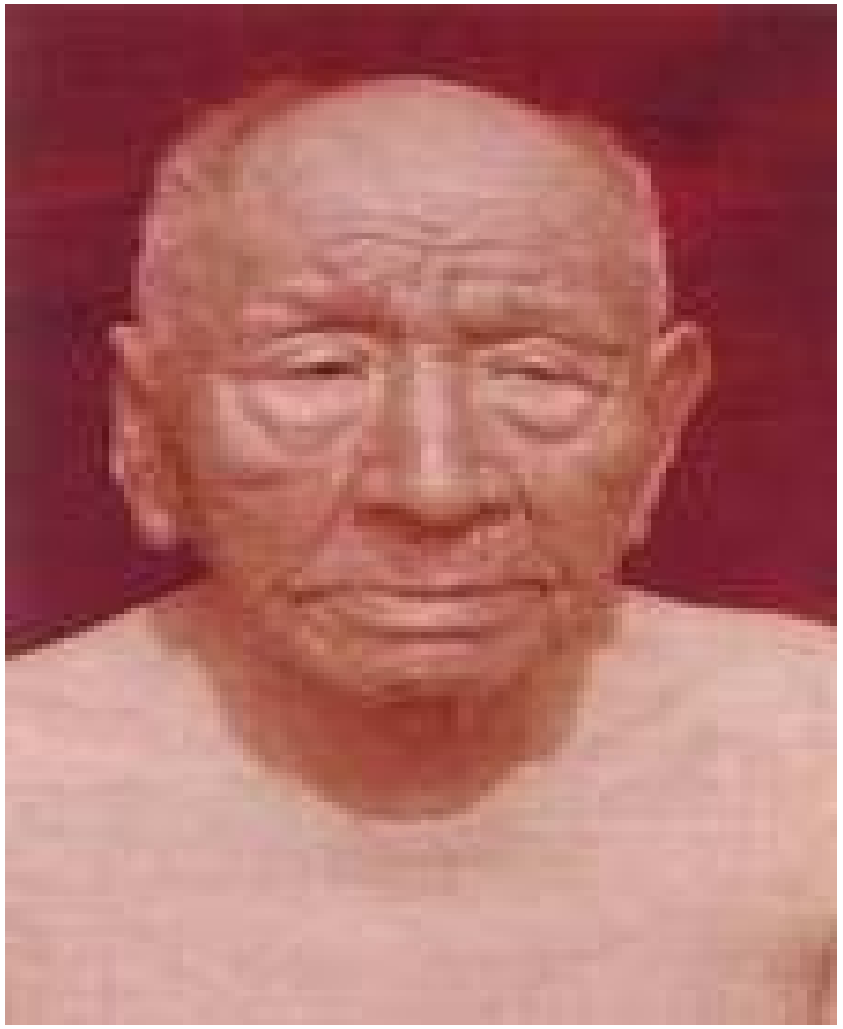


multiple hypopigmented patches





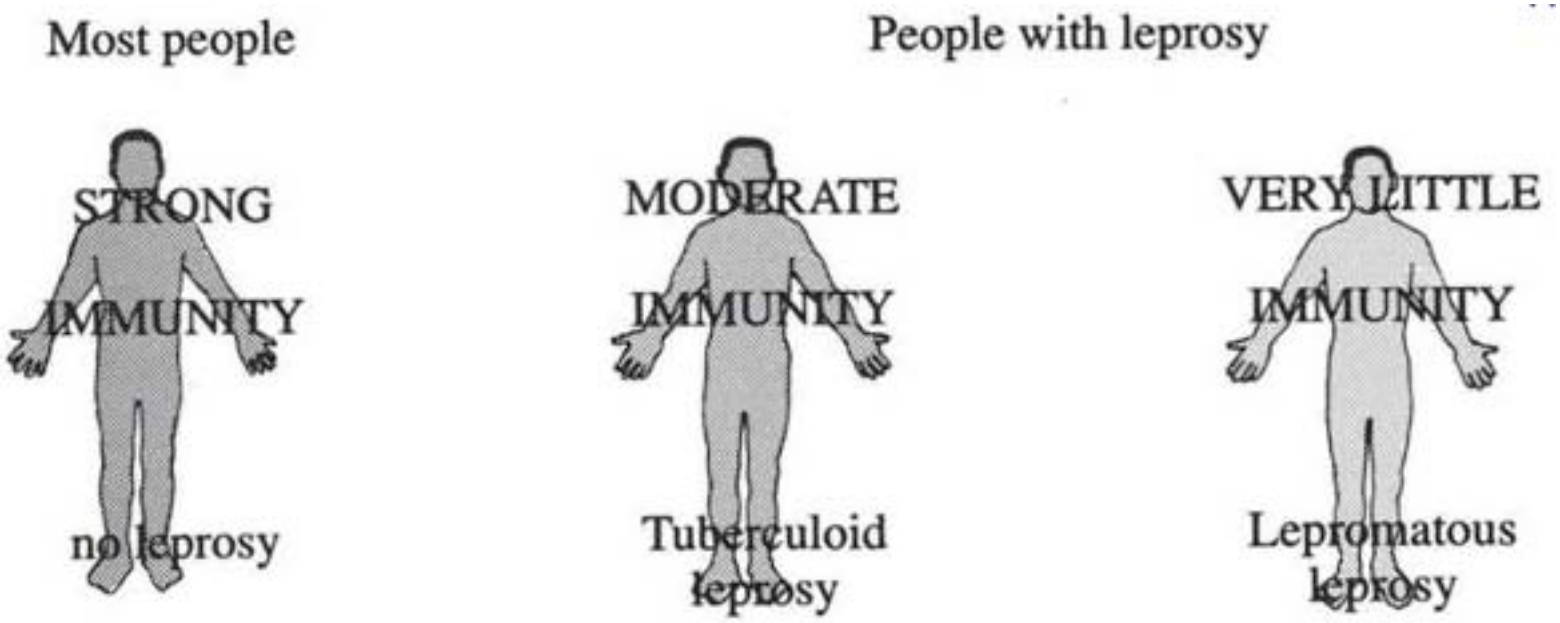
serious deformities caused by Leprosy



Clinical manifestations of leprosy **depend on the nature of the host's immune response to infection** and range from

lepromatous leprosy (uncontrolled replication with nerve damage from high-titer infection) to

tuberculoid leprosy (nerve and organ damage predominantly from the host granulomatous immune response)



Leprosy is classified using the following categories:

.- **Tuberculoid (TT)**

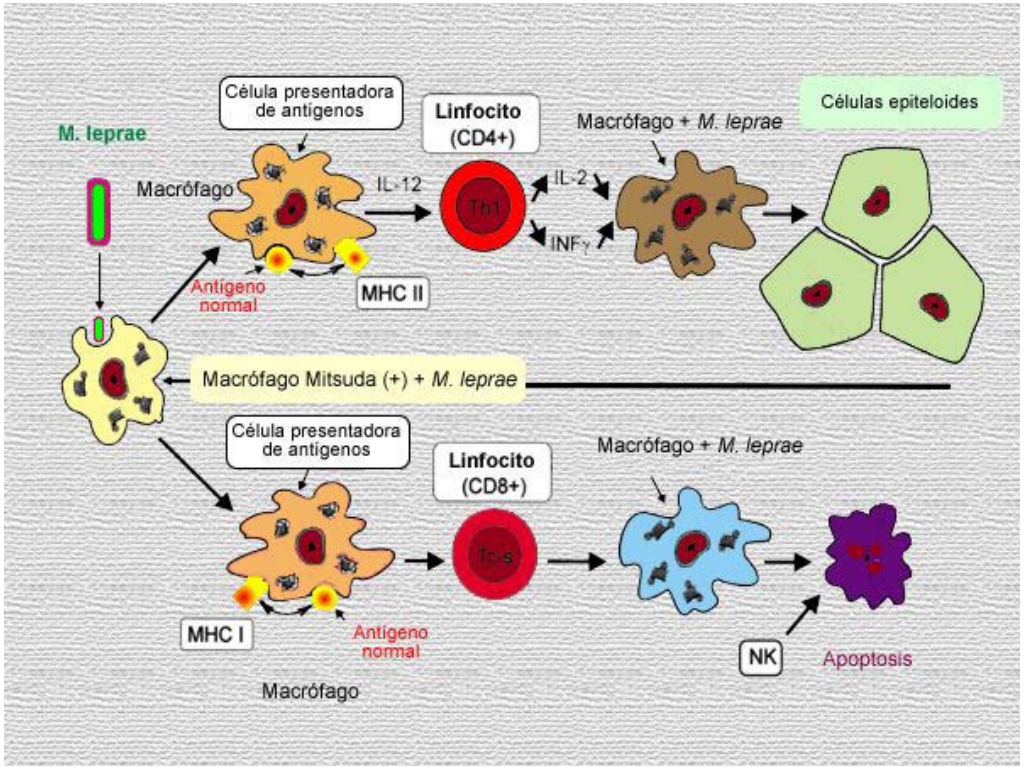
(a high degree of cell-mediated immunity and delayed hypersensitivity present with relatively few well-demarcated lesions)

.-**Borderline Tuberculoid (BT)**

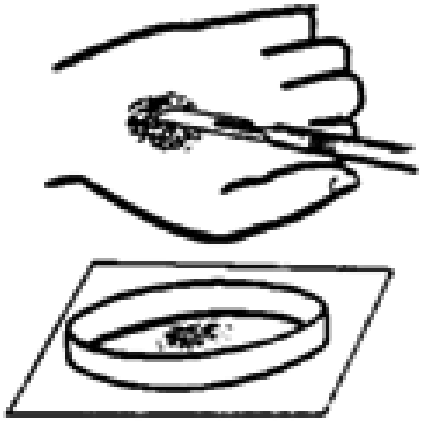
.-mid-borderline (BB)

.-Borderline Lepromatous (BL)

.-Lepromatous (LL)



(no apparent resistance to M. leprae present on the lepromatous end of the spectrum with numerous, poorly demarcated lesions)



taking a 'split skin smear' from a skin patch

Performance of PCR for detection of *M. leprae* DNA in urine

Leprosy status	Positive	Negative	Positivity (%)
Lepromatous	4/11	7/11	36.4
Tuberculoid	2/5	3/5	40
All	6/16	10/16	37.5
Healthy	0/8	8/8	0
Untreated	2/10	8/10	20
Treated	4/6	2/6	66.7

REACTIONAL STATES

Lepra reactions comprise several common immunologically mediated inflammatory states that cause considerable morbidity.

Type 1 Lepra reactions

In patients with borderline (BT, or TT) forms of leprosy but not in patients with pure lepromatous disease.

When precede the initiation of appropriate antimicrobial therapy, they are termed **downgrading reactions.** When they occur after the initiation of therapy, they are termed **reversal reactions**

Type 2 Lepra Reactions: Erythema Nodosum Leprosum*

Occurs exclusively in patients near the lepromatous end of the leprosy spectrum (BL-LL), affecting nearly 50% of this group.

***Erythema Nodosum** may precede leprosy diagnosis and initiation of therapy or follows the institution of chemotherapy

The most common features of ENL are crops of painful erythematous papules that resolve spontaneously in a few days to a week

Fever and malaise.

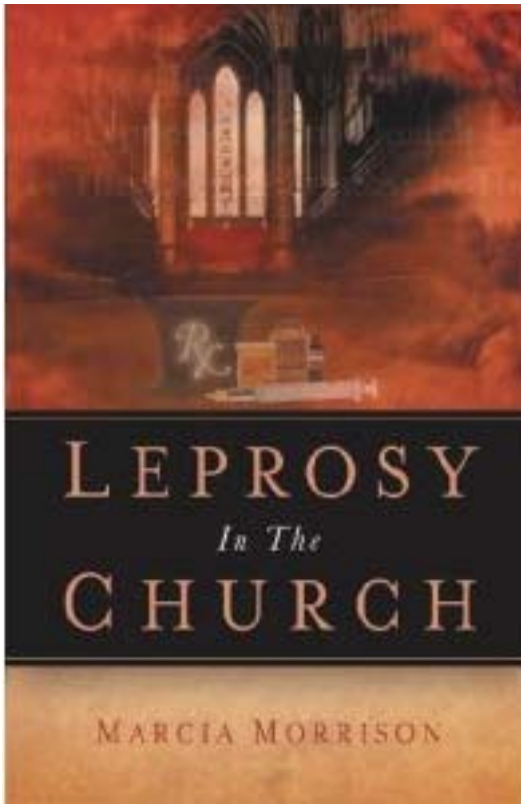
Lepra and The Bible

The disease most often cited. A feared disease in ancient times, and was a sick disgusting and unclean “unpure”.

Always seen as a punishment from God, ("God damned”)

The Old Testament had much legislation on leprosy. Only priests were responsible for determining their healing.

The lepers had to be separated from family and community and live isolated in caves and could not get close to the cities



The fact that Jesus approached and touched the leper was considered a violation of religious law

Many miracles are based on curing leprosy and some people believe that to strengthen their faith could improve their immunity and reestablish

Lepra and Dr. House

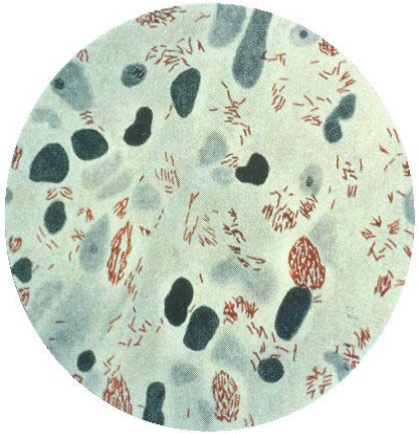
Chapter 13 serie 1 "The curse"

About a child that suffers a kind of deterorati
of clinical condition and skin lesions

Only at the end his father recognizes that hac
been long time ago in India following a "guru

and passed it to his son years later ….

TAKE HOME MESSAGES
(Leprosy in the XXI century)



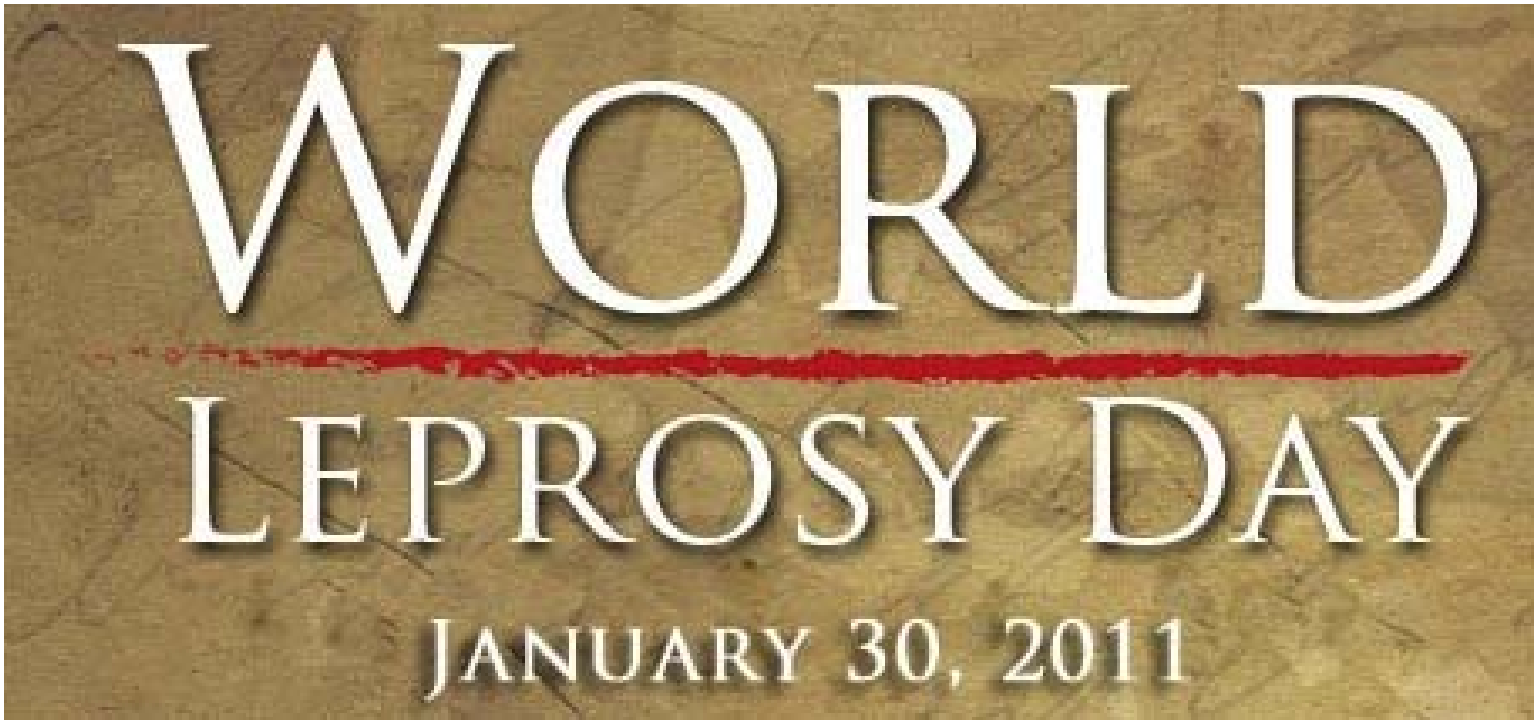
.- all over the world…

.- until 40 years latency…

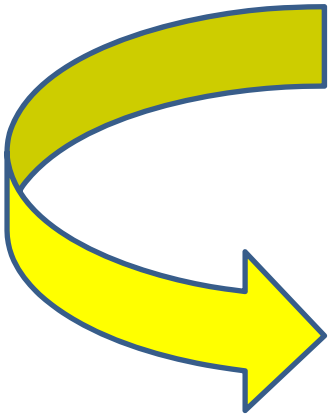
.- very different skin lesions…

.- mind with erythema nodosum..

.- biopsy and smear the diagnostic key…


WORLD
LEPROSY DAY
JANUARY 30, 2011

TRATAMIENTO agosto 2011

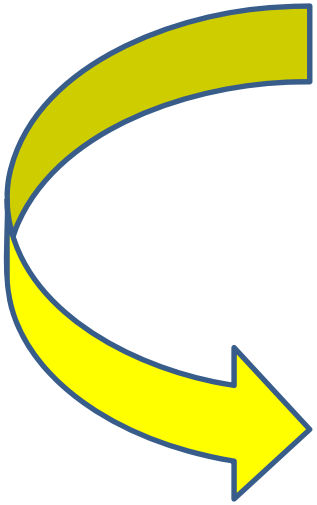


Rifampicina 600 mg al dia
Clofazimina 100 mg 1 comprimido días alternos
Dapsona 100 mg al día

Prednisona 20 mg al dia

Omeoprazol 20 mg 1 comprimido al día
Neurontin 600 mg (1-1-1)
Neurontin 300 mg (0-0-1)
Septim forte 1 comprimido cada 12h Sabado y Domingo

TRATAMIENTO septiembre 2011

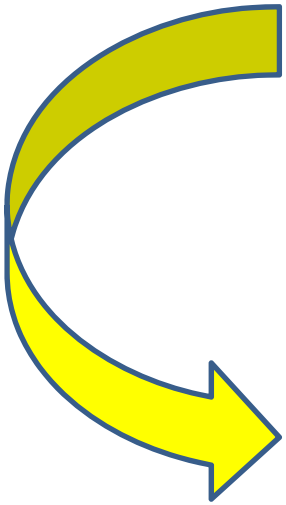


Rifampicina 600 mg al día
Dapsona 100 mg al día
Ofloxacino 400 mg cada 12h

Prednisona 1 mg/kg al día recidivando al descender la dosis a 0.5 mg/kg/día

TRATAMIENTO noviembre 2011

nuevo brote →



Nuevo brote de lesiones cutáneas dolorosas
+
Fiebre, astenia y anorexia (72horas)

No proceso infeccioso concomitante
A la EF: nódulos con superficie eritematosa en muslos , piernas , antebrazos y espalda
No úlceras, no púrpura.
Dolor en región maleolar derecha: inflamación del ciático poplíteo ext

Talidomida + anticonceptivos

PLAN AL ALTA:

Rifampicina 600 mg/día
Dapsona 100 mg /día
Ofloxacino 400 mg/12h

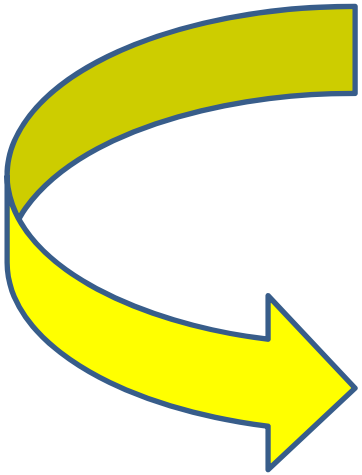
Talidomida 100 mg durante 10 días y luego (2.0.1)

Prednisona 10 mg (2.0.0) hasta el 21 Nov
Prednisona 10 mg (1.0.0) hasta el 24 Nov
Prednisona 10 mg días alternos

Septrim + Neurontin

En DIC 2011 se suspende tratamiento con Septrim y prednisona

TRATAMIENTO EVOLUCIÓN ENERO 2012



Baciloscopia en oreja , codo y pierna

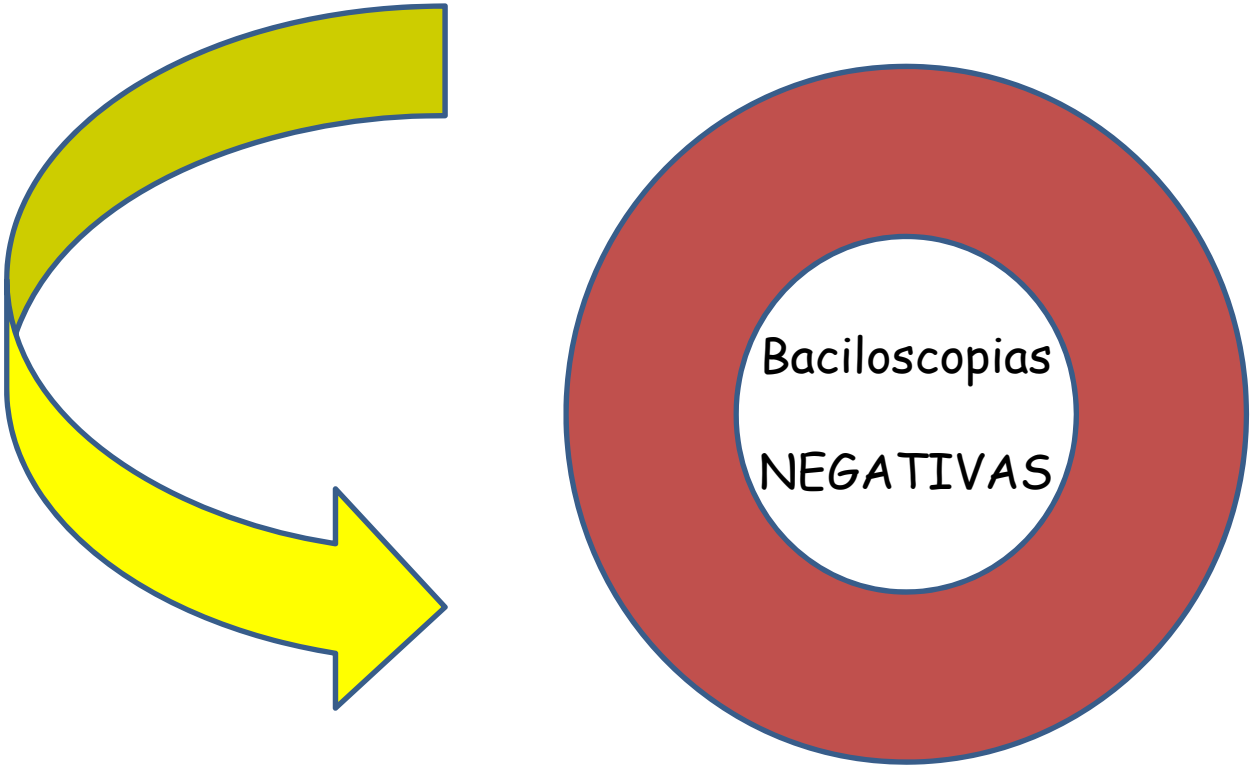
POSITIVA

Rifampicina + Ofloxacino + Dapsona
+
Talidomida 150 mg

marzo 2012

Neurológicamente bien ; alguna lesión cutánea nueva

TRATAMIENTO EVOLUCIÓN ABRIL 2012



MISMO TRATAMIENTO
REVISION EN 6 MESES

- Casi exclusivo de países en vías de desarrollo
  Asia , America y latinoamerica
  0,6-8 mill de individuos afectados
  600000 casos nuevos por año

- Incidencia máxima : 20-30 años
  Afectación varón-mujer 2:1

- Transmisión: via dudosa
  - Gotitas nasales
  - Suelo
  - Insectos vectores.

En países endémicos : existe un 10% de posibilidades de contagio por contacto domestico

En países no endémicos: un 1% de posibilidades.

CLINICA

- Periodo de incubación 2- 40 años(lo más frecuente 6-7 años)
-variedades:
    - Tuberculoide polar (TT)
    - Tuberculoide limitrofe (BT)
    - Tubercuolide Semilimitrofe (BB)
    - Lepromatosa limitrofe (BL)
    - Lepra lepromatosa polar (LL)

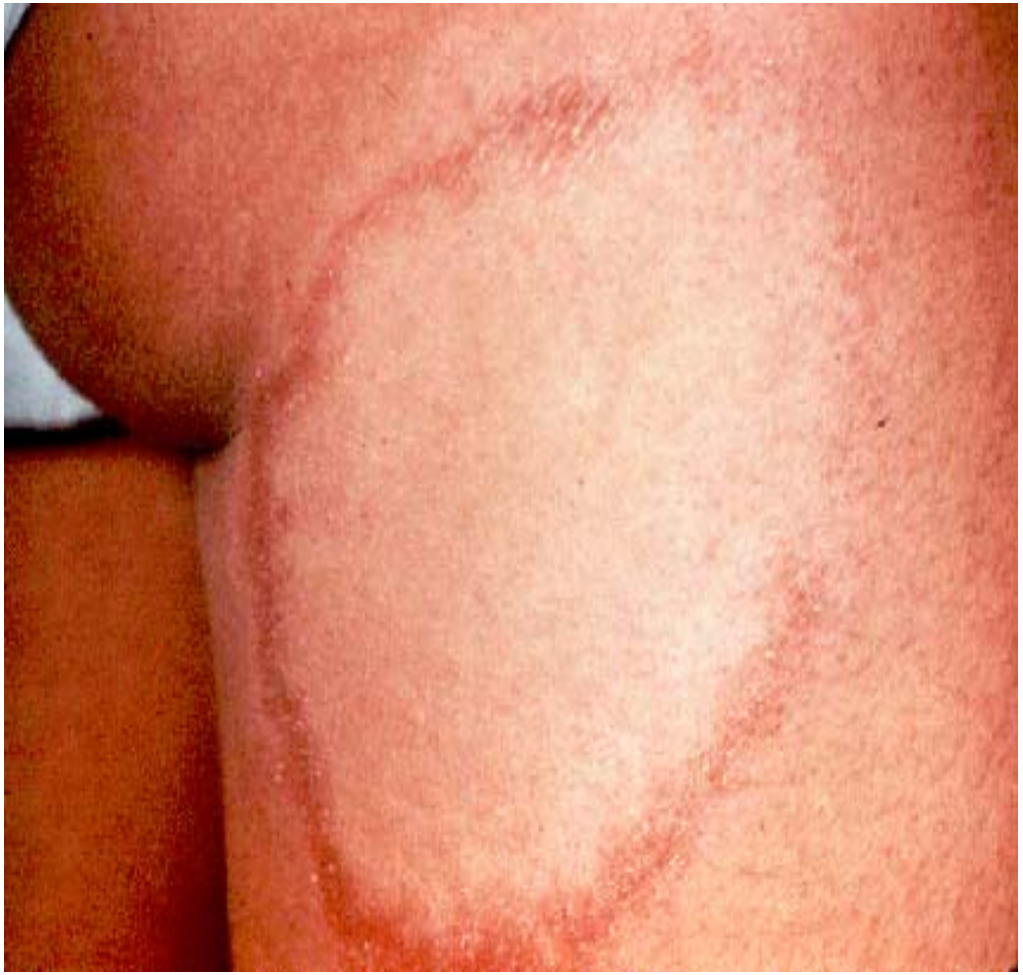
a)FORMA TUBERCULOIDE (TT y BT) Africa e India

-Menos grave ;
-Síntomas dermatologicos:

máculas o placas hipopigmentadas hipoestésicas , con bordes eritematosos , carentes de glandulas sudorípadaras y foliculoso pilosos

-Síntomas del sistema nervioso periférico:

Engrosamiento de nervios perifericos sobre todo:
-Cubital - ciático popliteo externo
-Retroauricular - tibial pos terior



Tuberculoid lesion with a raised, well defined margin.
Courtesy of James L Krahenbuhl, Phd and Robert R Jacobson, MD, PhD.

1.Las células T desgarran el perineuro y destruyen las células de Schwann
2. Fibrosis del epineuro y sustitución del endoneuro por granulomas y necrosis caseosos

¡! OTROS DATOS: PPD positivo
La proporcion cd4: cd8 es de 2:1

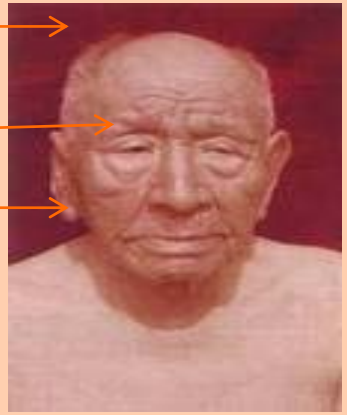
b) FORMA LEPROMATOSA

-Distribución simétrica de nódulos cutáneos

-Placas elevadas o infiltración difusa de la dermis

-<u>Signos típicos:</u>

- **Facies leonina**
- **Pérdida del borde lateral de cejas y pestañas**
- **Lóbulos de orejas péndulas**
- **Piel seca**



-se aislan bacilos en :

- Cualquier órgano excepto:
  - pulmones y SNC

-PPD negativo ; proporción cd8:cd4 2:1

- Principales sintomas afectan a:

1.Neuropatia distal y simetrica
2.Afectación de vias respiratorias superiores
3.Afectación de la cámara anterior del ojo
4.Afecatción testicular

b) Reacciones de tipo 2 ERITEMA NODOSO LEPROSO

- Ocurren únicamante en el extremo lepromatoso
- Pueden ocurrir antes del tratamiento , pero en el 90% ocurre al iniciar la terapia
- Los síntomas habituales suelen ser:
  - Malestar general
  - Fiebre intensa
  - Lesiones eritematosas
  - Nódulos dolorosos
  - Anemia , leucocitosis
  - Elevación de transaminasas

  -neuritis
  -adenitis
  -uveitis
  -orquitis
  - glomerulonefritis
- Biopsia: signos de paniculitis o vasculitis. Exceso de PMN.

•Ojo!!!

- Fenómeno de Lucio: en pacientes del Caribe; brotes de úlceras bien delimitadas.

Biopsia isquemia de epidermis y dermis superficial.

- **COMPLICACIONES DE LA LEPRA:**

a) **NEUROPATIA:**

↳ que afecta a

HIPOSTESIA

↳ y respeta a

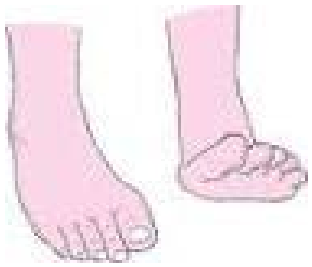
Tacto discrimatorio
Dolor
Receptores del calor

Sensibilidad vibratoria
Sensibilidad postural

📖 El nervio mas afectado es el cubital -> **mano en garra**

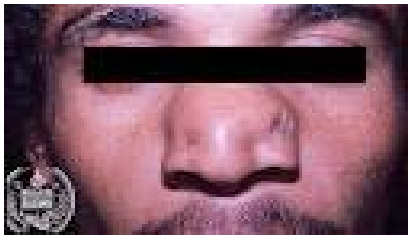
📖 El 2° mas afectado es el ciático poplíteo externo

→ **Pie péndulo**



- Úlceras en los metatarsianos

b) NARIZ



En la LL : invasión de mucosa nasal

epistaxis

destrucción del cartílago nasal (nariz en silla de montar)

anosmia

c) OJOS

Lagoftalmia e insensibilidad corneal por parálisis de pares craneales.

En la LL: cámara anterior invadida por bacilos

- uveitis cataratas o glaucoma

En la lámpara de hendidura imagen de córnea en rosario.

d) TESTICULOS

En la LL : orquitis

Se produce aumento de LH y FSH ; disminución de testosterona
aspermia o hipospermia

e) AMILODOSIS

En la LL : hepática y renal

f) ABSCESOS DE LOS NERVIOS

En las formas de BT.

Sobre todo afecta al cubital

DIAGNÓSTICO

Biopsia

Ojo!!!!!!:

- En la LL se produce ☐ hiperglobulinemia difusa

que provoca *ANA , VDRL falsamente positivos*

- En la forma tuberculoide las lesiones a v

  - Son atípicas
  - No son hipostesicas
  - No contienen granulomas

DX con 2 de 3

ANTICUERPO CONTRA ANTIGENO GLICOLIPIDO FENÓLICO

- En la LL un 95% tiene AC a

sin embargo sólo el 60% de las tuberculoides los tienen

TRATAMIENTO

- Dapsona (50-100 mg/dia)
- Clofazimina (50-100 mg/dia, 100 mg tres veces por semana 0 300 mg al mes)
- Rifampicina (600 mg al dia o mensulaes)

DAPSONA

- En monoterapia origina recidivas
- Si déficit de Deshidrogenasa 6P hemólisis

A pesar de no tener déficit Hb baja 1 pto por 100ml

clofazimina

- coloración rojo oscuro de la piel

Recomendaciones de la OMS:

Pacientes con < 5 lesiones cutáneas - >paucibacilares

- Dapsona 100 mg dia
- rifampicina 600 mg mes

6 meses

Pacientes con 6 o más multibacilares 1 año

- Dapsona 100 mg dia
- clofazimina 50 mg dia
- rifampicina 600mg/mes
- clofazimina 300mg mes
- Dapsona 100 mg /mes

- Tratamiento de reacciones tipo 1

Prednisona 40-60 mg día mínimo 3 meses si neuritis o importante inflamación con riesgo de ulcerar

- Tratamiento reacciones tipo 2

Prednisona 40-60 mg día durante 1-2 semanas

Talidomida 100-300 mg día ojo !! con embarazos