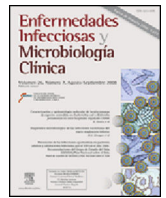




# Enfermedades Infecciosas y Microbiología Clínica

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## Scientific letter

### Management and clinical experience in Hansen disease's type 2 reaction in four cases<sup>☆</sup>



#### Manejo y experiencia clínica en eritema nudoso leproso en 4 casos

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, an intracellular microorganism bound with great tropism by the skin and peripheral nervous system. The classification system of Ridley and Jopling<sup>1</sup> describes 5 forms of disease based on the clinical, microbiological, histological and immunological characteristics of the patient; it establishes lepromatous leprosy (multibacillary form) and tuberculoid leprosy (paucibacillary form) as the 2 polarised ends of the clinical spectrum. Leprosy reactions are acute exacerbations of Hansen's disease (HD)<sup>2</sup> described in 30–50% of patients and are responsible for the mortality associated with this disease. Classically, 2 forms have been described: the type 1 or upgrading reaction, and the type 2 reaction or erythema nodosum leprosum (ENL).

We present 4 cases of ENL treated in our department from March 1999 to May 2019 (Table 1). They involve 3 males and one female, with a median age of 39 years. The diagnosis and follow-up of the ENL was carried out in our centre in all cases. Cases number 3 and 4 originated in Brazil, and the latter referred to a diagnosis of HD in a second-degree relative, while cases 1 and 2 were patients with non-imported HD. In 2 of the cases, the ENL presented as a form of disease onset without having yet started treatment with targeted multitherapy (MDT). In all of them, the skin examination showed multiple erythematous, indurated, painful nodules in the upper and lower extremities. Case 3 also presented fever, weight loss and watery rhinorrhea. The diagnosis of a pancreatic neoplasm, the implantation of a levonorgestrel releasing intrauterine device and the onset of MDT are the identifiable factors as possible triggers in these patients. The histological study of the lesions showed the presence of neutrophils (4/4), leukocytoclasia (2/4) and inflammatory infiltrate in the adipose panicle (4/4). Ziehl–Neelsen staining showed the presence of acid-alcohol resistant bacilli (AARB) in 2 cases. After diagnosis, all patients began

**Table 1**  
Clinical–epidemiological characteristics and classification of ENL cases.

	Case 1	Case 2	Case 3	Case 4
<i>Epidemiological characteristics</i>				
Sex	Male	Male	Female	Male
Age	45 years	41 years	25 years	37 years
Country of origin	Spain	Spain	Brazil	Brazil
Immunosuppression	No	Yes (HIV)	No	No
Family history of Hansen's disease	No	No	No	Yes (2nd degree relative)
Hansen's disease (year of diagnosis)	Multibacillary (1999)	Multibacillary (1992) (diagnosis in another centre)	Multibacillary (2011)	Multibacillary (2017)
Clinical cutaneous location of ENL	Upper limbs	Upper and lower limbs	Upper and lower limbs	Upper and lower limbs
<i>Histological characteristics in biopsy compatible with ENL</i>				
Ziehl–Neelsen staining	+++	Negative	+++	Negative
Neutrophils	Yes	Yes	Yes	Yes
Vasculitis	Not described	Yes	Yes	No
Panicle involvement	Yes	Yes	Yes	Yes
Treatment for Hansen's disease (start of treatment)	United States regimen (1999)	Unknown regimen (1992)	United States regimen (2011)	WHO regimen (2017)
Onset time of ENL in relation to treatment with polychemotherapy	Starting form (pretreatment)	Post-treatment	Starting form (pretreatment)	Intra-treatment
ENL specific treatment	Systemic corticotherapy Thalidomide	Systemic corticotherapy Thalidomide	Systemic corticotherapy Thalidomide	Systemic corticotherapy
ENL classification <sup>a</sup>	Chronic	Chronic	Chronic	Chronic
Predisposing factors	–	Pancreatic neoplasia	IUD	–

IUD: intrauterine device; ENL: erythema nodosum leprosum; WHO: World Health Organisation.

<sup>a</sup> World Health Organization.<sup>3</sup>

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**Fig. 1.** Clinical manifestations of cutaneous type 2 lepra reaction. (A) Subcutaneous, indurated and painful nodule in the auricular pavilion. (B) Nodule on the extensor face of the arm. (C) Erythematous oedematous plaques with central vesiculation, similar to erythema multiforme. (D) Violet-coloured erythematous papules that can evolve to necrosis and ulceration.

treatment with systemic corticosteroids (0.5 mg/kg/day), with case 3 requiring intravenous treatment at a higher dose. Given the strong tendency to recurrence, thalidomide treatment (200–400 mg/day depending on weight) was initiated in 3 of them, ignoring the evolution of case 1, due to loss to follow-up. As an adverse effect, drowsiness and the feeling of dizziness-instability were frequent at the beginning of treatment and with subsequent development of tolerance. In case 2, thalidomide was started at a dose of 400 mg/day, maintaining the same dose until clinical control, with a subsequent decrease of 50 mg/day every week, until complete suspension. In case 3, the patient experienced amenorrhoea at the beginning of treatment; she started at a dose of 200 mg/day that is currently maintained owing to recurrence if suspended. During follow-up, serial smears were performed with strictly negative results in all patients.

A type 2 lepra reaction is an acute inflammatory condition characteristic of multibacillary forms.<sup>4</sup> Leprea reactions occur as a result of the imbalance between the patient's immune system and the mycobacterium produced, in many cases, by the initiation of the targeted antibiotic treatment; however, multiple causes have been documented as triggers (drugs, infections, pregnancy, contraceptive treatment). Underlying type 2 is a Gell and Coombs type III hypersensitivity mechanism,<sup>4,5</sup> with the formation of circulating immunocomplexes that are deposited in the vascular wall. Subsequently, polymorphonuclear recruitment occurs<sup>6</sup> in addition to the subsequent leukocytoclastic vasculitis that can affect multiple organs and tissues (fever, arthritis, osteitis, myositis, iridocyclitis, rhinitis and the characteristic neuritis). Depending on the cutaneous tissue damage, we can find (Fig. 1) erythematous macules, erythema multiforme-like lesions, subcutaneous nodules, extensive purpura or even necrotic areas (Lucio phenomenon,

typical of patients with diffuse lepromatous leprosy).<sup>7,8</sup> The treatment includes the non-suspension of MDT, the prevention of new outbreaks by avoiding triggers (precaution with hormonal contraception) explaining the situation to the patient, and avoiding therapeutic abandonment. Systemic corticosteroids should be used at doses of 0.5–1 mg/kg/day, with a decrease of 10 mg/every 15 days and, in the case of cortico-dependence or no response, thalidomide<sup>9</sup> can be used as first-line treatment (with the mandatory combination of dual contraception in women of childbearing age). Effective alternatives include clofazimine and the use of anti-TNF in isolated cases published with good response.<sup>10</sup>

The duration of the ENL is not established, and it can occur before, during and up to several years after the end of the MDT treatment, so it should be considered as a complication of the disease in the control and long-term follow-up of these patients.

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## Spinal infection caused by a defective strain of *Streptococcus intermedius* diagnosed by multiplex-PCR<sup>☆</sup>



### Infección espinal por una cepa defectiva de *Streptococcus intermedius* diagnosticada mediante PCR multiplex

We present a case of spinal infection due to a defective strain of *Streptococcus intermedius*, whose diagnosis was facilitated by the use of multiplex PCR.

The patient was a 70-year-old male with type 2 diabetes mellitus admitted for 15-day low back pain with deterioration of his general condition and fever. He denied previous trauma. On examination, he presented pain on palpation in the lumbar spine with negative sacroiliac maneuvers, and in the analysis, he presented leukocytosis of  $23.9 \times 10^9/l$  (84.2% neutrophils) with C-reactive protein of 23.24 mg/dl. Empirical treatment with ceftriaxone was initiated.

The MRI performed 2 days later showed images compatible with erosive septic arthritis of the left interapophyseal lumbar facets at L4–L5 level and several epidural and paravertebral collections compatible with abscesses. Surgery was performed to drain the paravertebral collections, and samples were sent to microbiology.

Gram staining showed a high number of polymorphonuclear leukocytes, but no microorganisms. Cultures were made on agar-blood and agar-chocolate plates (incubated in CO<sub>2</sub>), Schaedler medium (anaerobiosis) and enriched thioglycolate broth. After 18 h of incubation no medium showed growth, so a portion of the sample was diluted with physiological serum and a multiplex PCR was performed (BCID, FilmArray<sup>®</sup>, Biofire), with a positive result for *Streptococcus* spp., being negative for *S. pyogenes*, *S. agalactiae* and *S. pneumoniae*.

After 48 h of incubation, all solid media remained negative and a Gram stain of the thioglycolate broth showed gram-positive cocci in chains, despite which no growth was obtained in the subcultures to solid media.

On suspicion of a nutritionally deficient strain, new subcultures of the broth were made, placing paper discs (BBLTM TaxoTM) impregnated with 0.001% pyridoxine hydrochloride on the plates. After nocturnal incubation, satellite colonies appeared around the discs (Fig. 1).

A portion of the thioglycolate broth was inoculated in a vial of anaerobic blood culture (BD BACTEC Plus Anaerobic/F), which showed growth at 33 h of incubation. After subcultures of this vial, sufficient growth was achieved in the habitual media, without the need to be supplemented for the subcultures or for carrying out the identification and antibiogram tests.

Identification was made using the API<sup>®</sup> 20 Strep system (bioMérieux), with a 91.2% success rate for *S. intermedius*, coinciding with that obtained by MALDI-TOF (Bruker) and was confirmed at the National Centre for Microbiology.

In the antibiogram with discs and gradient strips, the strain showed sensitivity to penicillin G, amoxicillin, cefotaxime, erythromycin and clindamycin.

This microbiological finding led to the suspicion of an odontogenic origin of the infection, consulting with the maxillofacial surgery department, which proceeded to extract 7 affected teeth. A transesophageal echocardiogram ruled out the existence of vegetation. The patient evolved favorably, with resolution of the condition after treatment with ceftriaxone IV for 20 days and subsequently oral amoxicillin, until 6 weeks were completed.

*S. intermedius* is part of the oropharyngeal microbiota, the gastrointestinal tract and the genitourinary tract.<sup>1</sup> More than 40% of clinical isolates come from dental plaque, with haematogenous spread having been reported in both surgical and conservative procedures,<sup>2</sup> and is a major cause of serious infections, including

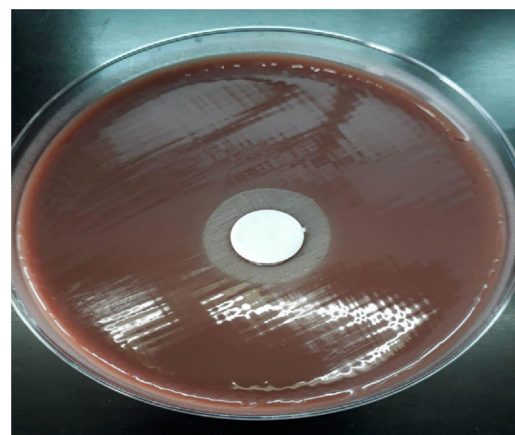


Fig. 1. Agar-chocolate plate showing satellitism around a disk impregnated with 0.001% pyridoxine hydrochloride.

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