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Case Report Open Access

A case of borderline leprosy revealed by immunosuppressive treatment for systemic lupus erythematous

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Abstract

Leprosy, or Hansen's disease (HD), is an endemic mycobacterial infection caused by acid-fast bacilli (*M. leprae complex, including M. leprae e M. lepromatosis*) mainly involving the skin and the peripheral nerves. The means of transmission is not fully understood; individuals with sufficient exposure and susceptibility to *M. leprae complex* may develop a broad range of clinical manifestations, which vary depending upon the host's ability to mount an acquired immune response to infection. The spectra of immunological mechanisms can make the symptoms and lab findings similar to those of connective tissue disorders. Here we report a case of 31-year-old man, traveling from Ghana to Italy in 2016; the initial clinical findings (bullous erysipelas of the hands and hypotrophy of the hypotenar region with the flexion of the fourth and fifth proximal interphalangeal joints) suggested Hansen's disease, but unfortunately, the skin biopsies were negative for mycobacteria. Afterwards, over the following six years, the biochemical and hystopathological data together with the symptoms developed by the patient, have been evaluated separately by the various specialists (dermatologists, rheumatologists and nephrologists), with final diagnosis of lupus. From here, clinicians started immunosuppressive treatment, without any clinical improvement. The absence of acid-fast bacilli in the skin biopsies and the lack of neurological manifestations (like loss of sensitivity) delayed the diagnosis until the general conditions of the patient worsened (increase of proteinuria, generalized oedema, recurrence of skin ulcers, appearance of annular lesions on the back); he was transferred to Referral Hospital to be tested for polymerase chain reaction (PCR). The clinical, serological and histological similarities between leprosy and autoimmune diseases may lead to erroneous and delayed diagnosis, with potential clinical and emotional sequelae requiring long-life care.

Keywords: mycobacteria, skin ulcers, membranous glomerulonephritis, connectivitis, traveller, PCR

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Introduction

Leprosy is a chronic granulomatous disease caused by infection of *Mycobacterium leprae/lepromatosis*, mainly involving the skin, the peripheral nerves and mucosa of the upper respiratory tract [1,2]; however, the clinical picture is highly related to individual's immune response. The respiratory route is probably the main vehicle of transmission; nasal discharge from untreated patients with lepromatous (multibacillary) disease frequently contains large numbers of bacilli [3,4].

Individuals with sufficient exposure and susceptibility to *leprosy* may develop a broad range of clinical manifestations, which vary depending on the host's ability to mount an acquired immune response to infection [5,6]; the full-blown disease is preceded by a long period of incubation (from 5 to 20 years), and its multisystemic nature makes the diagnosis challenging, especially in non-endemic contexts.

Leprosy is still considered a highly neglected tropical disease. Despite the efforts for elimination and the availability of treatment since 1981, it remains prevalent in many regions of the world (mainly Brazil, India and Indonesia but it is still transmitting in more than 120

countries); 174.087 new cases are reported in 2022, increasing by 23% compared with 2021. With increasing international travel, patients are now diagnosed everywhere in the Western world, often after a long delay[2, 3]; generally, very little attention is paid to leprosy in the medical training; the non-awareness, even among the specialists who may see patients at second or third level, is the main reason for misleading the diagnosis.

Case Presentation

We describe a case of 31-y-old man traveling from Ghana to Italy in 2016. At the arrival, the patient complained bullous erysipelas of the hand and the medical files reported hypertension. Given the retractile aspects of the hands and some hypo-pigmented areas, clinicians have started investigations to rule out leprosy, although sensitivity was preserved. The first skin biopsy was not conclusive, excluding acid-fast bacilli and granuloma. (See Figure 1). Therefore, the patient started the routine health screening for asylum seekers to detect communicable diseases.

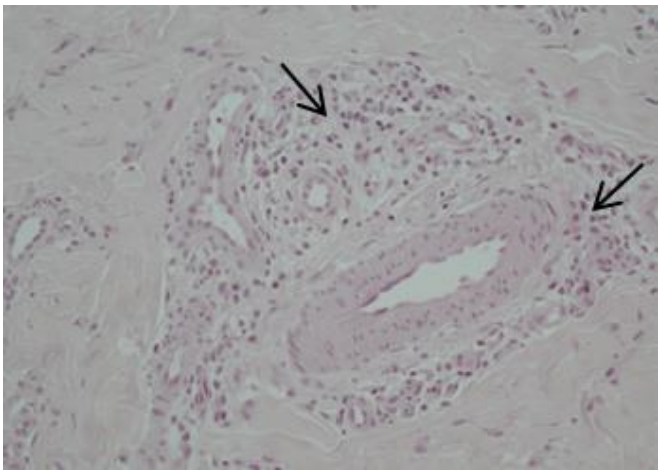

Figure 1: skin biopsy with perivascular infiltrates

To exclude tuberculosis, clinicians performed a thoracic CT scan and it showed bullous dystrophy of the lungs, multiple lymphadenopathies and hepatic calcifications (see Figure 2). Then, the bronchoscopy did not show acid-fast bacilli or other signs of mycobacterial infection; indeed, they proceed with surgical biopsies (lung and lymph nodes) were done, showing chronic non-granulomatous lymphadenitis, but still not acid-fast bacilli were found (see Figure 3 and 4). Regarding the lab tests, we detected ANA antibodies, consumption of complement, LAC, nephrosic proteinuria; the other clinical findings (Raynaud's phenomenon, skin nodules) also supported the hypothesis of connectivitis; therefore, nephrologists started treatment with colchicine, hydroxychloroquine and low dosage of corticosteroids. However, during the following weeks, we observed increase of proteinuria, appearance of skin ulcers and peripheral oedema; given this clinical worsening, renal biopsy showed membranous glomerulonephritis (see Figure 5).

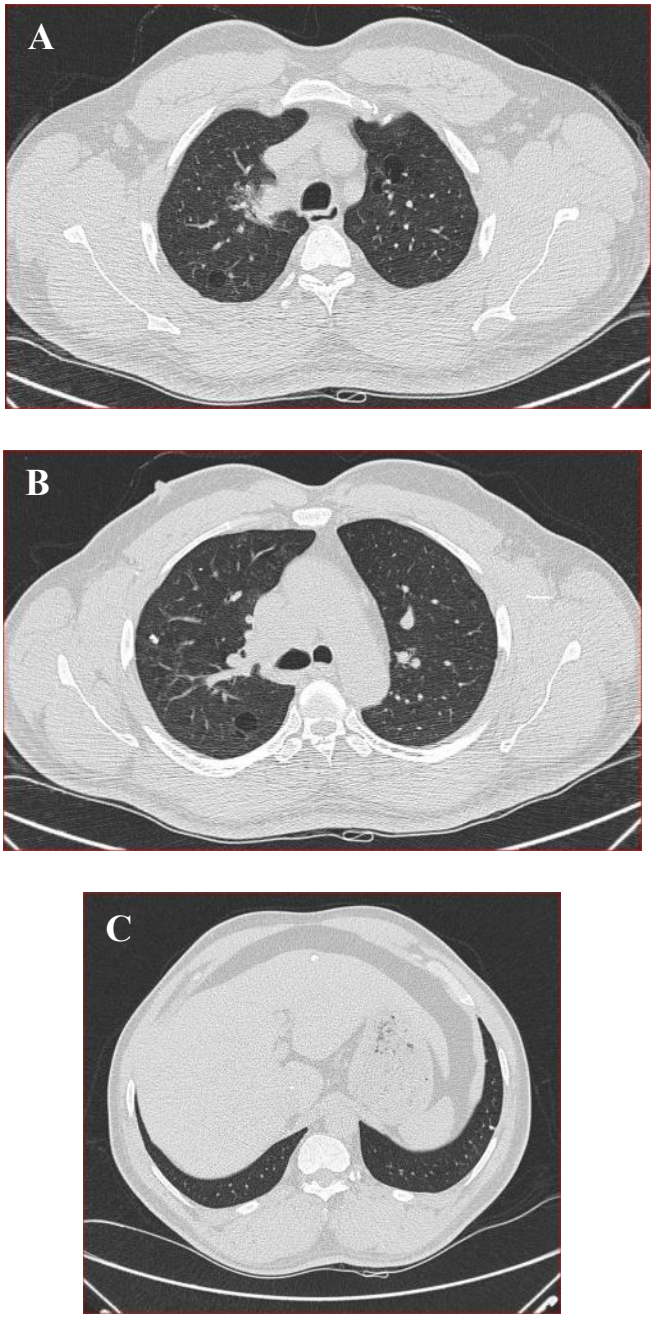

Figure 2. A. lymphatic tissue in Barety space with associated-pneumonia and bullous dystrophy in transverse CT section. **B.** another transverse CT section showing enlarged lymphadenopathies in Barety space. **C.** hepatic calcifications in transverse CT section.

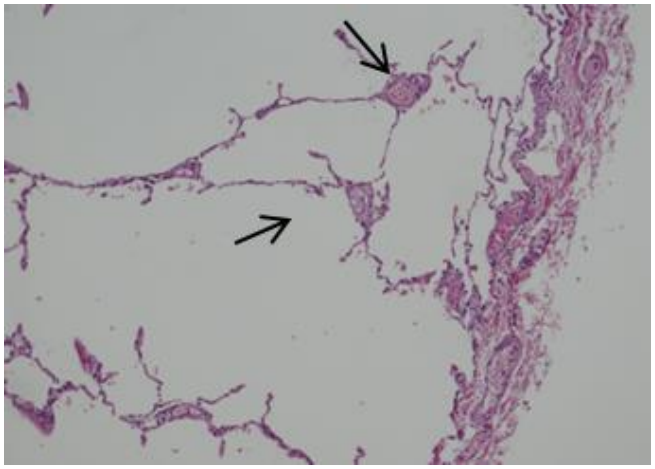

Figure 3: lung with haemorrhagic alveolitis and emphysema.

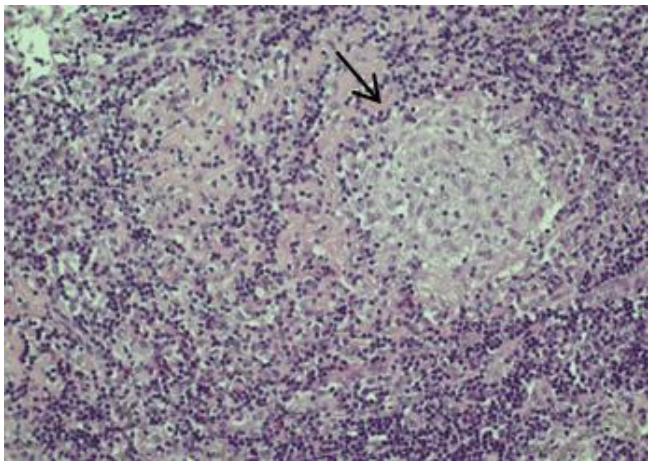

Figure 4: lymph node biopsy with granuloma

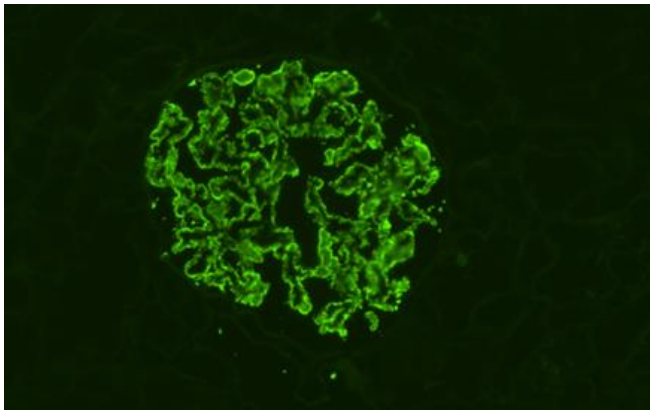

Figure 5: histochemistry technique showed membranous glomerulonephritis in 5 – 6 glomeruli (parietal granular model of high intensity for IgG, weak/moderate for C3, weak for IgM and C1q, traces for IgA).

Indeed, the definitive diagnosis of lupus was established and the initial empiric treatment was replaced by a combination of immunosuppressive drugs (mofetil mycophenolate, methotrexate, and increased dosage of steroids). However, the conditions were worsening during the last admission in the hospital, and many annular desquamative lesions appeared in the back; despite the absence of bacilli in all biopsies performed over time, clinicians reconsidered leprosy once more. The patients was sent to the Referral Centre where the diagnosis of leprosy borderline group) was possible only by PC of skin lesions, while the direct examinations for acid-fast bacilli was always negative; the final classification was borderline group B. The patient interrupted immunosuppressive treatment. Combination of dapsone, rifampicin and clofazimine has been effective to control the disease. During the following weeks, the patient was gradually improving, with reduction of oedema and healing of the ulcers; however, the complete functionality of the hands was not restored.

Discussion

The initial absence of typical symptoms (like loss of sensitivity) and lack of acid-fast bacilli in histological samples, associated with the heterogeneous and unstable manifestations typical of the borderline form, were misleading for clinicians, focused on connective tissue diseases. The patient has taken therapy for systemic lupus erythematous, refractory to glucocorticoids and immunosuppressive treatment. The differential diagnosis between leprosy and immune-mediated rheumatic diseases can represent a great challenge, since the infection can reproduce not only clinical manifestations but also laboratory findings [8]. Furthermore, rheumatic diseases and leprosy can also coexist: the immunosuppressive treatments (including biologic drugs) are the paradigm in the management of autoimmune and inflammatory conditions; however, to date, there are not consistent data or guidelines about assessment of leprosy before starting the treatment [7]. However, one of the challenges in diagnosing leprosy is simply to consider this disease in the list of differential diagnoses, particularly in non-endemic countries where leprosy is extremely rare [3]; unfortunately, the delayed diagnosis can cause irreversible damages that may require lifelong care. It is not uncommon to see patients been correctly diagnosed after years from the initial clinical evaluation, often after treatment for mistaken dermatological or rheumatic diseases, including lupus, sarcoidosis, scleroderma and various types of skin ulcers [9,10,11]. Many confounding

factors can play a crucial role, including laboratory data; for example, the pathogenic role of autoantibodies like rheumatoid factor (RF) and ANA is not clear but also can contribute to a misleading diagnosis[17]. The skin involvement can also be present in a variety of diseases, ranging from the most common (tinea corporis, Lyme's disease, psoriasis, erythema multiform, lichen planus) to a rare conditions (fixed drug eruptions, immunoglobulin A vasculitis, secondary syphilis, annular granuloma). Awareness among healthcare professionals (mainly the specialists involved in the diagnostic processes), should be supported and encouraged.

In the table 1 are resumed the most important diagnostic tools [3]; the sensitivity and specificity data are obtained from Bangladeshi and Indian cohorts (slit skin smear test and skin biopsy test) [12,13], or are result of systematic reviews and meta-analysis (lepromin, serological tests, PCR) [14,15]. it's important to remark that the accuracy of skin biopsy examination depends on several variables (for example the appropriate selection of the location for biopsy, the representative sample size, and the experience of the pathologist in leprosy examination) and it can be challenging if it is not performed by trained professionals in this particular field. The PCR has higher sensitivity and specificity, but is available only in reference centres. However, in non-endemic countries, PCR should be considered an essential diagnostic tool, because the scarcity of patients makes less reliable all the techniques that are depending of the operator's experience.

Table 1. Comparisons between the sensitivity and specificity among the various diagnostic tests for leprosy [3].

Diagnostic tests	Sensitivity (%)	Specificity (%)
Slit skin smear test	50	100
Skin biopsy test	49-70	70-72
Lepromin test	20-25 (low dose) 10-15 (high dose)	95-100 (low dose) 60-70 (high dose
PCR	67.9-81.5	91.4-96.5
Serological tests	55-71.8	86.9-93.9

Conclusion

The clinical and serological similarities between patients with leprosy and connective tissue disorders may lead to erroneous diagnosis and leprosy can imitate many different conditions [16]. Patients with leprosy can present with predominant rheumatic manifestations, refractory to glucocorticoids and immunosuppressive therapy, as we have shown in our patient. Leprosy has not been eradicated and misdiagnosis can be frequent; the correct identification of the disease can take several years, especially in non-endemic areas [9, 10]. It is necessary to increase medical practitioner awareness in order to reach an early diagnosis, start proper treatment and reduce the morbidity and irreversible sequelae [17].

Highlights

What Is Already Known?

The clinical and serological similarities between patients with leprosy and connective tissue disorders are many and various, and especially in non-endemic countries the diagnosis can be delayed for a long time, with important sequelae. Further confounding the distinction is the possibility that patients may truly have both disease concurrently, and leprosy can also act as a trigger for lupus reactivation; however, its associations is still not fully explored.

What Does This Study Add?

In special patient populations who are candidates for immunosuppressive therapies, it may be necessary to exclude the coexistence of lepromatous disease. Furthermore, especially in non-endemic countries and in selected cases, PCR is to be considered the reference diagnostic tool which allows shortening the diagnosis time and the risk of sequelae for the patient.

Authors' Contributions

All authors contributed equally to this study.

Conflict of Interest Disclosures

The authors declared no potential conflicts of interest with respect to Research, authorship, and/or publication of this article.

Ethical Approval

The patient gave permission for the presentation of his case reports and followed ethical considerations of the declaration of Helsinki.

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