Quiz

Correct answer to the quiz. Check your diagnosis

Case report

An unexpected leprosy diagnosis in Nordic patient with skin lesions

Arnhild Binde[1], Johannes Hendricus van der Stoep[1], Camilla Sivesind Mehlum[2], Monika Aneta Dzieniecka[1]

[1]Department of Pathology, Innlandet Hospital, Lillehammer, Norway
[2]Department of Microbiology, Innlandet Hospital, Lillehammer, Norway

Leprosy is a rare chronic infectious disease that can be challenging to diagnose in non-endemic settings due to limited clinical experience among physicians and its marked clinical heterogeneity. We report the case of leprosy in a Nordic patient with an extensive travel history who presented with cutaneous lesions, nasal congestion, and peripheral neurological symptoms. Although the histopathological findings were not fully specific, modified Ziehl-Neelsen staining revealed numerous acid-fast bacilli within the tissue samples. *Mycobacterium leprae* was subsequently confirmed by molecular analyses. To minimise diagnostic delay and prevent disease progression, we provide an overview of the histopathological features of leprosy and discuss relevant differential diagnoses.

Key words: leprosy, *Mycobacterium leprae*, skin lesions, peripheral neuropathy, dermatopathology.

Introduction

Leprosy (Hansen's disease) is a chronic infectious disease caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*. Since the introduction of multidrug therapy in the 1980s, the global incidence has declined substantially [1].

Early detection is crucial to mitigating clinical complications, but this may be challenging in low-endemic regions where awareness among clinicians and pathologists is limited [2]. This case report aims to highlight the histopathological features of leprosy and discuss important differential diagnoses to reduce diagnostic delays and prevent disease progression.

Case report

A 63-year-old man was admitted to an outpatient clinic with a generalised rash. His symptoms included erythematous, non-pruritic lesions with a focal nodular component that gradually spread from the lower extremities to the trunk and upper extremities. He also reported a "pillow-like" sensation in both feet, blue discolouration of his toes, a cough and nasal congestion with bloody discharge.

His medical history was notable for seronegative polyarthritis over a two-year period with multiple therapeutic agents, including adalimumab, administered for approximately 18 months. A detailed retrospective review of his medical records revealed

involvement of the metatarsophalangeal and metacarpophalangeal joints, as well as synovitis of the wrists and bursitis of the elbows and right knee.

The patient had travelled extensively, visiting Nepal, India, and multiple Latin American countries since the mid-1980s. During the past five years, he had travelled to China, Korea, Ukraine and Dubai, and visited Uganda twice during the last year.

Material and methods

The Department of Pathology received two surgical specimens: a 5 mm punch biopsy from a skin lesion on the thigh and, later, three 3 mm biopsies from the nasal mucosa.

Formalin-fixed, paraffin-embedded samples from the skin and nasal mucosa were processed using standard protocols. Tissue sections (3.5 μm thick) were obtained for ancillary techniques, including HE using Roche HE600 and modified Ziehl-Neelsen stain (AFB III Staining Kit) using the Roche BenchMark Special Stains system.

A real-time polymerase chain reaction (PCR) for *Mycobacterium leprae* was performed on the nasal mucosa biopsy. In addition, 16S rDNA sequencing and RipSeq mixed software were used to detect and identify bacterial DNA in biopsies of the nasal mucosa and skin. Material from both sites was submitted for general and mycobacterial culture.

Results

Histological examination of the skin biopsy revealed a dermal and subcutaneous lymphohistiocytic infiltrate with an asymmetrical discrete outline of granulomatous inflammation surrounding nerves, adnexal structures, small and large vessels and arrector pili muscles. A preserved "Grenz zone" of sparing in the papillary dermis was noted as well as distended histiocytes whose vacuolated cytoplasm exhibited a bluish-grey tinge (Figure 1). The nasal mucosa biopsy demonstrated similar histological features, including an infiltrate of vacuolated histiocytes associated with fibrosis. The epithelial surface was ulcerated (Figure 2). Modified Ziehl-Neelsen staining revealed abundant acid-fast bacteria within histiocytes (Figure 3).

Mycobacterium leprae was detected by 16S rDNA sequencing in both nasal and skin biopsies. Species-specific real-time PCR confirmed the presence of *Mycobacterium leprae* in samples collected from the nasal mucosa. Mycobacterial cultures were negative, consistent with the inability of *Mycobacterium leprae* to grow in artificial media [3].

Based on the clinical presentation, histopathological and microbiological findings, a diagnosis of multibacillary (World Health Organization – WHO, classification) and borderline lepromatous leprosy (Ridley-Jopling classification) was established.

Discussion

Diagnosing leprosy in non-endemic areas is challenging. In Europe, the disease is rare, with only 53 new cases reported in 2022, resulting in limited diagnostic experience among clinicians and pathologists [4]. The most common clinical symptoms include skin lesions and signs of peripheral nerve involvement. According to the WHO, leprosy may be diagnosed if at least one of the following is present: marked loss of sensation in a hypopigmented or reddish skin lesion; thickening or enlargement of a peripheral nerve with sensory loss and/or motor weakness; or microscopic detection of mycobacteria in a skin smear [5].

Several classification systems have been proposed in the literature; but the Ridley-Jopling system and WHO systems are the most widely applied [6]. The Ridley-Jopling system categorised leprosy based on the host's immune response to *Mycobacterium leprae* and *Mycobacterium lepromatosis*, ranging from tuberculoid to lepromatous forms. It includes five categories: tuberculoid, borderline tuberculoid, mid-borderline, borderline lepromatous, and lepromatous leprosy [7]. Many patients initially present with an intermediate (borderline) form, which may shift over time due to disease progression or treatment response. Histopathological features vary considerably, from well-defined granulomatous inflammation in the tuberculoid form to poorly defined infiltrates dominated by foamy macrophages in lepromatous leprosy. In the latter form, numerous bacilli are typically visualised using modified Ziehl-Neelsen staining, whereas in tuberculoid leprosy, bacteria are scarce and often difficult to detect [8].

The World Health Organization classification system is simple to implement and widely adopted for therapeutic guidance. It differentiates between paucibacillary and multibacillary leprosy based on clinical features and, when available, slit skin-smear results demonstrating acid-fast bacilli. In our case, the constellation of findings was most consistent with multibacillary borderline lepromatous leprosy.

Notably, the host immune response to *Mycobacterium leprae* and *Mycobacterium lepromatosis* differs significantly among individuals, and immunocompetent persons may develop lepromatous leprosy [9]. In the present case, the patient's treatment with adalimumab likely predisposed him to developing a multibacillary form of the disease [10].

In low-endemic regions, diagnosis is difficult due to the wide variability of its clinical and histopathological presentations. Cutaneous manifestations are frequently non-specific, and may include mild erythematous rashes, pigmentary changes, plaques, ma-

cules, papules and nodules [11]. Differential diagnoses are extensive, and it is beyond the scope of this article to provide an entire list of skin conditions with similar histological features. Tuberculoid leprosy must be distinguished from sarcoidosis, tuberculosis, leishmaniasis and secondary syphilis [8]. Neurotropic granulomatous and lymphohistiocytic infiltrates are highly suggestive of tuberculoid leprosy. For lepromatous

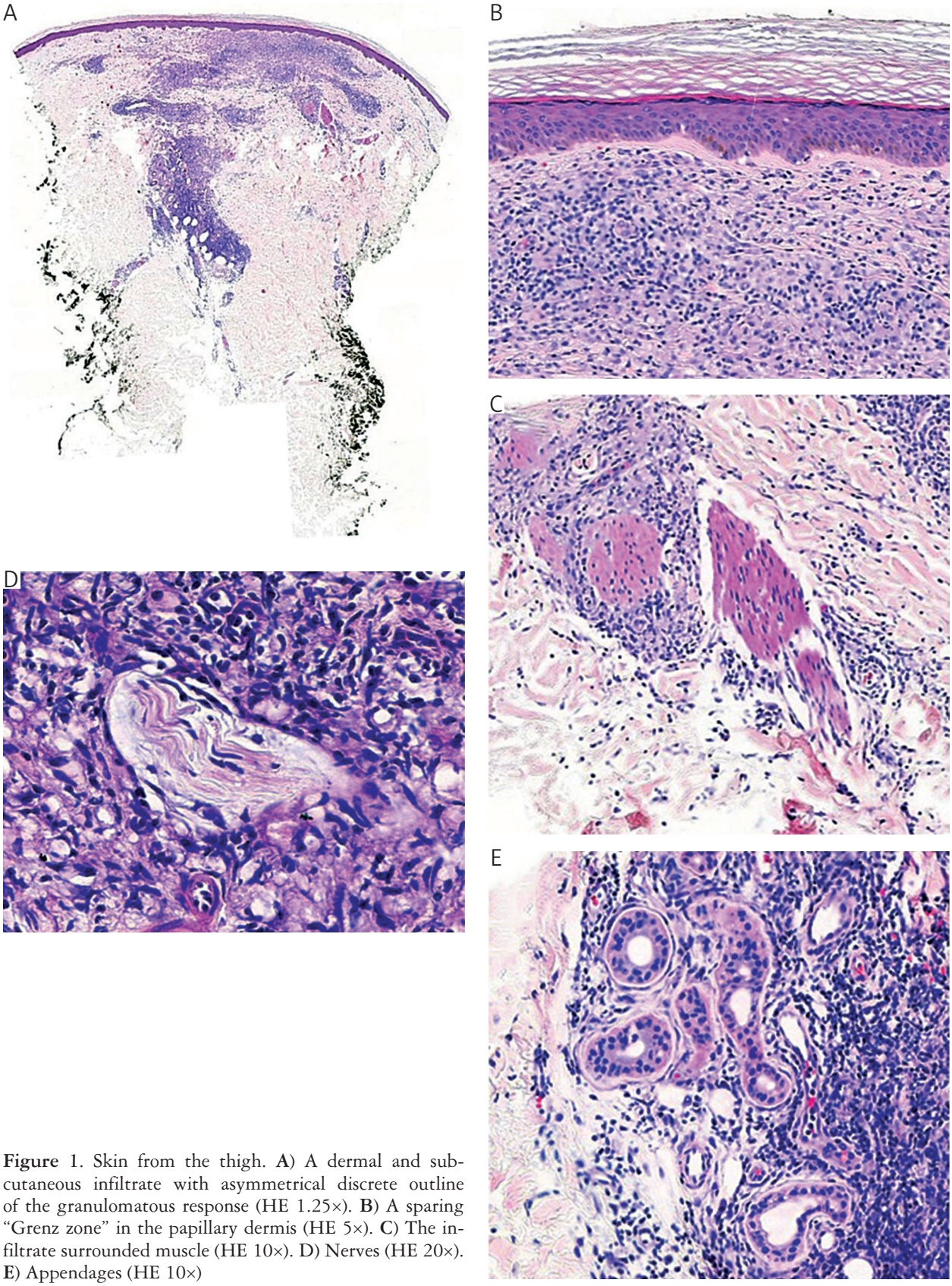

Figure 1. Skin from the thigh. **A**) A dermal and subcutaneous infiltrate with asymmetrical discrete outline of the granulomatous response (HE 1.25×). **B**) A sparing "Grenz zone" in the papillary dermis (HE 5×). **C**) The infiltrate surrounded muscle (HE 10×). D) Nerves (HE 20×). **E**) Appendages (HE 10×)

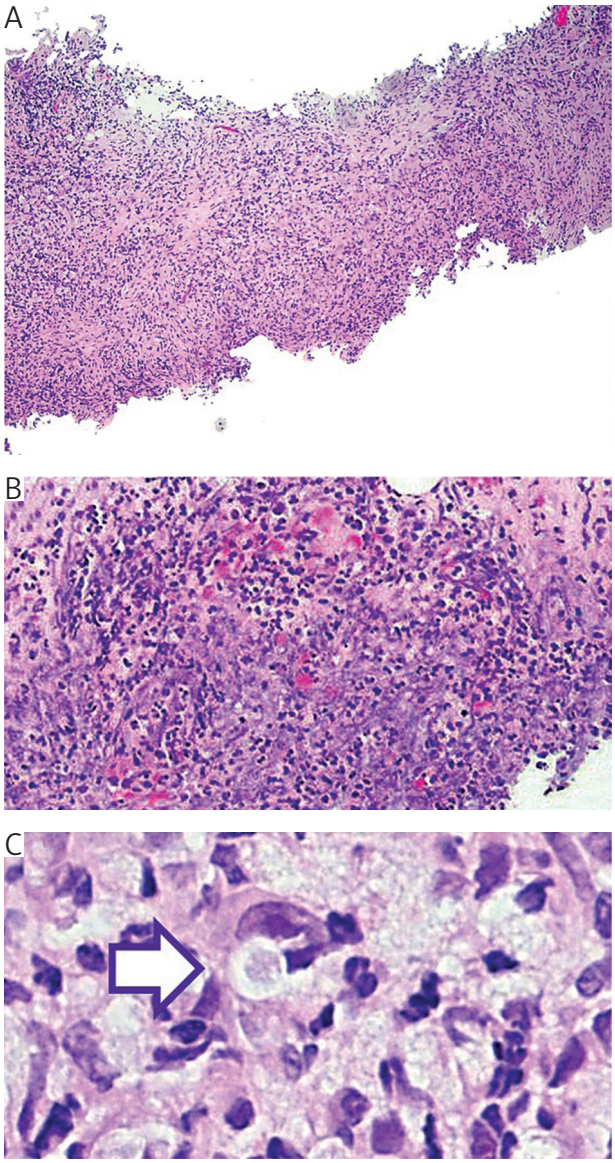

Figure 2. Nasal mucosa. Lymphohistiocytic infiltrate with fibrosis. **A**) Low power view (HE 10×). **B**) Ulcerated surface with neutrophils (HE 20×). **C**) Vacuolated histiocytes (HE 20×)

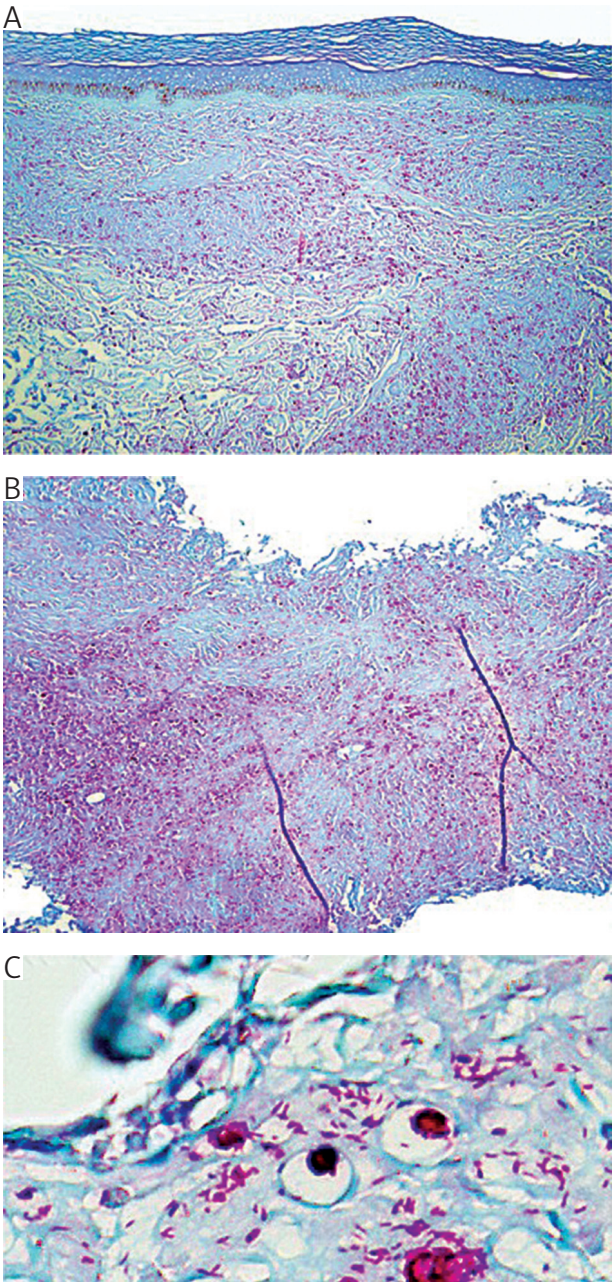

Figure 3. **A**) Large numbers of acid-fast bacteria in the skin (ZN 10×). **B**) Large numbers of acid-fast bacteria in the nasal mucosa (ZN 10×). **C**) Macrophages distended with large groups of leprosy bacilli (globi) in nasal mucosa (ZN 40×)

leprosy, differential diagnoses include xanthomas and xanthogranulomas, some forms of dermal leishmaniasis, paraffinoma, and, rarely, infections caused by other atypical mycobacteria (in the late stage) [8]. Virchow cells (large foamy histiocytes) and a "Grenz zone" further suggest the diagnosis of lepromatous leprosy. Special staining with modified Ziehl-Neelsen may reveal acid-fast organisms, thereby strengthening the suspicion of leprosy.

Conclusions

This article reports an unexpected diagnosis of leprosy in a patient residing in a non-endemic region. Despite the absence of recent exposure, the patient had an extensive travel history that included multiple visits to highly endemic areas, many of which occurred decades earlier. Given that leprosy may remain latent and clinically silent for up to 20 years, the delayed onset of symptoms observed in this case is biologically plausible [12]. Following histopathological confirmation, infectious disease specialists determined that the patient's arthritis and bursitis likely represented early extra-cutaneous manifestations of leprosy that preceded the appearance of cutaneous lesions [10]. Moreover, the existing literature has documented exacerbations of lepromatous disease in individuals receiving TNF-α inhibitors, highlighting an additional diagnostic challenge.

Although leprosy remains rare in Europe, increasing international mobility and migration from endemic regions may contribute to a gradual rise in incident cases. Accordingly, clinicians should maintain a high index of suspicion when evaluating patients presenting with unexplained dermatological or neuropathic findings, particularly when a history of travel to endemic areas is elicited [5].

Histopathological assessment of a skin biopsy, including modified Ziehl-Neelsen staining, continues to represent the diagnostic gold standard. Definitive confirmation and species-level characterisation should be supported by molecular techniques, which are strongly recommended in contemporary diagnostic practice [13]. Early recognition and appropriate diagnostic workup remain essential for timely initiation of therapy and the prevention of long-term morbidity.

Disclosures

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Address for correspondence

Arnhild Binde
Department of Pathology
Innlandet Hospital
P.O. Box 990
2629 Lillehammer, Norway
Phone: +47 61 27 21 48
e-mail: arnhild.binde@sykehuset-innlandet.no