SHORT COMMUNICATION

Diagnostic Challenges of Neurosyphilis: A Case of Lues Maligna with Neuropsychiatric Symptoms

Gabrielė JONAUSKAITĖ[1], Inga ČESNAVIČIŪTĖ[2], Justė GAVELYTĖ[2], Raimonda MCGLONE[2] and Tadas RAUDONIS[2]
[1]Vilnius University, Faculty of Medicine, Vilnius, Lithuania, and [2]Faculty of Medicine, Vilnius University, Institute of Clinical Medicine, Clinic of Infectious Diseases and Dermatovenereology, Vilnius, Lithuania. Email: gabriele.jonauskaite@mf.stud.vu.lt
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Lues maligna (malignant or ulceronodular syphilis) is a rare, aggressive form of secondary syphilis caused by the spirochaete *Treponema pallidum*, characterised by deep ulcerative lesions and systemic involvement, predominantly in immunocompromised individuals (1). *T. pallidum* may also involve the central nervous system, resulting in neurosyphilis at any stage of infection (2, 3). Early neurosyphilis may be asymptomatic but can later progress to a wide array of manifestations, including meningeal, cerebrovascular and even neuropsychiatric symptoms (4). The diagnostic process of neurosyphilis remains complex due to the lack of clear diagnostic criteria. Non-treponemal cerebrospinal fluid (CSF) tests, such as the Venereal Disease Research Laboratory test (VDRL) and the rapid plasma reagin test (RPR), are frequently used to confirm neurosyphilis. However, given their low sensitivity, negative test results cannot reliably exclude neurosyphilis (5).

CASE PRESENTATION

A 37-year-old man presented with a generalised rash, which had persisted for 2 months. The eruption reportedly began on the nape, subsequently spreading diffusely, and was accompanied by episodes of fever up to 39.9°C. After a consultation at the outpatient clinic, malignant syphilis was suspected, and the patient was referred to a tertiary-level hospital.

Physical examination revealed multiple infiltrated nodules, several ulcerated and covered with necrotic crusts (**Fig. 1**). Multiple skin lesions were noted on the back, including a 2.5 cm crater-like ulcer with firm edges on the right scapula (Fig. 1D). On the

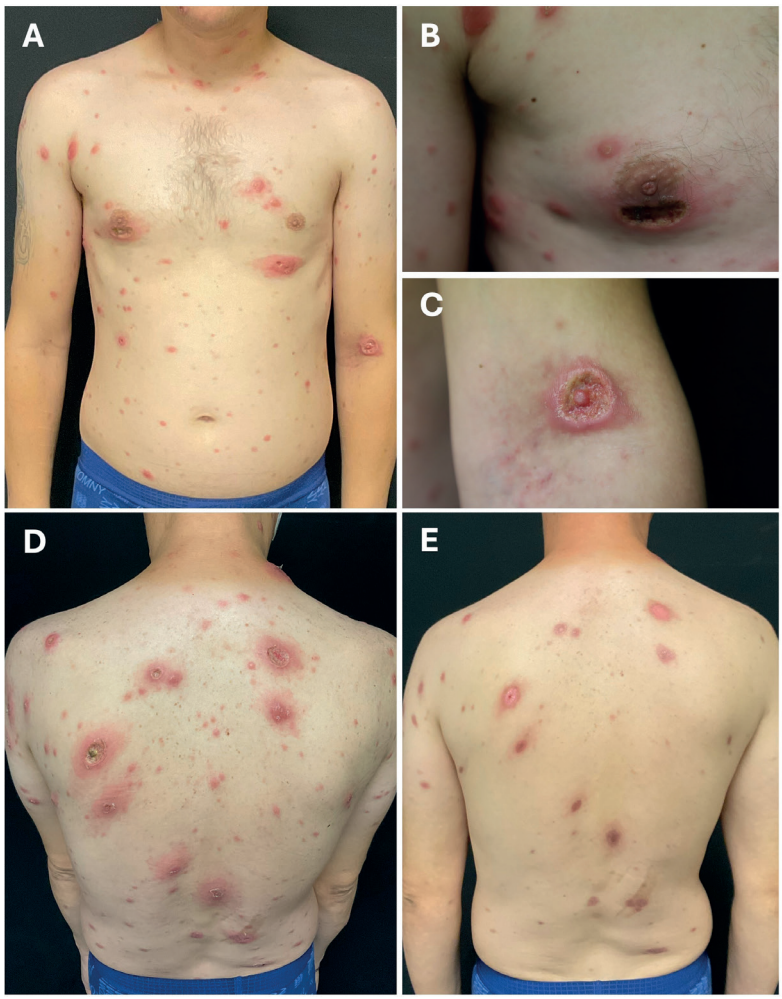

Fig. 1. (A) Anterior torso with multiple erythematous lesions before treatment. (B) Necrotic breast ulcer. (C) Ulcerated nodule in the antecubital fossa. (D) Posterior torso with large, ulcerated lesions before treatment. (E) Light erythematous macules and post-inflammatory pigmentation on the back 23 days after starting intravenous benzylpenicillin.

scrotum, 1–1.5 cm nodules with eroded centres were observed. Enlarged and painful cervical and inguinal lymph nodes were palpated. During the examination, the patient was hostile towards the hospital staff, dismissive and reluctant to cooperate. Due to anticipated non-compliance with hospital regulations suggesting a short hospital stay, suspected comorbid sexually transmitted infections (STIs), and uncertain tolerance to high-dose benzylpenicillin in the context of elevated liver enzymes, doxycycline (100 mg twice daily) was initiated along with local disinfection and antibiotic creams. After the first dose, the patient developed a fever of up to 38°C.

The patient denied casual sexual encounters and intravenous drug use; however, he did not deny engaging in same-sex sexual activity and alcohol abuse. Medical records included multiple emergency visits for alcohol intoxication. A complete blood count showed macrocytic hyperchromic anaemia (haemoglobin 119 g/L, mean corpuscular volume 116.3 fL, mean corpuscular haemoglobin 39.1 pg). Tests for STIs showed positive RPR (titre 1:128) and *T. pallidum* haemagglutination assay (TPHA) (4+) values. CSF analysis revealed *T. pallidum* antibodies (s/co value 14.01), along with positive TPHA (4+), negative VDRL and normal cell count, protein and glucose levels. Based on the clinical presentation, serum and CSF examination results, strong suspicion of neurosyphilis remained. Tests for other STIs (urethral and pharyngeal PCR swabs, hepatitis and HIV serology) were negative.

Gastroenterological evaluation revealed chronic liver disease (ALT 105 U/L, AST 101 U/L, GGT 523 U/L, ALP 193 U/L) related to alcohol abuse, but no contraindications to high-dose benzylpenicillin. Psychiatric assessment identified alcohol-related mental and behavioural disorders but could not reliably exclude neurosyphilis. During hospitalisation, the patient was recommended addiction treatment, administered diazepam and tiapride for withdrawal symptoms, and quetiapine or chlorprothixene for sleep disturbances.

Because of suspected neurosyphilis, intravenous aqueous crystalline benzylpenicillin (3 million international units (IU) 6 times daily) was initiated, and doxycycline was discontinued after 6 days. The patient was discharged after 12 days due to non-adherence to hospital rules but continued weekly intramuscular benzathine benzylpenicillin injections at the Day Care Centre (2.4 million IU for 3 weeks). The therapeutic response was favourable, with marked cutaneous improvement, regression of ecthymatous lesions and surrounding erythema, wound contraction and development of post-inflammatory pigmentation (Fig. 1E). Thirty-five days after initiating treatment, the RPR titre decreased from 1:128 to 1:64, accompanied by improved demeanour, reduced hostility and acknowledgement of prior non-compliance with hospital regulations.

DISCUSSION

Cutaneous manifestation. In this patient, syphilis presented atypically, with infiltrated erythematous nodules, some of them resembling ecthymas with ulcerated and necrotic masses, suggesting malignant syphilis. Most patients with malignant syphilis are HIV-positive, while HIV-negative individuals, such as the presented patient, may have other comorbidities, including hepatitis and alcoholism (6). The patient met Fisher's criteria, commonly used to diagnose malignant syphilis: gross rash morphology (ulceronodular skin lesions), high-titre serological tests for syphilis, rapid clinical response to antibiotic therapy, and developed a high-grade fever, which was interpreted as a Jarisch–Herxheimer reaction (7).

Neurosyphilis. According to a study by Lin et al. (8), neuropsychiatric symptoms may be the primary manifestation of neurosyphilis, often leading to misdiagnosis. The reported patient exhibited dangerous and irresponsible behaviour, impaired impulse control and hostility, which mildly improved following benzylpenicillin treatment. Psychiatric consultation recommended symptomatic management, abstinence and addiction treatment. Given the patient's history with alcohol, distinguishing between alcohol-induced neurocognitive impairment and neuropsychiatric symptoms caused by intrathecal *T. pallidum* invasion proved to be challenging, as both conditions may have overlapped. In light of the clinical and laboratory findings, treatment was initiated to prevent this complication from remaining unaddressed. Although rare, cases of malignant syphilis complicated with neurosyphilis have been reported in the literature (1, 9). In a study by Zhu et al., neurosyphilis was found in approximately 30% of patients with malignant syphilis, significantly higher than the 13.1% observed in patients with secondary syphilis (10).

Diagnosis and treatment. Syphilis was confirmed based on positive RPR (a high titre of 1:128 indicated a relatively recent infection) and positive TPHA. However, the diagnostic process of neurosyphilis remains complex due to the lack of standardized testing and definitive guidelines, relying instead on a combination of symptoms, findings and laboratory results (4). According to the European guidelines on the management of syphilis, CSF examination is indicated in cases of neurological, ocular or auricular involvement, or when tertiary syphilis is suspected. Centers for Disease Control and Prevention (CDC) guidelines also recommend against CSF testing when asymptomatic neurosyphilis is suspected (11, 12).

In the reported case, CSF analysis was performed due to atypical presentation, suspected neurological involvement and the possibility of late, or even tertiary, syphilis. CSF results showed positive TPHA and T. pallidum antibodies but negative VDRL, no pleocytosis and no changes in protein or glucose levels. While TPHA is sensitive, it is non-specific to neurosyphilis. A positive VDRL test is more specific and helps to confirm neurosyphilis, but with a sensitivity of 67–72%, a negative test result does not always exclude it (4). CSF pleocytosis is reported to be sensitive but non-specific to neurosyphilis and may be influenced by HIV status, neurosyphilis type and the diagnostic criteria used. Finally, elevated CSF protein may support the diagnosis of neurosyphilis but is considered the least reliable marker (13).

According to German guidelines, probable neurosyphilis is diagnosed when a positive serum TPHA, T. pallidum particle agglutination assay (TPPA), or fluorescent treponemal antibody (FTA) test is accompanied by 2 of the following: chronic or subacute neuropsychiatric symptoms; increased CSF cell count or blood-CSF

barrier disruption; positive effect of antibiotic therapy on clinical course and CSF findings (14). In this case, although the CSF examination showed no blood-CSF barrier disruption, positive serum TPHA, neuropsychiatric symptoms and mild clinical improvement after treatment supported a diagnosis of probable neurosyphilis. As neurosyphilis could not be reliably excluded, an intensive antibiotic treatment regimen was initiated. CDC advises intravenous therapy with 18–24 million units of benzylpenicillin daily for 10–14 days in disseminated infections, such as neurosyphilis (11). Accordingly, the patient received 18 million units of benzylpenicillin daily, resulting in marked regression of cutaneous lesions and mild improvement in neuropsychiatric symptoms.

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