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SYPHILIS SHOULD NOT BE OVERLOOKED IN ANY INDIVIDUAL, IRRESPECTIVE OF THEIR CONDITION

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ABSTRACT

Introduction: Syphilis remains a significant challenge in public health, largely because of its diverse clinical manifestations, often resulting in underdiagnosis especially among patients with neurogenic disability.

Case description: We present a case of neurosyphilis in a 63-year-old patient with a spinal cord injury. Despite syphilis being a well-established sexually transmitted infection, the exacerbation of neurological and dermatological symptoms during physical examination prompted an investigation into alternative causes beyond the patient's pre-existing paraparesis, ultimately resulting in the diagnosis of neurosyphilis.

Conclusion: This case highlights the importance of considering syphilis as a potential diagnosis in individuals regardless of their medical history.

KEYWORDS

Neurosyphilis, tetraparetic, sexually transmitted infection, roseoliform exanthema, meningoradiculitis

LEARNING POINTS

- The incidence of syphilis cases is on the rise, presenting an ongoing challenge.
- Faced with atypical neurological symptomatology, it is necessary to know how to investigate and discuss tertiary syphilis.
- In the event of neurological worsening in a neuro-injured patient, it is necessary to know how to discuss a curable diagnosis.

INTRODUCTION

In recent years, there has been a resurgence of syphilis. The decline in exposure to its various manifestations has led to challenges in diagnosing a disease that was once well-recognised[1-3]. With the increasing rates of syphilis, cases of neurosyphilis have likely risen as well[4]. The global population could be contaminated, even in patients with disability. Despite some attention to this rising incidence, there remains a striking delay in diagnosis and subsequent treatment of this infectious disease[5-7]. This delay is even more pronounced when the patient does not fit the typical profile for a sexually transmitted disease.

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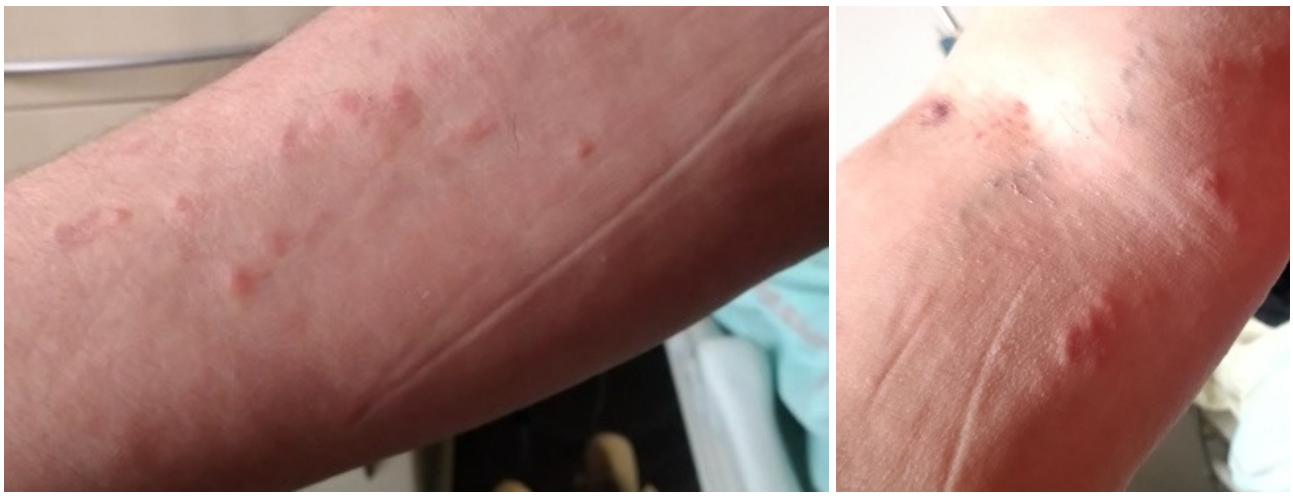

Figure 1. Physical examination revealed a rash resembling roseola on the trunk and back, along with erythematous-squamous papules on both arms and upper limbs, leaving behind pink scars.

CASE DESCRIPTION

In September 2022, a 63-year-old male with a medical history of infantile paraparesis, which had been progressively worsening over the previous four years, with hypertension and gout, presented to the department of infectious diseases. He reported a 15-day history of multiple painless, non-itchy plaques. Physical examination revealed a rash resembling roseola on the trunk and back, with erythematous-squamous papules on both arms and upper limbs, leaving behind pink scars *(Fig. 1)*. He also exhibited spastic weakness and worsening sensory loss in the lower extremities. The patient recalled experiencing a sore throat with ulcers in the mouth, a rash on the palms of hands and feet, and inflammatory joint pain in the upper limbs without swelling. There had been a single episode of eye floaters without vision loss or pain six months prior, which resolved on its own within a few days. Since then, he noted a decline in his condition marked by weakness, pain and paraparesis of the lower extremities. The patient denied any recent travel, lived in an urban area and did not report any tick bites. Laboratory analyses including routine blood examination, liver and kidney function tests were normal. To exclude any neurological pathologies, brain and spinal MRI were performed showing only minor leukoaraiosis with no signs of neurological compression or stroke. Electromyography showed signs of bilateral axonal lesions with delayed central motor conduction to both legs compatible with myeloradiculitis. Ophthalmological evaluation was unremarkable. A complete CT-scan eliminated a deep infectious focus and neoplastic involvement. The aetiologies of roseoliform exanthema are mainly infectious, therefore a complete infectious assessment was undertaken; a cerebrospinal fluid polymerase chain reaction test ruled out *Borrelia burgdorferi* infection, and other possible aetiologies such as tuberculosis, herpes simplex virus 1 and 2, varicella-zoster virus, enterovirus, Epstein-Barr virus and cytomegalovirus. No evidence for vasculitis or collagen vascular disorders was found. Anti-nuclear antibodies such as ds-DNA (antibodies against single and double-stranded DNA), and autoantibodies to extractable nuclear antigens such as anti–Sjögren's-syndrome-related antigen A or complement levels were normal.

The new-patient interview revealed unprotected sexual activity since beginning of 2022. Given the unprotected sexual intercourse, serological tests for HIV, hepatitis B surface antigen and anti-HCV (hepatitis C virus) were performed and came back negative. Finally, syphilis testing (reactive venereal disease research laboratory, VDRL) returned positive with an index of 1/256. Moreover, the patient tested negative for other sexually transmitted diseases such as *Chlamydia trachomatis* and gonorrhoea.

A lumbar puncture revealed clear fluid with slightly increased protein levels (525 mg/l) and 20 cells/µl, predominantly lymphocytes (79%), and monocytes (11%), with *Treponema pallidum* antibodies. The *T. pallidum* antibody levels were 1 UI/ml in the cerebrospinal fluid (CSF) and 1/256 units in the serum. A diagnosis of neurosyphilis was made, and intravenous crystallised penicillin G (24 million units/day) was administered for 14 days. After 72 hours of anti-syphilitic treatment, the patient developed an extension of cutaneous lesions on the trunk and face, consistent with a Herxheimer reaction or drug-induced allergy *(Fig. 2)*. Topical steroids were prescribed, resulting in clinical improvement, and penicillin G treatment was continued with a favourable outcome: skin lesions disappeared, and neurological impairment decreased.

Reassessment after three months of treatment revealed an improvement in the patient's general condition, with restored motor function and regression of all skin lesions. Syphilis serological control found a decrease in the index with a VDRL of 1/4 after 6 months and 1/2 after one year.

DISCUSSION

Neurosyphilis arises from the invasion of the central nervous system by *T. pallidum* and can occur at any stage of syphilis[8]. The initial stage of syphilis, characterised by genital chancre, often goes unnoticed. The secondary stage typically presents with a transient roseoliform skin rash, while the

subsequent asymptomatic latent stage can persist for several years. Neurological invasion occurs rapidly, affecting approximately 30% of patients during the primary stage, often without symptoms[8,9]. However, symptomatic cases – which typically arise within 12 months post-infection – often manifest as acute meningitis, frequently involving the basilar region and can lead to cerebral vessel thrombosis. Hydrocephalus accompanied by increased intracranial pressure has also been reported. Late neurological manifestations, such as tabes dorsalis and general paresis, typically arise 10–30 years after infection, but can occur earlier in immunocompromised individuals[10]. While those cases have declined since the penicillin era, physicians should remain vigilant for atypical presentations, including epilepsy, ocular symptoms, stroke and confusion, which have become more prevalent.

For a neuro-injured patient, all these symptoms can be part of their neurological stage and can be neglected or can also be caused by other irritative stimuli. Thus, neurological worsening in a neuro-injured patient must lead to discussions about a curable diagnosis before ruling on progression of the underlying disease. Faced with atypical neurological symptomatology, with a negative aetiological assessment, it is necessary to know how to investigate and discuss sexually transmitted disease and especially tertiary syphilis, which can appear a long time after the infection and be responsible for a polymorphous picture. The essential diagnostic test is a lumbar puncture, with evidence of intrathecal antibody synthesis and positive VDRL. CSF laboratory abnormalities are commonly found in individuals with early syphilis, regardless of whether they exhibit neurological signs or symptoms. No single laboratory test can definitively confirm or rule out a diagnosis of neurosyphilis. Instead, the current best practice for diagnosing neurosyphilis relies on a combination of clinical history, physical examination findings, serum antibody tests and CSF analysis.

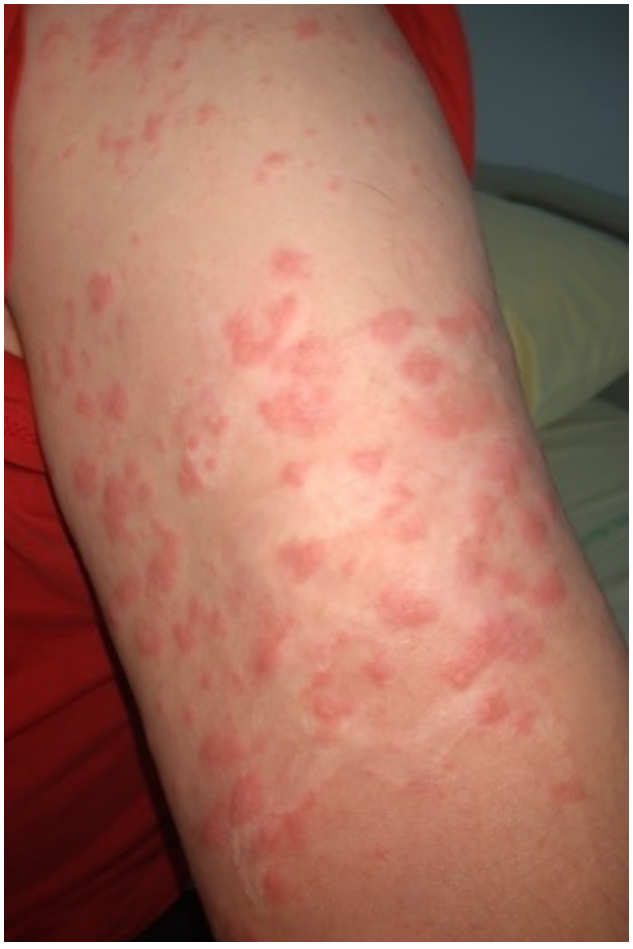

Figure 2. After 72 hours of anti-syphilitic treatment, the patient developed an extension of cutaneous lesions on the trunk and face, consistent with a Herxheimer reaction.

A recent review by Hamill et al. outlines the key clinical features of both early and late (tertiary) neurosyphilis. It discusses the clinical significance of an asymptomatic patient, examines the indications for CSF examination, evaluates the performance characteristics of various CSF assays including treponemal and lipoidal antibodies, and discusses the role of imaging[11].

Clinical observations suggest that most cases of neurological invasion and CSF abnormalities in asymptomatic individuals likely either resolve or do not progress with non-neurosyphilis antibiotic regimens. Symptomatic neurosyphilis is rare, even without universal CSF examinations. There is currently no evidence to support treating neurosyphilis at any stage in individuals without clinical neurological findings. Furthermore, it remains uncertain whether treating asymptomatic neurosyphilis with IV penicillin improves long-term outcomes. According to the Centers for Disease Control and Prevention (CDC) guidelines, CSF examination should be conducted in patients with clinical signs or neurological involvement, patients with lipoidal serological titres showing a sustained fourfold increase following appropriate therapy, and patients diagnosed with gummatous or cardiovascular syphilis[12]. However, CSF examinations are not recommended for individuals presenting solely with ocular or optic signs without neurological symptoms[12]. While people living with HIV have a higher risk of neurosyphilis, the overall risk is likely small, especially in the era of antiretroviral therapy.

Treatment recommendations for neurosyphilis are largely based on case series, retrospective studies, pharmacokinetic/pharmacodynamic data and clinical experience, as opposed to robust clinical trials. The optimal duration of therapy has not been studied in a trial setting, but clinical experience suggests that 10–14 days of penicillin is usually sufficient[13]. The role of corticosteroids in neurosyphilis management is uncertain, and routine use is not recommended by the CDC[12]. Post-treatment monitoring should involve regular VDRL titre checks every three months until it becomes undetectable – a process that can take up to 24 months, particularly in people living with HIV. Finally, doxycycline taken as pre- or post-exposure prophylaxis within 72 hours of potential exposure has been shown to reduce incident syphilis by approximately 70%[14]. However, unanswered questions remain regarding potential harms, including antimicrobial resistance in sexually transmitted infections[15].

CONCLUSION

The incidence of syphilis cases is on the rise, presenting an ongoing challenge despite the availability of effective treatments, diagnostic tests and educational public health initiatives. This case serves as a reminder that due to the typically prolonged disease course, resulting from diagnostic delays and the diverse affected organ systems with their respective symptoms, syphilis is often referred to as 'the great imitator'. This characteristic leads to significant delays in both diagnosis and subsequent treatment. While the majority of new syphilis infections are diagnosed in men who have sex with men or sex workers, our case highlights that the diagnostic of syphilis should not be disregarded in any individual, regardless of their circumstances.

REFERENCES

1. Kojima N, Klausner JD. An update on the global epidemiology of syphilis. *Curr Epidemiol Rep* 2018;**5**:24–38.
2. Fenton KA, Breban R, Vardavas R, Okano JT, Martin T, Aral S, et al. Infectious syphilis in high-income settings in the 21st century. *Lancet Infect Dis* 2008;**8**:244–253.
3. Schmidt R, Carson PJ, Jansen RJ. Resurgence of syphilis in the United States: an assessment of contributing factors. *Infect Dis (Auckl)* 2019;**12**:1178633719883282.
4. Staritsky LE, van Aar F, Visser M, op de Coul ELM, Heijne JCM, Götz HM, et al. Sexually transmitted infections in the Netherlands in 2019. RIVM; 2020 [cited 2024 Feb 4]. Available from: https://rivm.openrepository.com/handle/10029/623857
5. Heijstek MW, Goslings WR, Shamelian S. Koorts en exantheem als manifestatie van het secundaire stadium van syfilis [Fever and exanthema as manifestations of the second stage of syphilis]. *Ned Tijdschr Geneeskd* 2006;**150**:1342–1346.
6. Chen SY, Johnson M, Sunenshine R, England B, Komatsu K, Taylor M. Missed and delayed syphilis treatment and partner elicitation: a comparison between STD clinic and non-STD clinic patients. *Sex Transm Dis* 2009;**36**:445–451.
7. Bissessor M, Fairley CK, De Guingand D, Bradshaw CS, Chen MY. Delay in the diagnosis of early syphilis among men who have sex with men: need for greater community and health provider education. *Int J STD AIDS* 2009;**20**:52–53.
8. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med* 2020;**382**:845–854.
9. Moore JE, Faupel M. Asymptomatic neurosyphilis V. A comparison of early and late asymptomatic neurosyphilis. *Arch Derm Syphilol* 1928;**18**:99–108.
10. Ropper AH. Neurosyphilis. *N Engl J Med* 2019;**381**:1358–1363.
11. Hamill MM, Ghanem KG, Tuddenham S. State-of-the-art review: neurosyphilis. *Clin Infect Dis* 2023;**78**:e57–e68.
12. Workowski KA, Bachmann LH. Centers for Disease Control and Prevention's Sexually Transmitted Diseases Infection Guidelines. *Clin Infect Dis* 2022;**74**:S89–94.
13. Idsoe O, Guthe T, Willcox RR. Penicillin in the treatment of syphilis. The experience of three decades. *Bull World Health Organ* 1972;**47**:1–68.
14. Luetkemeyer AF, Donnell D, Dombrowski JC, Cohen S, Grabow C, Brown CE, et al. Postexposure doxycycline to prevent bacterial sexually transmitted infections. *N Engl J Med* 2023;**388**:1296–1306.
15. Traeger MW, Mayer KH, Krakower DS, Gitin S, Jenness SM, Marcus JL. Potential impact of doxycycline post-exposure prophylaxis prescribing strategies on incidence of bacterial sexually transmitted infections. *Clin Infect Dis* 2023;ciad488.