

Sepsis or Jarisch-Herxheimer Reaction? A Case of Clinical Overlap

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1. Abstract

The Jarisch-Herxheimer reaction (JHR) is an acute inflammatory response that may occur after initiating anti-microbial therapy for spirochetal infections, most notably syphilis. Its clinical presentation often involving fever, hypotension, and systemic symptoms can closely mimic sepsis, posing a diagnostic challenge. This case report aims to illustrate the importance of recognizing JHR, particularly in immunocompromised individuals, and distinguishing it from true infectious processes to avoid unnecessary interventions. We report the case of a 39-year-old immunosuppressed female with a recent diagnosis of secondary syphilis, treated with a single intramuscular dose of benzathine penicillin G. Within 18 hours of treatment, she was admitted to the emergency department with high fever, rash, hypotension, and altered mental status. Laboratory testing, neuroimaging, and comprehensive infection screening were performed. Empirical antibiotic therapy and sepsis protocols were initiated in accordance with early warning scores. Despite initial concern for sepsis, diagnostic work-up revealed negative blood and urine cultures, normal procalcitonin levels, and no identifiable infectious focus. The patient's clinical status improved spontaneously within 36 hours, with resolution of fever and rash. The temporal relationship between penicillin administration and symptom onset, coupled with the exclusion of alternative diagnoses, confirmed the diagnosis of JHR. This case highlights the diagnostic complexity of JHR in immunocompromised patients, particularly in the context of rising syphilis rates. Timely recognition of JHR is essential to avoid misdiagnosis and overtreatment. Increased awareness and education are critical to improving outcomes in spirochetal infection management.

2. Introduction

Syphilis is a chronic, systemic infectious disease primarily transmitted through sexual contact [1]. The transmission of syphilis occurs mainly through sexual contact, whether oral, vaginal, or anal. Additionally, the disease can be transmitted from mother to child during pregnancy, with a fetal mortality rate exceeding 40% [2].

Syphilis is caused by *Treponema pallidum*, a bacterium from the genus *Treponema*, which is part of the *Treponemataceae* family.

T. pallidum has a spiral shape with 10 to 20 coils, measuring approximately 5–20 micrometers in length and only 0.1 to 0.2 micrometers in thickness. Interestingly, this bacterium lacks a cell membrane and is instead surrounded by an outer envelope. The flagella of *T. pallidum* emerge from the distal end of the bacterium, extending along the external longitudinal axis, allowing it to move by rotating its body around these filaments [3-6]. Most people infected with syphilis do not show visible symptoms, which significantly contributes to the persistence of the disease's transmission chain. The asymptomatic nature makes it difficult to identify and treat syphilis carriers, allowing the infection to spread more easily. If not properly diagnosed and treated, syphilis can progress over several years, resulting in severe systemic complications that affect multiple organs and body systems. These complications can include neurological damage, cardiovascular issues, and other potentially fatal health problems [7,8]. In 2022, the World Health Organization (WHO) estimated 8 million new syphilis cases among adults aged 15–49 worldwide. Prevalence is especially high among gay men and other men who have sex with men (7.5%) compared to 0.5% in the general male population. Some countries report a growing number of cases in this group, including congenital syphilis. Globally, there were an estimated 700,000 cases of congenital syphilis in 2022, resulting in 150,000 fetal deaths and stillbirths, 70,000 neonatal deaths, 55,000 preterm or low-birth-weight births, and 115,000 infants with clinical signs of the disease [9]. In Brazil, in 2023, 242,826 cases of acquired syphilis were reported, resulting in a detection rate of 113.8 cases per 100,000 inhabitants. In the same year, 86,111 cases of syphilis in pregnant women were recorded, with a rate of 34.0 cases per 1,000 live births. Although there have been advances, congenital syphilis remains a significant challenge, with 25,002 cases reported in 2023, as well as an incidence rate of 9.9 cases per 1,000 live births and 196 infant deaths [10]. The natural progression of syphilis is characterized by alternating periods of activity, with various clinical, immunological, and histopathological manifestations (primary, secondary, and tertiary syphilis), and periods of latency, known as latent syphilis. Additionally, syphilis can be classified as recent if diagnosed within one year of infection, and as late if diagnosed after one year. Syphilis progresses through different stages, each

marked by distinct clinical manifestations. In the primary stage, it is characterized by the formation of an ulcer in the genital or perianal area. In the secondary stage, various symptoms emerge, mainly affecting the skin. After a latency period, which can last several decades, the disease may progress to more advanced stages, significantly affecting the skin, heart, and nervous system [11]. Primary syphilis typically presents as a hard chancre at the site of inoculation about three weeks after infection. It begins as a pink papule that becomes ulcerated, painless, and non-inflammatory, with firm edges and a clean, serous base. Within 1–2 weeks, bilateral, painless lymphadenopathy appears. In 90–95% of cases, chancres are genital—on the foreskin, glans, or urethra in men, and on the labia, vaginal wall, or cervix in women. Often asymptomatic, it may go unnoticed. Extragenital sites include the anus, mouth, tongue, breasts, and fingers. The lesion resolves spontaneously in 4–5 weeks without scarring [6,12]. The diagnosis of syphilis requires an integrated approach that combines clinical data, diagnostic test results, a history of previous infections, and an investigation of recent high-risk sexual exposures. A thorough assessment of the patient's sexual history is crucial to clarify the diagnosis, requiring professional skills and the assurance of appropriate confidentiality. Diagnostic methods include direct examinations and immunological tests. Direct examinations involve the detection of *T. pallidum* in biological samples collected directly from primary and secondary lesions. These procedures are essential to confirm the presence of the syphilis-causing bacterium and to guide proper treatment [13–15]. The earliest methods developed to diagnose syphilis were complement fixation reactions, such as the Wassermann and Kahn tests, which used materials extracted from tissues, making standardization difficult [16]. With diagnostic advancements, these methods were replaced by tests like the VDRL (Venereal Disease Research Laboratory), which uses purified antigens derived from lecithin, cholesterol, and cardiolipin. The VDRL typically becomes positive between five and six weeks after infection and two to three weeks after the appearance of the primary chancre, though it may not detect early syphilis. In secondary syphilis, it is highly sensitive, but its effectiveness decreases in the later stages of the disease. Despite its usefulness, the VDRL, a non-treponemal test, is not specific and may yield false positives [17]. Treponemal tests detect antibodies specific to *T. pallidum*, such as those identified by rapid immunochromatographic assays, which require minimal infrastructure. These tests remain positive in about 85% of individuals for life and cannot distinguish between active and past infection. In contrast, non-treponemal tests (e.g., VDRL) detect non-specific anti-cardiolipin antibodies, making them useful for screening and monitoring treatment response, and complementary to treponemal tests [7,18]. Following a positive treponemal or non-treponemal test for syphilis, immediate treatment with benzathine benzylpenicillin is recommended in specific cases, including pregnant women, victims of sexual violence, individuals at risk of being lost to follow-up, those presenting signs of primary or secondary syphilis, and those without a prior diagnosis. Treatment after the initial positive result does not replace the need for further testing, clinical-laboratory follow-up, or treating sexual partners [13]. Within the first 24 hours of penicillin treatment, the Jarisch-Herxheimer Reaction (JHR) may occur, especially in cases of primary and secondary syphilis. This reaction manifests with worsening skin lesions (i.e., erythema, pain, itching), along with fever, malaise, headaches, and joint pain. While antipyretics can relieve these symptoms, there's no evidence they prevent the reaction [19,20]. The JHR occurs in approximately 10% to 35% of patients treated for syphilis and is characterized by an acute, self-limited febrile response within the first 24 hours after initiating therapy for *T. pallidum* infection. Although transient, its presentation—including fever, chills, myalgia, headache, and exacerbation of skin lesions—may be misinterpreted as disease progression, particularly given syphilis's reputation as the “great imitator.” Similar reactions have been reported in other spirochetal infections, such as Lyme disease and relapsing fever, where symptoms typically resolve within

a few hours after starting antimicrobial therapy [21].

Case reports suggest that JHR can induce uterine contractions during pregnancy and lead to complications like acute respiratory distress, liver and kidney dysfunction, myocardial injury, hypotension, meningitis, altered consciousness, seizures, or even stroke [22]. Research indicates that similar reactions occur in other spirochetal diseases, such as leptospirosis and borreliosis, presenting with symptoms like headaches, myalgia, arthralgia, and laboratory abnormalities, such as leukocytosis with lymphopenia. These reactions usually start 4 to 12 hours after treatment initiation and have been observed with antibiotics like erythromycin, amoxicillin, tetracycline, quinolones, and penicillin. Symptoms typically subside within 6 to 12 hours, and analgesics and antipyretics are commonly used for relief. The efficacy of corticosteroid pretreatment in preventing JHR remains a subject of debate. In pregnant women, the reaction can lead to adverse outcomes such as preterm birth or fetal demise, especially if the fetus is already infected. This case describes a rare manifestation of the JHR in a patient with secondary syphilis and underlying immunosuppression [23–27]. This case reports a rare form of the JHR in a patient with secondary syphilis and under immunosuppression.

2. Case Description

A 39-year-old female patient presented to the emergency department of Roraima General Hospital (HGR), the main public healthcare facility in Boa Vista, Roraima, Brazil. She exhibited high-grade fever (40 °C), chills, diffuse morbilliform rash (Figure 1A), generalized malaise, and hypotension. Over the preceding 10 days, she reported progressive worsening of the rash, along with asthenia, arthralgia, and fatigue. Additionally, she complained of a severe, diffuse headache without visual disturbances. On examination, the patient appeared lethargic, anxious, and confused, with normal respiratory effort, tachycardia (heart rate: 120 bpm), and hypotension (80/50 mmHg). In light of this clinical presentation, sepsis was suspected. Empirical antibiotic therapy with ceftriaxone was promptly initiated. Blood and urine cultures were obtained, and computed tomography (CT) scans of the brain, chest, and abdomen were performed to investigate possible sources of infection. The patient's partner informed the medical team that she had been receiving care at an infectious disease clinic following a recent diagnosis of secondary syphilis. At the time of hospital admission, her Venereal Disease Research Laboratory (VDRL) titer was 1:128. She had received a single intramuscular dose of benzathine penicillin G (2,400,000 IU) approximately 18 hours prior to admission. Her medical history included systemic arterial hypertension and overweight status, as well as a kidney transplant performed in 2016 and a cholecystectomy in 2017. She was on immunosuppressive therapy consisting of azathioprine, tacrolimus, and prednisone, and was under regular follow-up in São Paulo, SP, Brazil. Additionally, she had a prior ICU admission one year earlier due to sepsis of urinary origin. She denied tobacco use and alcohol consumption. Given the recent administration of benzathine penicillin and the acute onset of fever, hypotension, rash exacerbation, and systemic symptoms within 18 hours, a Jarisch-Herxheimer reaction (JHR) was considered. This reaction is known to occur following antibiotic treatment for spirochetal infections and can resemble sepsis, particularly in immunocompromised individuals. Initial laboratory tests showed a white blood cell count of $6.65 \times 10^3/\mu\text{L}$, hemoglobin of 10.90 g/dL, platelets at $217.00 \times 10^3/\mu\text{L}$, C-reactive protein (CRP) of 50.3 mg/dL, and negative rapid tests for HBsAg, anti-HCV, and anti-HIV. Urinalysis was normal, and a hemoparasite test was negative. Due to the severe headache, neurosyphilis was suspected, and a lumbar puncture was performed; however, cerebrospinal fluid (CSF) analysis ruled out this hypothesis. Brain, abdominal, and chest imaging revealed no changes related to the current clinical condition, except for reduced-sized kidneys with signs of advanced chronic

nephropathy, and a renal graft in the left iliac fossa with typical characteristics (Figure 2C-F). The patient's immunosuppressive regimen including azathioprine, tacrolimus, and prednisone may have amplified the inflammatory response, potentially intensifying the severity or duration of the JHR. Blood and urine cultures were negative, and procalcitonin levels were normal (<0.12 ng/mL). During hospitalization, the patient showed satisfactory clinical improvement, with continued empirical antibiotic therapy until infections were ruled out. Spontaneous clinical improvement was observed within 36 hours, despite ongoing empirical antibiotic therapy and the absence of identifiable infectious foci. This evolution, in the context of recent penicillin administration and systemic symptoms, was consistent with a Jarisch-Herxheimer reaction. Characterized by acute fever, chills, hypotension, headache, and worsening rash following treatment initiation, JHR is a transient inflammatory response triggered by the rapid destruction of spirochetes and release of proinflammatory mediators. The patient remained under observation for three more days before discharge, with improvement in her general condition, resolution of the morbilliform rash (Figure 1B), and remained afebrile.

3. Discussion

The Jarisch-Herxheimer reaction (JHR) was initially observed in the late 19th century by Austrian dermatologist Adolf Jarisch, who reported a worsening of skin lesions in a syphilis patient following treatment with a mercury-based medication. In the early 20th century, German dermatologist Karl Herxheimer documented a similar response, further contributing to the characterization of this reaction [28]. The JHR is an acute, self-limiting inflammatory response that typically occurs within 24 hours of initiating antibiotic therapy for spirochetal infections such as syphilis, Lyme disease, leptospirosis, and relapsing fever [22]. Clinically, JHR manifests with fever, chills, head-ache, myalgia, tachycardia, hypotension, and a transient exacerbation of existing skin lesions. Although generally benign, its presentation can closely resemble sepsis, posing significant diagnostic

challenges, particularly in critically ill or immunocompromised patients [29]. In the present case, a 39-year-old immunosuppressed female developed systemic symptoms including high fever, hypotension, and mental confusion approximately 18 hours after receiving intramuscular benzathine penicillin G for secondary syphilis. Given her immunosuppressive therapy and prior history of urosepsis, the initial clinical impression favored sepsis, prompting the initiation of empirical antibiotic therapy and comprehensive diagnostic evaluations. However, the temporal association between antibiotic administration and symptom onset, coupled with negative blood and urine cultures and normal procalcitonin levels, supported the diagnosis of JHR. The pathophysiology of JHR is believed to involve the rapid lysis of spirochetes following antibiotic treatment, leading to the release of endotoxin-like substances and pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-8 (IL-8). This cytokine surge precipitates the acute inflammatory response characteristic of JHR. Symptoms typically resolve within 6 to 12 hours; however, in this case, resolution occurred after 36 hours, which is longer than the usual course [30]. Notably, the patient's ongoing immunosuppressive regimen including azathioprine, tacrolimus, and prednisone did not mitigate the severity of the reaction. This observation contrasts with the expectation that immunosuppressed individuals might experience attenuated inflammatory responses due to their diminished immune function [31]. The differential diagnosis between JHR and sepsis is particularly challenging due to overlapping clinical features such as fever, tachycardia, and hypotension [32]. Key distinguishing factors include the timing of symptom onset relative to antibiotic administration and the absence of an identifiable infectious source. In this case, the prompt recognition of JHR prevented unnecessary interventions and highlighted the importance of clinical vigilance. Brazil has been experiencing a resurgence of syphilis cases in recent years. In 2023, 242,826 cases of acquired syphilis were reported, reflecting a significant increase from previous years [10]. This rising incidence underscores the need for heightened awareness and

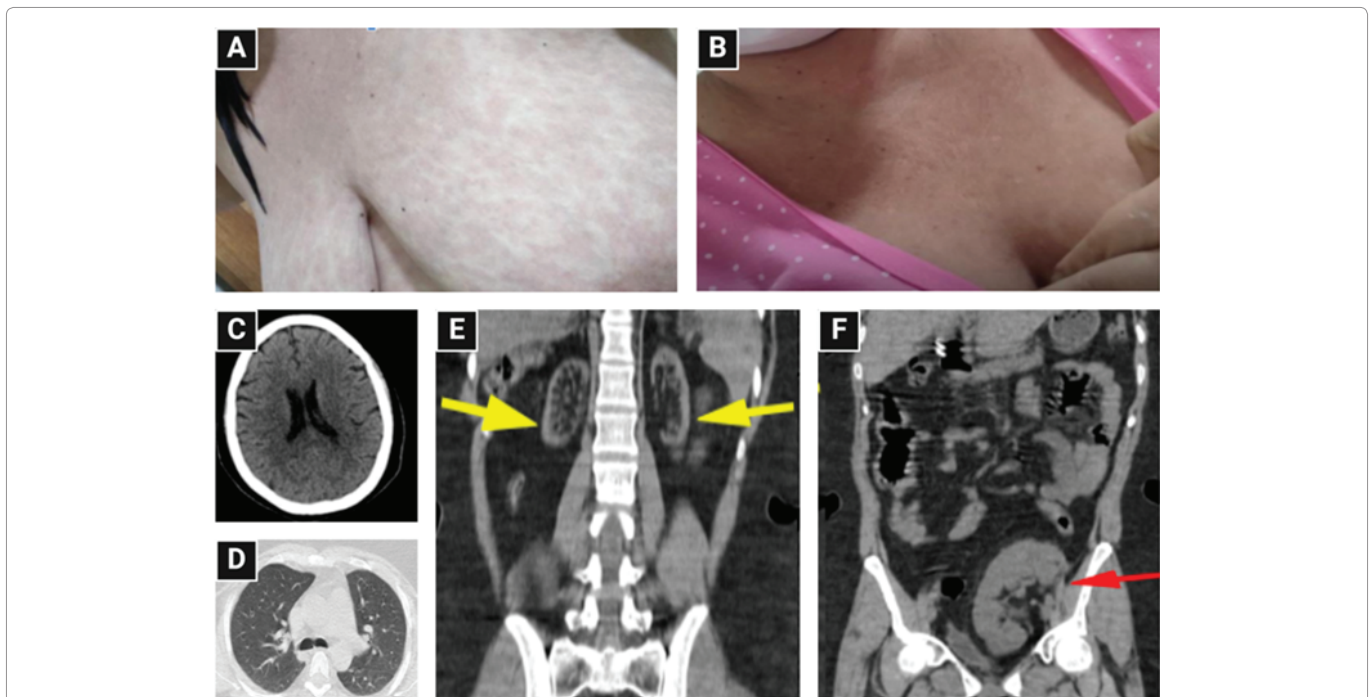


Figure 1: Clinical and radiological findings of the patient. (A) Morbilliform rash at admission. (B) Improvement of the morbilliform rash after 36 hours. (C) Cranial CT scan showing: Normal cortical sulci and brain cisterns for the patient's age. The brain parenchyma exhibits normal morphology and attenuation. No significant midline shift is observed, and there are no signs of intra- or extra-axial collections or masses. (D) Chest CT showing: Absence of pleural effusion. Mild reticular and ground-glass opacities in the subpleural region of the middle lobe, nonspecific. The rest of the lung parenchyma is without significant consolidations. (E) Abdominal CT, sagittal view, showing: Small kidneys with signs of advanced chronic nephropathy. (F) Abdominal CT, sagittal view, showing: Renal graft in the left iliac fossa with typical characteristics.

education among healthcare professionals regarding syphilis and its complications, including JHR. Misinterpretation of JHR as sepsis can lead to unnecessary treatments and increased healthcare costs, emphasizing the importance of accurate diagnosis and appropriate management. In summary, the JHR is a transient inflammatory response that can closely mimic sepsis [32]. Distinguishing between JHR and sepsis is critical to ensure appropriate patient management and avoid unnecessary interventions. This case highlights the importance of considering JHR in the differential diagnosis following antibiotic treatment for spirochetal infections, particularly in regions with high syphilis prevalence.

5. Conclusions

This case underscores the critical importance of recognizing the Jarisch-Herxheimer reaction (JHR) as a potential cause of acute clinical deterioration following antibiotic treatment for spirochetal infections. In immunocompromised patients, where baseline risk for severe infections is high, the presentation of JHR may closely mimic sepsis, leading to diagnostic uncertainty and potentially unnecessary interventions. Timely identification-grounded in careful clinical judgment and an understanding of the reaction's pathophysiology-is essential to avoid overtreatment and improve patient safety. As syphilis continues to rise in prevalence, particularly in endemic settings such as Brazil, the ability of clinicians to distinguish JHR from true systemic infections is not only a matter of individual patient care, but also a public health priority. Greater awareness and continued education are vital to ensuring accurate diagnosis, appropriate resource use, and optimal outcomes in the management of syphilis and its complications. Institutional Review Board Statement: The study was approved by the Research Ethics Committee of the Federal University of Roraima, under protocol number CAAE 84002424.0.0000.5302 (ap-proved on 24 March 2025). Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper.

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