Acute pustular eruption following a Jarisch-Herxheimer reaction in the treatment of syphilis

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INTRODUCTION

The Jarisch-Herxheimer reaction (JHR) is an acute febrile inflammatory reaction that sometimes follows the treatment of syphilis and other spirochete infections with antibiotics. Although first described over a century ago, relatively little is still known about this adverse event. It is thought that antimicrobial therapy renders the dividing spirochetes susceptible to phagocytosis, with consequent release of lipoproteins, cytokines, and immune complexes.[1] Symptoms present within 2 hours of antimicrobial administration and include fever, chills, vasodilation with flushing, tachycardia, mild hypotension, and possible worsening of skin lesions.[2] The reaction is typically self-limited and resolves within 24 hours. Here, we report a patient with syphilis treated with penicillin who developed an acute JHR with a sustained, generalized rash believed to be either a flare of psoriasis or acute generalized exanthematous pustulosis (AGEP).

Abbreviations used:

AGEP:	acute generalized exanthematous pustulosis
JHR:	Jarisch-Herxheimer reaction
TNF-α:	tumor necrosis factor-α

CASE REPORT

A 31-year-old black man with a self-reported history of psoriasis came to the emergency department with a widespread eruption that began after penicillin treatment for syphilis. The patient had also previously been diagnosed with syphilis in 2010 and was treated with penicillin at that time without complications. He described an erythematous, scaly eruption on his trunk and arms, sparing his elbows and knees, occurring intermittently for the past few years that typically cleared within a few days after applying clobetasol. One month previous, he noticed what appeared to be his usual psoriasis flare; however, it was not resolving with clobetasol. He was subsequently diagnosed with his second episode of syphilis and treated with 2 intramuscular benzathine penicillin G injections. He had also recently completed a 10-day course of doxycycline and was 10 days into a 1-month course of tetracycline. A few hours after each penicillin injection, he reported arthralgia, myalgia, fever, chills, headache, and worsening of the rash. Examination revealed erythematous plaques with central hyperkeratosis and collarettes of scale and numerous scattered pustules covering >90% of his body surface area (Fig 1). The patient was admitted for supportive care.

A skin biopsy indicated a subcorneal neutrophilic pustule consistent with AGEP or pustular psoriasis (Fig 2). Workup revealed positive rapid plasma reagin and venereal disease research laboratory tests. Human immunodeficiency virus, hepatitis B virus, hepatitis C virus, and QuantiFERON-TB Gold (Quest Diagnostics, Madison, NJ) screening tests were all negative. In addition, mutations were absent in the *IL-36RN* gene, which encodes the interleukin 36 receptor antagonist implicated in both AGEP and pustular psoriasis.[3] The patient was

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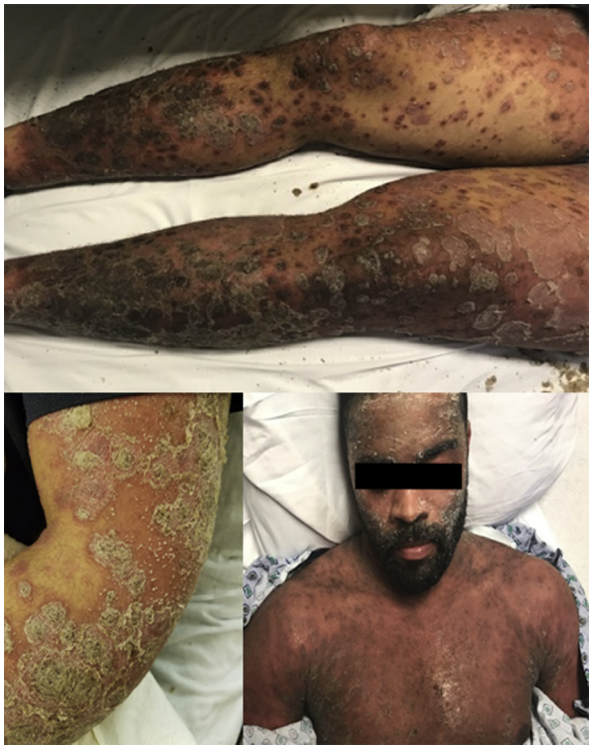

Fig 1. Jarisch-Herxheimer reaction in a patient with syphilis. Diffuse erythematous pustules and plaques with central hyperkeratosis and collarettes of scale are seen on >90% of the body surface area.

febrile throughout admission; after 7 days, the fever subsided and the patient was discharged. Given the severity of his reaction, the patient was instructed to follow-up with his primary care physician to determine if further treatment was necessary. One month after discharge, he saw a dermatologist and his skin improved substantially with topical fluocinonide. Two months after hospitalization, the patient saw an infectious disease specialist, who was concerned that his latent syphilis was not adequately treated because he only received 2 of the 3 planned shots of penicillin along with only 10 days of doxycycline. He was restarted on a 1-month course of doxycycline, upon which a generalized clinical plaque-type psoriasis flare was observed in the same distribution as his prior skin eruption, only this time without fever or other systemic systems. Currently, the patient is in the process of obtaining acitretin through an assistance program.

DISCUSSION

Syphilis, a genital ulcerative infection caused by the bacteria *Treponema pallidum*, can have serious potential complications when left untreated. The mainstay of treatment, regardless of stage, is penicillin G. A well-established, predictable complication

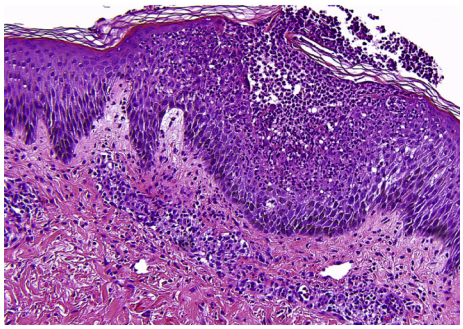

Fig 2. Skin biopsy demonstrating subcorneal neutrophilic pustule. These findings are consistent with either acute generalized exanthematous pustulosis or pustular psoriasis. (Hematoxylin-eosin stain; original magnification: ×20.)

is the JHR, occurring in approximately 10% of all patients treated for syphilis.[4]

Rash is a characteristic finding in the second stage of syphilis, classically a diffuse macular or papular rash involving the trunk, extremities, and potentially the mucosal surfaces, palms, and soles. These lesions can worsen with a JHR, manifesting as acute vascular congestion, neutrophilic infiltrates, and edema, but the exacerbation is transient and resolves within 24 hours.[5] This is in contrast to the sustained, progressive, and severe exacerbation seen in our case. It is often difficult to distinguish AGEP from pustular psoriasis because they can present with similar histologic and clinical findings. A case of AGEP has been described in a patient with psoriasis after administration of etanercept, a tumor necrosis factor-α (TNF-α) inhibitor.[6] Certain features favor the diagnosis of pustular psoriasis, including the longer duration of fever and pustules, history of psoriasis, generalized eruption, lack of prior reaction to penicillin, and presence of arthralgias, all of which were present in our patient.[7] Furthermore, the patient flared with clinical psoriasis upon re-exposure to syphilis treatment, notably without systemic symptoms. Still, we cannot state whether this was definitively pustular psoriasis or AGEP. To the best of our knowledge, there are no reported cases in the literature of a JHR causing a new onset or exacerbation of psoriasis.

The treatment of JHR is supportive. There are currently no agents routinely administered prophylactically to prevent or ameliorate JHR. In a study performed by Fekade et al,[8] patients with spirochete (*Borrelia*) infections pretreated with sheep polyclonal Fab fragments against TNF-α immediately before penicillin injection had fewer clinically evident JHRs than those pretreated with nonspecific sheep antibodies. However, a definitive conclusion remains questionable as

biologic therapies can take time to establish effect in the body. TNF-α is a critical proinflammatory cytokine elevated in JHR, and is also common to many inflammatory diseases, including psoriasis.[9,10] If pretreatment with TNF-α inhibitors does indeed have the ability to suppress JHR, it seems reasonable that JHR might trigger TNF-α production and the onset of TNF-α—mediated conditions (AGEP or psoriasis). We hypothesize this played a role in our patient's cutaneous flare. Further research is warranted to establish this relationship.

When treating spirochete infections with antibiotics, providers should be prepared for and warn patients of the possibility of JHR and its complications. Pretreatment with immunotherapy such as TNF-α inhibitors should be considered, especially in patients with a history of psoriasis. Further research is needed to investigate the role of targeted immune therapy to prevent JHR and its possible sequelae.

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