Palisaded neutrophilic and granulomatous dermatitis associated with ledipasvir/sofosbuvir

Mary Elizabeth Reed Shenk, MHSA, Kimberly Marie Ken, MD, Kara Braudis, MD, and Kristen Heins Fernandez, MD
Columbia, Missouri

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INTRODUCTION

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is a cutaneous reaction pattern seen in association with systemic diseases and rarely with infections or medications.[1] Typical clinical presentation includes tender, erythematous-to-violaceous papules, plaques, or nodules affecting extensor and acral surfaces, most commonly the elbows and hands.[1,2] Histopathologic examination of the lesions can vary, and the disease is thought to occur along a continuum, with early lesions histologically resembling leukocytoclastic vasculitis with dense neutrophilic infiltration and more established lesions consisting of palisaded histiocytes and small granulomas with trapping of collagen and neutrophilic debris.[1] Late lesions are thought to simulate granuloma annulare (GA) with fibrosis and granulomas surrounded by collagen and mucin.[2]

Ledipasvir/sofosbuvir (LDV/SOF) is a novel, oral, direct-acting antiviral medication used to treat chronic hepatitis C (HCV). Compared with conventional treatment for HCV, LDV/SOF offers improved tolerability and efficacy with limited adverse reactions.[3] Adverse reactions of the drug can include cutaneous eruptions[4]; however, to our knowledge, there are no previous case reports of LDV/SOF-induced PNGD. Here, we present a case of PNGD associated with LDV/SOF.

Abbreviations used:

GA:	granuloma annulare
HCV:	hepatitis C virus
INF:	interferon
LDV/SOF:	ledipasvir/sofosbuvir
PNGD:	palisaded neutrophilic and granulomatous dermatitis

CASE REPORT

A 65-year-old man with a medical history of HCV diagnosed 6 years prior, cerebrovascular accident, hypertension, type II diabetes mellitus, hyperlipidemia, and peripheral vascular disease presented to our dermatology clinic for consultation concerning a rash present on his bilateral hands along with conjunctival erythema for nearly 4 weeks. Associated symptoms included pain, tenderness, and pruritus of his skin lesions and occasional ocular pruritus. He denied rash elsewhere on his body. No therapy for his rash had been initiated.

Current medications included amlodipine, cholecalciferol, clopidogrel, glipizide, glyburide, hydrochlorothiazide, insulin glargine, LDV/SOF, metformin, omeprazole, oxybutynin, sildenafil, simvastatin, and tamsulosin. LDV/SOF had been the only recent medication change, which was started 4 days before the onset of his skin findings and conjunctivitis. Given the timeline, a drug reaction to LDV/SOF was suspected.

On examination, he had tender erythematous papules and nodules with a violaceous center on his right volar hand and digits (Fig 1, *A*), tender erythematous papules and nodules on his right dorsal hand and lateral digits (Fig 1, *B*), and erythematous papules with central hemorrhagic crusting on his left fourth dorsal, proximal digit. He

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Correspondence to: Kristen Heins Fernandez, MD, One Hospital Drive, MA111, Columbia, MO 65212. E-mail: fernandezk@health.missouri.edu.
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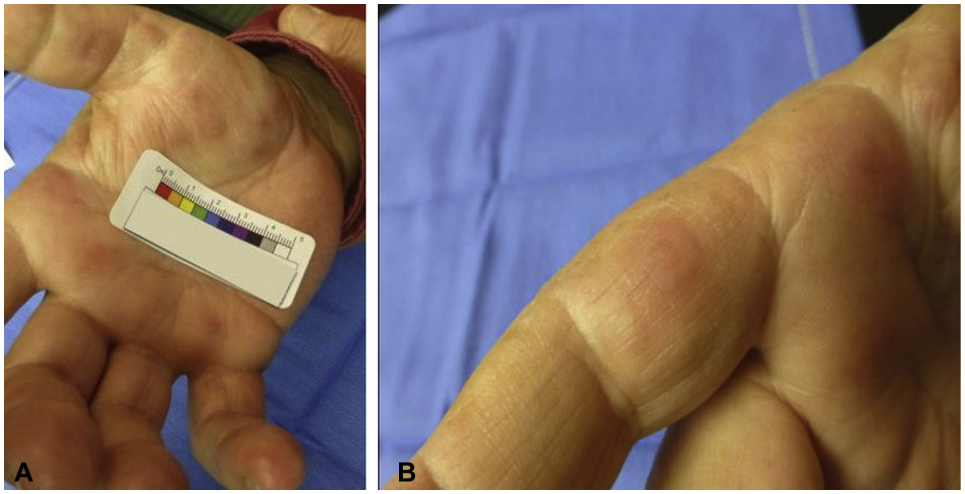

Fig 1. **A**, PNGD: Multiple erythematous nodules on the palm. **B**, PNGD: Erythematous nodules on the right lateral digit and palm.

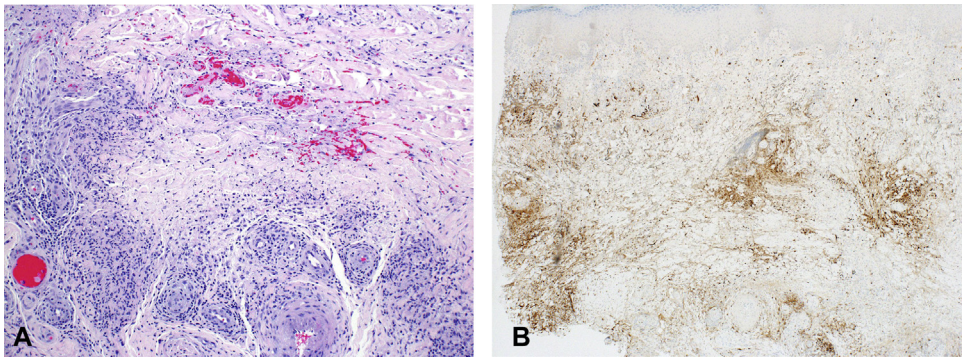

Fig 2. **A**, PNGD: Nodular and palisaded collections of histiocytes with multinucleated histiocytes and associated lymphocytes. **B**, PNGD: Scattered mononuclear cells within areas of granulomatous infiltration. (**A**, Hematoxylin-eosin stain; **B**, Myeloperoxidase stain; original magnifications: **A**, ×10; **B**, ×4.)

had bilateral scleral injection of his medial eyes. No oral lesions or erosions were present.

Two punch biopsies were obtained from his right proximal and right distal second palmar digit. Histopathology of both specimens found nodular and palisaded collections of histiocytes with some multinucleated histiocytes and associated lymphocytes in the dermis (Fig 2, *A*). Foci of interstitial mucin and some loss of elastic fibers were present. A myeloperoxidase stain highlighted scattered mononuclear cells within areas of granulomatous infiltration (Fig 2, *B*). Based on the biopsy results and clinical pathologic correlation, PNGD was diagnosed.

The patient was started on clobetasol 0.05% ointment for affected areas. After discussions with the hepatology department, it was decided to continue LDV/SOF. His treatment was shortened to 8 weeks instead of 12 because of significant ankle pain and edema, without cutaneous abnormality. At the end of his LDV/SOF treatment, only postinflammatory desquamation remained. The rash has not recurred, and his HCV viral load is undetectable.

DISCUSSION

The diagnosis of PNGD can be challenging, as the clinical and histologic presentation can vary. PNGD occurs along a spectrum of cutaneous granulomatous reactions, also including interstitial granulomatous dermatitis and interstitial granulomatous drug reaction; there is often overlap between these entities, further complicating the diagnosis.[1] The tender erythematous papules and nodules found on our patient's hands are clinically characteristic of PNGD.[1] Histologically, our case is consistent with late findings of PNGD, which can resemble GA, with

palisaded granulomas surrounding degenerated collagen and mucin.[2]

PNGD associated with drug reactions are relatively uncommon. Allopurinol was the first known drug-induced case of PNGD to be reported in the literature.[5] Rosenbach and English[1] cited tumor necrosis factor inhibitors and allopurinol as the most common medications known to be associated with PNGD. The timeline for PNGD eruption after drug initiation has been reported to be 2 to 3 weeks for allopurinol[5] and up to 22 months for tumor necrosis factor inhibitors.[6] Although our suspected drug reaction occurred after only 4 days, given the limited reports of drug-induced PNGD, this quick timeline does not necessarily argue against a drug association.

Cutaneous adverse reactions associated with LDV/SOF have been reported in 2.4% to 7% of cases,[3,4,7] and rarely LDV/SOF has been discontinued in certain cases because of severe skin disorders.[7] Tadokoro et al[7] reported a case of a steroid-responsive grade 3, morbilliform drug eruption of the face and upper extremities appearing 9 days after initiating LDV/SOF. The LDV/SOF package insert lists "skin rashes, sometimes with blisters or angioedema-like swelling" as the only cutaneous reactions, which were identified during postmarket experience.[8] No cutaneous reactions clinically or histologically resembling PNGD have been described in association with LDV/SOF.

Cutaneous granulomatous reactions have been associated with HCV and interferon (INF) therapy, previously widely used in its treatment. The cutaneous manifestations of HCV vary, and vasculitis is most commonly seen histologically, although palisading granulomatous inflammation is another common histologic finding in these patients.[9] El-Khalawany et al[10] described 18 HCV patients treated with INF who had cutaneous granulomatous reactions. Histologically, these reactions were most often consistent with sarcoidosis, although interstitial granulomatous reaction and interstitial granulomatous drug reaction were also described.[10] However, these reports do not associate PNGD, specifically, with HCV or INF therapy.

Together the clinical and pathologic findings of PNGD are reported as associated with LDV/SOF treatment, as supported by a comprehensive literature search. However, it is possible that some of the cutaneous adverse reactions associated with LDV/SOF treatment may have been PNGD but were not biopsied or further evaluated because of the mild nature and/or short duration of LDV/SOF treatment, which is generally 12 weeks. Palisading granulomatous inflammation has been noted histologically in the setting of chronic HCV; thus, it is possible that PNGD may be associated with immune activation against HCV in the setting of LDV/SOF treatment. Perhaps the development of PNGD during HCV treatment is a good prognosticator, as our patient had an undetectable HCV viral load and was thus cured of HCV with only 8 weeks of treatment.

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