

BRIEF ARTICLES

Drug Induced Autoimmunity Related Neutrophilic Dermatitis by Calcium Channel BlockersMaulik M. Dhandha, MD¹, Markiza Cooper, MD², M. Yadira Hurley, MD³, Sofia Chaudhry, MD³¹Maine Dartmouth Family Medicine Residency, Augusta, ME²Mayo Clinic, Department of Dermatology, Jacksonville, FL³Saint Louis University, Departments of Dermatology, Saint Louis MO**ABSTRACT**

Autoimmunity Related Neutrophilic Dermatoses (ARND) is a recently described entity characterized by urticarial papules and plaques with histology showing a neutrophilic perivascular and interstitial infiltrates with leukocytoclasia, along with variable vacuolar interface dermatitis. We report a 38 year old Caucasian female with a ten year history of lupus who presented with pruritic urticarial papules and plaques on the face, trunk, upper extremities and thighs. The onset occurred 10 days after she started a calcium channel blocker (CCB), diltiazem. Histopathology revealed scattered dyskeratotic keratinocytes, vacuolar interface dermatitis, and a sparse perivascular and interstitial mixed infiltrate of neutrophils within the dermis. There was focal leukocytoclasia, dermal edema, and rare eosinophils. The patient initially improved with prednisone taper, but flared again upon starting a different CCB, verapamil. Exposure to certain medications such as CCB in the setting of autoimmune connective tissue disorder may be the inciting trigger for a neutrophilic dermatoses. Future studies may provide further information on the pathogenesis of ARND and cutaneous drug eruption in the setting of SLE.

INTRODUCTION

Autoimmunity Related Neutrophilic Dermatitis (ARND) is a recently described clinical-histopathological entity. In the setting of an autoimmune connective tissue disease (AICTD), these patients develop a nonbullous urticarial eruption that does not resolve within 72 hours. Histology is characterized by an interstitial neutrophilic infiltrate with leukocytoclasia along with a variable degree of vacuolar interface dermatitis.¹ The nomenclature of ARND encompasses multiple prior case reports

and series that describe a similar condition by different terminology, including nonbullous neutrophilic dermatosis (NBND), nonbullous Sweet-like neutrophilic dermatosis, and nonbullous neutrophilic lupus erythematosus (NBNLE). It has primarily been reported in the setting of lupus, but has also been associated with rheumatoid arthritis and dermatomyositis.¹⁻⁶ Herein we report a unique case of ARND in a patient with systemic lupus erythematosus (SLE), whose eruption appears to have been triggered by starting a calcium channel blocker (CCB), given that the patient subsequently flared on a different CCB. To

November 2019 Volume 3 Issue 6

the best of our knowledge, there have been no prior reports of drug induced ARND. Our patient was a 38 year-old Caucasian

CASE REPORT

female who presented to dermatology with a three day history of pruritic pink edematous urticarial papules coalescing into plaques on her face, trunk, upper extremities and thighs (Fig. 1 and 2). Her mucous membranes were unremarkable, and she denied any joint pain/swelling, fevers and increased sun exposure. She had a history of class IV Lupus Nephritis diagnosed 10 years prior, but her lupus had since been well controlled on only hydroxychloroquine 200 mg twice a day. (She was off hydroxychloroquine for one month due to insurance issues, but it was restarted two days prior to the eruption.) Her other medications included bupropion and diltiazem, the latter being started 10 days prior to her eruption. The clinical differential diagnosis of her eruption included a flare of her SLE, autoimmunity related neutrophilic dermatosis, a class four drug hypersensitivity, and urticaria.

She was started on systemic corticosteroids while awaiting biopsy results. Diltiazem was discontinued since it was a possible culprit, while hydroxychloroquine was continued. Her histology revealed scattered dyskeratotic keratinocytes and vacuolar interface dermatitis (Figure 3). There was a sparse perivascular and interstitial mixed infiltrate composed predominantly of neutrophils within the dermis (Figure 4). There was focal leukocytoclasia and associated dermal edema. There was no fibrinoid necrosis of the vessels. There were sparse eosinophils within the infiltrate (Figure 5). The differential diagnoses for this histology included non-bullous neutrophilic lupus erythematosus, a neutrophilic dermatosis, and a drug eruption.

Given the neutrophilic infiltrate, she was started on dapsone as her systemic steroid was tapered. Autoimmune work up revealed positive anti-histone (1.7), ANA (speckled), and anti-dsDNA (30) antibodies. Her skin continued to clear as her steroid dose was slowly tapered. After she had been on 20mg of prednisone daily for five days, she had a sudden severe flare of her eruption. At this time we learned that another provider had restarted her on another calcium channel blocker, verapamil, prior to the flare. Her prednisone dose was again increased to 60mg daily, and we had the new CCB changed to an ACE-inhibitor. Because of the flare, Rheumatology also started her on mycophenolate mofetil as a steroid sparing agent. However, as her prednisone dose was again tapered off over 3 months, she did not experience a flare. Dapsone was then stopped. Mycophenolate Mofetil was also slowly tapered over 8 months by Rheumatology. Patient has not had any flares since getting off the medications.

Figure 1. Pruritic edematous urticarial papules coalesced into plaques on face, neck, chest and upper arms.



SKIN

Figure 2. Pruritic edematous urticarial papules coalesced into plaques on the back.



Figure 3. Vacuolar Interface Dermatitis with superficial perivascular and interstitial neutrophilic infiltrate (10x).

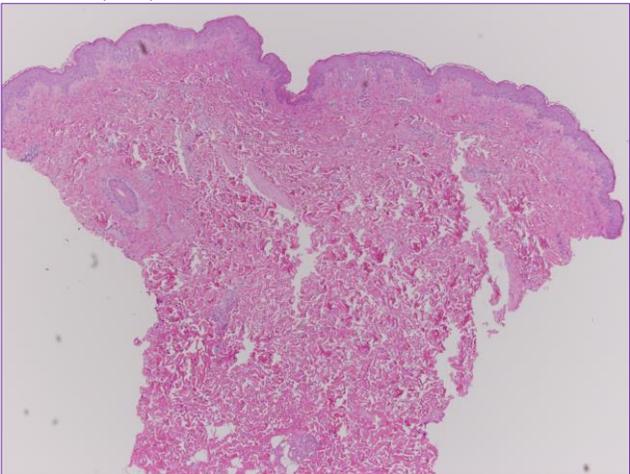


Figure 4. Vacuolar Interface Dermatitis with superficial perivascular and interstitial neutrophilic infiltrate (40x).

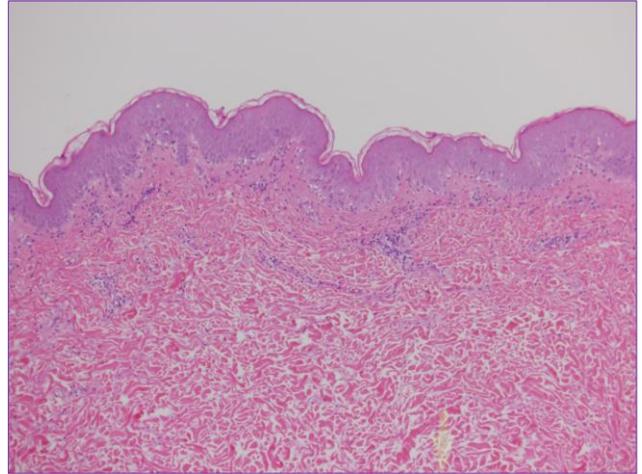
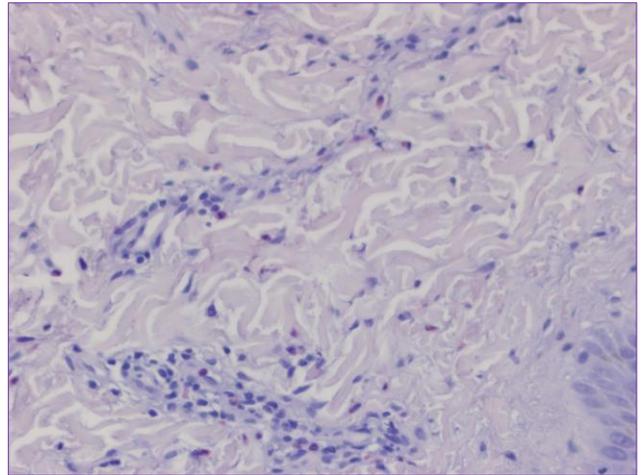


Figure 5. Sirius Red staining showing rare eosinophils in the infiltrate (100x).



DISCUSSION

The patient's eruption of urticarial papules and plaques in the setting of lupus, combined with a histology of a predominantly neutrophilic perivascular and interstitial infiltrates with leukocytoclasia and vacuolar interface dermatitis is most consistent with autoimmunity related neutrophilic dermatosis (ARND). However, unlike prior reports, our patient had a new preceding medication: a calcium channel blocker. Her eruption had a sudden, severe flare when she was re-exposed to second calcium channel blocker. The acute onset of the eruption 10 days after the initial exposure to calcium channel blocker along with the severe flare after re-exposure with another CCB indicate that her eruption may have been drug induced. The sparse eosinophils within the biopsy may also indicate a drug hypersensitivity reaction. Although the main other differential diagnosis was a flare of her lupus erythematosus, the fact that she flared with re-exposure to another CCB makes this less likely.

Our case demonstrates that the exposure to certain medications, such as CCBs, may be the inciting trigger for a neutrophilic dermatosis that present as ARND. However this effect may be restricted to non-dihydropyridine CCBs, as this patient was only exposed to this class of CCBs. Additional studies are needed to further understand the pathogenesis of ARND and cutaneous drug eruptions in the setting of autoimmune connective tissue diseases.

Conflict of Interest Disclosures: M. Yadira Hurley and Maulik M. Dhandha have participated in clinical trials in the past.

Funding: None

Corresponding Author:

Maulik M. Dhandha, MD
Maine Dartmouth Family Medicine Residency
Dermatology
#340 Ballard Center, 6 Chestnut Street, Augusta, ME
Email: maulikdhandha@gmail.com

References:

1. Saeb-Lima M, Charli-Joseph Y, et al. Autoimmunity-related neutrophilic dermatosis: a newly described entity that is not exclusive of systemic lupus erythematosus. *Am J Dermatopathol* 2013;35(6):655-60. [PMID: 23518639]
2. Hau E, Vignon Pennamen MD, Battistella M, et al. Neutrophilic skin lesions in autoimmune connective tissue diseases: nine cases and a literature review. *Medicine (Baltimore)*. 2014 Dec;93(29):e346. [PMID: 25546688]
3. Brinster NK, Nunley J, Pariser R, et al. Nonbullous neutrophilic lupus erythematosus: a newly recognized variant of cutaneous lupus erythematosus. *J Am Acad Dermatol*. 2012;66:92-97. [PMID: 22050914]
4. Pavlidakey P, Mills O, Bradley S, et al. Neutrophilic dermatosis revisited: an initial presentation of lupus? *J Am Acad Dermatol*. 2012;67:e29-e35. [PMID: 21907449]
5. Gleason BC, Zembowicz A, Granter SR. Non-bullous neutrophilic dermatosis: an uncommon dermatologic manifestation in patients with lupus erythematosus. *J Cutan Pathol*. 2006;33:721-725. [PMID: 17083690]
6. Satter EK, High WA. Non-bullous neutrophilic dermatosis within neonatal lupus erythematosus. *J Cutan Pathol*. 2007;34:958-960. [PMID: 18001424]