Urticaria and a rare mutation: An unusual case of neutrophilic urticarial dermatosis

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INTRODUCTION

Neutrophilic urticarial dermatosis (NUD) is a rare condition characterized by a transient urticarial eruption typically accompanied by systemic symptoms including fever and arthralgias. About 50 cases have been described in the literature to date.[1] The histology is unique, showing a neutrophilic interstitial, perivascular and/or perieccrine infiltrate with leukocytoclasia. Notably, it lacks leukocytoclastic vasculitis.[1-4] In this case, we discuss a 59-year-old white woman with NUD who harbored a novel heterozygous mutation for NLR Family Pyrin Domain Containing 3 (*NLRP3*) gene. This gene provides instructions for the protein synthesis of cryopyrin.

Abbreviations used:

CAPS:	cryopyrin- associated periodic syndromes
IL:	interleukin
NUD:	neutrophilic urticarial dermatosis
NLRP3:	NLR family pyrin domain containing 3

CASE REPORT

A 59-year-old white woman with a medical history of chronic myelogenous leukemia (treated with dasatinib, a tyrosine kinase inhibitor), renal cell carcinoma (status post partial nephrectomies), diabetes mellitus type II, and hypothyroidism presented to clinic with a 10-month history of a painful skin eruption, polyarthralgia, fevers, and fatigue. A review of systems also found that she had bilateral partial sensorineural hearing loss. On physical examination, there were large, red, thin, erythematous plaques on the flanks, lateral thighs, abdomen, and lower legs (Fig 1). The patient reported that lesions persisted for 24 to 72 hours. Initially, allergic contact dermatitis was diagnosed. However, her symptoms persisted despite use of antihistamines and topical steroids and avoiding allergens. At a subsequent visit, a biopsy was performed which found a primarily dermal infiltrate composed of perivascular, perieccrine, and interstitial neutrophils with focal leukocytoclasia. Neither vasculitis nor edema was observed (Fig 2, *A* and *B*). Serology testing found an elevated C-reactive protein and mildly elevated

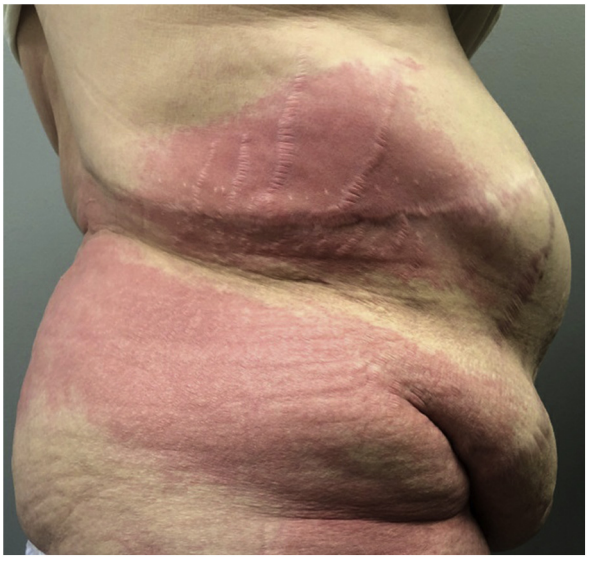

Fig 1. On physical examination, broad, large thin erythematous plaques were present on the abdomen, bilateral flanks, lower back, and lower legs.

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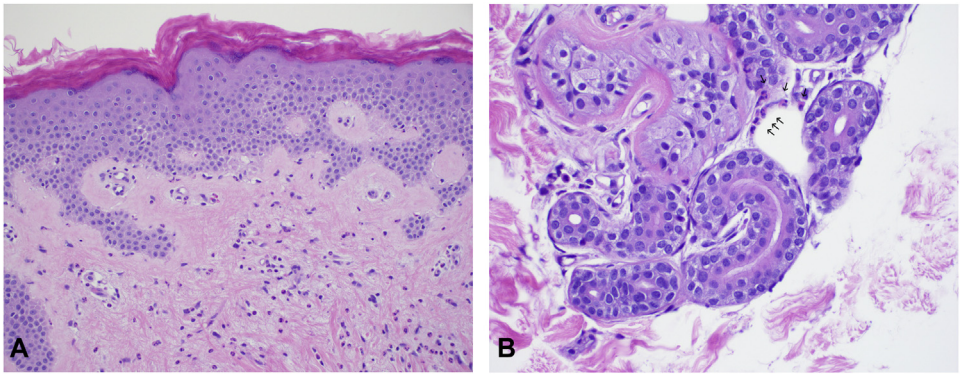

Fig 2. **A**, Neutrophils are seen lining the dermoepidermal junction. There is also an interstitial and perivascular neutrophilic infiltrate present within the dermis. **B**, Neutrophils are also visualized around and infiltrating eccrine glands.

ferritin. Rheumatoid factor, antinuclear Antibodies, cyclic citrullinated peptide, complements, and urine and serum protein electrophoreses were all unremarkable. Ultimately, genetic testing found that the patient had a unique heterozygous mutation in *NLRP3* (c. 1976C>A). Neutrophilic urticarial dermatosis associated with a cryopyrin-associated disorder was the final diagnosis. Dasatinib was held, dapsone was initiated, and the patient's symptoms resolved.

DISCUSSION

NUD was initially described in 1985. A histopathologic review of biopsies from 241 patients with urticaria found that a small subset (10%) had infiltration with neutrophils without vasculitis. These specific cases were coined *neutrophilic urticaria*. It was later noted that this condition was often associated with an elevated sedimentation rate and leukocytosis. Currently, NUD is recognized as a rare condition characterized by a transient urticarial eruption sometimes associated with fevers, polyarthralgia, and a rich neutrophilic dermal infiltrate. It has a distinct reaction pattern associated with systemic diseases such as adult-onset Still disease, systemic lupus erythematosus, Schnitzler syndrome, and autoinflammatory diseases (ie, cryopyrin-associated periodic syndromes [CAPS]).[1,2,4,5] Unlike other neutrophilic dermatoses, such as Sweet syndrome, NUD histologically lacks dermal edema.[3] Although leukocytoclasia may be present, vessel wall alteration is not seen. This finding contrasts with those of urticarial vasculitis. Furthermore, unlike common urticaria, the infiltrate is predominately or entirely neutrophilic. Previous studies suggest that the neutrophils in NUD tend to line or infiltrate the epithelia of the epidermis, hair follicles, and sebaceous and eccrine glands.[4] One study termed this phenomenon *neutrophilic epitheliotropism*, which proved to be of high sensitivity (83.1%).[3] Similarly, in our case, neutrophils can be seen both lining the dermoepidermal junction as well as infiltrating eccrine glands (Fig 2, *B*).

Our patient's serologic work up was unrevealing for other causes of NUD such as systemic lupus erythematosus, Schnitzler syndrome, or Still disease. Given the clinical suspicion for cryopyrin-associated periodic syndrome, genetic testing was proposed. Results showed a novel heterozygous mutation in *NLRP3* suggesting that she has a form of CAPS. The 3 major cryopyrinopathies include familial cold autoinflammatory, Muckle-Wells, and CINCA/NOMID syndromes. These autoinflammatory diseases characteristically feature episodic fevers and widespread neutrophilic urticarial dermatoses. Although familial cold autoinflammatory and CINCA/NOMID appear in childhood, Muckle-Wells syndrome can manifest at any age.

CAPS are mediated by autosomal dominant gain-of-function heterozygous mutations altering protein synthesis of cryopyrin, an essential component of inflammasomes. This enables the autocatalytic activation of inflammatory caspases. Activation of these caspases causes an uncontrolled overproduction of interleukin (IL)-1β,[4,6] leading to a cascade of unrestrained cytokines. Furthermore, recent studies found that IL-1 potentiates T helper-17 activity including neutrophil recruitment into the skin.[7] A study by Meng et al[8] showed that the skin of mice with a *NLPR3* mutation had a neutrophil-rich infiltrate. These mice also demonstrated a T helper-17—predominant profile, confirmed by mRNA analysis and real-time polymerase chain reaction.[9]

Patients with CAPS typically respond well to IL-1 inhibitors such as anakinra. However, our patient was started on dapsone, 25 mg/d, while genetic testing was pending. Dapsone was selected as an interim therapeutic agent because it inhibits myeloperoxidase, thus, is very effective in treating neutrophilic dermatoses. Ultimately, the patient had a

favorable response after 2 weeks of treatment, with complete resolution of her urticarial eruption. Considering her medical history, to avoid further immunosuppression, the decision was made to continue dapsone and reserve anakinra for progression of symptoms. Her dasatinib was also held. Of note, a variety of tyrosine kinases have been implicated in *NLRP3* inflammasome activation.[7] Hence, it is possible that dasatinib may have played a role in unmasking the patient's underlying disorder, thus accounting for her late presentation. This case ultimately highlights the wide differential diagnosis considered for persistent urticarial eruptions, especially in the setting of systemic symptoms. In rare cases such as ours, thorough serologic and genetic testing may be appropriate to establish a diagnosis.

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