

Neutrophilic Urticaria With Systemic Inflammation

A Case Series

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Importance: Predominantly neutrophilic infiltrates are seen in a subset of patients with urticaria. The lesions tend to be less itchy and poorly responsive to standard therapy, including antihistamines. We describe 2 patients having neutrophilic urticaria with systemic inflammation (NUSI) without known connective tissue disorder or malignancy. We propose the term *NUSI* to help classify a previously undefined multisystemic inflammatory entity likely mediated by interleukin 1 (IL-1).

Observations: Patient 1, a 47-year-old woman, was seen with urticaria and associated night sweats, fevers, and polyarticular arthritis. Acute-phase reactants were elevated with worsening of symptoms. Initial treatment with a combination of topical and systemic corticosteroids, antihistamines, and immunosuppressants was unsuccessful.

A 100% clinical resolution was achieved with anakinra, an IL-1 receptor antagonist. Patient 2, a 24-year-old woman, was seen with urticaria and associated joint pain and swelling. Initial treatment included a combination of antihistamines, colchicine, and dapsone. Only colchicine provided moderate benefit but was stopped because of significant gastrointestinal tract discomfort. Anakinra was initiated; the patient achieved 100% control while receiving daily therapy.

Conclusions and Relevance: The diagnosis of NUSI is important to consider in patients who are seen with antihistamine-resistant urticaria in combination with systemic inflammatory symptoms. Interleukin 1 blockade is a viable option for therapy.

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THE PATHOGENESIS OF CONVENTIONAL urticaria is related to stimuli that promote mast cell degranulation and can act immunologically through the IgE receptor, or they are independent of the IgE receptor and bind directly to the mast cell. Conventional urticaria tends to be effectively treated with antihistamine therapy. Histopathologically, urticaria is characterized by a sparse perivascular and interstitial infiltrate composed of a mixture of lymphocytes, eosinophils, and neutrophils.¹ The term *neutrophilic urticaria* was initially proposed for a subtype of urticaria in which the infiltrate is composed predominantly of neutrophils.² Based on the findings of a few small studies,²⁻⁴ it is estimated that approximately 4% to 18% of patients with urticaria demonstrate infiltrates that are composed predominantly of neutrophils, constituting neutrophilic urticaria. Neutrophilic urticaria displays clinical features that are not typical of conventional urticaria: the lesions tend to be less pruritic, may be painful, and are generally poorly responsive to

standard therapy, including antihistamines.⁵ The pathogenic mechanism of neutrophilic urticaria has yet to be elucidated, but the lack of therapeutic response to antihistamine therapy suggests a pathway that does not involve mast cell degranulation.

Kieffer et al⁶ described 9 patients with what they characterize as a particular variant of neutrophilic urticaria, for which they proposed the term *neutrophilic urticarial dermatosis* (NUD). In NUD, patients clinically exhibit erythematous macules or slightly raised papules or plaques. The edematous papules and plaques often seen in conventional urticaria are not a feature of this entity. Furthermore, NUD differs histopathologically from conventional neutrophilic urticaria in that the infiltrate is denser and leukocytoclasia is present. Degenerative collagen bundles are also frequently seen in this entity. In fact, the authors propose that NUD is a type of neutrophilic dermatosis, more so than a variant of urticaria. Many of the patients with NUD were noted to have an associated connective tissue disorder, such as systemic lupus erythematosus (SLE),

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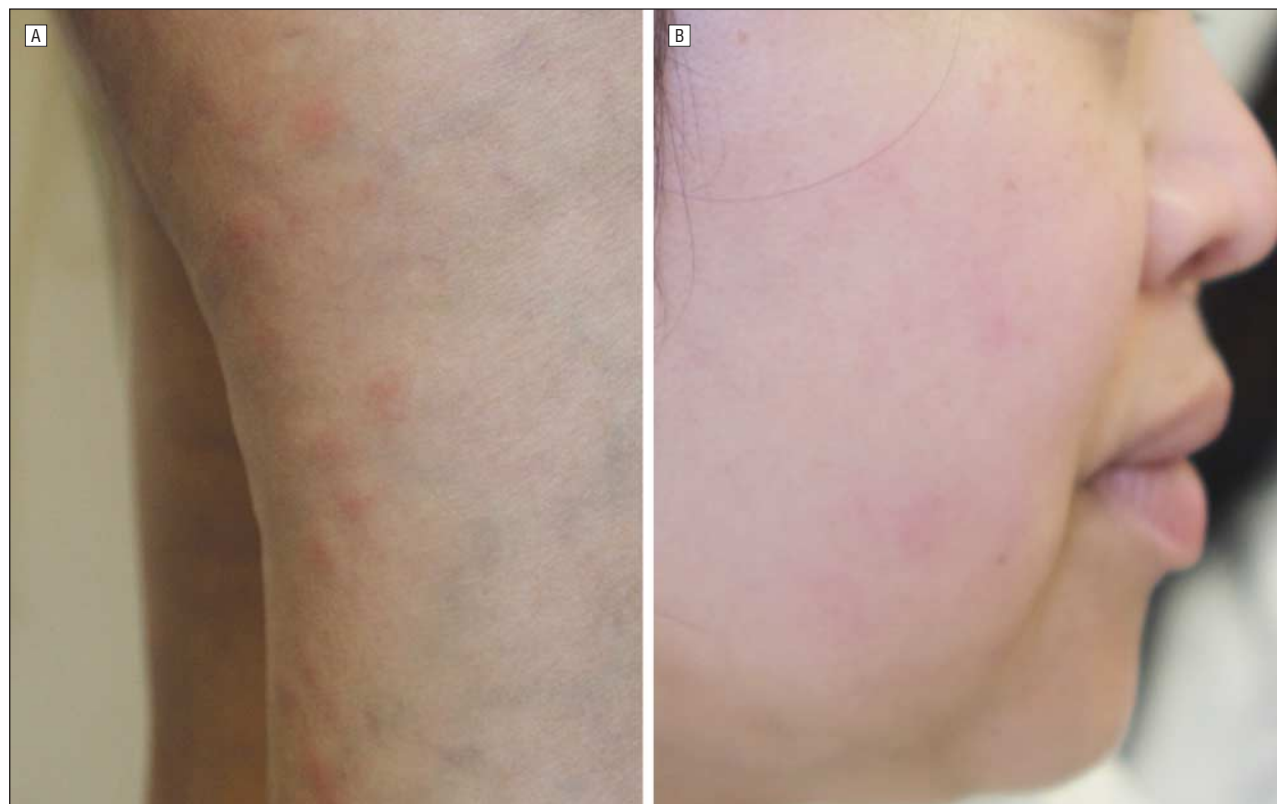


Figure 1. Clinical findings in patient 1. A, Urticated papules and plaques. B, Evanescent pink macules.

Schnitzler syndrome, or adult-onset Still disease (AOSD).^{6,7} Recent reports of nonbullous neutrophilic infiltrates in SLE likely represent the same entity as NUD.^{6,8-10}

In this study, we describe 2 patients having urticarial lesions with biopsy specimens showing neutrophilic infiltrates, who also were seen with extracutaneous symptoms likely mediated by interleukin 1 (IL-1) and not associated with a known inflammatory disease. We propose the term *neutrophilic urticaria with systemic inflammation* (NUSI) for the disease in these patients. This new term is intended to describe a spectrum of diseases that includes neutrophilic urticaria and highlights the role of IL-1 in driving this particular inflammatory process.

REPORT OF CASES

CASE 1

A 47-year-old Vietnamese woman was seen in the dermatology clinic with a 10-day history of a fixed, burning, and itchy rash on her anterior right thigh. The patient had been referred from the rheumatology clinic, where she was being seen for symmetric inflammatory arthritis of the wrist, metacarpophalangeal, and knee joints. Skin examination revealed a 15 × 15-cm erythematous plaque without surface change on the right thigh (**Figure 1**). Four months later, the patient was seen with a new, 2-week history of diffuse, burning, and pruritic wheals on the limbs, each lasting less than 24 hours. The rash was associated with night sweats, fevers, and exacerbation of her inflammatory arthritis. Physical exami-

nation revealed evanescent pink papules and plaques on the extremities. Consecutive biopsy specimens of both lesions showed sparsely cellular superficial and deep perivascular and interstitial infiltrate composed mostly of neutrophils with a few admixed eosinophils. No evidence of vasculitis was noted (**Figure 2**). Her inflammatory arthritis was initially attributed to seronegative rheumatoid arthritis because she had a low positive rheumatoid factor level at 21.0 IU/mL. However, onset of skin symptoms and a negative anticyclic citrullinated peptide antibody result (a more specific test for rheumatoid arthritis¹¹) prompted evaluation for alternative connective tissue diseases. Adult-onset Still disease was thought to be unlikely in the setting of normal ferritin and liver transaminase levels, and the patient demonstrated no other major or minor features as described in the classification criteria for AOSD by Yamaguchi et al.¹² The patient had a moderate-titer antinuclear antibody, but she did not meet the criteria for SLE diagnosis as defined by the American College of Rheumatology revised 1997 classification.¹³ She had a positive Sjögren syndrome antibody as well but had no sicca symptoms to meet the clinical criteria for a diagnosis of that syndrome.¹⁴ The results of serum protein electrophoresis and immunofixation electrophoresis were normal, which excluded Schnitzler syndrome. The patient also had persistent microcytic anemia, but hematologic evaluation (including bone marrow biopsy) revealed no malignancy.

The patient's arthritis was initially treated with prednisone (5 mg/d) and methotrexate (15 mg/wk), which provided minimal control, and she continued to expe-

rience mild to moderate synovitis. Initial treatment of her rash included topical triamcinolone acetonide ointment, 0.1%, and daily sedating and nonsedating oral antihistamines, including hydroxyzine hydrochloride (10 mg), loratadine (10 mg), and doxepin hydrochloride (10 mg), all of which provided minimal control of the patient's itch. Methotrexate was discontinued because it was not proving effective in controlling the patient's arthritis, and there was concern that it may have been exacerbating her anemia. The patient was subsequently treated with prednisone to dosages as high as 20 mg/d to attempt to control her cutaneous symptoms and her arthritis. She was also treated with hydroxychloroquine sulfate at dosages of up to 400 mg/d for 1 year, and daily antihistamines were continued. This treatment regimen provided temporary resolution of both her rash and arthritis. However, on tapering prednisone, her symptoms returned and persisted during the next 2 years, with ongoing urticaria involving the trunk, limbs, and face, as well as recurrence of fixed, red, burning, pruritic lesions on her lower extremities. Biopsy of the fixed lesions showed histopathological findings similar to those in prior biopsy specimens. Her fever and inflammatory arthritis also progressed, with significant limitation of activities of daily living. Acute-phase reactants were elevated throughout the course of her presentation, with erythrocyte sedimentation rates and C-reactive protein levels as high as 81 mm/h and 139.2 mg/L, respectively (to convert C-reactive protein level to nanomoles per liter, multiply by 9.524). Because of the evidence of neutrophilic inflammation, colchicine (1.2 mg/d) and dapsone (≤ 50 mg/d) were sequentially tried but were ineffective. She was treated with a trial of subcutaneous etanercept (50 mg/wk) to control her worsening synovitis. However, etanercept was discontinued because of severe exacerbation of the patient's urticaria and synovitis and the development of fevers. Following this exacerbation, anakinra (an IL-1 receptor antagonist) was initiated at a dosage of 100 mg subcutaneously daily. Within days, the patient had dramatic improvement of symptoms. However, she developed significant injection-site eruptions, of which a biopsy specimen showed a superficial and mid-dermal perivascular and interstitial infiltrate of lymphocytes, neutrophils, and eosinophils. Given that all other cutaneous lesions had resolved at this point, these eruptions were presumed to be injection-site reactions and not persistence of her primary condition. Anakinra was initially withheld but was then continued, despite the local reactions, because of the significant positive effect of the therapy. The injection-site reactions resolved after 1 month, and the patient remained asymptomatic with ongoing daily anakinra therapy. When anakinra was withheld and when doses were missed on 2 subsequent occasions because of a supply shortage of the medication, she had marked recrudescence of her symptoms, including severe joint pain and fevers, with erythrocyte sedimentation rate and C-reactive protein elevations to 78 mm/h and 200 mg/L, respectively. She has achieved complete clinical resolution since restarting daily anakinra.

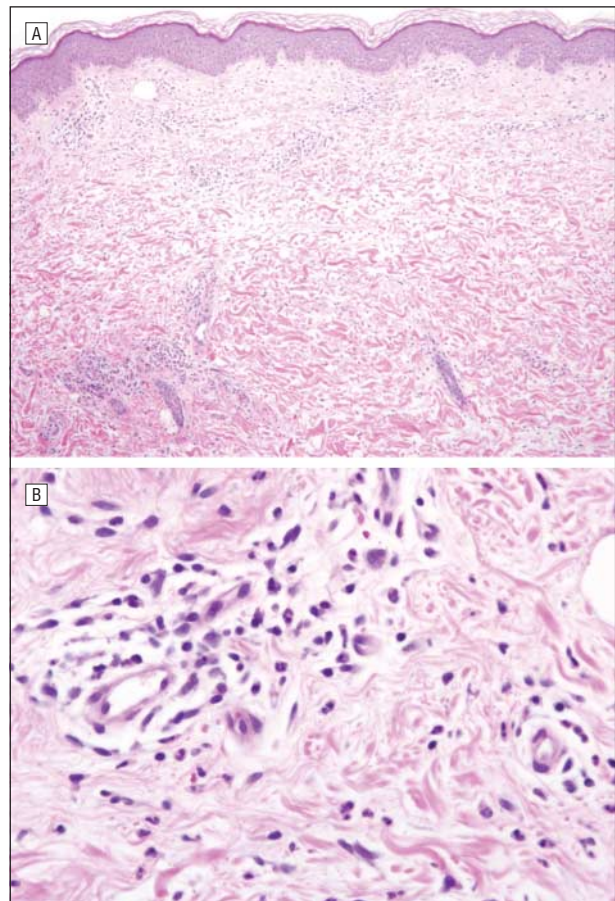


Figure 2. Histopathological findings in patient 1. A, Low-power view highlighting sparsely cellular superficial and deep perivascular and interstitial infiltrate composed mostly of neutrophils (hematoxylin-eosin, original magnification $\times 4$). B, Higher magnification confirming that most of the cells within the infiltrate are neutrophils (hematoxylin-eosin, original magnification $\times 40$).

CASE 2

A 24-year-old woman of white race/ethnicity was seen with a 6-month history of urticarial rash with associated inflammatory joint pain in the ankles and knees without swelling. Her skin lesions were pruritic, and painful edematous papules and plaques had occurred on her face, trunk, limbs, palms, and soles and had always resolved within 24 hours, with no apparent bruising. Diurnal variation of her rash and rheumatological symptoms were observed, with increasing severity throughout the day. In addition, cold seemed to precipitate the rash. The skin lesions and symptoms did not respond to daily antihistamine therapy with cetirizine hydrochloride (10 mg) or with diphenhydramine hydrochloride (100 mg). Before presentation to the dermatology clinic, she had also been treated with prednisone, with dosages of up to 20 mg/d, which provided minimal relief of both rash and joint pain. Her arthralgias had been previously treated with diclofenac sodium (150 mg/d) and propoxyphene napsylate (50 mg/d)-acetaminophen (325 mg/d) as needed, with moderate control of pain. Skin examination revealed pink papules and plaques ranging between 2 and 20 mm (some in linear array) diffusely on the trunk, back, chest, and extremities, with moderate edema of the plaques on the

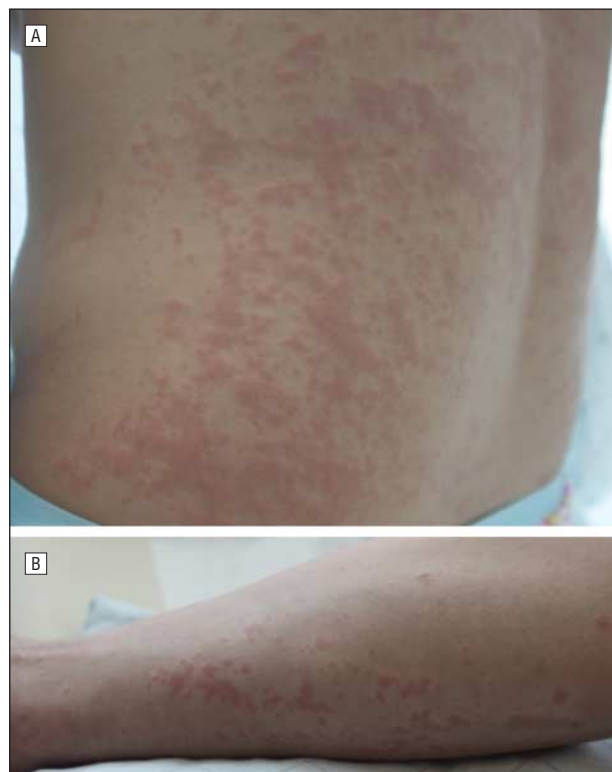


Figure 3. Clinical findings in patient 2. A, Urticated papules and plaques on the back. B, Figurate and edematous papules on the volar forearm.

back (**Figure 3**). Dermographism was not elicited on pressure testing, and cold provocation with an “ice cube” test was negative.¹⁵ A biopsy specimen of a representative lesion revealed a sparse perivascular and interstitial infiltrate of lymphocytes and neutrophils. Scant leukocytoclastic debris was also apparent (**Figure 4**). Review of the patient’s previous laboratory studies revealed erythrocyte sedimentation rate and C-reactive protein elevations as high as 87 mm/h and 172.2 mg/L, respectively. The patient also had persistent normocytic anemia. Schnitzler syndrome and SLE were excluded because she had no paraproteinemia and had a negative antinuclear antibody and Sjögren syndrome antibody. Adult-onset Still disease was thought to be unlikely with no fevers, a normal ferritin level, and none of the other major or minor features noted as described in the criteria by Yamaguchi et al.¹² Genetic testing was conducted, with no mutations found in *NLRP3* (Online Mendelian Inheritance in Man 606416), the gene implicated in cryopyrin-associated periodic syndrome. The patient was initially treated with hydroxyzine (25 mg/d) and colchicine (1.2 mg/d), later increased to 2.4 mg/d. Colchicine provided significant but incomplete improvement of the patient’s arthritis and rash but was stopped after 6 weeks of use because of diarrhea. Colchicine was replaced with dapsone (50 mg/d), which provided no relief of symptoms. Five months after initial presentation, the patient developed frank polyarticular synovitis of the wrists, metacarpal phalangeal joints, proximal interphalangeal joints, and ankles. Radiographs were negative for erosions or periarticular osteopenia. Methotrexate (15 mg/d) was tried, without benefit. Anakinra (100 mg/d subcutane-

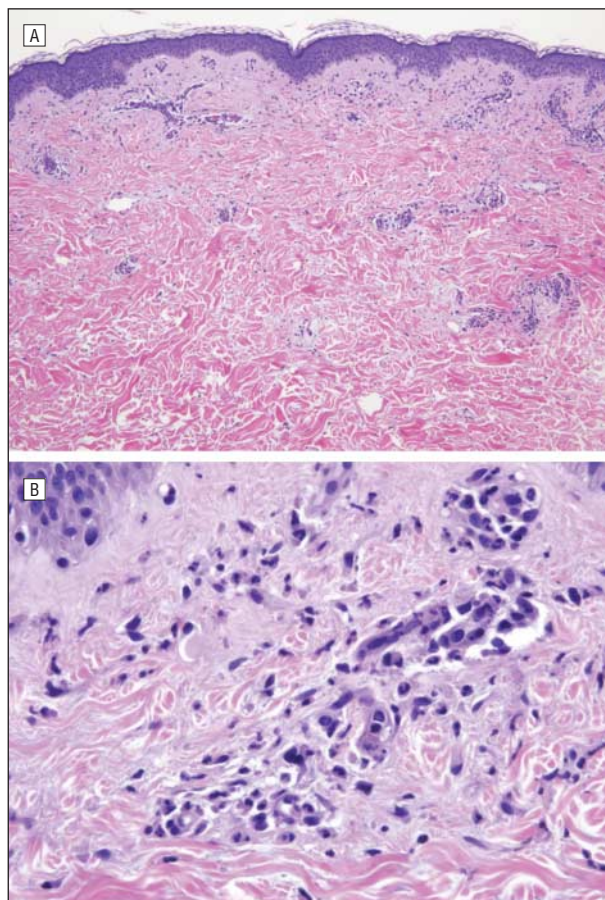


Figure 4. Histopathological findings in patient 2. A, Low-power view showing a sparse perivascular and interstitial infiltrate of lymphocytes and neutrophils (hematoxylin-eosin, original magnification $\times 4$). B, Higher magnification confirming that most of the lesional cells are neutrophils and displaying slight leukocytoclastic debris (hematoxylin-eosin, original magnification $\times 40$).

ously) was subsequently initiated. The patient experienced immediate response to anakinra and had complete remission of her symptoms, including resolution of anemia. On attempting to taper the anakinra frequency, she again developed signs and symptoms of urticaria and inflammatory back pain. She has had complete clinical resolution since resuming daily anakinra therapy.

COMMENT

The cases reported herein represent a previously undefined multisystemic inflammatory entity known as NUSI. Although these cases differ in severity, we believe that they represent variations of the same process. In NUSI, abrupt onset of neutrophilic urticaria occurs in tandem with inflammatory arthritis and other systemic symptoms, and complete control of symptoms is achieved with IL-1 blockade.

The response to treatment seen in the patients described herein implicates IL-1 dysregulation and the activation of the inflammasome in the pathogenesis of NUSI. In addition, the clinical similarity of NUSI to cryopyrin-associated periodic syndrome, characterized

by congenital IL-1 β excess, leads us to believe that NUSI is primarily driven by IL-1 β , which is a potent proinflammatory cytokine regulated by the *NLR* genes. These genes, including *NLRP3*, are involved in the formation of protein complexes, or inflammasomes, as a response to certain stimuli. The inflammasomes initiate an inflammatory cascade by activating the caspase proteins, which cleave the inactive cytoplasmic precursor of IL-1 β to form active IL-1 β . In this manner, upregulation of *NLR* genes causes increased levels of caspases and, in turn, increased levels of IL-1 β , resulting in inflammation and clinical symptoms.¹⁶ In cryopyrin-associated periodic syndrome, mutations in the *NLRP3* gene lead to IL-1 β excess and resulting inflammation and urticaria via the mechanism already described.¹⁷⁻¹⁹ In NUSI, no known congenital mutation leads to the dysregulation of the IL-1 β pathway. Rather, dysregulation of this pathway occurs later in life and is of unknown origin.

Partial response to colchicine in patient 2 is further evidence of inflammasome activation: while colchicine is known to reduce inflammatory symptoms by disabling neutrophil binding to endothelial cells, it also acts to prevent release of IL-1 β .^{20,21} Colchicine, at tolerable dosages, was insufficient to control the patient's symptoms, but both patients had complete resolution of symptoms with direct IL-1 blockade.

The presentation of urticaria with systemic inflammatory symptoms, including small joint pain, necessitates investigation for connective tissue disease, urticarial vasculitis, and Schnitzler syndrome, as well as possible genetic testing if a periodic fever syndrome is suspected. Urticarial vasculitis was excluded in these patients because of the absence of histopathological evidence of vasculitis in their skin biopsy specimens. In addition, the lesions in urticarial vasculitis usually last longer than 24 hours,^{7,22} whereas individual lesions resolved within 24 hours in both patients described herein. Schnitzler syndrome was similarly excluded given the lack of paraproteinemia in both patients. The polyarticular synovitis observed in NUSI can be seen in certain types of connective tissue diseases, including SLE and rheumatoid arthritis. However, urticaria is not typical of either condition. Systemic lupus erythematosus can be associated with NUD, which seemed unlikely clinically and histopathologically in these cases because both patients had edematous papules and plaques and because the infiltrates in both patients' biopsy specimens were sparser than those typical of NUD.⁶ In addition, SLE can be associated with hypocomplementemic urticarial vasculitis.²³ However, complement levels were normal in both patients, and there was no evidence of vasculitis. Furthermore, SLE seemed unlikely because elevated C-reactive protein level and leukocytosis, which both patients had, are not typical of active SLE disease in the absence of acute infection or serositis.²⁴⁻²⁶ Adult-onset Still disease is a known autoinflammatory entity that shares many clinical features with NUSI, both cutaneous and extracutaneous symptoms. However, the key characteristics of AOSD (eg, elevated ferritin levels, transaminitis, and cyclical fevers) were not seen in the patients described herein and are not a feature of NUSI.

The clinical similarity of NUSI with other autoinflammatory diseases underscores the possibility of a shared pathogenesis among all these diseases, centered on IL-1 dysregulation with subsequent neutrophil-driven inflammation. Response to IL-1 blockade has been observed in cases of AOSD, Schnitzler syndrome, acute febrile neutrophilic dermatosis, pyoderma gangrenosum, non-complementemic urticarial vasculitis, and even neutrophilic panniculitis.^{22,27-34} It is feasible that these diseases fit on a spectrum, with cutaneous symptoms progressing from varied severity of neutrophilic urticaria, with or without vasculitis, to include acute febrile neutrophilic dermatosis and perhaps pyoderma gangrenosum. Although IL-1 blockade was not tried in the patients with NUD described by Kieffer and colleagues,⁶ it is likely that NUD also fits on this spectrum.

The possibility of cross talk between the innate and adaptive immune systems in NUSI also cannot yet be discounted. Both of the patients described herein had complete resolution with IL-1 blockade. However, autoimmune processes were suspected in both of them. Autoimmune diseases (eg, SLE) have been associated with neutrophilic dermatoses, specifically NUD,^{6,8} and it is feasible that the spectrum of IL-1 dysregulation includes overlap between autoinflammatory and autoimmune processes.

The diagnosis of NUSI is important to consider in patients who are seen with antihistamine-resistant urticaria in combination with systemic inflammatory symptoms. It creates a designation for a presentation of IL-1 dysregulation that does not fit under the umbrella of cryopyrin-associated periodic syndrome, nor fully meets the criteria for a known autoinflammatory or autoimmune disease. The distinction of NUSI will aid in improved diagnosis and treatment of affected individuals. Neutrophilic urticaria with systemic inflammation is likely misdiagnosed as urticarial vasculitis and other neutrophilic dermatoses.^{35,36} In addition, as seen in patient 1, NUSI and other IL-1-driven inflammatory conditions can be exacerbated by the use of anti-tumor necrosis factor agents.³⁶ Consideration of NUSI in patients with fitting presentations would steer care away from these agents and toward a trial of IL-1 blockade, a response to which may be seen immediately. Interleukin 1 antagonists (eg, anakinra or canakinumab), which traditionally are not standard therapy for neutrophilic dermatoses, urticarial vasculitis, or connective tissue diseases, are viable treatments for NUSI.

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