

Neutrophilic Urticarial Dermatitis



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KEYWORDS

- Neutrophilic urticarial dermatosis • NUD • Classic urticaria • Neutrophilic urticaria
- Urticarial vasculitis • Sweet syndrome • Schnitzler syndrome • Adult-onset Still's disease

KEY POINTS

- Neutrophilic urticarial dermatosis (NUD) commonly coexists with inflammatory systemic diseases, but this association is not obligatory.
- Diagnosis of NUD and its distinct accompanying condition necessitates a meticulous evaluation of the clinical manifestations, histologic features, and laboratory findings.
- Management of NUD depends on the clinical context and associated systemic disease.

INTRODUCTION

Clinically, neutrophilic urticarial dermatosis (NUD) is characterized as pink to reddish urticarial eruption consisting of flat or slightly raised, pruritic or nonpruritic macules, papules, or plaques that resolve within 24 hours.^{1,2} Histologically, it is characterized by an intense neutrophilic interstitial and perivascular infiltrate with no blood vessel damage or significant edema.³ Recently, extension of neutrophils into the epidermis, hair follicles, sweat glands, and sebaceous glands, a term referred to as neutrophilic epitheliotropism, has been identified as a sensitive and specific histopathologic clue for NUD.³ Its typical extracutaneous signs include fever or arthralgia.²

The clinical criteria of NUD are¹.

- (1) Recurrent or chronic cutaneous eruptions consisting of macules, papules, or plaques.
- (2) Individual lesions resolve within 48 hours.
- (3) Pruritic or nonpruritic lesions.

The histologic criteria of NUD are¹.

- (1) Diffuse dermal neutrophilic infiltrate with interstitial involvement.
- (2) Absence of significant vessel wall alteration (particularly fibrinoid necrosis).
- (3) Absence of significant dermal edema.

NUD is typically associated with systemic diseases such as Schnitzler syndrome, adult-onset Still's disease, cryopyrin-associated periodic syndromes, and lupus erythematosus (LE).⁴ Since NUDs identification in 2009, there have been reports of its associations with other conditions such as systemic-onset juvenile arthritis, Sjögren syndrome, primary biliary cirrhosis, inflammatory bowel disease, serum sickness-like drug reaction, post-streptococcal rheumatic disease, and acral acquired cutis laxa associated with IgA multiple myeloma.⁴ Rarely, the clinical and histologic presentations of NUD can present without associated systemic diseases.⁵

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DISEASES COMMONLY ASSOCIATED WITH NEUTROPHILIC URTICARIAL DERMATOSIS PATTERN

Schnitzler Syndrome

Schnitzler syndrome is a rare, late-onset, acquired autoinflammatory multisystemic disease.^{6,7} It was first described in 1972 by the French dermatologist, Liliane Schnitzler, and there have been around 300 published global cases since then.^{2,8} It has a marginal predominance in men, and its mean age of onset is 51 years; the youngest reported patient began experiencing urticaria at 13 years old.⁸

Schnitzler syndrome is defined by monoclonal gammopathy (usually IgM or sometimes IgG) and recurrent, nonpruritic urticarial rash that is neutrophil rich on biopsy, plus at least two of these abnormalities: bone pain, lymphadenopathy, intermittent fever, leukocytosis, hepatomegaly and/or splenomegaly, arthralgias or arthritis, and an elevated erythrocyte sedimentation rate.^{6,9} Other abnormalities include peripheral neuropathy, weight loss, headache, elevated inflammatory markers, and fatigue.⁷ Patients may also develop lymphoproliferative diseases and amyloid A (AA) amyloidosis may occur in rare instances, if not properly treated.¹⁰ There are two sets of diagnostic criteria called the Lipsker and Strasbourg criteria. However, the Strasbourg criteria as described in **Box 1** are the most recent and its validity has been confirmed.^{2,11}

The first clinical presentation of Schnitzler syndrome is recurrent urticarial lesions consisting of red or rose-colored macules or slightly elevated papules and plaques that may become confluent (**Fig. 1**).^{6,8} Individual lesions last less than 24 hours and resolve without sequelae.⁶ These eruptions are typically nonpruritic, though they can be moderately pruritic.^{6,8} They usually occur on the trunk and extremities—sparing the head and neck regions, and angioedema and dermographism are rare.^{6,8} There are reports of worsening skin lesion following heat or cold exposure, alcohol consumption, stress, work, or physical exercise.^{2,8} Patients may exhibit neurologic symptoms such as vertigo or delirium during the recurrent inflammatory episodes.¹²

The histopathology of urticarial skin lesions in Schnitzler syndrome includes various patterns described as sparse perivascular inflammation, NUD, or leukocytoclastic vasculitis.⁶ Histopathology of a plaque in its early stages reveals normal epidermis, dermal neutrophilic infiltrate of variable density, and clusters of neutrophils around sweat ducts.⁸ In addition, interstitial neutrophils are distributed along collagen bundles and leukocytoclasia is present.⁷

Box 1

Strasbourg diagnostic criteria of Schnitzler syndrome^{2,11}

Obligat criteria

- Chronic urticarial rash and
- Monoclonal IgM or IgG gammopathy

Minor criteria

- Recurrent fever^a
- Bone morphology anomalies with or without bone pain^b
- A neutrophilic dermal infiltrate on skin biopsy^c
- Hyperleukocytosis and/or elevated CRP^d

Definite diagnosis if

- Two obligat criteria AND at least two minor criteria if IgM and three minor criteria if IgG

Probable diagnosis if

- Two obligat criteria AND at least one minor criteria if IgM and two minor criteria if IgG

^a Must be greater than 38°C and otherwise unexplained. Occurs usually—but not obligatory—together with the skin rash.

^b As assessed by bone scintigraphy, MRI or elevation of bone alkaline phosphatase.

^c Corresponds usually to the entity described as “neutrophilic urticarial dermatosis” (Medicine 2009; 88: 23–31); absence of fibrinoid necrosis and significant dermal edema.

^d Neutrophils greater than 10,000/mm³ and/or CRP greater than 30 mg/L.

The etiology of Schnitzler syndrome is not established.⁶ It is considered an acquired autoinflammatory disorder due to elevated levels of pro-inflammatory cytokines such as interleukin (IL)-1 α , IL-1 β , IL-6, and tumor necrosis factor (TNF)- α .^{6,8,13} Therefore, drugs targeting the IL-1 pathway are effective therapeutic options.⁸ Anakinra is the first drug of choice for Schnitzler syndrome.¹⁴ Alternative therapies such as rilonacept (IL-1 receptor decoy), canakinumab (anti-IL-1 β monoclonal antibody), and tocilizumab (anti-IL-6 monoclonal antibody) are also suitable options.^{6,13,14} About 15% to 20% of patients with Schnitzler will develop a lymphoproliferative disorder such as Waldenström’s macroglobulinemia; thus, regular monitoring for monoclonal gammopathy is crucial.¹⁵

Adult-Onset Still’s Disease

Adult-onset Still’s disease (AOSD) is a systemic inflammatory disorder that is often difficult to

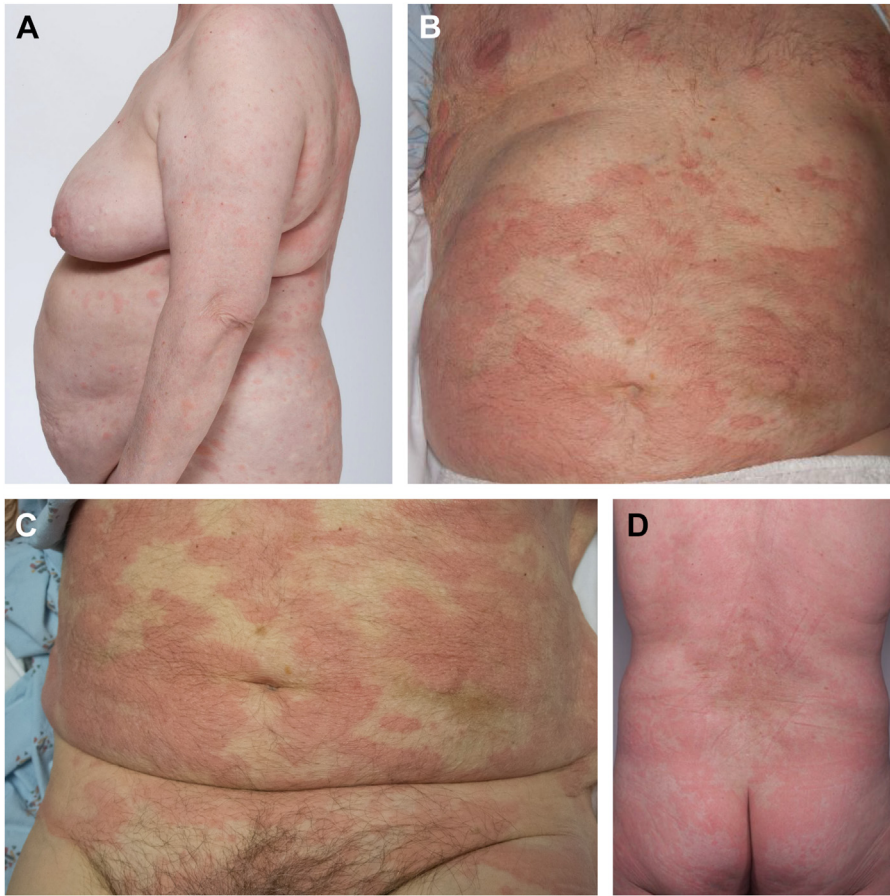


Fig. 1. (A) Urticarial papules and plaques on the trunk and upper extremity of a female with Schnitzler syndrome. (B) Confluent urticarial plaques on the trunk of an 80-year-old man with 8-month history of recurrent fevers, rashes, lymphadenopathy, arthralgias, confusion, and delirium. (C) Urticarial papules on the trunk and extremities of a 56-year-old with recurrent nonpruritic urticaria, elevated ESR/CRP, febrile sensation, and recurrent vertigo. (D) Urticarial papules and plaques on the trunk of a male with Schnitzler syndrome.

diagnose. It typically affects young adults around 30 years of age and is slightly more commonly seen in women over men; rarely, it is seen in adults more than 60 years old.¹⁶ The exact etiology of AOSD is unknown; however, there is a connection between genetically predisposed hosts and auto-inflammatory disorders triggered by macrophage cell activation and TH1 cytokines such as IL-1, IL-2, IL-6, IL-18, TNF- α , and interferon- γ .¹⁶

AOSD is clinically characterized by high-spiking fever, polyarthralgia/arthritis, a salmon-pink evanescent rash, lymphadenopathy, liver dysfunction, and splenomegaly.¹⁷⁻¹⁹ The characteristic salmon-pink evanescent rash is a major diagnostic finding with high sensitivity and specificity as it presents in about 87% of patients with AOSD (Fig. 2).^{17,20} Some markers of disease activity include elevated levels of ferritin, IL-6, and IL-18.^{17,21-25} The histologic findings of the typical evanescent rash reveal a relatively

sparse perivascular mixed inflammatory infiltrate containing neutrophils with little karyorrhexis.^{17,19} Acute lesions are more likely to have the perivascular neutrophilic infiltrate, whereas chronic lesions may display keratin whorls in the stratum corneum and dyskeratotic keratinocytes scattered through the epidermis.^{17,26,27}

The two most common symptoms in patients with AOSD are recurrent episodes of high-spiking fevers that typically flare in the late afternoon and an asymptomatic macular exanthem that is salmon-pink in color.¹⁷⁻¹⁹ The salmon-pink evanescent rash is most frequently seen on the trunk and extremities and often demonstrates the Koebner phenomenon.^{17-19,28} Additional symptoms commonly include arthritis, pharyngitis, lymphadenopathy, liver dysfunction, hepatomegaly, and splenomegaly.¹⁷⁻¹⁹ Specifically, bilateral ankylosing carpal arthritis is a distinctive feature of AOSD.²⁹

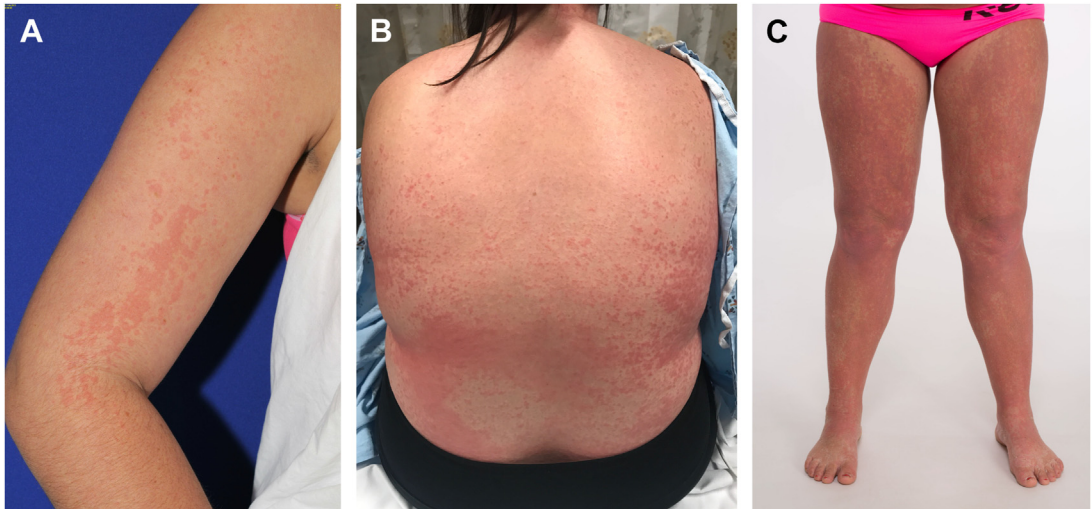


Fig. 2. (A) Coalescing urticarial papules and thin plaques on the upper arm of a young female with AOSD. (B) Coalescing urticarial papules and plaques on the trunk of a 31-year-old female with AOSD. (C) Confluent urticarial papules and plaques on the lower extremities of a woman with AOSD.

Yamaguchi's criteria for a classification of AOSD include both the major and minor criteria.^{17,19} The major criteria consist of the following: (1) fever of $\geq 39^{\circ}\text{C}$, lasting ≥ 1 week; (2) arthralgia lasting ≥ 2 weeks; (3) typical rash (ie, macular or maculopapular nonpruritic salmon-pink eruption usually appearing during fever); and (4) leukocytosis ($\geq 10,000/\text{mm}^3$) including 80% more of granulocytes.¹⁹ The minor criteria consist of the following: (1) sore throat; (2) lymphadenopathy and/or splenomegaly; (3) liver dysfunction; and (4) negative rheumatoid factor (RF) and negative antinuclear antibody (ANA).¹⁹ An individual must meet ≥ 5 criteria including ≥ 2 major criteria for a diagnosis of AOSD.¹⁹ When considering a diagnosis of AOSD, it is important to exclude other potential causes of the systemic symptoms such as infection (eg, sepsis and infectious mononucleosis), malignancy (eg, malignant lymphoma), and rheumatic disease (eg, polyarteritis nodosa and rheumatoid vasculitis with extra-articular features).¹⁹

The treatment of AOSD is mostly targeted toward controlling acute systemic symptoms. Many patients respond well to nonsteroidal anti-inflammatory drugs (naproxen 500 mg twice daily) and oral corticosteroids (0.5–1 mg/kg daily).^{30–32} Methotrexate and intravenous immunoglobulin can be considered when patients are unable to taper corticosteroids.^{30–32} For severe or chronic disease, various biologic agents that inhibit inflammatory signaling pathways such as TNF- α (eg, infliximab, adalimumab, etanercept), IL-1 (eg, anakinra), and IL-6 (eg, tocilizumab) can be helpful.^{30–32} In addition, rituximab has been reported to improve refractory disease (**Box 2**).³²

Cryopyrin-Associated Periodic Syndromes

Cryopyrin-associated periodic syndromes (CAPS) are rare hereditary autoinflammatory conditions representing a spectrum of disease severity.^{2,33,34} They include three clinical phenotypes associated with gain-of-function mutations in the NLRP3 gene (NOD-like receptor family, pyrin domain containing 3) that encodes for cryopyrin—a regulatory protein that forms intracellular protein complexes called inflammasomes.^{5,35,36} Defects of the inflammasomes increase its activity and the

Box 2

Yamaguchi's criteria for a classification of adult-onset Still's disease¹⁹

Major criteria

1. Fever of $\geq 39^{\circ}\text{C}$, lasting ≥ 1 week
2. Arthralgia lasting ≥ 2 week
3. Typical rash (ie, macular or maculopapular nonpruritic salmon-pink eruption usually appearing during fever)
4. Leukocytosis ($\geq 10,000/\text{mm}^3$) including 80% more of granulocytes

Minor criteria

1. Sore throat
2. Lymphadenopathy and/or splenomegaly
3. Liver dysfunction
4. Negative RF and negative ANA

Classification of AOSD requires ≥ 5 criteria including ≥ 2 major criteria.

conversion of inactive IL-1 β precursor into active IL-1 β .^{5,36}

CAPS incidence in the United States is about 1 in 1,000,000 people and it has a prevalence of 300 to 500 individuals.³⁷ They are inherited in an autosomal-dominant pattern.³³ Its diagnostic criteria as specified in **Box 3** include elevated inflammatory markers (C-reactive protein [CRP]/serum amyloid A [SAA]) plus two or more of CAPS typical symptoms: urticaria-like rash, cold- or stress-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms (arthralgia/arthritis/myalgia), chronic aseptic meningitis, and skeletal abnormalities (epiphyseal overgrowth/frontal bossing).³⁵

The three clinical phenotypes of CAPS in order of increasing severity are familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome/neonatal-onset multi-system inflammatory disease (CINCA/NOMID).⁵ They are also called “cryopyrinopathies” and are identified as a continuum of a singular disorder.³⁷ All three phenotypes present with urticarial rash, NUD, childhood onset, fever, joint pain, persistent neutrophilia, and elevated inflammatory markers (CRP, SAA, and neutrophil protein S100A12).^{5,35} Histologically, CAPS lesions reveal a perivascular or perieccrine neutrophilic infiltrate.³⁷

FCAS, the mildest CAPS, was first reported in 1940. It presents at birth or during the first 6 months, though there are late-onset cases.^{34,37} It is clinically defined by recurrent fever, arthralgia, and an intermittent cold-induced urticaria-like rash.^{34,37} The maculopapular and typically non-pruritic (can be itchy and/or painful) rash is usually the first noticeable sign, and it begins one or 2 hours after exposure to cold temperatures.³⁷

Box 3

Diagnostic criteria of cryopyrin-associated periodic syndrome³⁵

Mandatory criteria

Raised inflammatory markers (CRP/SAA)

Plus ≥ 2 of 6 CAPS typical signs/symptoms:

Urticaria-like rash

Cold/stress-triggered episodes

Sensorineural hearing loss

Musculoskeletal symptoms (arthralgia/arthritis/myalgia)

Chronic aseptic meningitis

Skeletal abnormalities (epiphyseal overgrowth/frontal bossing)

Histologically, FCAS presents as sparse interstitial neutrophilic infiltrate in the reticular dermis.³⁷ Common clinical symptoms include conjunctivitis, nausea, and muscle pain, whereas headache, sweating, drowsiness, and amyloidosis are seen in less than 5% of patients.³⁷

In 1962, Muckle and Wells first described the intermediate phenotype, MWS.³⁶ Like FCAS, it is characterized by fever, arthralgia, and an urticaria-like rash.^{36,37} However, the urticaria-like rash is also induced by stress or exercise in addition to cold temperatures.^{36,37} Sensorineural hearing loss is common as it is associated with 70% of cases, and conjunctivitis in MWS is usually associated with episcleritis and iridocyclitis.³⁷ Its characteristic AA amyloidosis usually begins with proteinuria and

Box 4

Systemic lupus international collaborating clinics criteria⁴²

Clinical Criteria

Acute cutaneous lupus

Chronic cutaneous lupus

Oral/nasal ulcers

Nonscarring alopecia

Synovitis

Serositis

Renal

Neurologic

Anemia

Leukopenia/lymphopenia

Thrombocytopenia

Immunologic Criteria

ANA

Anti-dsDNA antibody

Anti-Smith antibody

Antiphospholipid antibodies

Lupus anticoagulant

Anticardiolipin

Beta-2-glycoprotein

Low complement

Definite diagnosis if

Fulfillment of at least four criteria (at least one clinical criterion and one immunologic criterion),

OR

Lupus nephritis is present with ANA or anti-dsDNA antibodies

leads to the most serious complication of renal dysfunction in about 25% of patients.³⁷ MWS symptoms are typically chronic and last for 2 to 3 days.³⁷

In the early 1980s, Prieur, Giscelli, Hassink, and Goldsmith first described the most severe phenotype, CINCA/NOMID.^{38,39} This syndrome emerges due to de novo mutations.³⁶ The main feature of CINCA/NOMID is a neonatal onset of cutaneous symptoms, along with end-organ damage and a triad of arthropathy, chronic urticaria, and central nervous system (CNS) abnormalities.³⁶ These CNS abnormalities range from hearing loss to chronic aseptic meningitis and results in mental retardation.^{36,37} Related symptoms include chronic headaches, irritability in young children, vomiting, and papilledema on fundoscopy.³⁷ Premature birth is common and one-third of children have early stages of amyloidosis that worsens with age and atypical facies—frontal prominence, facial hypoplasia, and saddle nose.³⁷ Patients with CINCA/NOMID can develop osteoarthropathy mainly of the large joints and overgrowth of epimetaphyseal cartilage mainly of the long bones.³⁷ Osseocartilaginous overgrowth in the patella and



Fig. 3. Young woman with lupus erythematosus who presented with urticarial papules and NUD on histopathology.

Box 5

Recommended laboratory tests if neutrophilic urticarial dermatosis is diagnosed²

Complete blood count (CBC)

CRP

ESR

Immunofixation serum protein electrophoresis

Ferritin ± glycosylated ferritin

Antinuclear antibodies, anti-dsDNA antibodies, anti-Ro/SSA antibodies, anti-La/SSB antibodies

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distal femur is a distinct feature and supports a diagnosis of CINCA/NOMID when present.³⁷

There are no fixed distinctions between FCAS, MWS, and CINCA/NOMID as they share similar features.³⁷ Their clinical manifestations can be significantly improved by the inhibition of IL-1 β .³³ The three effective treatments for CAPS include anakinra (IL-1 receptor antagonist), rilonacept (soluble IL-1 decoy receptor), and canakinumab (anti-IL-1 β monoclonal antibody).³⁷ Patients who are unable to tolerate daily injections of anakinra can use rilonacept or canakinumab due to their longer half-lives.³⁷



Fig. 4. Edematous urticarial plaques on trunk of patient with common urticaria.

Lupus Erythematosus

LE is a chronic, polygenic, autoimmune inflammatory disease characterized by various clinical manifestations and the production of humoral antibodies against parts of cell nucleus.^{5,40,41} Systemic LE is typically diagnosed using the systemic lupus international collaborating clinics criteria.⁴² As depicted in **Box 4**, it requires a fulfillment of at least four criteria: one clinical criteria and one immunologic criteria or a sole criteria of lupus nephritis in the presence of ANA or anti-double-stranded DNA (dsDNA) antibodies.⁴²

Patients present clinically with widely distributed rose or red macules or slightly elevated papules (**Fig. 3**).⁴³ These lesions are mostly present on the trunk and rarely involve the face and limbs.^{2,43} The histologic findings of LE is similar to that of NUD—marked neutrophilic interstitial and perivascular infiltrate with leukocytoclasia, but no significant edema or fibrinoid necrosis of blood vessels.^{2,43}

Sometimes, mild vacuolization of the basement membrane and a lupus band may be present which can lead to a missed NUD diagnosis.²

The laboratory findings of NUD in a setting of LE are the same as those usually seen in LE and they include elevated erythrocyte sedimentation rate (ESR), hypergammaglobulinemia, antinuclear antibodies, and anti-dsDNA, anti-Sjögren syndrome antigen A (Ro/SSA), and anti-Sjögren syndrome antigen B (La/SSB) antibodies.² An elevated CRP without serositis, thromboembolic events, or infection is a rare sign in LE.²

NUD occurs before the diagnosis or during the course of LE.⁵ In patients with LE, NUD typically presents with fever and joint pain.^{5,43} Other associated symptoms include paresthesia, sore throat, abdominal pain, and episcleritis.² Koebner phenomenon may occur in remarkably rare instances.² The triad symptoms of a rash, fever, and joint pain are usually misdiagnosed as a classic lupus flare and thus treated with ineffective

Table 1
Histopathology of urticarial dermatosis^{1,2,4,6,45,47–50}

Dermatosis	Clinical Findings	Histopathologic Findings
Classic urticaria	<ul style="list-style-type: none"> • Urticarial plaques are typically red and pruritic • Lesions can recover in 2–3 h and usually without residual pigmentation • Lesions respond to antihistamines • Angioedema may be present 	<ul style="list-style-type: none"> • Perivascular, mainly mononuclear cell inflammation, with/without eosinophils (Fig. 5) • Dermal edema
Neutrophilic urticaria	<ul style="list-style-type: none"> • Individual urticarial lesions may be present for 24 h or less, several days, or more 	<ul style="list-style-type: none"> • Vascular and perivascular neutrophilic inflammation, with/without eosinophils (Fig. 6) • Dermal edema
Neutrophilic urticarial dermatosis	<ul style="list-style-type: none"> • Pink to reddish urticarial eruptions consisting of flat or slightly raised, pruritic or nonpruritic macules, papules, or plaques • Individual lesions resolve within 24 h • Probable association with dermatographism • May present with a burning sensation in the skin • Associated with fever or arthralgia 	<ul style="list-style-type: none"> • Perivascular and interstitial neutrophilic inflammation with/without eosinophils (Fig. 7) • Leukocytoclasia
Urticarial vasculitis (leukocytoclastic vasculitis)	<ul style="list-style-type: none"> • Painful, pruritic, or burning lesions • Lesions persist more than 24 h • May include palpable purpura and angioedema • Residual hyperpigmentation following resolution 	<ul style="list-style-type: none"> • More perivascular than interstitial neutrophilic inflammation, with/without eosinophils (Fig. 8) • Leukocytoclasia • Fibrinoid necrosis of small vessels • Endothelial swelling • Hemorrhage
Sweet syndrome	<ul style="list-style-type: none"> • Erythematous or purplish papules and nodules • Raised plaques • Edematous lesions • May be associated with fever, joint pains, or episcleritis 	<ul style="list-style-type: none"> • Significant dermal edema • Intense neutrophilic infiltrate typically in the superficial dermis

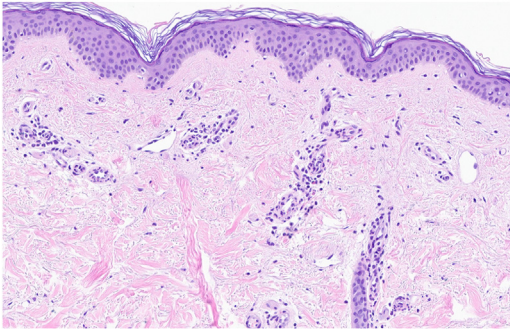


Fig. 5. Dermal edema, perivascular lymphocytes, neutrophils and eosinophils. Intraluminal neutrophils present. (Hematoxylin-eosin stain; X20).

immunosuppressive therapies.^{5,43} The treatment of choice includes neutrophil migration inhibitors such as dapsone and colchicine.^{5,43,44}

RECOMMENDED LABORATORY TESTS IF NEUTROPHILIC URTICARIAL DERMATOSIS IS DIAGNOSED

A diagnosis of NUD must be followed by a screening for systemic disease (**Box 5**).² However, there are rare instances in which NUD occurs in isolation.² Screening for systemic diseases associated with NUD should be performed at initial diagnosis and if the disease worsens,² although it can arise during the course of an existing systemic disease.²

DIFFERENTIAL DIAGNOSIS OF NEUTROPHILIC URTICARIAL DERMATOSIS

It is important to differentiate between NUD, classic urticaria, neutrophilic urticaria, urticarial vasculitis/leukocytoclastic vasculitis, and Sweet syndrome as NUD is usually associated with inflammatory disorders.⁴ Classic urticarial plaques

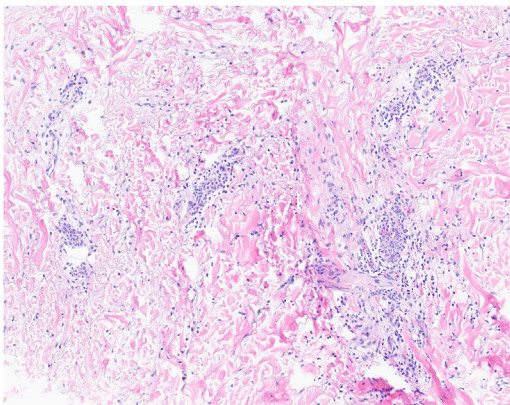


Fig. 6. Perivascular neutrophilic infiltrate with minimal interstitial spread and without leukocytoclasia (Hematoxylin-eosin stain; X20).

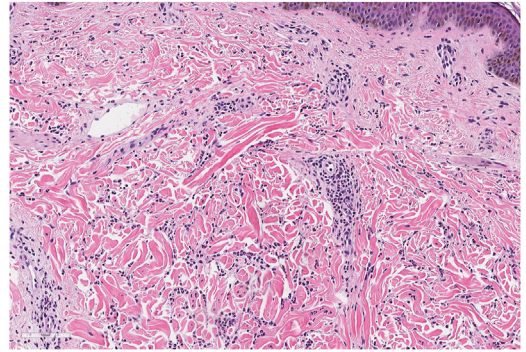


Fig. 7. Neutrophilic perivascular and interstitial infiltrate with leukocytoclasia; there is no vasculitis (Hematoxylin-eosin stain; X20).

are typically red and pruritic (**Fig. 4**).⁴⁵ The clinical lesions resolve without residual pigmentation, may be associated with angioedema, and respond to antihistamines.⁴⁵ However, NUD does not respond to antihistamine therapy and may present with a burning sensation in the skin.⁴ Histologically, they both feature a lymphocytic, neutrophilic, or a mixed dermal infiltrate.^{1,4}

Neutrophilic urticaria has a defined histologic entity, but its clinical aspects have been poorly understood.⁴⁶ Unlike NUDs individual lesions which resolve in 24 hours, neutrophilic urticaria presents with urticarial lesions that resolve in 24 hours or less, several days, or more.^{46,47} It has a strong association with dermographism as compared with NUD.^{46,47} Along with NUD, they both feature a neutrophil-rich perivascular infiltrate.^{4,6} However, neutrophilic urticaria lacks the interstitial inflammation and leukocytoclasia seen in NUD.^{4,6}

Urticarial vasculitis consists of long-lasting urticarial rashes.⁴⁸ It may present with angioedema and fever similar to NUD, but may be associated with palpable purpura which is not seen in NUD.⁴⁹ NUD is different from urticarial vasculitis due to its absence

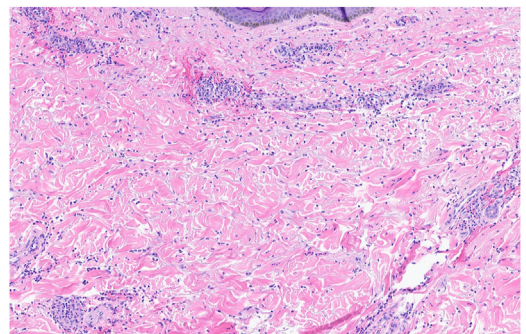


Fig. 8. Leukocytoclasia, perivascular and interstitial neutrophils, fibrinoid necrosis of vessel walls, hemorrhage, and edema of dermis (Hematoxylin-eosin stain; X20).

of fibrinoid necrosis of small vessels, endothelial cell swelling, and extravasation of erythrocytes.⁶

Sweet syndrome, also called acute febrile neutrophilic dermatosis, is a distinct entity but with many similarities to NUD.^{2,50} Clinically, Sweet syndrome's lesions are more edematous and raised than NUD.² Its papules and nodules are erythematous or purplish and consist of raised plaques.² Like NUD, it may present with fever or joint pains.² Sweet syndrome is histologically different from NUD primarily by the presence of edema in its superficial dermis and its denser neutrophilic infiltrate (**Table 1**).²

SUMMARY

NUDs etiology is not well established and its association with several systemic diseases suggests a link to autoinflammation.⁵ Diagnosis of NUD and its accompanying condition requires a rigorous analysis of clinical, histologic, and laboratory findings.⁵ Its treatment is determined by the clinical symptoms and underlying disease.⁵ Neutrophil migration inhibitors and IL-1 antagonists are found to be effective therapies against NUD.⁵ Further histopathological analysis of cases identified as "urticaria vasculitis" will likely reveal more patients presenting with NUD.²

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CLINICS CARE POINTS

- Screening for neutrophilic urticarial dermatosis (NUD) at initial onset via a rigorous analysis of the clinical presentation, histopathologic features, and laboratory results determines the specific therapeutic management. Antihistamines should at least be used initially, though they are usually ineffective.
- In patients with Schnitzler syndrome or cryopyrin-associated periodic syndrome, interleukin-1 antagonists such as anakinra, rilonacept, or canakinumab are the most effective treatments.
- Anakinra or tocilizumab is preferred in severe or chronic states of adult-onset Still's disease over first-line therapy nonsteroidal anti-inflammatory drugs, corticosteroids, or methotrexate.

- In NUD associated with lupus erythematosus, antineutrophilic agents such as dapsone and colchicine are treatments of choice as immunosuppressants are ineffective and result in multiple adverse effects.

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