Neutrophilic Urticarial Dermatosis

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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 are[1].

(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 are[1].

(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]

Obligate 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 obligate criteria AND at least two minor criteria if IgM and three minor criteria if IgG

Probable diagnosis if

- Two obligate 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/mm^3 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 proinflammatory cytokines such as interleukin (IL)-1α, IL-1β, 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-1β 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

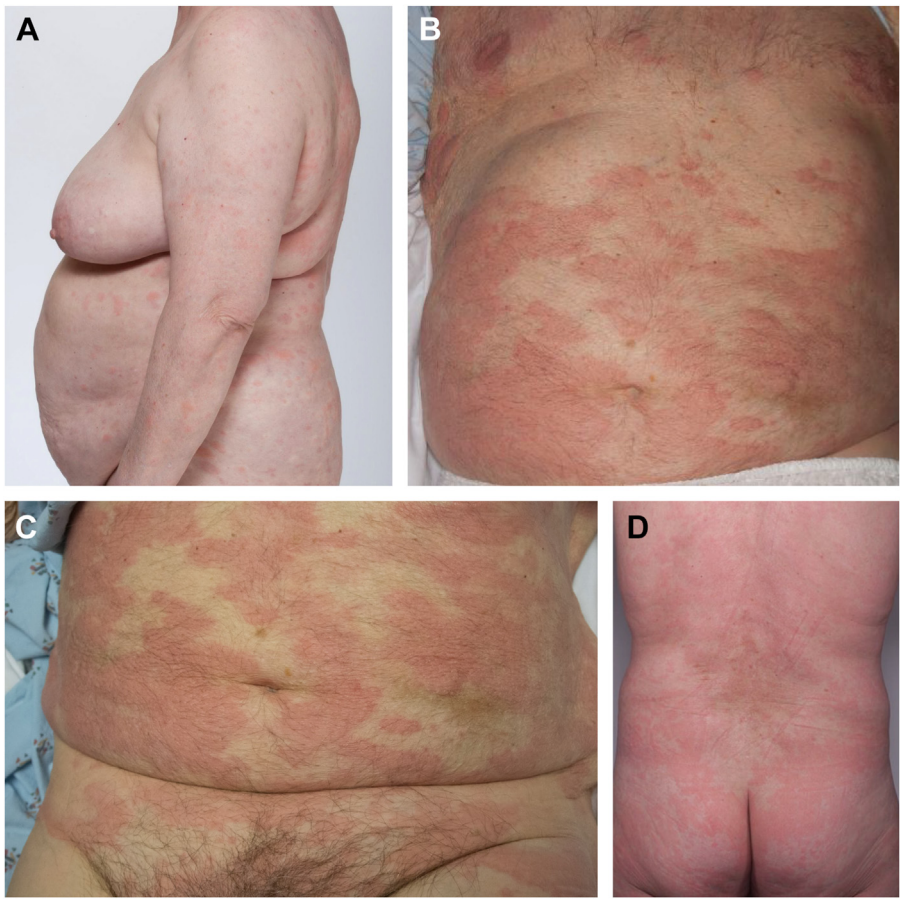

Fig. 1. (*A*) Urticarial papules and plaques on the trunk and upper extremity of a female with Schnitzler syndrome. (*B*) Confluent urticarial plaques on the trunk of an 80-year-old man with 8-month history of recurrent fevers, rashes, lymphadenopathy, arthralgias, confusion, and delirium. (*C*) Urticarial 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 autoinflammatory 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]

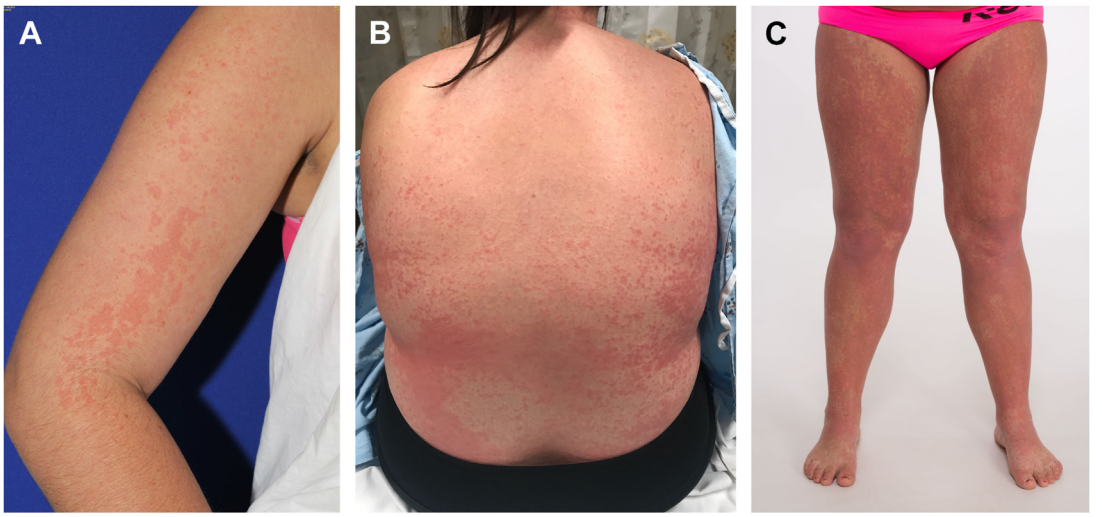

Fig. 2. (*A*) Coalescing urticarial papules and thin plaques on the upper arm of a young female with AOSD. (*B*) Coalescing urticarial papules and plaques on the trunk of a 31-year-ol female with AOSD. (*C*) Confluent urticarial papules and plaques on the lower extremities of a woman with AOSD.

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 ≥39°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 (≥10,000/mm3) 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 (CAPSs) 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 disease[19]

Major criteria

1. Fever of ≥39°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 (≥10,000/mm3) 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-1β precursor into active IL-1β.[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 multisystem 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 nonpruritic (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 syndrome[35]

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 criteria[42]

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

Box 5
Recommended laboratory tests if neutrophilic urticarial dermatosis is diagnosed[2]

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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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-1β.[33] The three effective treatments for CAPS include anakinra (IL-1 receptor antagonist), rilonacept (soluble IL-1 decoy receptor), and canakinumab (anti-IL-1β 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]

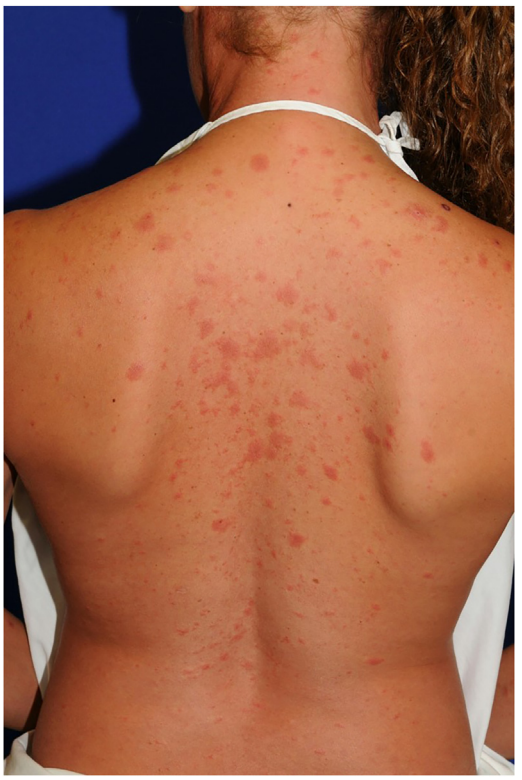

Fig. 3. Young woman with lupus erythematosus who presented with urticarial papules and NUD on histopathology.

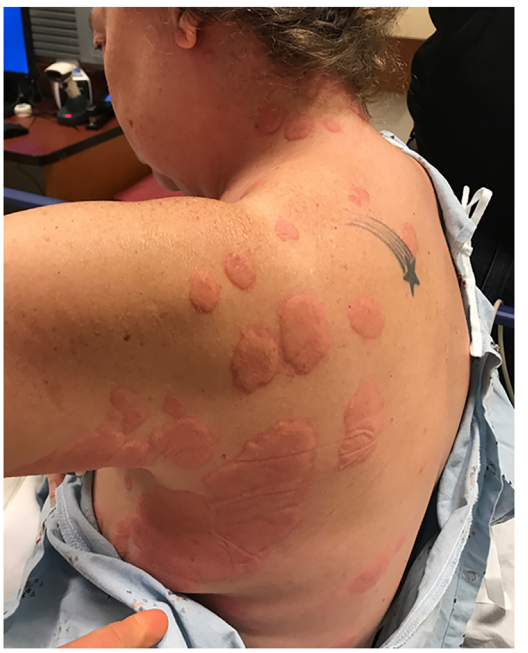

Fig. 4. Edematous urticarial plaques on trunk of patient with common urticaria.

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 remarkedly 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	• 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	• Perivascular, mainly mononuclear cell inflammation, with/without eosinophils (**Fig. 5**) • Dermal edema
Neutrophilic urticaria	• Individual urticarial lesions may be present for 24 h or less, several days, or more	• Vascular and perivascular neutrophilic inflammation, with/without eosinophils (**Fig. 6**) • Dermal edema
Neutrophilic urticarial dermatosis	• 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 dermographism • May present with a burning sensation in the skin • Associated with fever or arthralgia	• Perivascular and interstitial neutrophilic inflammation with/without eosinophils (**Fig. 7**) • Leukocytoclasia
Urticarial vasculitis (leukocytoclastic vasculitis)	• Painful, pruritic, or burning lesions • Lesions persist more than 24 h • May include palpable purpura and angioedema • Residual hyperpigmentation following resolution	• More perivascular than interstitial neutrophilic inflammation, with/without eosinophils (**Fig. 8**) • Leukocytoclasia • Fibrinoid necrosis of small vessels • Endothelial swelling • Hemorrhage
Sweet syndrome	• Erythematous or purplish papules and nodules • Raised plaques • Edematous lesions • May be associated with fever, joint pains, or episcleritis	• Significant dermal edema • Intense neutrophilic infiltrate typically in the superficial dermis

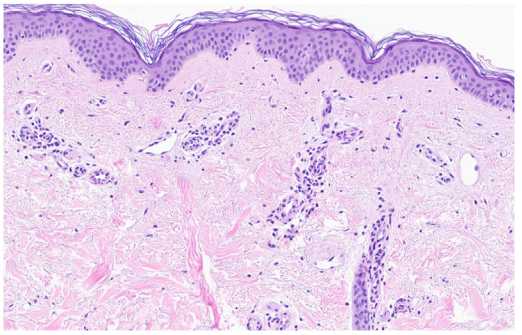

Fig. 5. Dermal edema, perivascular lymphocytes, neutrophils and eosinophils. Intraluminal neutrophils present. (Hematoxylin-eosin stain; X20).

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] alhough 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

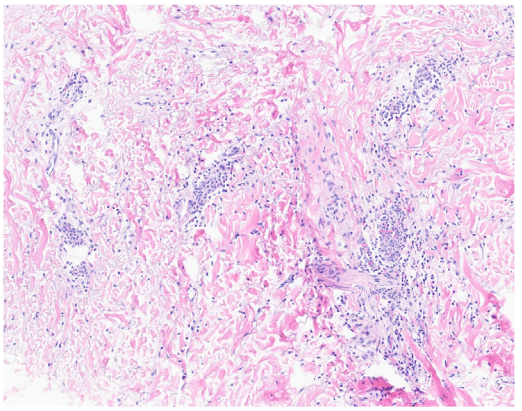

Fig. 6. Perivascular neutrophilic infiltrate with minimal interstitial spread and without leukocytoclasia (Hematoxylin-eosin stain; X20).

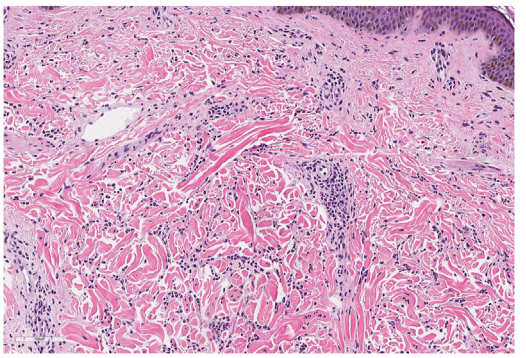

Fig. 7. Neutrophilic perivascular and interstitial infiltrate with leukocytoclasia; there is no vasculitis (Hematoxylin-eosin stain; X20).

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

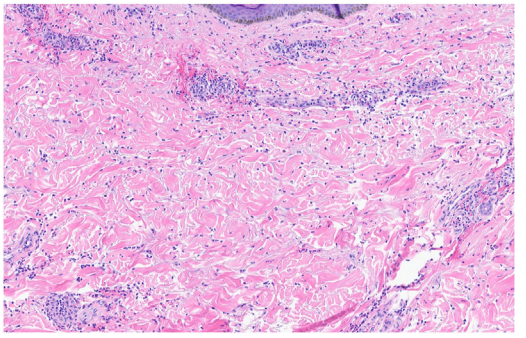

Fig. 8. Leukocytoclasia, perivascular and interstitial neutrophils, fibrinoid necrosis of vessel walls, hemorrhage, and edema of dermis (Hematoxylin-eosin stain; X20).

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.

REFERENCES

1. Kieffer C, Cribier B, Lipsker D. Neutrophilic Urticarial Dermatosis: A Variant of Neutrophilic Urticaria Strongly Associated With Systemic Disease. Report of 9 New Cases and Review of the Literature. Medicine 2009;88(1).
2. Gusdorf L, Lipsker D. Neutrophilic urticarial dermatosis: A review. Ann Dermatol Venereol 2018; 145(12):735–40.
3. Salam A, Papalexopoulou N, White JM, et al. Neutrophilic urticarial dermatosis: a novel association with poststreptococcal rheumatic disease. Clin Exp Dermatol 2018;43(3):311–4.
4. Gusdorf L, Lipsker D. Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond. J Eur Acad Dermatol Venereol 2020;34(4):685–90.
5. Gillihan R, Farahbakhsh N, Motaparthi K. Neutrophilic Urticarial Dermatosis Without Underlying Systemic Disease. J Clin Aesthet Dermatol 2020;13(3): 20–1.
6. Sokumbi O, Drage LA, Peters MS. Clinical and histopathologic review of Schnitzler syndrome: the Mayo Clinic experience (1972-2011). J Am Acad Dermatol 2012;67(6):1289–95.
7. Al-Hakim A, Mistry A, Savic S. Improving Diagnosis and Clinical Management of Acquired Systemic Autoinflammatory Diseases. J Inflamm Res 2022; 15:5739–55.
8. Lipsker D. The Schnitzler syndrome. Orphanet J Rare Dis 2010;5:38.
9. Ryan JG, De Koning HD, Beck LA, et al. IL-1 blockade in Schnitzler syndrome: ex vivo findings correlate with clinical remission. J Allergy Clin Immunol 2008;121(1):260–2.
10. Efthimiou P, Petryna O, Nakasato P, et al. New insights on multigenic autoinflammatory diseases. Ther Adv Musculoskelet Dis 2022;14. 1759720x221 117880.
11. Gusdorf L, Asli B, Barbarot S, et al. Schnitzler syndrome: validation and applicability of diagnostic criteria in real-life patients. Allergy 2017;72(2): 177–82.
12. Tolkachjov SN, Wetter DA. Schnitzler Syndrome With Delirium and Vertigo: The Utility of Neurologic Manifestations in Diagnosis. J Drugs Dermatol JDD 2017; 16(6):625–7.
13. Bhutani M, Shahid Z, Schnebelen A, et al. Cutaneous manifestations of multiple myeloma and other

plasma cell proliferative disorders. Semin Oncol 2016;43(3):395–400.
14. Kano Y, Sugihara M. Schnitzler Syndrome Presenting as a Fever of Unknown Origin with Elevated Alkaline Phosphatase Levels. Intern Med 2023; 62(9):1361–4.
15. van Leersum FS, Potjewijd J, van Geel M, et al. Schnitzler's syndrome - a novel hypothesis of a shared pathophysiologic mechanism with Waldenström's disease. Orphanet J Rare Dis 2019;14(1): 151.
16. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, et al. Adult-onset Still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. Medicine (Baltim) 2014;93(2):91–9.
17. Lee JY, Yang CC, Hsu MM. Histopathology of persistent papules and plaques in adult-onset Still's disease. J Am Acad Dermatol 2005;52(6): 1003–8.
18. Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971;30(2):121–33.
19. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19(3):424–30.
20. Ohta A, Yamaguchi M, Tsunematsu T, et al. Adult Still's disease: a multicenter survey of Japanese patients. J Rheumatol 1990;17(8):1058–63.
21. Schwarz-Eywill M, Heilig B, Bauer H, et al. Evaluation of serum ferritin as a marker for adult Still's disease activity. Ann Rheum Dis 1992;51(5):683–5.
22. Rooney M, David J, Symons J, et al. Inflammatory cytokine responses in juvenile chronic arthritis. Br J Rheumatol 1995;34(5):454–60.
23. Scheinberg MA, Chapira E, Fernandes ML, et al. Interleukin 6: a possible marker of disease activity in adult onset Still's disease. Clin Exp Rheumatol 1996;14(6):653–5.
24. Hoshino T, Ohta A, Yang D, et al. Elevated serum interleukin 6, interferon-gamma, and tumor necrosis factor-alpha levels in patients with adult Still's disease. J Rheumatol 1998;25(2):396–8.
25. Kawaguchi Y, Terajima H, Harigai M, et al. Interleukin-18 as a novel diagnostic marker and indicator of disease severity in adult-onset Still's disease. Arthritis Rheum 2001;44(7):1716–7.
26. Lübbe J, Hofer M, Chavaz P, et al. Adult-onset Still's disease with persistent plaques. Br J Dermatol 1999;141(4):710–3.
27. Suzuki K, Kimura Y, Aoki M, et al. Persistent plaques and linear pigmentation in adult-onset Still's disease. Dermatology 2001;202(4):333–5.
28. Joy M, Wittner L, Ellis S. A challenging diagnosis of adult-onset Still's disease in the setting of raised anti-streptolysin O titres. Rheumatol Adv Pract 2019;3. © The Author(s) 2019. Published by Oxford University Press on behalf of the British Society for Rheumatology.
29. Mitrovic S, Fautrel B. Clinical Phenotypes of Adult-Onset Still's Disease: New Insights from Pathophysiology and Literature Findings. J Clin Med 2021;10(12).
30. Giampietro C, Ridene M, Lequerre T, et al. Anakinra in adult-onset Still's disease: long-term treatment in patients resistant to conventional therapy. Arthritis Care Res 2013;65(5):822–6.
31. Ortiz-Sanjuán F, Blanco R, Calvo-Rio V, et al. Efficacy of tocilizumab in conventional treatment-refractory adult-onset Still's disease: multicenter retrospective open-label study of thirty-four patients. Arthritis Rheumatol 2014;66(6):1659–65.
32. Belfeki N, Smiti Khanfir M, Said F, et al. Successful treatment of refractory adult onset Still's disease with rituximab. Reumatismo 2016;68(3):159–62.
33. Levy R, Gérard L, Kuemmerle-Deschner J, et al. Phenotypic and genotypic characteristics of cryopyrin-associated periodic syndrome: a series of 136 patients from the Eurofever Registry. Ann Rheum Dis 2015;74(11):2043–9.
34. Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. Clin Exp Dermatol 2008;33(1):1–9.
35. Kuemmerle-Deschner JB, Ozen S, Tyrrell PN, et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). Ann Rheum Dis 2017;76(6): 942–7.
36. Yu JR, Leslie KS. Cryopyrin-associated periodic syndrome: an update on diagnosis and treatment response. Curr Allergy Asthma Rep 2011;11(1):12–20.
37. Miyamae T. Cryopyrin-associated periodic syndromes: diagnosis and management. Paediatr Drugs 2012;14(2):109–17.
38. Prieur AM, Griscelli C. Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation. J Pediatr 1981;99(1):79–83.
39. Hassink SG, Goldsmith DP. Neonatal onset multisystem inflammatory disease. Arthritis Rheum 1983;26(5):668–73.
40. Mok C, Lau C. Pathogenesis of systemic lupus erythematosus. J Clini Pathol 2003;56(7):481–90.
41. Kuhn A, Ruzicka T. Classification of Cutaneous Lupus Erythematosus. In: Kuhn A, Lehmann P, Ruzicka T, editors. Cutaneous lupus erythematosus. Berlin, Heidelberg: Springer; 2005.
42. Tiao J, Feng R, Carr K, et al. Using the American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) criteria to determine the diagnosis of systemic lupus erythematosus (SLE) in patients with subacute cutaneous lupus erythematosus (SCLE). J Am Acad Dermatol 2016;74(5):862–9.
43. Gusdorf L, Bessis D, Lipsker D. Lupus erythematosus and neutrophilic urticarial dermatosis: a retrospective study of 7 patients. Medicine 2014;93(29).
44. Lipsker D, Saurat J-H. Neutrophilic cutaneous lupus erythematosus. Dermatology 2008;216(4):283.

45. Kayiran MA, Akdeniz N. Diagnosis and treatment of urticaria in primary care. North Clin Istanb 2019;6(1):93–9.
46. Toppe E, Haas N, Henz BM. Neutrophilic urticaria: clinical features, histological changes and possible mechanisms. Br J Dermatol 1998;138(2):248–53.
47. Peters MS, Winkelmann RK. Neutrophilic urticaria. Br J Dermatol 1985;113(1):25–30.
48. Kolkhir P, Grakhova M, Bonnekoh H, et al. Treatment of urticarial vasculitis: A systematic review. J Allergy Clini Immunol 2019;143(2):458–66.
49. Venzor J, Lee WL, Huston DP. Urticarial vasculitis. Clin Rev Allergy Immunol 2002;23(2):201–16.
50. Cohen PR. Sweet's syndrome - A comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis 2007;2(1):34.