

REVIEW ARTICLE

Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond

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Abstract

Neutrophilic urticarial dermatosis (NUD) has been described in 2009. Clinically, it is an eruption of rose or red macules or slightly elevated plaques, vanishing within 24 h. It occurs mostly on the trunk and the limbs. Extracutaneous signs such as fever or joint pain can be associated. The histopathological findings are a dense perivascular and interstitial infiltrate of neutrophils with leucocytoclasia but without vasculitis. It is often associated with other systemic diseases such as Schnitzler syndrome, adult-onset Still disease (AOSD), cryopyrin-associated periodic syndrome (CAPS) and Lupus erythematosus (LE). The pathogenesis of NUD is not well established but its association with CAPS and AOSD suggests that NUD is linked to autoinflammation. The management of NUD depends on the clinical findings and the potential associated systemic condition. Neutrophil migration inhibitors, such as dapsone or colchicine, and IL-1 antagonists, in particular, anakinra, are the main therapeutic options for the treatment of NUD. The prognostic value of NUD, especially when occurring in the setting of LE is not known and needs to be further investigated.

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Conflict of interest

None.

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None.

Introduction and epidemiology

In 2009, neutrophilic urticarial dermatosis (NUD) was reported by one of us.¹ Two factors contributed to the description of this entity. First, a long history and tradition in Dermatopathology in our Department. Second, the fact that one of us has shown interest in a rare disease called Schnitzler syndrome² for more than 20 years. In the late 90's, we observed that patients suffering from Schnitzler syndrome had clinically an urticarial eruption but displayed histologically a neutrophilic infiltrate, that was very different from the findings usually seen in common urticaria. We, therefore, decided to collect the cases corresponding clinically to an urticarial eruption and histologically to a dense neutrophilic infiltrate, which we did for 10 years. In 2009, we thoroughly analysed those patients. Of initially 24 collected patients, only 9 patients with a very homogenous clinicopathological presentation remained in the end. Those patients were described as NUD. Interestingly, 7 of those 9 patients had an associated systemic disorder: adult-onset Still disease (AOSD, 3 cases), systemic lupus erythematosus (SLE, 3 cases) and Schnitzler syndrome (1 case).

Since its original description, NUD has been accepted as an autonomous entity. Numerous new cases have been reported, and associated diseases have been confirmed and expanded.^{1,3–20} Table 1 summarizes the associated diseases that have been published since our original publication in 2009. NUD can also occur without any underlying disease, as an entity on its own.

Pathogenesis and associated diseases

The pathogenesis of NUD is not well established, but its association with other systemic diseases for which the pathogenesis is better known provides some clues.

For instance, the association with AOSD, Schnitzler syndrome and most of all with CAPS, which is a monogenic autoinflammatory syndrome, suggests that NUD is linked to autoinflammation, in other words to actors of the innate immune system of myeloid lineage.

Associated systemic diseases are common in the setting of neutrophilic dermatosis, but there are probably some differences in regard to disease association between Sweet syndrome/pyoderma gangrenosum and neutrophilic urticarial dermatosis. The

Table 1 Cases of NUD and associated diseases since its original description in 2009

Associated diseases	N° of cases (%) N = 119	References
Schnitzler syndrome	50	Kieffer et al. ¹ ; Asahina et al. ³ ; Sokumbi et al. ⁵ ; Broekaert et al. ¹¹ ; Gusdorf et al. ¹⁴ ; Faggioli et al. ¹⁵ ; Rowczenio et al. ²⁰
SLE	21	Kieffer et al. ¹ ; Hau et al. ⁹ ; Gusdorf et al. ¹⁰ ; Broekaert et al. ¹¹ ; Lee et al. ¹⁷
AOSD	10	Kieffer et al. ¹ ; Hartig et al. ⁷ ; Broekaert et al. ¹¹ ;
SOJA	9	Broekaert et al. ¹¹ ; Stringer et al. ¹⁹
Systemic inflammation NOS	9	Broekaert et al. ¹¹
CAPS	5	Kolivras et al. ⁴ ; Broekaert et al. ¹¹ ; Herbert et al. ¹²
None	4	Kieffer et al. ¹ ; Belani et al. ⁶
Sjögren disease	3	Broekaert et al. ¹¹
Primary biliary cirrhosis	2	Broekaert et al. ¹¹
Inflammatory Bowel disease	2	Broekaert et al. ¹¹ ; Hou et al. ¹⁶
Serum sickness-like drug reaction	2	Nguyen et al. ¹³
Poststreptococcal rheumatic disease	1	Salam et al. ¹⁸
Acral acquired cutis laxa associated with IgA multiple myeloma	1	Kluger et al. ⁸

AOSD, adult-onset Still disease; CAPS, cryopyrin-associated periodic syndromes; (S)LE, (systemic) lupus erythematosus; NOS, not otherwise specified; SOJA, systemic-onset juvenile arthritis.

former are mainly associated with malignancies, myelodysplastic syndromes and inflammatory bowel disease, whilst NUD has been mainly associated with AOSD, Schnitzler syndrome, CAPS and lupus erythematosus so far.

Cryopyrin-associated periodic syndromes

Cryopyrin-associated periodic syndrome include three partially overlapping autosomal-dominant phenotypes: familial cold autoinflammatory syndrome, Muckle-Wells syndrome and CINCA/NOMID (chronic infantile neurological cutaneous and articular syndrome/Neonatal-onset multisystem inflammatory disease). They belong to the group of monogenic autoinflammatory syndromes.²¹ CAPS are caused by gain-of-function (GOF) mutations in the *NLRP3* gene (NOD-like receptor family, pyrin domain containing 3). *NLRP3* encodes a protein called cryopyrin. GOF mutations in *NLRP3* lead to an upregulation of inflammasome activity with an increased conversion of the biologically inactive IL-1 β precursor into active IL-1 β .

The three disorders share some common features such as a childhood onset, urticarial rash, joint pain and fever. All patients have persistent neutrophilia and raised acute phase protein. Cutaneous findings may be typical of NUD and may lead to the diagnosis, especially in atypical cases with a late-onset disease or in the absence of a familial history.¹²

Schnitzler syndrome

Schnitzler syndrome is a rare, adult-onset disease with approximately 300 cases described around the world. The required hallmarks for the diagnosis are a monoclonal IgM gammopathy and an urticarial rash corresponding to the definition of NUD. Variant Schnitzler syndromes with a monoclonal IgG component have been described, but some of them are probably mosaic

CAPS syndromes.²² The neutrophilic infiltrate in skin biopsy belongs to the Strasbourg diagnostic criteria.^{2,14,23} The role of IL-1 signalling in the disease's pathogenesis is highlighted by treatment response to anakinra, an anti-IL-1 receptor antagonist, which is immediate and complete, except for the monoclonal component that persists. No germline pathogenic mutations have been identified so far in patients with Schnitzler syndrome, but somatic mosaicism of *NLRP3* involving the myeloid lineage has been reported in two patients with variant Schnitzler syndrome.²² Yet, these results were not confirmed in a larger cohort of patients with Schnitzler syndrome.²⁰

Adult-Onset Still disease and juvenile idiopathic arthritis

Adult-onset Still disease is a rare non-familial, non-heritable systemic inflammatory disease. A classic clinical triad including high spiking fever, arthralgia and an erythematous evanescent rash is characteristic. Usually, an evanescent salmon-coloured maculopapular cutaneous eruption appears during the fever spike. It is part of the Yamaguchi criteria,²⁴ and skin biopsy is not mandatory. NUD is observed in about 22% of AOSD cases.²⁵ It can occur initially with the other signs of AOSD, or during the course of the disease after a few months. IL-1 β has been implicated in the pathogenesis of AOSD.²⁶ An IL-1 blockade is effective in some patients,²⁷ especially those with high fever and rash, in refractory diseases²⁸ and those with life-threatening cytokine storm and myocarditis.²⁹ NUD has also been reported as the presenting feature systemic juvenile idiopathic arthritis,¹⁹ a closely related if not similar entity.

Lupus erythematosus

Lupus erythematosus is a polygenic autoimmune disease characterized by the presence of non-organ-specific humoral

autoantibodies. Recently, the role of neutrophils in the pathophysiology of LE has emerged.³⁰ Neutrophils are commonly observed in the infiltrate of early and evolving cutaneous lesions of LE. Many neutrophilic dermatoses have been reported in the context of LE such as Sweet syndrome or pyoderma gangrenosum.¹⁰ Some variants of cutaneous LE are neutrophilic diseases such as bullous LE or amicrobial pustulosis of skin folds. These observations suggest that some cutaneous manifestations of LE involve an autoinflammatory mechanism.

When occurring in the setting of LE, NUD is often associated with fever and joint pain and thus very often misdiagnosed as a classic lupus flare, leading to increase in immunosuppressive therapies that will not be helpful in this situation. NUD can precede the diagnosis of LE or can arise during the course of LE. Antinuclear antibodies are always positive, and anti-Ro/SSA and anti-La/SSB antibodies are frequently present.¹⁰

Marshall's syndrome (Neutrophilic dermatosis with postinflammatory cutis laxa)

The initial rash of some cases of Marshall syndrome is a NUD (see below).

Other reported associations

Neutrophilic urticarial dermatosis has been reported in association with other diseases. Amongst those, two cases of serum sickness-like drug reaction (SSLR) have been reported.¹³ It has also been reported as a feature of poststreptococcal rheumatological disease.¹⁸ Furthermore, associations with primary Sjögren syndrome, primary biliary cirrhosis or inflammatory bowel disease are also described.^{11,16} A few cases of NUD in the context of IgA gammopathy, the isotype most commonly associated with neutrophilic dermatoses^{31,32} have also been reported.⁸

Clinical features

An urticarial eruption, i.e. an erythematous macular and/or palpable rash that resolves without sequels within 24 hours, is a

very common situation. The most common cause is acute or chronic urticaria (or hives). However, some clinical features allow the clinician to suspect NUD rather than urticaria. Lack of itching, or only slight pruritus, is the first sign that should raise suspicion, and the presence of mostly homogenous, not or only barely raised non-confluent rose or red lesions is another distinguishing feature (Fig. 1). When those rather unusual clinical findings are present, a cutaneous biopsy should be performed. Purpura, a hallmark of urticarial vasculitis, is not present, and lesions are usually not oedematous, whilst they always are in Sweet syndrome. Pain and burning sensation are unusual. Individual lesions resolve within 24 to 48 h without scarring, nor residual pigmentation. The eruption can either be chronic or recurrent.

Extracutaneous signs are very frequent, even in the absence of an underlying systemic condition. Fever, myalgia and fatigue are the most common signs encountered in patients with NUD. Less frequently, chest or abdominal pain can be observed.

Histopathology

The microscopic characteristics of NUD are a dermal neutrophilic infiltrate with substantial interstitial spreading and leucocytoclasia. By definition, there are no signs of vasculitis such as fibrinoid necrosis of vessel walls and no significant oedema of the dermis. These last two criteria are essential to distinguish NUD from urticarial vasculitis and from Sweet syndrome.

A mild to dense neutrophilic infiltrate in the papillary and the reticular dermis is observed (Fig. 2). Neutrophils are typically arranged in a single file along with the collagen bundles (Fig. 3). When the infiltrate is dense, foci of necrobiotic collagen bundles can be found. Neutrophils can also be located within the epithelia of sweat glands.⁴ They can also be seen in the epidermis or in the hair follicle epithelia, especially if NUD is associated with LE.⁴ Leucocytoclasia and diapedesis are common, but there is no fibrinoid necrosis of vessel walls and no extravasation of erythrocytes.



Figure 1 Neutrophilic urticarial dermatosis. Rose to red macules and barely raised papules or plaques in a patient occurring in the context of Schnitzler syndrome.

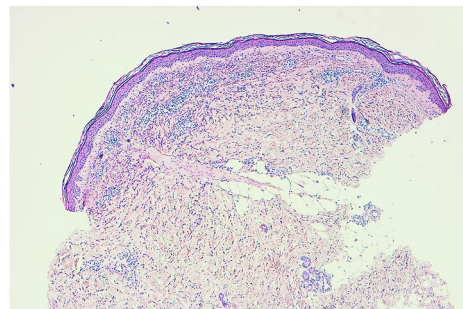


Figure 2 Neutrophilic urticarial dermatosis. Neutrophilic infiltrate of the dermis with substantial interstitial spreading. Absence of significant dermal oedema.

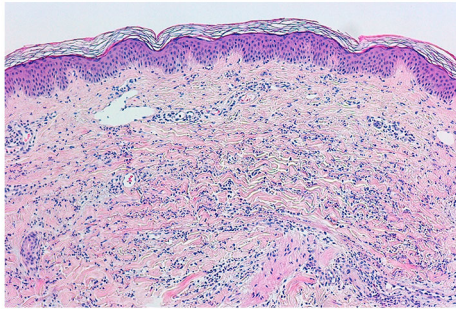


Figure 3 Neutrophilic urticarial dermatosis. Interstitial neutrophilic infiltrate of the dermis, with leucocytoclasia but without vasculitis. Neutrophils seem to spread along collagen bundles.



Figure 4 Urticarial vasculitis. Red papules and plaques leaving yellow purpuric and yellowish macules.

Other findings

Peripheral blood leucocytosis with neutrophilia is the most common abnormality in patients with NUD. Nonspecific inflammatory markers such as erythrocyte sedimentation rate (ESR) and CRP level are frequently elevated. In the absence of an associated systemic condition, renal or hepatic involvement has not been described.

Differential diagnosis

Chronic spontaneous urticaria

Chronic spontaneous urticaria is defined as the occurrence of spontaneous wheals and/or angio-oedema for longer than 6 weeks.³³ Clinically, the typical lesions are very itchy rose or red papules or plaque. Angio-oedema can be associated, as well as dermatographism. The individual lesions last a few hours and disappear without a sequel. The presence of fever or arthritis should lead to reconsider the diagnosis. If a skin biopsy is performed urticaria is characterized by dermal oedema. Blood vessels and lymphatics may be dilated but without alteration of the vessel walls. There is a mild cellular infiltrate in the dermis, mainly around the vessels. Neutrophils and eosinophils may be more prominent in acute urticaria and delayed-pressure urticaria.³⁴

Neutrophilic urticaria

Neutrophilic urticaria was reported in 1985 by Peters and Winkelmann.³⁵ The methodology of their study was to review

consecutive skin biopsy of a patient with a clinical presentation of common urticaria. They found a minority of patient with a neutrophilic perivascular infiltrate. However, leucocytoclasia and interstitial component were lacking. Furthermore, the neutrophilic infiltrate was never as intense as in NUD, and it never displayed the same pattern of interstitial spreading.

Urticarial vasculitis

Urticarial vasculitis is the main differential diagnosis of NUD. It is defined as an urticarial rash with histological signs of leucocytoclastic vasculitis (Table 2). It is divided into 2 groups according to complement levels: normocomplementemic or hypocomplementemic urticarial vasculitis (HUV). HUV is very often associated with other conditions such as LE (McDuffie syndrome), primary Sjögren's syndrome and monoclonal gammopathy.³⁶ The diagnosis is usually suspected when the lesions last more than 24 h and resolve to leave a purpuric patch (Fig. 4). Burning sensation and pain are usually reported. Fibrinoid necrosis of vessel walls is present and rules out the diagnosis of NUD.

Sweet syndrome

Sweet syndrome is the most frequent neutrophilic dermatosis. It is characterized by the abrupt onset of sometimes painful, oedematous and erythematous papules, plaques or nodules on the skin. The lesions can be violaceous and are much more oedematous and raised than those seen in NUD. Fever is frequent, and other organs can be involved.³⁷ Many underlying conditions are

Table 2 Histopathological features of typical lesions of neutrophilic urticarial dermatosis, Sweet syndrome and urticarial vasculitis

	Neutrophilic urticarial dermatosis	Sweet syndrome	Urticarial vasculitis
Histopathological features of typical lesions†	Neutrophilic dermal infiltrate with substantial interstitial spreading; absence of confluence of neutrophils; leucocytoclasia without vessel wall necrosis. No oedema.	Dense and confluent neutrophilic infiltrate of the dermis. Substantial oedema in the upper dermis. Some foci of vessel wall involvement can occur as an epiphenomenon.	Angiocentric neutrophilic infiltrate with no or minor interstitial spreading. Vessel wall fibrinoid necrosis and foci of thrombosis.

†Depending on type of lesions, especially the moment in the life of lesions when biopsy was taken, there can be some overlap between these entities.

described, in particular, inflammatory bowel disease, infections, haematologic malignancies, and solid tumours.³⁸ Histologically, there is a dense infiltrate of neutrophils in the upper and mid-dermis with a prominent oedema of the upper dermis (Table 2).

Neutrophilic dermatosis with postinflammatory cutis laxa (Marshall syndrome)

Marshall syndrome was first described in 1966,³⁹ mainly in paediatric patients. The primary lesion is a red papule that quickly extends and becomes bluish in the centre. Then the central area becomes wrinkled. Urticarial lesions have been reported.⁴⁰ Skin biopsy reveals a subepidermal oedema with a slight neutrophilic infiltration. The inflammation is more important in the reticular dermis, particularly around blood vessels. In the late stages, elastic fibres are almost totally absent and the remaining ones are thinner and fragmented. Aortitis and other fatal cardiovascular diseases were described in association with neutrophilic dermatosis and postinflammatory cutis laxa.^{41,42} The initial rash of a few cases of Marshall syndrome is an authentic NUD.

Palisaded neutrophilic granulomatous dermatitis

Palisaded neutrophilic granulomatous dermatitis is a rare condition. It is typically associated with autoimmune diseases,⁴³ lymphoproliferative disorders⁴⁴ or drug-reactions.⁴⁵ Clinical features are tender, erythematous to violaceous papules, plaques or nodules affecting the extensor surface; a central depression is characteristic. The skin biopsy shows an interstitial granuloma annular-like neutrophilic infiltrate; a necrotizing extravascular granulomatous process with basophilic degeneration of collagen bundles allows diagnosis. Leucocytoclasia and small-vessel vasculitis are probably almost always initially present.⁴⁶

Management

The management of NUD depends on the clinical findings and the potentially associated diseases. If NUD occurs without any known underlying condition, the first step is to investigate a potential association. Clinical examination should be complete. Laboratory evaluation should include a complete blood count, CRP, and ESR, serum protein electrophoresis, ferritinemia and measurement of antinuclear, anti-Ro/SSA and anti-La/SSB antibodies.

If NUD occurs as a proper disease, first-line therapy should rely on antihistamines, although they are not efficient in most cases. As second-line therapy, we recommend neutrophil migration inhibitors, such as dapsone, the most efficient drug in our experience, or colchicine.

Therapeutic dosage of dapsone ranges from 50 to 200 mg/day (maximum 2 mg/kg/day in children). The lowest effective dose should be given to minimize the possible side effects, namely haemolytic anaemia, methemoglobinemia or hypersensitivity (DRESS) syndrome.

Colchicine can be used with therapeutic dosage from 0.5 to 1 mg/day. At this dose, it is most of the time well tolerated. Information about the potentially lethal drug interaction with macrolides and pristinamycin should always be given to the patient and its general practitioner.

When NUD is occurring in the setting of Schnitzler syndrome or CAPS, IL-1 antagonists are the drugs of choice. Anakinra is a recombinant IL-1 receptor antagonist. Therapeutic dosage ranges from 50 to 100 mg/day in Schnitzler syndrome and from 100 to 400 mg/day in CAPS. The administration is subcutaneous, and the main adverse effects are injection site reactions and neutropenia. Neutropenia requires dose reduction or suspension of anakinra until blood count normalization.⁴⁷ The other IL-1 antagonists, canakinumab and rilonacept can also be used in CAPS.⁴⁸

When NUD occurs in the setting of an autoimmune disease such as LE, it is regularly misdiagnosed as a lupus flare. A dermatologist's look and a skin biopsy are then crucial to establish the correct diagnosis, especially since increasing immunosuppressive drugs is usually not helpful in this situation.¹⁰ Dapsone, or sometimes colchicine is generally the best therapeutic choices to control the symptoms.

The treatment of AOSD is often more complex, and a complete evaluation is needed, as the conventional treatments, such as nonsteroidal anti-inflammatory drugs, steroids, or methotrexate, may resolve the symptoms. Anakinra and tocilizumab can be valuable if the classical treatments are ineffective.²⁷ In this setting, a histopathological documentation of NUD could even be a predictor of a response to anakinra.

Unresolved questions

The frequency of a histopathological picture of NUD during common urticaria, which is never biopsied in real life, is not known. Therefore, NUD remains a clinicopathological diagnosis. In the same way, a rigorous histopathological analysis of cases labelled 'urticarial vasculitis' could possibly allow reclassifying a certain number of patients as NUD. The same observation can be made about serum sickness-like reaction.

The prognostic signification of NUD when occurring in the setting of LE is not known and needs to be further investigated.

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