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# Neutrophilic urticarial dermatosis preceding adult-onset Still disease

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## Abstract

Neutrophilic urticarial dermatosis is a distinct entity strongly associated with underlying autoinflammatory disease. The pathogenesis of this condition has been considered to center around interleukin-1. We report a young woman with neutrophilic urticarial dermatosis who presented with a recurrent urticarial rash for two years prior to the onset of other systemic features including persistent fevers, sore throat, leukocytosis, elevated ferritin, and splenomegaly. She was ultimately diagnosed with adult-onset Still disease and responded well to treatment with systemic corticosteroids. Although neutrophilic urticarial dermatosis is known to occur in the setting of systemic symptoms and disease, its occurrence preceding the onset of systemic inflammation is less well-described in current literature.

*Keywords: adult-onset, neutrophilic urticaria, Still disease, urticarial dermatosis*

## Introduction

Neutrophilic urticarial dermatosis (NUD) is a rare and distinct clinic-pathologic entity. It is characterized clinically by recurrent eruptions of slightly elevated pink or reddish macules and plaques that recede within 24 hours. A rich neutrophilic dermal infiltrate with leukocytoclasia but without vasculitis are its typical histological features [1]. Neutrophilic

urticarial dermatosis occurs in the setting of systemic symptoms and autoinflammatory disease [1-3].

## Case Synopsis

A 25-year-old woman was referred for a persistent urticarial rash of one month duration. During the same period she experienced daily high-grade fevers with a sore throat, malaise, and myalgia. She reported similar eruptions occurring intermittently over the last two years which were only mildly pruritic and responded partially to antihistamines. No triggers were identified and these eruptions receded without residual hyperpigmentation. Examination showed faint urticated macules and plaques with minimal edema over her upper limbs which were mildly pruritic (**Figure 1**). She was treated with high-dose antihistamines but with poor response.



**Figure 1.** Clinical photo of left arm showing faint urticated macules and plaques with minimal edema.

Histology from a skin punch biopsy done at presentation showed a predominantly neutrophilic perivascular infiltrate with extension into the epidermis. There was increased mucin deposition from the superficial to mid reticular dermis (**Figure 2**). No eosinophils were seen on histology. There was no obvious leukocytoclasia or diapedesis. Direct immunofluorescence was unremarkable. Her clinical and histological features were consistent with a diagnosis of NUD. Laboratory tests revealed an elevated neutrophil count of  $14.2 \times 10^9/L$ , mildly raised aspartate transaminase of 66U/L (normal 12-42U/L), elevated ferritin levels of 8736UG/L, C-reactive protein of 255mg/L, and erythrocyte sedimentation rate of 104mm/h. An extractable nuclear antibody profile was positive for anti-Ro antibody. Rheumatoid factor, antinuclear antibody, and double-stranded antibody titers were negative. A myeloma panel returned negative. Computed tomography of her chest, abdomen, and pelvis revealed mild splenomegaly with no other abnormalities. Subsequently, a diagnosis of adult-onset Still disease (AOSD) was made, supported by the Yamaguchi criteria (**Box 1**). She was treated with oral prednisolone 30mg once daily by consulting rheumatologists with clinical and biochemical improvement. Her urticarial eruption resolved during subsequent clinic review one month later.

#### Box 1. Yamaguchi criteria.

##### Major criteria

- 1) Fever  $\geq 39^\circ C$  persisting for  $\geq 1$  week
- 2) Arthralgia/arthritis persisting for  $\geq 2$  weeks
- 3) Non-pruritic, salmon-pink, macular or maculopapular rash during fever
- 4) Leukocytosis  $\geq 10 \times 10^9/L$  ( $>80\%$  neutrophils)

##### Minor criteria

- 1) Sore throat
- 2) Lymphadenopathy and/or splenomegaly (clinical or ultrasound)
- 3) Raised hepatic enzymes (after exclusion of other causes)
- 4) Negative rheumatoid factor and antinuclear antibodies

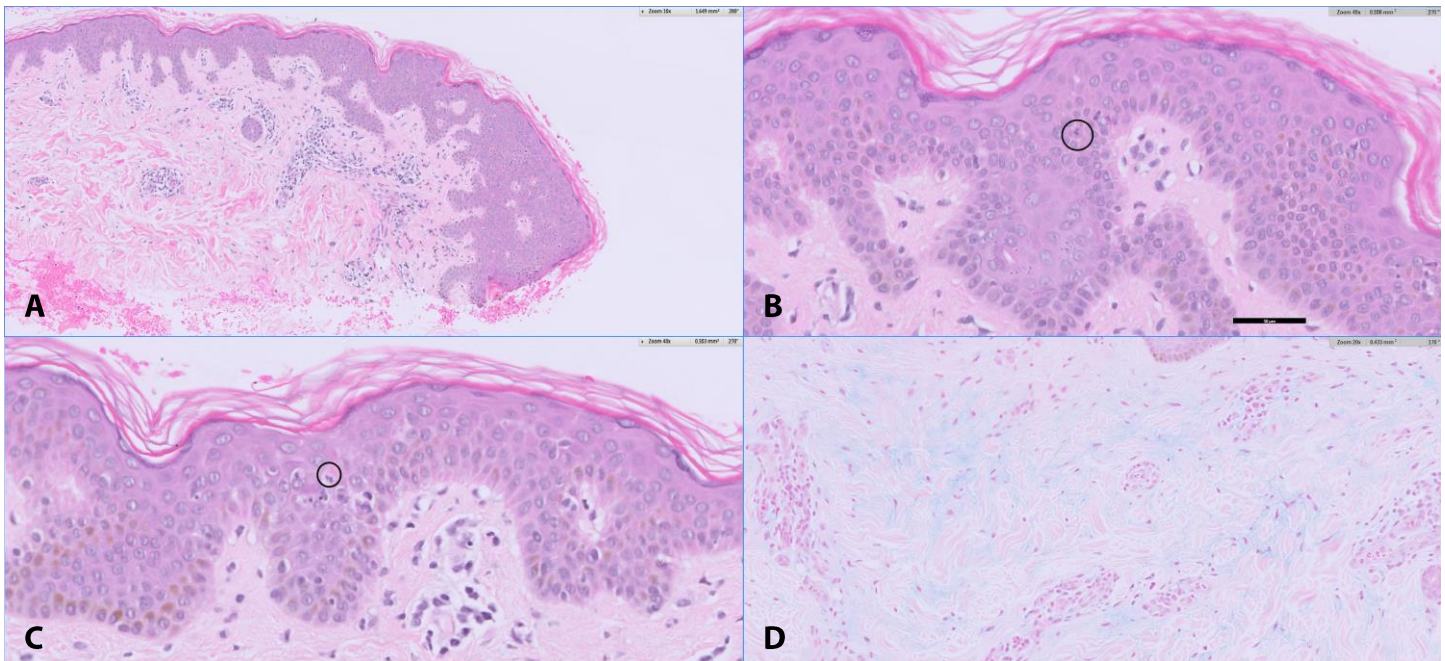
##### Exclusion criteria

- 1) Infections, in particular sepsis and infectious mononucleosis
- 2) Malignancy, in particular lymphoma
- 3) Other rheumatic diseases, in particular polyarteritis nodosa and vasculitides with extra-articular features

$\geq 5$  criteria are required,  $\geq 2$  must be major, with no exclusion criteria.

## Case Discussion

Neutrophilic urticarial dermatosis is strongly associated with underlying autoinflammatory disease and has been reported in cases of AOSD, systemic lupus erythematosus, Schnitzler syndrome, and cryopyrin-associated autoinflammatory syndromes [1,2]. The pathogenesis of this phenomenon has been proposed to center around



**Figure 2.** H&E histopathology: **A)** Dermal perivascular neutrophilic infiltrate, 40 $\times$ ; **B, C)** intra-epidermal neutrophils (black circles), 40 $\times$ . **D)** Alcian blue staining demonstrates mucin deposition in superficial to mid dermis, 40 $\times$ .

interleukin-1 [2]. It has been theorized that inherited hyperactivation of the inflammasome pathway such as seen in NLRP3 gain-of-function mutation could play a pathophysiological role [3].

The differential diagnosis of NUD includes classical urticaria and urticarial vasculitis. We summarize the distinguishing features between these three entities in [Table 1](#). Compared to urticaria, edema and pruritus are less marked in NUD and response to antihistamines is generally poorer [1, 4]. Unlike urticarial vasculitis, post-inflammatory hyperpigmentation and purpura do not occur in NUD [1]. Histological features of urticarial vasculitis such as leukocytoclastic vasculitis, fibrinoid necrosis of the vessel walls, and extravasation of red blood cells are also absent in NUD [1].

Neutrophilic epitheliotropism was appreciated in our patient. It describes a histopathological reaction pattern of a perivascular and interstitial neutrophilic infiltrate focally extending into the epithelia of the epidermis and adnexae. It is a highly sensitive (83.1%) and moderately specific (74.3%) feature of NUD [5]. Additionally, increased mucin deposition in the reticular dermis was observed in our case. This feature has been found to be associated with lupus erythematosus and might potentially apply to other connective tissue disorders [6].

The association between NUD and underlying systemic inflammation has been well-established in recent literature. Most cases reported NUD occurring in the setting of autoinflammatory disease and extracutaneous symptoms [1,2,4]. Interestingly, our patient experienced recurrent urticarial eruptions over a period of two years prior to the development

of systemic symptoms and a formal diagnosis of AOSD. Although a skin biopsy was only performed at the end of two years, the morphology of her rash, a history of mild pruritus with partial response to antihistamines, and permanent resolution of cutaneous symptoms following treatment for AOSD suggest a diagnosis of NUD from initial onset rather than common urticaria. Neutrophilic urticarial dermatosis preceding the onset of systemic inflammation is less well described in current literature. A review of published cases of NUD in the setting of AOSD showed that the urticarial eruptions have tended to occur in association with systemic signs and symptoms, except for one case where the rash preceded systemic symptoms by one year ([Table 2](#)), [4,7-8]. It is possible that NUD could precede systemic autoinflammatory disease by a duration of months to years. This observation bears medical significance because NUD could herald the onset of systemic disease and patients who present with NUD should be followed-up for the development of autoinflammatory disease.

## Conclusion

Recognition of NUD as a distinct entity is crucial for timely diagnosis of underlying systemic disease. Neutrophilic urticarial dermatosis could precede systemic inflammation. Patients who present with NUD should be followed-up for subsequent development of autoimmune disease.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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**Table 1.** Clinical and histological differences between urticaria, NUD and urticarial vasculitis.

Features	Urticaria	NUD	Urticarial vasculitis
Morphology	Edematous papules, plaques	Faint urticated macules, slightly-raised papules or plaques	Edematous papules, plaques Post inflammatory hyperpigmentation and purpura
Symptoms	Marked pruritus	Mild pruritus	Pain or burning sensation
Duration	Few hours	24-48 hours	>24 hours
Angioedema	Possible	Rare	Possible
Systemic/extracutaneous	Rare	Frequent—arthralgia, fever	Frequent—livedo, arthralgia, fever
Dermographism	Frequent	Possible	Possible
Response to high-dose antihistamines	Frequent	Rare or partial	Partial
Associations	Rare	Frequent—AOSD, systemic lupus erythematosus (SLE), Schnitzler syndrome, cryopyrin-associated autoinflammatory syndromes	Frequent—30% associated with connective tissue disease (SLE, Sjogren syndrome), cryoglobulinemia, viral infections, malignancies, drugs
Histology	Variable dermal edema. Perivascular inflammatory infiltrate consisting of neutrophils, eosinophils, lymphocytes, mast cells	Predominant neutrophilic infiltrate. Lacks dermal edema Neutrophilic epitheliotropism [5]	Leukocytoclastic vasculitis, fibrinoid necrosis of the vessel walls, extravasation of red blood cells

**Table 2.** Published cases of neutrophilic urticarial dermatosis (or a rash corresponding to neutrophilic urticarial dermatosis) in association with adult-onset Still disease.

Case	Demographics	Clinical features	Reference
1	28/ F	Transient and nonpruritic rose macules and papules on trunk and upper limbs in evening for 2 months, in association with fever, myalgia, polyarthritis, pharyngitis, diarrhea and hepatomegaly	[4]
2	33/ M	Rose and transient macules and papules on trunk and limbs for 1 month, in association with fever, polyarthritis, odynophagia and lymphocytic meningitis	[4]
3	57/ F	Recurrent evening eruption with red, small wandering and nonpruritic papules on trunk and limbs (duration of rash not specified), in association with fever, odynophagia arthralgia and myalgia	[4]
4	42/ M	Nonpruritic urticarial rash as well as chills, fever, myalgia, arthralgia and fatigue (duration of rash not specified, associated hepatitis B)	[4]
5	52/ F	Mildly pruritic evanescent salmon-pink urticarial eruption on extremities and trunk for 3 years. High grade fevers for 2 years, associated with arthralgia, fatigue, sore throat, lymphadenopathy and hepatomegaly	[7]
6	53/ M	Disseminated nonpruritic urticarial rash in association with recurrent fever, weight loss, arthralgias and fatigue (duration of symptoms not specified, probable AOSD)	[8]