Overview of Neutrophilic Biology, Pathophysiology, and Classification of Neutrophilic Dermatoses

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KEYWORDS

• Neutrophilic dermatoses neutrophils • Autoinflammation • Myeloid neoplasm

KEY POINTS

- Neutrophilic dermatoses (NDs) are a heterogeneous group of inflammatory skin conditions characterized by a primitive infiltrate of the skin by neutrophils without evidence of infection.
- The most well-defined NDs include pyoderma gangrenosum, Sweet's syndrome, subcorneal pustular dermatosis, neutrophilic eccrine hidradenitis, amicrobial pustulosis of the folds, generalized pustular psoriasis, and neutrophilic urticarial dermatosis.
- The pathogenic mechanisms of the various NDs involves autoinflammation, neutrophilic dysfunction and clonal somatic mutation and differentiation of the myeloid cells as encountered in myeloid neoplasm.

INTRODUCTION

Neutrophilic dermatoses (NDs) are a heterogeneous group of inflammatory skin conditions characterized by a primitive infiltrate of the skin by neutrophils without evidence of infection.[1,2] Clinical presentations of ND are polymorphic, including pustules, bullae, abscesses, papules, nodules, plaques, and ulcers, and almost any organ system can be involved, giving rise to the term of "neutrophilic disease."[3] The most well-defined NDs include pyoderma gangrenosum (PG), Sweet's syndrome (SS), subcorneal pustular dermatosis (SPD), neutrophilic eccrine hidradenitis (NEH), amicrobial pustulosis of the folds (APF), generalized pustular psoriasis, and neutrophilic urticarial dermatosis (NUD).[1,2] Although each entity may present within an overlapping clinically and/or pathologically spectrum, making diagnosis and management difficult.

Nowadays, NDs are classified based on the localization of neutrophils within the skin and clinical features.[3] The pathogenic mechanisms of the various NDs are not well understood, and studies on ND pathophysiology in humans are limited. However, the discoveries on the innate immune system such as the inflammasome physiology or neutrophilic diversity, and the emergence of the concept of autoinflammation in humans allowed us to understand those diseases better.[4,5]

Indeed, ND's clinical and pathophysiological features have significant overlap with disorders included within the spectrum of autoinflammatory diseases that manifest as relapsing periods of sterile tissue inflammation including the skin.[2,6,7]

Also, a great number of patients with ND suffer from another underlying condition such as hematological malignancies, autoinflammatory diseases, inflammatory bowel disease, and connective tissue diseases.[2,8–10] As the skin is not the only organ targeted by the activated neutrophils, and as many organs may be involved by a similar sterile inflammation, the term "neutrophilic disease" has

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been proposed.[3] Recent findings suggest that NDs are due to 2 main mechanisms: (i) a polyclonal hereditary activation of the innate immune system (polygenic or monogenic) and (ii) a clonal somatic activation of myeloid precursor cells as encountered in myeloid.[1,7,11,12]

First, we will provide an overview of neutrophilic biology, then explain the latest findings in the pathophysiology of ND, and finally we will present a classification of these diseases.

OVERVIEW OF NEUTROPHILIC BIOLOGY

Neutrophils are key players of innate immunity; they are the most abundant type of white blood cells in the circulation and are produced in the bone marrow.[13] Once released into the bloodstream, they circulate until they are needed to fight infection or respond to tissue damage. Once within the tissue, neutrophils are activated to perform multiple innate immune responses including phagocytosis, release a variety of proinflammatory mediators, including cytokines, chemokines, and reactive oxygen species.[14,15] These mediators promote the recruitment of other immune cells, such as monocytes and lymphocytes, and contribute to the destruction of pathogens. Neutrophils can also release neutrophil extracellular traps (NETs) – a web-like structures composed of DNA, histones, and antimicrobial proteins that play a role in trapping and clearing infectious agents.[16]

Neutrophils are primarily known for their role in the immune response, they also play a role in maintaining the health of the skin at steady state by clearance of apoptotic cells and debris and promote cell proliferation and wound healing.[17]

Neutrophils are short-lived cells, with a lifespan of only a few days. After they have performed their function, they undergo apoptosis, which is a programmed cell death.[18] Once they have undergone apoptosis, they are phagocytosed by other immune cells, such as macrophages, and are eliminated from the body promoting anti-inflammatory immune responses due to retention of granular and cytoplasmic components intracellularly.[18]

PATHOPHYSIOLOGY OF NEUTROPHILIC DERMATOSIS

Immune Dysregulation in Neutrophilic Dermatoses

Studies have revealed complex gene expression profiles in the skin of patients with ND suggesting activation of inflammasomes (interleukin [IL]-1β), dysregulation of the innate immune system (IL-17, IL-23, IL-36, TNFα, INF-γ), and recruitment and activation of neutrophils (IL-8, IL-17, granulocyte colony-stimulating factor [G-CSF]).

- The lesional skin of PG has showed overexpression of IL1β, IL-8, IL-17, IL-23, IL-36, and TNFα.[19,20]
- IL-1β, IL-6, and IL-8, IL-17, and TNFα are also elevated in the lesional skin of other NDs such as SS and APF.[19,21,22]
- Serum of patients with SS have significantly elevated IL-1 and INF-γ.[23]
- A role for G-CSF – a hormone cytokine that stimulates neutrophils' survival, proliferation, and differentiation – has been highly suggested in SS. Indeed G-CSF drugs, used in neutropenia, are a common cause of drug-induced SS and higher serum levels of G-CSF have been described in patients with active SS compared with SS patients with nonactive disease.[24]
- Matrix metalloproteinases (MMP)-2 and MMP-9 are overexpressed in inflammatory infiltrate of PG and may lead to tissue damage.[25]

NEUTROPHILIC DYSFUNCTION IN NEUTROPHILIC DERMATOSES

Although neutrophils play a crucial role in the immune response to infection and inflammation, they can also contribute to tissue damage in certain conditions including ND. In normal condition, after they have performed their function, neutrophils undergo apoptosis, promoting immunosuppressive response in the phagocyte and anti-inflammatory regulation: IL10 and TGFβ increase whereas TNFα, IL6, G-CSF, IL8, and IL17 downregulate recruitment and activation of neutrophils. The anti-inflammatory response relies on a long-lasting presence of apoptotic neutrophils.[26]

Certain infectious or inflammatory diseases including ND can trigger lytic forms of neutrophil death, which allows the release of proinflammatory cytokines and granular proteins that may worsen local tissue injury and sustain the inflammation.[18] Abnormal NETs release and NETosis – a form of lytic, proinflammatory death related to NETs release – has been showed to increase into the skin of patients with ND.[27]

- Increased in NET release has been demonstrated in SS, PG, SPD, hidradenitis suppurativa (HS), and NUD compared with control skin.[28–30]
- NETotic neutrophils are present in HS lesions, particularly in the lesional tunnel, and the degree of NETs and the severity of HS are positively correlated.[31]

- A study showed that more than 50% of neutrophils infiltrating the skin in the setting of PG exhibit NET formations.[28–30]
- Circulating neutrophils from PG and HS patients spontaneously undergo NETosis.[28,31]
- The sera of patients with HS are unable to degrade NETs induced in healthy neutrophils.
- Autoantibodies against citrullinated proteins derived from NET components have been detected in patients with HS.[31]
- There is a colocalization of IL-1 and TNFα in NETs of SS and PG.[28–30]

NEUTROPHILIC DERMATOSES AND AUTOINFLAMATION

ND-related syndromic diseases belong to systemic autoinflammatory diseases: a family of genetic disorders characterized by aberrant antigenic-independent activation of the innate immune system pathways.[5] Several NDs occur as clinical manifestations of autoinflammatory diseases (**Table1**), for example,

- SS is seen in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome and SS-like (erysipelas-like skin lesion) in patients with familial Mediterranean fever;[32,33]
- PG occurred in the context of autoinflammatory syndromes induced by mutation of the *proline-serine-threonine phosphatase interacting protein 1* (*PSTPIP1*) gene such as PAPA (pyogenic arthritis, PG, and acne), as well as in the context of pyrin-associated autoinflammation with ND caused by mutations in exon 2 of *MEFV* and A20 haploinsufficiency (*TNFAIP3*).[34,35]
- NUD occurred in cryopyrin-associated periodic syndrome (a monogenic autoinflammatory diseases related to *NLRP3* inflammasome) and Schnitzler syndrome or Still's disease (polygenic acquired diseases that probably primarily involve autoinflammatory pathways).[36]
- Deficiency of IL-1 receptor antagonist (IL1RN, deficiency of interleukin-1 receptor antagonist) and deficiency of the IL-36 receptor antagonist (IL-36RN/IL1F5 deficiency of IL-36 receptor antagonist) are monogenic diseases with skin pustular phenotypes.[37,38]

By extension some authors propose that ND by themselves should be considered as autoinflammatory diseases as they both share common clinical manifestations (such as fever or arthralgias), dermatopathological features (intense infiltration by neutrophils within the skin), cytokine profiles, and therapeutic approaches.[1,6,7]

PATHERGY

Eventually, NDs share the pathergy phenomenon, a skin condition in which a trauma such as surgical incisions leads to the development of skin lesions or ulcers that may be resistant to healing. This condition is well known in Behçet's disease, but it may also be seen in SS, PG, or neutrophilic necrotizing cellulitis.[39–41] Thus, postoperative PG is often misdiagnosed as wound infection, and pathergy may complicate wound debridement.[42,43]

Trauma and skin injuries release cytokines like IL36 and IL8 and dangers signals promoting innate immune response and may drive ND.[44]

SOMATIC MUTATION, AUTOINFLAMMATION

Recently, somatic mosaic *NLRP3* variations have been described in patients who presented with reminiscent late-onset urticaria with NUD. Whereas patients were refractory to antihistaminic drugs, steroids, and colchicine, they dramatically responded to IL-1β antagonist anakinra.[45,46] A new syndrome named Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome, was recently described. VEXAS is due to myeloid-restricted, somatic missense mutation in codon 41 of *UBA1 gene*, an X-linked gene that encodes the enzyme that initiates ubiquitination.[47] These mutations in *UBA1 gene* led to production of catalytically deficient cytoplasmic UBA1 and activation of multiple innate immune pathways. This syndrome includes SS, relapsing polychondritis, polyarteritis nodosa, giant-cell arteritis, MDS, and multiple myeloma.[47] Moreover, a lot of polygenic and multifactorial diseases included in the spectrum of autoinflammation, are associated with ND such as inflammatory bowel disease or spondylarthritis.[9,42,48] In addition, *MEFV* variation has been detected in 2 patients with MDS and SS.[49]

LEUKEMIC CELLS AND NEUTROPHILIC DERMATOSIS

Leukemic cells, under various stimuli, are able to differentiate into clonally restricted well-differentiated cells.[50] For example, preleukemic cells HL-60 can differentiate in vitro into granulocytes after stimulation with retinoic acid.[51] In clinical hematology, this phenomenon is responsible of the differentiation syndrome, a potentially fatal complication of treatment inducing maturation of myeloid blast in the setting of acute myeloid leukemia (AML), such as all-trans retinoic acid or

Table 1
Autoinflammatory disease and associated neutrophilic skin conditions

Diseases		Protein and Related Gene	Mode of Inheritance	Type of Neutrophilic Dermatosis
Autoinflammatory diseases caused by excessive interleukin-1 signaling, production, and secretion				
Familial Mediterranean fever Pyrin-associated autoinflammation with neutrophilic dermatosis		*MEFV* Pyrin MEFV (exon 4) Pyrin	Autosomal recessive (AR)	Erysipelas-like skin lesion "Sweet-like" Acne, aseptic abscesses, pyoderma gangrenosum
Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)		*TNFRSF1A* TNF receptor-1A	Autosomal dominant (AD)	Migratory edematous rash "Sweet-like"
Hyperimmunoglobulin D syndrome (HIDS)		*MVK* Mevalonate kinase	AR	Erythematous macules and edematous papules (neutrophilic urticaria), aphthous ulcers
Cryopyrin-associated periodic syndromes	Neonatal-onset multisystem inflammatory disease	*NLRP3* Cryopyrin	AD	Urticarial papules and plaques (neutrophilic urticarial dermatosis); aphthous ulcers
	Muckle–Wells syndrome			Urticarial papules and plaque (neutrophilic urticarial dermatosis)
	Familial cold autoinflammatory syndrome (FCAS)			Cold-induced urticarial papules and plaques (neutrophilic urticarial dermatosis)
FCAS type 2		*NLRP12* Monarch-1	AD	Neutrophilic urticarial dermatosis
Deficiency of interleukin-1 receptor antagonist		*IL1RN* IL-1 receptor antagonist	AR	Pustules within areas of erythema – appearance similar to pustular psoriasis, pyoderma gangrenosum
Pyogenic arthritis, PG, and acne (PAPA) PG, acne, and HS (PASH) syndrome PAPASH (PAPA + PASH) syndrome		*PSTPIP1* Proline-serinethreonine phosphataseinteracting protein-1	AD	Pyoderma gangrenosum Acne Hidradenitis suppurativa Aseptic abscesses Pathergy

Majeed syndrome	*LPIN2* Lipin 2	AR	Pustular dermatitis
Autoinflammation with infantile enterocolitis	*NLRC4* NLRC4 inflammasome	AR	Neutrophilic urticarial dermatosis, aphthous ulcers
Interferon mediated autoinflammatory diseases			
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome or proteosome-associated autoinflammatory syndrome	*PSMB8* Proteasome subunit, beta type 8	AR	Sweet syndrome, neutrophilic panniculitis
Autoinflammatory diseases caused by nuclear factor kappa B (NF-κB) dysregulation			
CAMPS (CARD14 mediated pustular psoriasis)	*CARD14 gene* Caspase recruitment domain-containing protein 14	AD	Generalized pustular psoriasis
Deficiency of IL-36 receptor antagonist	*IL36RN* IL-36 receptor antagonist	AR	Pustules within areas of erythema – resembles generalized pustular psoriasis
OTULIN-related autoinflammatory syndrome	*OTULIN* M1-specific deubiquitinase OTULIN	AR	Nodular panniculitis and lipodystrophy, pustular and scarring rash
VEXAS syndrome	*UBA1* Ubiquitin-activating enzyme (E1)	Myeloid-restricted, somatic missense mutation	Sweet syndrome
A20 haploinsufficiency	*TNFAIP3* A20	AD	Oral ulcers, genital ulcers, erythematous papules, folliculitis, pathergy
Famillial necrotizing neutrophilic cellulitis	*NFKB1 (p.R157X)*	AR	Neutrophilic necrotizing cellulitis
Autoinflammatory diseases caused by enzymatic defects in innate and adaptive immune cell-signaling pathways			
PLCG2-associated antibody deficiency and immune dysregulation Autoinflammation and PLCG2 associated antibody deficiency and immune dysregulation	*PLCG2* Phospholipase C, γ2	AD	Erysipelas-like skin lesion “Sweet-like”, neutrophilic urticaria

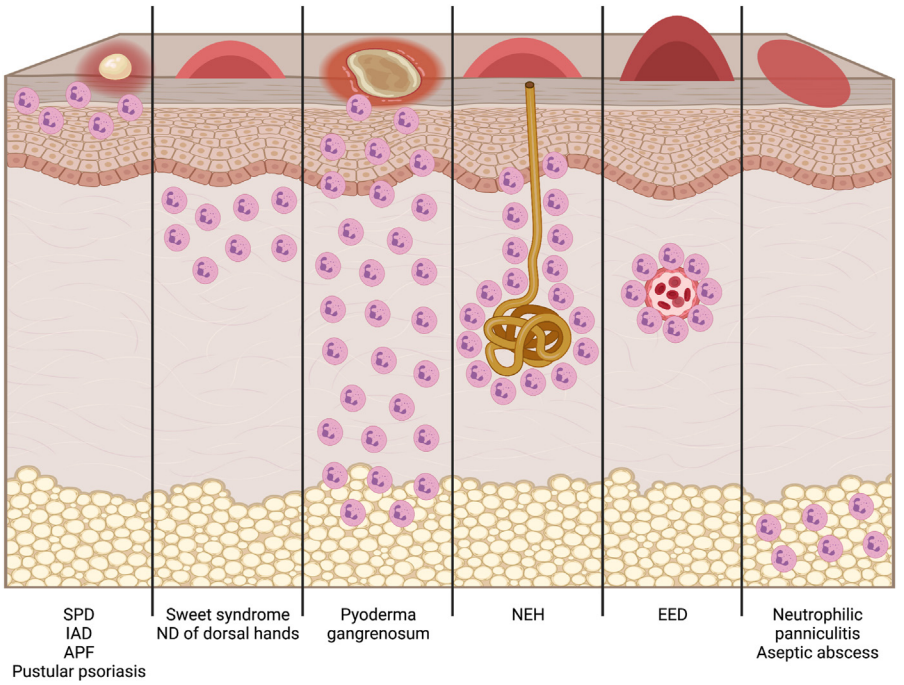

Fig. 1. Schematic of main neutrophilic dermatoses in accordance with neutrophils localization within the skin. APF, aseptic pustulosis of the folds; EED, erythema elevatum diutinum; IAD, intercellular IgA dermatoses; ND, neutrophilic dermatosis; NEH, neutrophilic eccrine hidradenitis; SPD, superficial pustular dermatoses. (Created with BioRender.com.)

inhibitor of FLT3. In the setting of myeloid neoplasm, historically, NDs were classified as "nonspecific"/paraneoplastic disorder whereas leukemia cutis (skin infiltration of AML blast cells) was classified as specific. This dichotomic classification has been questioned because: (i) ND occurs under different treatments inducing myeloid cell differentiation; (ii) ND as well as leukemia cutis predominate in AML with prominent monocytic component; (iii) several cases of mixtures of tumoral myeloid cells and mature neutrophils have been reported.[52] Since then, cytogenetic and molecular investigations have demonstrated that SS neutrophils and AML blast cells have a common precursor, suggesting a differentiation of tumoral cells into neutrophils within the skin in AML-associated SS.[11,53,54] Considering these findings, a disease spectrum from leukemia cutis to AML-associated SS might be suspected. Likewise, patients with MDS may develop skin involvement by immature myeloid dysplastic cell as myelodysplasia cutis, or infiltration by more mature clonal cells leading to mature SS neutrophils.[11,54,55] This also suggests in MDS a disease spectrum ranging from myelodysplasia cutis to MDS-associated classical SS.[55]

Moreover, Zakine and colleagues showed, in a case series study of 8 men with VEXAS syndrome, that skin infiltrates were made of a mixture of neutrophils and immature myeloid cells and that the *UBA1* mutation was found in cutaneous lesions in those patients, suggesting that the inflammatory skin manifestations found in VEXAS syndrome might be a direct consequence of the clonal infiltration of the skin rather than just a proinflammatory activation state.[12] The differentiation of myeloid cells into skin infiltrating neutrophils may be due to a specific skin immunologic environment that allows cell maturation.[56]

CLASSIFICATION OF NEUTROPHILIC DERMATOSIS

In 2006, Vignon-Pennamen and Wallach proposed a classification of the numerous NDs based on the localization of neutrophils within the skin (**Fig. 1**).[3] There are associations, transitions, and overlap of forms between these entities.

Epidermal/Superficial Neutrophilic Dermatoses: Pustulosis

- *Superficial neutrophilic dermatoses: SPD and intercellular IgA dermatoses (IAD):* The SPD is characterized by subcorneal, nonfollicular, unilocular pustules filled with neutrophils. There is no epidermal spongiosis in SPD

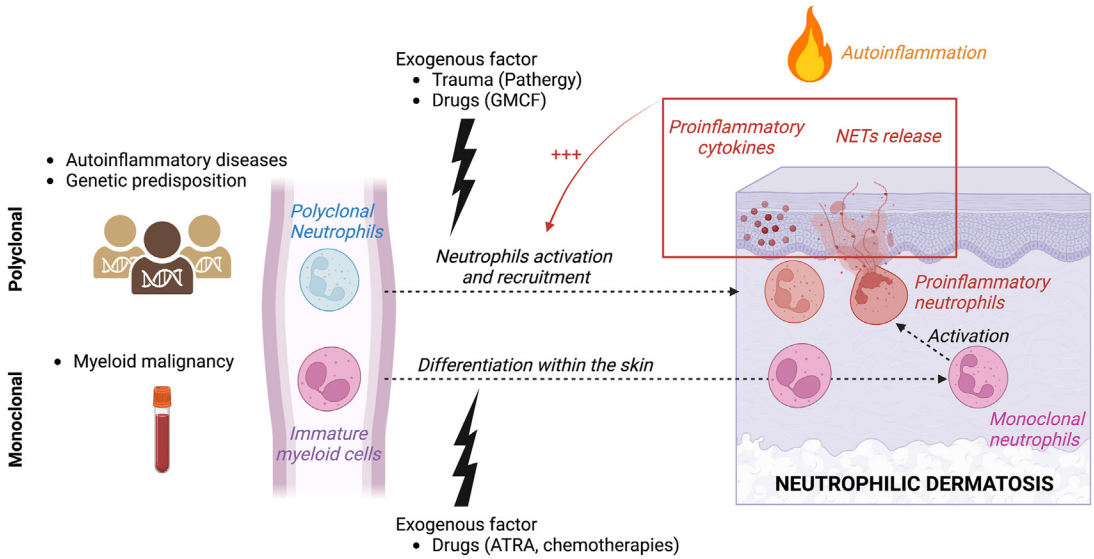

Fig. 2. Schematic of neutrophilic pathophysiology. There are 2 main mechanisms: (i) a polyclonal hereditary activation of the innate immune system: (a) polygenic like in inflammatory bowel diseases and (b) monogenic like in CAPS. (ii) Clonal somatic activation of myeloid cells as encountered in myelodysplastic syndromes. Once the proinflammatory neutrophils are within the skin, they release neutrophil extracellular traps, proinflammatory cytokines, and die by NETosis promoting inflammation of the skin, more neutrophils recruitment and activation, and skin tissue damage. In the setting of myeloid neoplasms, neutrophilic dermatoses are a direct consequence of clonal infiltration of the skin due to the ability of myeloid cells to differentiate. Those monoclonal neutrophils may bear proinflammatory mutations inducing inflammation and tissue damage. (Created with BioRender.com.)

unlike in pustular psoriasis. Acantholysis may be present in older lesions as a secondary change. Direct immunofluorescence studies for IAD staining should be performed to distinguish antibody-mediated subtype of SPD or variants of pemphigus.

- *Aseptic pustulosis of the folds:* Histologic examination reveals subcorneal or intraepidermal spongiform pustules with primarily periadnexal and perivascular neutrophilic infiltration of the dermis and no evidence of infection or vasculitis.[57] Direct immunofluo-rescence is usually negative.
- *Pustular psoriasis:* Pathology shows neutrophilic collections occurring in the stratum corneum and associated with spongiosis.

Dermal Neutrophilic Dermatoses: en Plaque

- *Sweet syndrome:* The characteristic histologic features of SS include prominent edema in the superficial dermis, dense and diffuse infiltrate of neutrophils in the upper and mid-dermis sparing the epidermis, leukocytoclasia, and endothelial swelling without vasculitis. Risk for malignancy may be elevated in patients with the histiocytoid variant of SS.[58] In this histologic variant, the infiltrate is composed of immature myeloid cells mixed with few mature neutrophils.
- *Neutrophilic eccrine hidradenitis:* NEH pathology shows neutrophils surrounding and infiltrating the eccrine gland with occasional intraductal abscess formation.[59] Syringosquamous metaplasia of sweat glands and fibrosis of adjacent dermis may occur. A variable degree of necrosis of the epithelial cells is usually present.
- *Palmoplantar NEH:* Relationship to physical activity and hyperhidrosis is speculated, potentially resulting in eccrine duct obstruction and rupture leading to inflammation. Differential diagnoses of palmoplantar NEH are plantar urticaria, plantar erythema nodosum, erythema multiforme, SS, chilblains, and pool palms.
- *Erythema elevatum diutinum:* The pathologic findings in erythema elevatum diutinum (EED) correlate with the age of the lesion at the time of biopsy. Early lesions show leukocytoclastic vasculitis.[60] Middle age lesions show a diffuse dermal infiltrate composed of histiocytes, lymphocytes, aggregates of neutrophils, and vasculitis. Lastly, old age lesion is characterized by a storiform fibrosis, sometimes with foci of neutrophils, neutrophilic vasculitis, and macrophage infiltration.

Deep Neutrophilic Dermatoses: Abscess and Ulceration

- *Pyoderma gangrenosum:* Earliest lesions of PG show perifollicular inflammation and intradermal abscess formation. Then the lesions progress to ulceration, pathology shows epidermal and superficial dermal necrosis with an underlying neutrophilic infiltrate and abscess formation.[61]
- *Neutrophilic panniculitis:* Neutrophilic panniculitis (NP) is a rare condition that belongs to the group of ND and the lobular panniculitis. In this condition, there is a subcutaneous fat lobules accumulation of mature neutrophils. NP has been reported to be significantly associated with MDS[62] and other myeloid malignancies.[63]

SUMMARY

Neutrophils play a central role in ND as the main characteristic of ND is a dense skin infiltrate by neutrophils without infection.[1] Even a great clinical and pathologic diversity, their classification has been made simple by a pathologic classification based on the localization of the neutrophils within the skin. Although not fully understood, pathogenic mechanisms of the various NDs are thought to be multifactorial, with neutrophilic dysfunction (NETs release and NETosis), auto-inflammation, and genetic predisposition each playing a role (**Fig. 2**).[11,30] It has also been suggested that a part of ND found in the setting of myeloid neoplasm might be a direct consequence of the clonal infiltration of the skin rather than just a proinflammatory activation state, due to the myeloid cells ability to differentiation. Eventually recent research into the neutrophil biology has increased appreciation of neutrophils' heterogeneity with an ongoing categorization of neutrophils subsets, which might be involved in several inflammatory diseases.[64]

CLINICS CARE POINTS

- ND are a spectrum of inflammatory skin conditions characterized by polymorphous cutaneous lesions resulting from a sterile neutrophil-rich inflammatory infiltrate.
- A great number of patients with ND suffer from an underlying condition (such as hematological malignancy, inflammatory bowel disease, connective tissue diseases).
- Pathogenic mechanisms of the various ND are thought to be multifactorial, with neutrophilic dysfunction, auto-inflammation, and genetic predisposition each playing a role.
- ND are diagnoses of exclusion and physicians should always consider differential diagnoses, particularly skin infections.

CONFLICT OF INTEREST

None to declare.

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