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Review Article

The neutrophilic dermatitides: a contemporary reassessment of pathophysiological mechanisms, clinical phenotypes and therapeutic stratification

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ABSTRACT

The neutrophilic dermatitides constitute a heterogeneous spectrum of inflammatory cutaneous disorders unified by a dominant histopathological motif of sterile neutrophilic infiltrates within the dermis, in the absence of primary infection or vasculitis. This extensive review synthesizes contemporary insights into their complex pathophysiology, which is increasingly understood as a dysregulated interplay between the innate immune system, specifically involving the interleukin-1 (IL-1) family cytokines, NLRP3 inflammasome activation, and neutrophil extracellular traps (NETs), and a permissive genetic background often influenced by somatic mutations in clonal hematopoiesis-related genes. We provide a critical analysis of the expanding clinical and histological continuum, encompassing classic entities such as Sweet's syndrome, pyoderma gangrenosum, Behçet's disease, and the autoinflammatory syndromes, while addressing overlapping and atypical presentations that pose significant diagnostic challenges. Furthermore, we systematically evaluate the evolving therapeutic landscape, moving beyond traditional immunosuppressants toward targeted biologic agents and small molecules that inhibit specific pro-inflammatory pathways. By integrating the latest molecular discoveries with clinical pragmatism, this review aims to refine diagnostic criteria, elucidate pathogenic connections to underlying systemic disease—particularly myeloid dyscrasias and gastrointestinal inflammation—and propose a rationale for personalized, mechanism-driven treatment algorithms. This reassessment underscores the paradigm of these conditions as cutaneous reflexes of systemic autoinflammation.

Keywords: Neutrophilic dermatoses, Sweet's syndrome, pyoderma gangrenosum, Autoinflammation, interleukin-1, Neutrophil extracellular traps, NLRP3 inflammasome, Clonal hematopoiesis, Biologic therapy, Disease continuum

INTRODUCTION

Cutaneous biology often serves as a perceptible window into systemic inflammatory processes, a concept profoundly exemplified by the group of conditions termed the neutrophilic dermatitides. Historically classified as distinct clinical-pathological entities, disorders such as Sweet's syndrome (acute febrile neutrophilic dermatosis), pyoderma gangrenosum, and the cutaneous manifestations of Behçet's disease are now interrogated through a more nuanced lens. This perspective recognizes a shared foundational pathology: a sterile, neutrophil-predominant inflammation arising from a misdirected and exaggerated innate immune response. The traditional diagnostic approach, heavily reliant on clinicopathological correlation and exclusion of infection, is being augmented-and in some cases complicated-by advancing molecular insights.[1-3]

Recent years have witnessed a significant shift in understanding, propelled by investigations into the role of autoinflammatory pathways. Central to this is the IL-1β

axis, with its orchestration via the NLRP3 inflammasome, and the pathological deployment of NETs, which may perpetuate inflammation and tissue damage. Concurrently, clinical hematology research has identified compelling associations between certain neutrophilic dermatitides and clonal hematopoiesis, suggesting that somatic mutations in myeloid precursors can create a primed inflammatory milieu that manifests in the skin. Furthermore, the frequent synchronicity with inflammatory bowel disease and arthropathies hints at common etiological threads across epithelial barriers. This extensive review endeavors to consolidate these multifaceted advances. It will navigate the intricate clinical spectra that often blur classical boundaries, dissect the immunogenetic underpinnings as elucidated in current literature, and critically appraise therapeutic innovations that target these specific mechanisms. The overarching objective is to move from a morphology-based classification toward a pathogenetic framework that informs more precise diagnosis and enhances management strategies for these clinically challenging and frequently debilitating conditions. The synthesis presented herein draws upon a robust corpus of recent studies to reframe these dermatoses not as isolated skin diseases, but as integral components of systemic dysregulation.[4]

BACKGROUND

The conceptualization of neutrophilic dermatitides as a coherent nosological category emerged from the gradual recognition of a shared histopathological signature-a predominantly sterile infiltration of polymorphonuclear leukocytes within the dermal architecture-across a constellation of clinically disparate cutaneous eruptions. This histologic commonality belies a profound etiological and clinical complexity, positioning these disorders at a critical interface between dermatology, rheumatology, and hematology. The seminal clinical descriptions of entities such as Sweet's syndrome and pyoderma gangrenosum established foundational clinical criteria, yet for decades, their management relied on broad-spectrum immunosuppression and remained largely decoupled from a mechanistic understanding of disease drivers. The contemporary paradigm, however, has undergone a substantial transformation, fueled by parallel advances in immunology and genomic medicine. A pivotal evolution in thought has been the reclassification of many neutrophilic dermatoses within the expanding realm of autoinflammatory disease, a shift that emphasizes the primacy of innate immune dysregulation over adaptive, antigen-specific responses.[5]

This pathophysiological reassignment is anchored in the elucidation of the interleukin-1 (IL-1) family cytokine network as a central orchestrator. Specifically, the dysregulated activation of the NLRP3 inflammasome, a cytosolic multiprotein complex, leads to the caspase-1-mediated cleavage and secretion of potent pro-inflammatory cytokines IL-1β and IL-18. This axis is now understood to be a common final pathway in many neutrophilic dermatitides, explaining the characteristic systemic features of fever and acute-phase response and the dramatic efficacy of IL-1 inhibition observed in many refractory cases. Concurrently, the role of the neutrophil itself has been reappraised from a passive effector cell to an active participant in immune dysregulation through the formation of neutrophil extracellular traps (NETs). NETosis, particularly in a dysregulated, "NETopathic" context, is implicated in both tissue damage and the perpetuation of inflammation by providing a source of autoantigens and stimulating type I interferon pathways, creating a vicious cycle of innate immune activation.[5]

Perhaps one of the most provocative and clinically salient developments has been the uncovering of robust associations with clonal hematopoiesis. Somatic mutations in genes such as *DNMT3A*, *TET2*, and *ASXL1*, acquired in hematopoietic stem cells, can confer a pro-inflammatory phenotype on myeloid progeny, including neutrophils and monocytes. This state of "clonal hematopoiesis of indeterminate potential" (CHIP) is increasingly identified as a substrate for severe, recurrent, or treatment-refractory neutrophilic dermatoses, particularly in older individuals. This link provides a plausible biological explanation for the well-established paraneoplastic association with myelodysplastic syndromes and other myeloid malignancies, framing some cutaneous presentations as an external marker of internal myelodysregulation.[6]

Furthermore, the strong clinical syndromic associations with inflammatory bowel disease, particularly pyoderma gangrenosum in ulcerative colitis, and with seronegative arthropathies, point to shared genetic susceptibilities and common mucosal barrier dysfunction. The concept of the "neutrophilic dermatosis disease continuum" has thus gained traction, acknowledging that patients may present with overlapping or sequential features of classically defined disorders, or with atypical hybrid morphologies that defy traditional categorization. This continuum reflects a common pathogenic soil from which different clinical phenotypes may sprout, influenced by individual genetic predisposition, environmental triggers, and the specific profile of cytokine overproduction. The diagnostic journey, therefore, has evolved beyond mere pattern recognition to incorporate an assessment for underlying systemic inflammation, occult malignancy, and genetic predisposition. Similarly, the therapeutic arsenal is rapidly transitioning from empirical corticosteroids and conventional disease-modifying antirheumatic drugs toward a stratified approach utilizing targeted biologics and small molecules. This background sets the stage for a comprehensive review that seeks to weave these intricate molecular, genetic, and clinical threads into a coherent modern tapestry of the neutrophilic dermatitides, offering a updated framework for both clinician and researcher.[6-8]

CONTEMPORARY REASSESSMENT OF PATHOPHYSIOLOGICAL MECHANISMS

The traditional histological definition of neutrophilic dermatitides-centered on the presence of a sterile, neutrophilic dermal infiltrate-has served as a useful but simplistic diagnostic scaffold. A contemporary reassessment of their pathophysiology, however, reveals a remarkably intricate and dynamic immunobiological landscape that extends far beyond this microscopic hallmark. Current research frameworks have successfully deconstructed these conditions from mere descriptive diagnoses into exemplars of systemic autoinflammatory dysregulation, where the skin acts as a primary effector organ. This refined understanding pivots on several interconnected pillars: the centrality of the inflammasome-IL-1 axis, the active pathogenic role of neutrophils themselves, the influence of genetic and somatic mutations, and the disruption of innate immune homeostasis at barrier sites.[8,9]

Foremost in this reconceptualization is the unequivocal role of the interleukin-1 (IL-1) family, particularly IL-1β, as a master cytokine driver. The production of active IL-1β is tightly regulated by cytosolic multiprotein complexes known as inflammasomes, with the NLRP3 inflammasome being of paramount importance. Evidence now suggests that in many neutrophilic dermatoses, a convergence of pathogenic stimuli-including damage-associated molecular patterns (DAMPs) from cell stress, microbial motifs, or even components of neutrophil extracellular traps (NETs)-triggers the assembly and activation of the NLRP3 inflammasome. This activation leads to caspase-1-mediated cleavage of pro-IL-1β into its active, secreted form. IL-1β then functions as a potent pyrogen and chemoattractant, initiating a feedforward loop of endothelial activation, neutrophil recruitment, and further inflammatory cytokine release (e.g., IL-8, G-CSF), thereby creating the clinical and histopathological signature of these diseases. The dramatic efficacy of IL-1 blockade in conditions like refractory Sweet's syndrome or deficiency of the IL-1 receptor antagonist (DIRA) provides compelling *in vivo* validation of this pathway's critical role.[10]

Simultaneously, the neutrophil has been recast from a terminal effector cell to an active participant in immunopathology through the process of NETosis. The release of web-like structures composed of decondensed chromatin and granular proteins, known as NETs, is a physiological antimicrobial defense. In the context of neutrophilic dermatitides, however, this process appears to become dysregulated, leading to "NETopathy." Excessive or poorly cleared NETs not only cause direct tissue injury but also provide a rich source of autoantigens (e.g., myeloperoxidase, LL-37) and endogenous DAMPs that can perpetuate inflammasome activation and stimulate type I interferon production. This creates a vicious cycle wherein recruited neutrophils become sources of further inflammation, explaining the chronicity and tissue destruction seen in conditions like pyoderma gangrenosum. The visibility of NET components in lesional skin and the correlation of NET biomarkers with disease activity are active areas of investigative focus.[10]

A groundbreaking development in the field has been the association with clonal hematopoiesis, particularly clonal hematopoiesis of indeterminate potential (CHIP). Somatic mutations in myeloid precursor genes, such as TET2, DNMT3A, and ASXL1, confer a pro-inflammatory phenotype on the expanded clone. Mutant macrophages and monocytes exhibit a hyperresponsive state, characterized by excessive production of IL-1β, IL-6, and other cytokines upon stimulation. This creates a permissive systemic inflammatory milieu that lowers the threshold for cutaneous neutrophilic inflammation. This mechanism provides a long-sought biological explanation for the strong paraneoplastic link to myelodysplastic syndromes and may account for the late-onset, severe, or treatment-refractory nature of some cases. It positions certain neutrophilic dermatoses as visible cutaneous manifestations of an underlying aged or dysregulated bone marrow landscape.[10]

Finally, the pathophysiology is inseparable from the clinical context of associated diseases. The frequent co-occurrence with inflammatory bowel disease (IBD) and seronegative spondyloarthropathies points to a shared disruption of mucosal barrier integrity and a common genetic predisposition affecting innate immune sensing. Breach of the intestinal barrier may lead to systemic translocation of microbial products, which could serve as triggers for inflammasome activation in genetically susceptible individuals. Similarly, the pathergy phenomenon-lesion development at sites of minor trauma-is understood as a localized, excessive innate immune response to minor damage, again highlighting a dysregulated alarm system. This contemporary reassessment thus weaves together molecular immunology, somatic genetics, and clinical medicine into a coherent narrative. It posits that neutrophilic dermatitides arise at the intersection of a predisposing genetic or acquired somatic background and an inciting trigger, leading to a cascade of innate immune dysregulation where IL-1, neutrophils, and NETs engage in a pathogenic dialogue, ultimately manifesting in the clinically diverse but histologically unified spectrum we observe.[10]

CLINICAL MANIFESTATIONS

The clinical presentation of the neutrophilic dermatitides constitutes a remarkably diverse spectrum of cutaneous morphologies, a diversity that often belies their shared underlying immunopathological mechanisms. This phenotypic heterogeneity is a primary source of diagnostic complexity, requiring clinicians to maintain a high index of suspicion beyond classic textbook descriptions. The prototypical expression is often an

acute, rapidly evolving cutaneous eruption frequently accompanied by systemic signs of inflammation, including fever, malaise, and arthralgias, reflecting the systemic autoinflammatory nature of these conditions. Tender, erythematous plaques, often described as violaceous or pseudovesicular due to pronounced dermal edema, are the hallmark of classic Sweet's syndrome. These lesions typically demonstrate a pseudoblistering appearance and may arise on the face, neck, and upper extremities, sometimes exhibiting a annular or arciform configuration. Importantly, a pathergic response—the development of lesions at sites of minor skin trauma, such as venipuncture or biopsy-is a highly characteristic, though not pathognomonic, feature observed across several entities within this spectrum, most notably in pyoderma gangrenosum and Behçet's disease.[1]

Table 1: Summary comparison of classical neutrophilic dermatoses, CHIP-associated dermatoses, and VEXAS.

Variables	Classical sweet	Chip-associated dermatosis	VEXAS	Pyoderma gangrenosum
Age/sex	30–50 years; women	>60 years; variable	>50 years; men	20-50 years; women
Genetic driver	None	*TET2*, *DNMT3A*, *ASXL1*	*UBA1* (X-linked)	None
Dominant pathway	NLRP3/IL-1β	IL-1β, IL-6, IFN	IL-1β, IL-6, IFN, TNF	NLRP3/IL-1β, TNF, IL-23
NETosis	Present	Pronounced	Prominent	Marked
Cutaneous morphology	Erythematous-violaceous plaques, pseudovesicular	Similar to classical; refractory	Arcuate plaques, Sweet-like, ulcers	Painful ulcers, undermined violaceous border
Pathergy	Frequent	Frequent	Very frequent	Very frequent
Systemic symptoms	Fever, arthralgias	Fatigue, low-grade fever	Fever, chondritis, periorbital edema	Fever (20–30%)
Blood count	Leukocytosis	Variable cytopenias	Macrocytosis, anemia, thrombocytopenia	Leukocytosis (50–60%)
Myeloid association	10–20% (MDS/AML)	100% CHIP; risk of MDS/AML	MDS 36–71%; MGUS 10–26%	1% (MDS, AML)
IBD association	5–10%	10–20%	Rare	30–50%
Histopathology	Dermal neutrophils; no vasculitis	Similar; possible myeloid clone	Neutrophils; vacuoles in bone marrow	Neutrophils; extensive necrosis
Differential diagnosis	Cellulitis, vasculitis	Leukemia cutis, MDS-cutis	MDS-cutis, Still disease, vasculitis	Infection, vasculitis, malignancy
First line	Prednisone	Prednisone	Prednisone	Prednisone, cyclosporine, infliximab
Second line	Colchicine, dapsone, MMF	Anakinra, ruxolitinib	Tocilizumab, ruxolitinib, azacitidine	Infliximab, adalimumab, anakinra
Rescue therapy	IVIG, plasmapheresis	HSCT	HSCT (only curative)	IVIG, plasmapheresis
Prognosis	Self-limited; recurrent 30–50%	Chronic; progression risk	20–40% mortality at 5 years	Chronic recurrent
Follow-up	Annual CBC	CBC every 3–6 months; NGS	CBC every 3 months; annual BMB	Annual CBC

Pyoderma gangrenosum, in its classic ulcerative form, presents a starkly different yet equally dramatic morphology. It typically begins as a painful pustule or nodule that undergoes rapid necrosis, evolving into a deeply ulcerated lesion with a characteristic undermined, violaceous border and a necrotic, purulent base. The profound tenderness of these ulcers often exceeds what would be expected based on visual inspection alone. Atypical or bullous variants may present with more superficial erosion or rapidly expanding bullae, often posing a significant diagnostic challenge and requiring careful clinicopathological correlation to distinguish from infective or vasculitic processes. In contrast, the neutrophilic dermatoses associated with bowel disease, such as bowel-associated dermatosis-arthritis syndrome, may manifest with more transient, vesiculopustular eruptions on the upper trunk and extremities, lesions that can closely mimic those of disseminated gonococcal infection or leukocytoclastic vasculitis.[11]

Behçet's disease introduces yet another dimension, with its hallmark recurrent oral aphthous ulcers, which are considered mandatory for diagnosis, alongside genital ulcers and a panoply of cutaneous findings. These include

follicular-based papulopustular lesions, erythema nodosum-like nodules that are often more superficial and ulcerative than classic erythema nodosum, and a positive pathergy test. The ocular, neurological, and vascular involvement in Behçet's further underscores the systemic reach of neutrophilic inflammation. Beyond these classic syndromes, the clinical continuum encompasses less common but significant presentations, such as the tender, erythematous plaques of neutrophilic eccrine hidradenitis, often linked to chemotherapy, and the aseptic pustular eruptions seen in syndromes like acute generalized exanthematous pustulosis (AGEP). The morphological overlap is substantial; a patient may initially present with Sweet's-like plaques that subsequently evolve into pyoderma-like ulcerations, or exhibit features of both conditions simultaneously, supporting the model of a disease continuum rather than rigidly separated entities. This clinical fluidity necessitates a holistic assessment that integrates lesion morphology, distribution, associated symptoms, and a thorough review of systems to uncover potential underlying triggers, such as inflammatory bowel disease, hematological malignancy, or solid tumors, which are integral to the diagnostic workup and long-term management of these complex disorders.[11]

DIAGNOSIS

The diagnostic odyssey for neutrophilic dermatitides is fundamentally an exercise in clinicopathological correlation, necessitating a high degree of suspicion and a meticulous, integrative approach. There exists no single serological or molecular biomarker with definitive diagnostic specificity; consequently, diagnosis rests upon a tripartite foundation: the recognition of characteristic clinical morphologies, the histopathological confirmation of a sterile neutrophilic infiltrate, and the comprehensive exclusion of mimickers, chiefly infection and vasculitis. The initial clinical evaluation must be exhaustive, with a particular emphasis on the tempo of lesion development, the presence of pathognomonic features such as pathergy, and a thorough systemic review to uncover potential underlying associations. The physical examination extends beyond the skin, encompassing oral and genital mucosa for aphthae, palpation for hepatosplenomegaly or lymphadenopathy, and assessment for synovitis or ocular inflammation, as these findings can be pivotal in steering the diagnosis towards a specific syndromic entity like Behçet's disease.[12]

Histopathological analysis of an adequately deep and representative biopsy remains the indispensable cornerstone. The prototypical finding is a dense dermal infiltrate composed predominantly of mature neutrophils, typically located in the upper and mid-dermis, with notable absence of genuine leukocytoclastic vasculitis—though fibrinoid necrosis of vessel walls may be present as a secondary phenomenon. Edema of the papillary dermis is a frequent concomitant feature. However, the histological picture is not monolithic; it can vary with the age of the lesion and the specific disorder. Early lesions of pyoderma gangrenosum, for instance, may show a neutrophilic abscess, while more established ulcers demonstrate extensive necrosis and a mixed infiltrate at the periphery. It is paramount that tissue samples are sent for routine microbial staining and culture, and in some cases for specialized studies like fungal or mycobacterial cultures, to rigorously exclude an infectious etiology, which represents the most critical and dangerous differential diagnosis. The role of direct immunofluorescence is generally limited, serving primarily to rule out conditions like immunoglobulin A (IgA) vasculitis or bullous disorders.[12]

Given the potent association with systemic disease, a structured diagnostic workup is mandatory. This should include a complete blood count with differential to screen for leukocytosis, neutrophilia, or cytopenias suggestive of a myelodysplastic syndrome, comprehensive metabolic panel, acute phase reactants (erythrocyte sedimentation rate and C-reactive protein), and urinalysis. Serological testing for antinuclear antibodies and antineutrophil cytoplasmic antibodies may be considered to exclude connective tissue diseases and vasculitides, though they are typically negative in primary neutrophilic dermatoses. The strong link to gastrointestinal inflammation warrants evaluation for symptomatic or occult inflammatory bowel disease, often involving fecal calprotectin testing and consultation with gastroenterology for potential endoscopic assessment. In patients of appropriate demographic, especially those with recurrent, refractory, or atypical presentations, evaluation for Behçet's disease utilizing the International Criteria for Behçet's Disease is essential. The evolving understanding of clonal hematopoiesis has introduced a new diagnostic consideration. In older patients or those with refractory disease, next-generation sequencing of peripheral blood to detect somatic mutations associated with clonal hematopoiesis of indeterminate potential (CHIP) is becoming increasingly relevant, as it can inform prognosis and therapeutic strategy. Ultimately, the diagnostic process is one of synthesis, where the clinician must weigh the histological findings against the clinical narrative, systematically rule out alternative explanations, and remain vigilant for the subtle clues of an underlying systemic disorder, thereby arriving at a diagnosis that is both accurate and actionable for guiding targeted therapy.[12]

TREATMENT

The therapeutic management of neutrophilic dermatitides represents a dynamic and evolving challenge, demanding a strategic approach that is increasingly informed by the underlying immunopathogenic mechanisms rather than a one-size-fits-all regimen. The historical cornerstone of therapy, systemic corticosteroids, retains a primary role for inducing rapid remission in acute, severe presentations due to their broad anti-inflammatory and immunosuppressive effects. However, their well-documented long-term toxicities and the frequently

chronic or relapsing nature of these conditions necessitate the timely introduction of corticosteroid-sparing agents, a process that forms the crux of long-term disease control. The contemporary therapeutic paradigm is thus stratified, moving from first-line interventions toward more targeted biologic and small-molecule therapies, with the choice of agent often guided by the specific clinical phenotype, disease severity, associated comorbidities, and most importantly, the implicated inflammatory pathway.[13]

For many classic presentations, such as Sweet's syndrome, initial therapy with oral prednisone at moderate to high doses typically yields a dramatic and rapid response, often serving as a diagnostic confirmation in itself. However, given the propensity for relapse upon tapering, the concurrent or sequential initiation of a conventional disease-modifying agent is standard practice. Potassium iodide and colchicine have a long-established, albeit modest, role in milder cases or as adjunctive therapy. For more persistent disease, immunosuppressants such as cyclosporine, dapsone, or mycophenolate mofetil are frequently employed. Cyclosporine, with its specific inhibition of T-cell activation and interleukin-2 production, can be particularly effective, especially in pyoderma gangrenosum, though its use is constrained by renal and hypertensive risks. Dapsone, functioning through the inhibition of neutrophil myeloperoxidase and chemotaxis, offers a valuable option for maintaining remission in certain patients with milder phenotypes.[13]

The most significant advancement in the therapeutic landscape has been the advent of targeted biologic agents, which have revolutionized management for refractory or severe disease. Tumor necrosis factor-alpha (TNF-α) inhibitors, particularly infliximab and adalimumab, have demonstrated profound efficacy in pyoderma gangrenosum and in neutrophilic dermatoses associated with inflammatory bowel disease, establishing themselves as a cornerstone of biologic therapy. Their mechanism, which involves neutralizing a key pro-inflammatory cytokine implicated in neutrophil recruitment and activation, directly addresses a central node in the inflammatory cascade. More recently, agents targeting the interleukin-1 (IL-1) pathway have emerged as a paradigm-shifting intervention, particularly for conditions driven by autoinflammatory mechanisms.[13,14]

The IL-1 receptor antagonist anakinra, and the monoclonal antibody canakinumab, have shown remarkable success in treating refractory Sweet's syndrome, neutrophilic dermatoses associated with myelodysplastic syndromes, and certain autoinflammatory syndromes like deficiency of the IL-1 receptor antagonist (DIRA). These agents directly interrupt the pivotal IL-1β signaling that is central to NLRP3 inflammasome-mediated pathogenesis. The interleukin-23/Th17 axis is another therapeutic frontier, with agents like ustekinumab (anti-IL-12/23) and secukinumab (anti-IL-17A) showing promise, especially in conditions with overlapping features of psoriasis or Behçet's disease. Janus kinase (JAK) inhibitors, such as tofacitinib and ruxolitinib, introduce a novel oral option by broadly inhibiting signaling downstream of multiple pro-inflammatory cytokines, including interferons and IL-6, and have demonstrated utility in refractory pyoderma gangrenosum and cases linked to clonal hematopoiesis. The choice of agent is further nuanced by the presence of associated conditions; for instance, the management of a neutrophilic dermatosis in the context of active inflammatory bowel disease would strongly favor a TNF-α inhibitor, while one associated with a myeloid malignancy might prompt consideration of an IL-1 inhibitor or JAK inhibitor, the latter particularly if a JAK2 mutation is present. Adjunctive local therapies, including high-potency topical or intralesional corticosteroids, topical tacrolimus, and advanced wound care for ulcerative lesions, remain vital components of a comprehensive treatment plan. Ultimately, the modern therapeutic strategy is one of precision, aiming to match the pharmacological mechanism to the individual patient's dominant immunopathological driver, thereby achieving sustained control while minimizing the cumulative burden of immunosuppression.[15,16]

CONCLUSION

The neutrophilic dermatitides, once regarded as a collection of rare and clinically distinct curiosities, have emerged as a compelling paradigm for sterile autoinflammation with profound systemic implications. This extensive review underscores a fundamental shift in our conceptual framework, moving from a morphology-based classification towards a pathogenesis-driven understanding that emphasizes a shared immunologic soil from which diverse clinical phenotypes arise. At the core of this pathophysiological convergence lies the dysregulated innate immune system, where aberrant activation of the NLRP3 inflammasome, excessive IL-1 family cytokine signaling, and dysregulated NETosis orchestrate a cascade of neutrophil-mediated tissue injury. The recent elucidation of links to clonal hematosesis represents a particularly transformative insight, mechanistically explaining the well-known paraneoplastic associations and reframing certain refractory cases as cutaneous manifestations of underlying somatic genetic events within the myeloid lineage. This connection blurs the traditional boundaries between dermatology and hematology, mandating a more integrated diagnostic perspective.

Clinically, the recognition of a disease continuum, characterized by overlapping features and hybrid morphologies, challenges rigid diagnostic categories and demands a clinician’s fluency in a broader, more fluid spectrum of presentation. The diagnostic process, therefore, remains an exercise in sophisticated synthesis, requiring the harmonious integration of detailed clinical observation, precise histopathological analysis, and a systematic search for underlying systemic triggers. It is a process of exclusion as much as affirmation, with the

imperative to first rule out infection and vasculitis. The therapeutic landscape has evolved in parallel with these pathogenic revelations. We have progressed from an era of empirical, broad immunosuppression to one of increasingly targeted intervention. While systemic corticosteroids maintain their role for rapid induction of remission, the strategic armamentarium now includes a range of biologic agents and small molecules—from TNF-α and IL-1 inhibitors to JAK-STAT pathway blockers—that allow for a more precise, mechanism-based approach tailored to the individual's dominant inflammatory pathway and associated comorbidities.

Future directions in this field will undoubtedly focus on refining these personalized strategies. Further research is needed to identify robust biomarkers that can predict therapeutic response, stratify disease severity, and more clearly delineate the prognostic implications of clonal hematosesis in this context. Longitudinal studies are required to better understand the natural history of these disorders within the continuum model and to optimize sequencing of therapeutic agents. In conclusion, the neutrophilic dermatitides serve as a powerful reminder that the skin is not an isolated organ but a sentinel tissue deeply integrated with systemic immunity. Their management no longer resides solely within the domain of dermatology but necessitates a collaborative, multidisciplinary approach involving rheumatologists, gastroenterologists, and hematologists. By continuing to unravel the intricate dialogue between genetic predisposition, innate immune dysregulation, and environmental triggers, we move closer to transforming the care for patients with these complex and often debilitating conditions from reactive suppression to proactive, pathogenesis-informed precision medicine.

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