What Do Autoinflammatory Syndromes Teach About Common Cutaneous Diseases Such as Pyoderma Gangrenosum? A Commentary

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KEYWORDS

• Autoinflammation • Pyoderma gangrenosum • Neutrophilic dermatoses
• Pyogenic arthritis syndrome • Deficiency of interleukin 1 receptor agonist
• Familial Mediterranean fever • Cryopyrin-associated periodic syndrome

KEY POINTS

- Pyoderma gangrenosum (PG) is a neutrophilic dermatosis whose pathogenesis is poorly understood. Current PG treatments target a broad spectrum of immunologic mediators, including neutrophils, lymphocytes, and cytokines, with variable success.
- Many autoinflammatory disorders feature cutaneous eruptions, including several presentations of neutrophilic dermatoses.
- Emerging literature highlights the pathophysiologic similarities between autoinflammation and PG; common immunologic pathways shared between these 2 entities may result in alterations in neutrophil recruitment and/or homeostasis, leading to neutrophilic dermatoses.
- Although rare, autoinflammatory disorders may in turn inform the understanding of more common cutaneous disorders, including the neutrophilic dermatoses.

INTRODUCTION

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis marked by ulcerating skin lesions and a chronic or remitting disease course. Despite the recognition of this clinical entity almost 100 years ago by Brocq, the pathogenesis of PG remains poorly understood. Although recent research has begun to elucidate the pathogenesis and components involved in many neutrophilic dermatoses including PG, very little evidence exists that supports a rational therapeutic approach to this clinical entity.[1,2] To date, the conceptual framework of PG treatment has highlighted the equal importance of treating the inflammatory etiology of PG balanced with optimized wound care.[3] Often, multiple immunosuppressive agents are required to achieve remission or control over the progression of PG skin lesions; these agents target a broad array of inflammatory pathways likely involved in PG pathogenesis, including lymphocyte-directed therapy, neutrophil-directed therapy, and cytokine blockade. The broad nature of the available therapies, even in algorithmic format, reveals that there are still significant gaps in the current understanding of the disease.

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Autoinflammatory diseases commonly present with cutaneous manifestations, and many disorders of autoinflammation specifically present with neutrophilic dermatoses; new information on the molecular and cellular pathways underlying autoinflammation thus provides great insights into the understanding of neutrophilic dermatoses, especially PG. This article aims to offer a fresh perspective on the pathogenesis of PG with a focus on emerging and convergent concepts in the pathophysiology of neutrophilic dermatoses and autoinflammation. Specifically, this article offers a series of observations on the natural history of PG, highlighting similarities between PG, other neutrophilic dermatoses, and autoinflammatory disorders, to elucidate key pathways and common connections between the disorders. These observations emphasize the relevance of studying rare autoinflammatory syndromes, as they in turn inform the understanding of more common skin disorders such as PG.

OBSERVATION 1—NEUTROPHILIC DERMATOSES, INCLUDING PG, OCCUR IN ASSOCIATION WITH A BROAD SPECTRUM OF SYSTEMIC DISORDERS

It is well established that many neutrophilic dermatoses, including PG, occur in association with a broad spectrum of systemic conditions, such as malignancy, neutropenia, rheumatologic disease, infection, autoinflammatory syndromes, and immunodeficiency, in addition to being triggered by medications and pathergy. A key question is how such disparate processes result in, or associate with the common phenotype of PG. A unifying hypothesis is that these diseases converge on inflammatory pathways leading to alterations in the recruitment of neutrophils or changes in neutrophil homeostasis; however, a definitive common pathway remains elusive (**Fig. 1**A). Recent research has highlighted numerous pathways that likely play a role in the inflammation of PG, which will be reviewed here. Ultimately, identifying and targeting common inflammatory pathways would maximize the clinical approach to this disorder.

OBSERVATION 2—NEUTROPHILIC DERMATOSES OCCUR IN THE SETTING OF INHERITED DISEASES OF AUTOINFLAMMATION

A significant advancement in the understanding of neutrophilic dermatoses has emerged from the observation that many autoinflammatory syndromes feature neutrophilic dermatoses and that these present across a broad spectrum of clinical and histopathologic phenotypes. Autoinflammatory diseases are defined as a distinct group of disorders that stem from dysregulation of the innate immune system, leading to chronic episodic systemic inflammation with end-organ damage, excessive cytokine production, and typically lacking features of autoimmunity such as autoreactive lymphocytes or autoantibodies. Disorders of autoinflammation commonly present with cutaneous manifestations.[2,4,5] In fact, several monogenic inherited diseases of and likely acquired autoinflammatory syndromes include neutrophilic infiltration patterns in skin, including erysipelas-like dermatoses in familial Mediterranean fever (FMF), neutrophilic urticaria in cryopyrin-associated periodic syndromes (CAPS), and pustular dermatosis in the deficiency of interleukin (IL) 1-receptor antagonist (DIRA) syndrome, among others. The recent elucidation of the genetic and cellular basis of autoinflammation, although rare, thus reveals molecular pathways potentially relevant to more common neutrophilic dermatoses.

Importantly, a notable inherited autoinflammatory syndrome features PG as 1 of its hallmark symptoms. The rare syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) is associated with genetic mutations in the PSTPIP1 protein, resulting in excessive IL-1 signaling. PG lesions are an almost universal manifestation in patients with this syndrome, suggesting a key role for the IL-1 cytokine pathway in the pathogenesis of PG in at least a subset of patients. The recognition of IL-1 signaling pathways in PAPA syndrome has also greatly informed the treatment of this condition. IL-1 blockade has been shown to be an effective therapy for both bone and skin lesions in the syndrome of PAPA; Brenner and colleagues[6] reported successful treatment of PG in the setting of PAPA syndrome with the IL-1 blocking medication, anakinra. Additionally, treatment for this distinct class of diseases is largely directed at cytokine pathways such as tumor necrosis factor (TNF)-alpha and lymphocyte-directed therapy, including corticosteroids, methotrexate, and cyclosporine, suggesting additional putative mechanisms contributing to the pathogenesis of the disease.[6–8]

Use of an IL-1 receptor antagonist for the treatment of PG in PAPA syndrome exemplifies how recognizing the elevation of IL-1 stemming from PAPA mutations led to significant improvements in treating patients with this disease. IL-1 likely plays a central role in a number of diseases of autoinflammation. Emerging genetic information has illuminated that many of the genes underlying autoinflammatory disorders function within a common IL-1 signaling pathway; mutations in these genes