Dermatologic Manifestations of Monogenic Autoinflammatory Diseases

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KEYWORDS

• Autoinflammatory disorders • IL-1 • Type I interferon • Immune dysregulation
• Neutrophilic dermatoses • urticaria • Panniculitis

KEY POINTS

- Monogenic autoinflammatory disorders are hyperinflammatory conditions caused by single-gene mutations in innate immune regulatory pathways. They often present in infancy or early childhood; some can mimic infection or sepsis.
- Recognizing the clinical and histologic features is essential in initiating genetic testing, appropriate referral to make an early diagnosis, and to begin aggressive treatment to prevent organ damage and life-threatening consequences.
- Patients with interleukin (IL)-1–mediated disorders present with neutrophilic urticaria, pustulosis, and migratory rash, whereas interferon (IFN)-mediated disorders may present with panniculitis, livedo reticularis, or vasculitis.
- Anti–IL-1 therapy is the standard of care in treating the cryopyrinopathies (cryopyrin-associated periodic syndrome), and deficiency of IL-1 receptor antagonist and other IL-1–mediated conditions, including familial Mediterranean fever, hyperimmunoglobulinemia D syndrome, and tumor necrosis factor receptor–associated periodic syndrome.
- Discoveries of the genetic cause of novel autoinflammatory diseases suggest a role for type I IFN, IL-17, and IL-18; several have uncovered novel targets for therapeutic intervention.

INTRODUCTION

Autoinflammatory disorders are immune-dysregulatory conditions characterized by early onset, sterile systemic inflammatory episodes that include fever, rashes, joint pain, and features of disease-specific organ inflammation.[1] The term autoinflammatory was proposed by Daniel Kastner in 1999 after the discovery of the genetic causes of the familial Mediterranean

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Abbreviations and acronyms

ADA2	Adenosine deaminase 2
AGS	Aicardi-Goutières syndrome
AID	Autoinflammatory disease
ANA	Antinuclear antibody
CAMPS	CARD14-mediated psoriasis
CANDLE	Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperatures
CAPS	Cryopyrin-associated periodic syndrome
CINCA	Chronic infantile neurologic, cutaneous, and arthritis syndrome
CK	Creatinine kinase
CNS	Central nervous system
CRP	C-reactive protein
DADA2	Deficiency of adenosine deaminase 2 (ADA2)
DIRA	Deficiency of interleukin-1 receptor antagonist
DITRA	Deficiency of interleukin-36 receptor antagonist
EO-IBD	Early onset of inflammatory bowel disease
ESR	Erythrocyte sedimentation rate
FCAS	Familial cold autoinflammatory syndrome
FDA	US Food and Drug Administration
FMF	Familial Mediterranean fever
GOF	Gain of function
HA20	Haploinsufficiency of A20
HIDS	Hyperimmunoglobulinemia D and periodic fever syndrome
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
JMP	Joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy
LOF	Loss of function
MAS	Macrophage activation syndrome
MWS	Muckle-Wells syndrome
NLR	NOD-like receptor
NOMID	Neonatal-onset multisystem inflammatory disease
PAPA	Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome
PGA	Pediatric granulomatous arthritis
PLAID	PLCγ2-associated antibody deficiency and immune dysregulation
PRAAS	Proteasome-associated autoinflammatory syndrome
SAVI	Stimulator of interferon genes (STING)–associated vasculopathy with onset in infancy
SMS	Singleton-Merten syndrome
SPENCDI	Spondyloenchondrodysplasia with immune dysregulation
TNF	Tumor necrosis factor
TRAPS	TNF receptor–associated periodic syndrome

fever (FMF)[2,3] and of the tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS).[4]

Over the last 15 years the discovery of the genetic causes for several autoinflammatory diseases revealed gain-of-function (GOF) mutations in intracellular innate immune sensors (**Fig. 1**), including the interleukin (IL)-1 and IL-18 activating inflammasomes *MEFV*/pyrin, *NLRP3*/cryopyrin, and nod-like receptor (NLR) family CARD domain-containing protein 4 (*NLRC4*); *NLRC4* also leads to high IL-18 serum levels. Mutations in the NOD-like receptor NOD2/caspase recruitment domain family, member 15 (CARD15) cause constitutive nuclear factor kappa B (NF-κB) activation; and more recently mutations in the viral RIG-I–like receptors, *IFIH1/MDA-5*[5] and DDX58, or the adaptor molecule *TMEM173/STING*[6] encoding the stimulator of interferon genes (STING), are all linked to type I interferon (IFN) production and cause autoinflammatory phenotypes. Furthermore, loss-of-function (LOF) mutations in genes (ie, many of the enzymes) involved in protein or nucleic acid metabolism, cell transport, and other cellular homeostatic functions can lead to the accumulation of intracellular danger signals, which can trigger innate immune sensors and activate proinflammatory pathways (see **Fig. 1**). The