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# Periodic Fever Syndromes

# Definition

three or more episodes of unexplained fevers in a 6-month period, occurring at least 7 days apart

- These conditions may demonstrate strict periodicity or recur with varying intervals between attacks

- Specific genetic mutations have been linked to some syndromes, although the etiology of others remains obscure

# HEREDITARY AUTOINFLAMMATORY SYNDROMES

The term *autoinflammatory* has been used to describe a group of illnesses characterized by attacks of seemingly unprovoked inflammation without significant levels of either autoantibodies or antigen-specific T cells more characteristic of autoimmune disease

the autoinflammatory diseases represent disorders of the innate immune system

- In general, adaptive immunity plays a much more prominent role in the more classically recognized autoimmune disorders, such as systemic lupus erythematosus, whereas the monogenic autoinflammatory diseases are primarily inborn errors of innate immunity


| | | |
|---|---|---|
| INNATE immune system | **Immune dysregulation** | ADAPTIVE immune system |
| Monocytes, macrophages, neutrophils | **Predominant cell types** | T cells, B cells |
| IL-1, TNF, IFNαβ, IL-12, IL-23, (IL-17), IL-18 | **Cytokine targets used therapeutically** | IFNγ, IL-4, (IL-17), IL-6 |
| Neutrophil- and macrophage-mediated organ damage | **Pathogenesis of organ damage** | Autoantibody- or autoantigen-specific T cell–mediated organ damage |
| IL-1-mediated monogenic autoinflammatory diseases | **Disease examples** | Thyroiditis, rheumatoid arthritis, SLE, ALPS |

- Autoinflammatory diseases exhibit episodic or persistent inflammation characterized by an acute-phase response with elevation of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (AA)
- In some patients, untreated autoinflammatory disorders over time will lead to AA amyloidosis

- It is important to note that autoinflammatory disorders are rare, whereas fever in childhood caused by innocuous illness is very common
- The approach to a child with fevers should include :

✓a detailed history

✓physical examination, and

✓ limited laboratory investigations

to rule out other conditions that lead to fevers, including autoimmune disorders and malignancies

# CLASSIFICATION OF AUTOINFLAMMATORY DISORDERS

- *autosomal recessive :*

✓familial Mediterranean fever (**FMF**)

✓hyper-IgD with periodic fever syndrome (**HIDS**)

- *autosomal dominant :*
- **TRAPS**
- (**CAPS**), or cryopyrinopathies (**FCAS** ; **MWS**; **NOMID**)

(fever, neutrophilic urticaria-likeskin rash, and joint involvement)

# classification according to the predominant mechanism

- interleukin (IL)-1ß-activation diseases
- protein-folding disorders
- nuclear factor κB (NF-κB)–activation disorders
- interferonopathies
- other cytokine-signaling disorders
- complementopathies

- A variety of mendelian *autoinflammatory disorders* may or may not exhibit prominent fevers and are not considered periodic fever syndromes but do have continuous or repeated episodes of spontaneous inflammation with unique clinical characteristics :

**PAPA**; **DIRA** ; **Blau syndrome** ; **DADA2**

# interferonopathies

- inappropriate *interferon expression:*

- chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (**CANDLE**)

# Complex mode of inheritance

- **PFAPA**
- **CRMO**
- **systemic-onset juvenile idiopathic arthritis**
- **Behçet disease**
- **Crohn disease**

## BOX 47-1 Inheritance Patterns of the Hereditary Autoinflammatory Syndromes

### Autosomal Dominant Pattern

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
Familial cold autoinflammatory syndrome (FCAS)
Muckle–Wells syndrome (MWS)
Neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurological cutaneous and articular syndrome (CINCA)
Cyclic hematopoiesis (CH), also called cyclical neutropenia (CN)
Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA)

### Autosomal Recessive Pattern

Familial Mediterranean fever (FMF)
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)
Deficiency of interleukin-1 receptor antagonist (DIRA)
Deficiency of interleukin-36 receptor antagonist (DITRA)
Autoinflammatory diseases involving the immunoproteasome
Deficiency of adenosine deaminase 2 (DADA2)

## TABLE 47-1 Classification of the Hereditary Periodic Fever Syndromes[a]

| DISEASE | GENE (CHROMOSOME) | PROTEIN (SYNONYMS) |
|---|---|---|
| **IL-1β ACTIVATION DISORDERS (INFLAMMASOMOPATHIES)** | | |
| Familial Mediterranean fever (FMF) | *MEFV* (16p13.3) | Pyrin (marenostrin) |
| Hyperimmunoglobulin D with periodic fever syndrome (HIDS) | *MVK* (12q24) | Mevalonate kinase |
| Familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), neonatal-onset multisystem inflammatory disease (NOMID), chronic infantile neurological cutaneous and articular syndrome (CINCA) | *NLRP3/CIAS1* (1q44) | Nucleotide-binding domain, leucine-rich repeat, and pyrin domain containing protein (NALP3, Cryopyrin, PYPAF1) |
| Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) | *PSTPIP1* (15q24-25.1) | Proline serine threonine phosphatase-interacting protein (PSTPIP1); CD2-binding protein (CD2BP1) |
| Deficiency of the interleukin-1 receptor antagonist (DIRA) | *IL1RN (2q14.2)* | IL-1Ra |
| **PROTEIN FOLDING DISORDERS OF THE INNATE IMMUNE SYSTEM** | | |
| TNF receptor–associated periodic syndrome (TRAPS) | *TNFRSF1A* (12p13) | TNF receptor superfamily 1A (TNFRSF1A, TNFR1, p55, CD120a) |

## Table 188.1 Differential Diagnosis of Periodic Fever

**HEREDITARY**

See Table 188.2.

**NONHEREDITARY**

A. Infectious
   1. Hidden infectious focus (e.g., aortoenteric fistula, lung sequestration)
   2. Recurrent infection/reinfection (e.g., chronic meningococcemia, immune deficiency)
   3. Specific infection (e.g., Whipple disease, malaria)

B. Noninfectious inflammatory disorder:
   1. Adult-onset Still disease
   2. Systemic-onset juvenile idiopathic arthritis
   3. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
   4. Schnitzler syndrome
   5. Behçet syndrome
   6. Crohn disease
   7. Sarcoidosis

C. Neoplastic
   1. Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)
   2. Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma)
   3. Histiocytic disorders

D. Vascular (e.g., recurrent pulmonary embolism)
E. Hypothalamic
F. Psychogenic periodic fever
G. Factitious or fraudulent

**Table 188.2 Autoinflammatory Disorders**

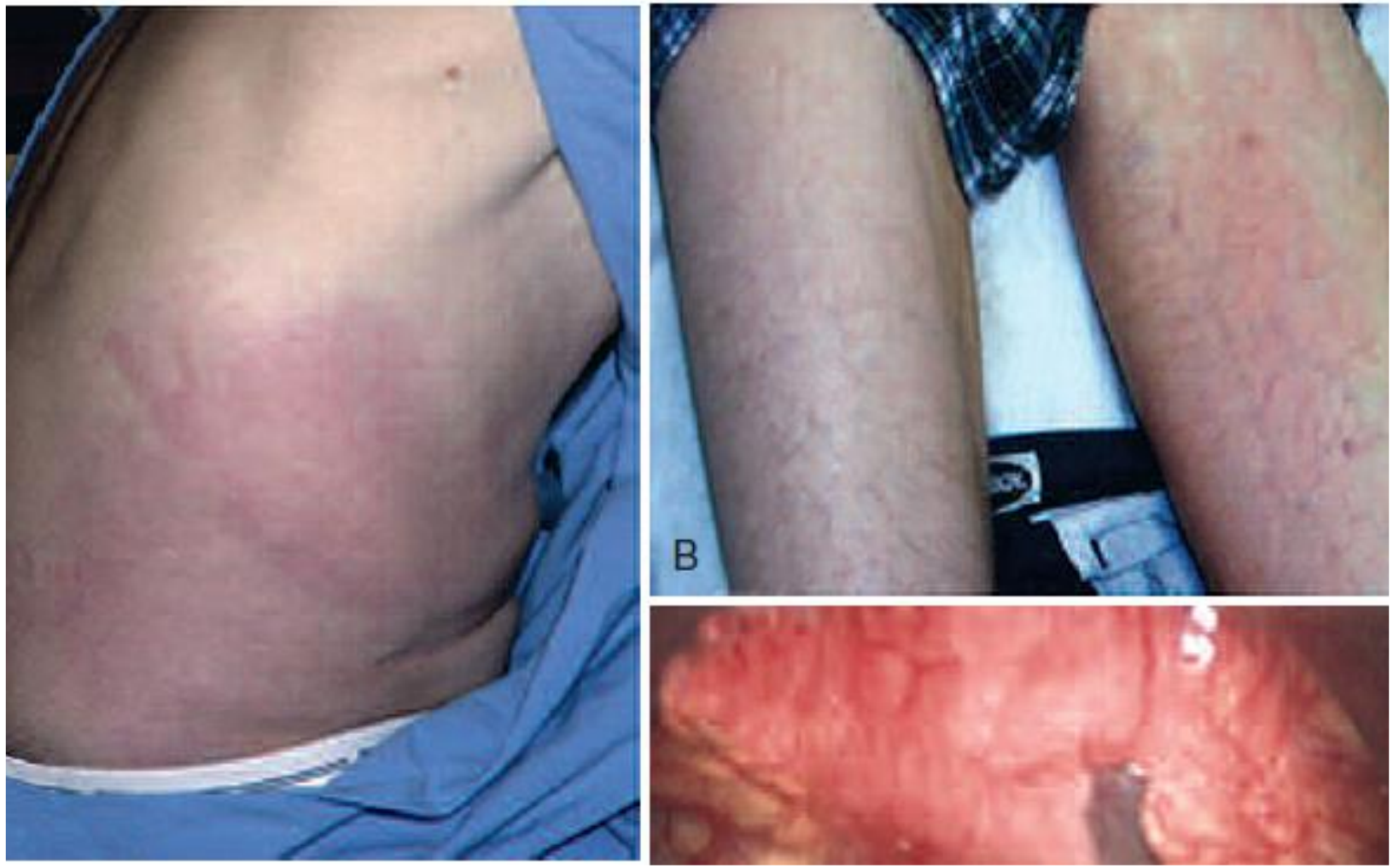
| DISEASE | GENETIC DEFECT/PRESUMED PATHOGENESIS | INHERITANCE | AFFECTED CELLS | FUNCTIONAL DEFECTS | ASSOCIATED FEATURES |
|---|---|---|---|---|---|
| Familial Mediterranean fever | Mutations of *MEFV* (lead to gain of pyrin function, resulting in inappropriate IL-1β release) | AR | Mature granulocytes, cytokine-activated monocytes | Decreased production of pyrin permits ASC-induced IL-1 processing and inflammation following subclinical serosal injury; macrophage apoptosis decreased | Recurrent fever, serositis, and inflammation responsive to colchicine. Predisposes to vasculitis and inflammatory bowel disease |
| Mevalonate kinase deficiency (hyper IgD syndrome) | Mutations of *MVK* (lead to a block in the mevalonate pathway). Interleukin-1β mediates the inflammatory phenotype | AR | | Affecting cholesterol synthesis; pathogenesis of disease is unclear | Periodic fever and leukocytosis with high IgD levels |
| Muckle–Wells syndrome | Mutations of *NLRP3* (also called *PYPAF1* or *NALP3*) lead to constitutive activation of the NLRP3 inflammasome | AD | PMNs, monocytes | Defect in cryopyrin, involved in leukocyte apoptosis and NF-κB signaling and IL-1 processing | Urticaria, SNHL, amyloidosis |
| Familial cold autoinflammatory syndrome | Mutations of *NLRP3* (see above)<br>Mutations of *NLRP12* | AD | PMNs, monocytes | Same as above | Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure |
| Neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) | Mutations of *NLRP3* (see above) | | PMNs, chondrocytes | Same as above | Neonatal-onset rash, chronic meningitis, and arthropathy with fever and inflammation |
| TNF receptor–associated periodic syndrome (TRAPS) | Mutations of *TNFRSF1A* (resulting in increased TNF inflammatory signaling) | AD | PMNs, monocytes | Mutations of 55-kDa TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF | Recurrent fever, serositis, rash and ocular or joint inflammation |
| Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome | Mutations of *PSTPIP1* (also called *C2BP1*) (affects both pyrin and protein tyrosine phosphatase to regulate innate and adaptive immune responses) | AD | Hematopoietic tissues, upregulated in activated T cells | Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response | Destructive arthritis, inflammatory skin rash, myositis |
| Blau syndrome | Mutations of *NOD2* (also called *CARD15*) (involved in various | AD | Monocytes | Mutations in nucleotide binding site of CARD15, possibly disrupting | Uveitis, granulomatous synovitis, campodactyly, ras |

## TABLE 39.1 Clinical, Demographical, and Genetic Features of Selected Monogenic Autoinflammatory Diseases

| | FMF | TRAPS | HIDS | FCAS | MWS | NOMID/CINCA | PAPA | DADA2 | SCAN4 | HA20 | CANDLE | SAVI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Taxonomy | Familial Mediterranean fever | Tumor necrosis associated periodic syndrome | Hyperimmunoglobulinemia D with periodic fever syndrome | Familial cold auto-inflammatory syndrome | Muckle–Wells syndrome | Neonatal-onset multisystem inflammatory disease/ chronic infantile neurological cutaneous and articular syndrome | Pyogenic arthritis with pyoderma gangrenosum and acne | Deficiency of adenosine deaminase 2 | Syndrome of enterocolitis and autoinflammation associated with mutation in *NLRC4* | Haplo in sufficiency of A20 | Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature | STING-associated vasculopathy with onset in infancy |
| New taxonomy* | | | Mevalonate kinase deficiency (MVD) mild | NLRP3-associated autoinflammatory disease *(NLRP3-AID)* mild | NLRP3-associated autoinflammatory disease *(NLRP3-AID)* moderate | NLRP3-associated autoinflammatory disease *(NLRP3-AID)* severe | *PSTPIP1-associated* arthritis, pyoderma gangrenosum & acne (PAPA) | | | | Proteasome-associated autoinflammatory syndrome (PRAAS) | |
| Inheritance | Autosomal recessive with gain-of-function mutations | Autosomal dominant | Autosomal recessive | Autosomal dominant | Autosomal dominant | Autosomal dominant or *de novo* | Autosomal dominant | Autosomal recessive | Gain of function mutation | Autosomal dominant | Autosomal recessive | Autosomal dominant or de novo |
| Ethnicity | Jewish, Arab, Turkish, Armenian, Italian | Any ethnic group | Dutch, French, other European | Mostly European | Northern European | Any ethnic group | Any ethnic group | Any ethnic group | Any ethnic group | Any ethnic group | Any ethnic group | Any ethnic group |
| Gene | *MEFV* | *TNFRSF1A* | *MVK* | *NLRP3* | *NLRP3* | *NLRP3* | *PSTPIP1/ CD2BP* | *ADA2* | *NLRC4* | *TNFAIP3* | *PSMB8* (and other proteasome genes) | *TMEM173* |
| Protein | Pyrin/ marenostrin | TNFRSF1A | Mevalonate kinase | NLRP3/ cryopyrin | NLRP3/ cryopyrin | NLRP3/ cryopyrin | PSTPIP1/ CD2BP1 | Adenosine deaminase 2 | NLRC4 | TNFAIP3 (A20) | PSMB8 | STING |
| Duration of episode | 1–3 days | Often >7 days | 3–7 days | Usually <24 hours | 2–3 days | Almost continuous, with exacerbations | Variable | Variable | Variable | Variable | Variable | Variable |
| Mucocutaneous | Erysipeloid erythema | Migratory rash, underlying myalgia | Nonmigratory maculopapular rash; vasculitis | Cold-induced urticaria-like rash | Urticaria-like rash | Urticaria-like rash | Cystic acne; PG | Livedo, vasculitic rash, Raynaud's | Cold-induced urticaria | Recurrent oral and/ or genital ulcers | Violaceous skin nodules or plaques, lipodystrophy | Cold-sensitive acral lesions, ulcerations, tissue loss |

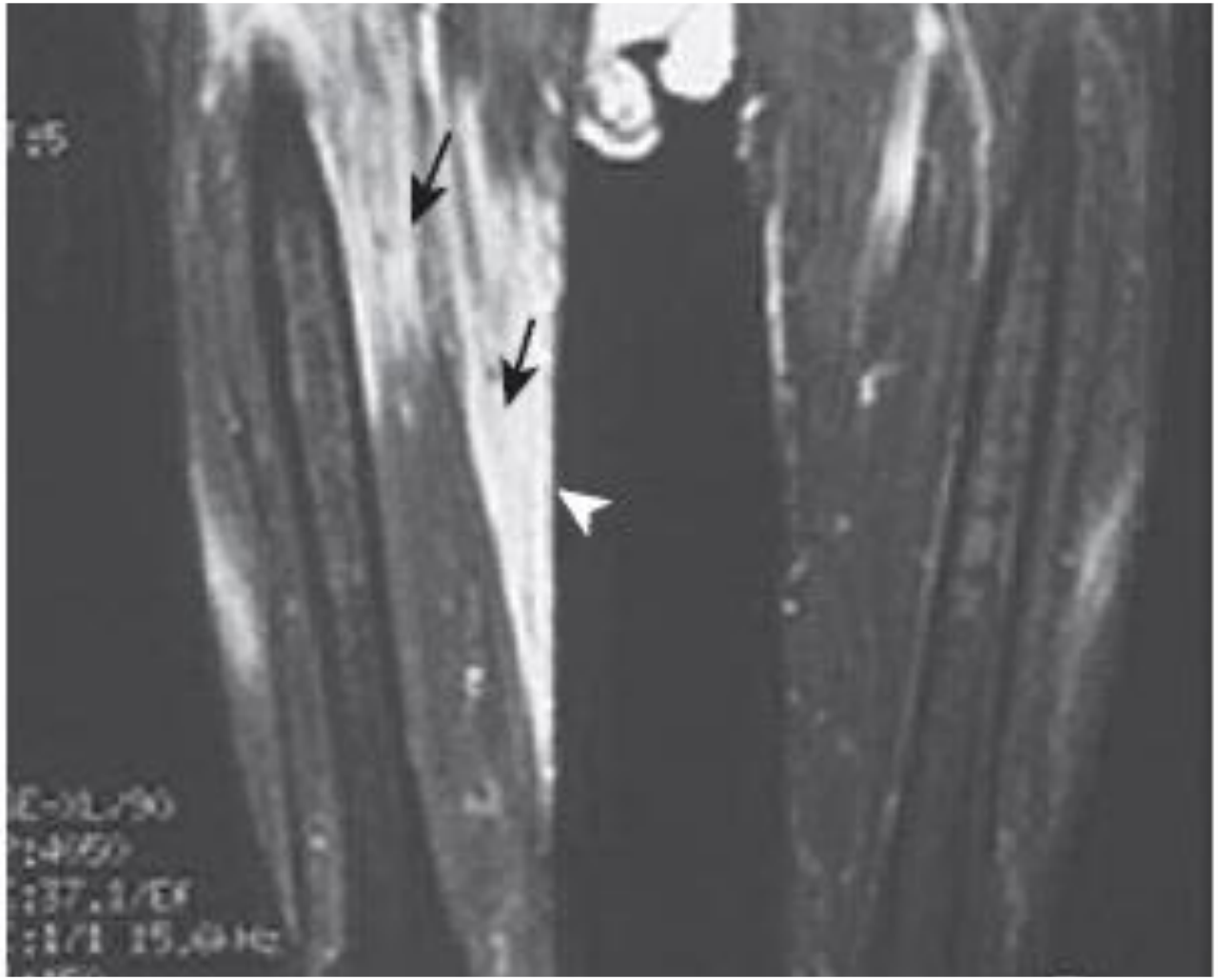
# TRAPS

Cutaneous findings associated with TRAPS may consist of macular areas of erythema on the torso **(A)** or on an extremity **(B)**.



# TRAPS

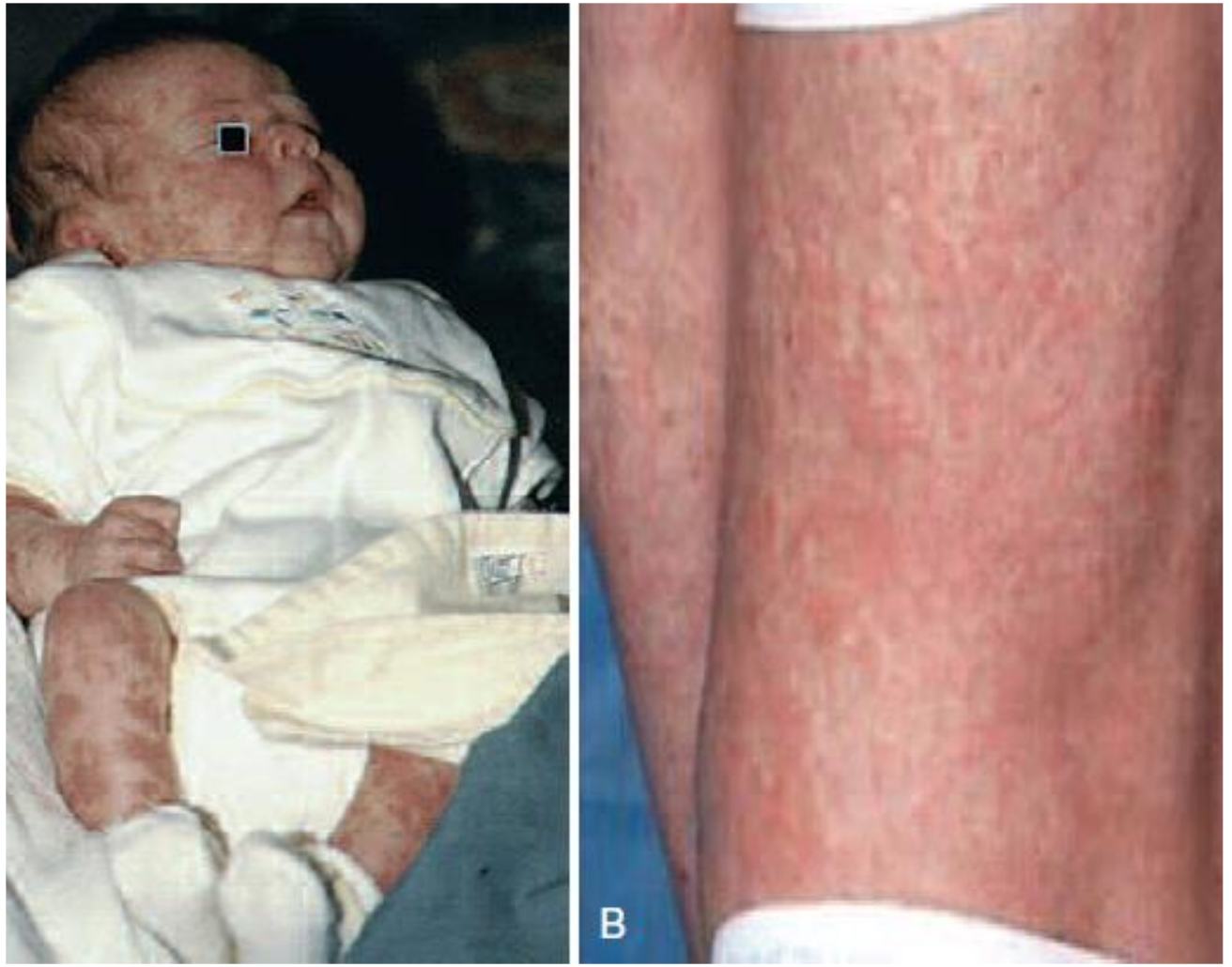
Sagittal views of the proximal thighs of a TRAPS patient demonstrating edematous changes within muscle compartments *(black arrows)*, here and extending to the skin *(white arrows)*



# NOMID

An urticaria-like rash is usually present at birth or during the first months of life. B, The

rash is nonpruritic and papular



# NOMID

Joint involvement in NOMID is most commonly asymmetrical and chiefly involves the knees.

A, The arthropathy can cause gross deformity of the joints with contractures. B, A hallmark of NOMID is a bizarre enlargement of the ossified portions of the epiphyses of the involved joints