AEDV HIGHLIGHTS
24th World Congress of Dermatology (WCD)

10-15 JUNIO 2019
Milán

#WCD2019
Systematic and autoimmune disease

Raquel Rivera
*Dermatologia. HU 12 de Octubre MAdrid*
SY : Autoinflammatory Diseases

Plenary S: How Autoantigens Drive Cutaneous Disorders
When to suspect an “inflammatory” periodic fever?

- Early onset (usually)
- Rapid appearance of fever without evident signs (and history) of respiratory or urinary tract infections
- Elevation of acute phase reactants with normalization in the inter-critical intervals
- Complete wellbeing in the inter-critical intervals
- Periodicity (not mandatory) / lack of seasonality
- Stereotypic manifestations (“it is his/her typical episode!”)
Classic hereditary fevers: FMF, TRAPS, mevalonato kinase deficiency: presentations and treatment.
Marco Gattorno

Cluster study (canakinumab)
Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes


DOI: 10.1056/NEJMoa1706314
TARGETING IL-36 IN DITRA SYNDROME

A phase 1 proof-of-concept study involving seven patients who presented with a generalized pustular psoriasis flare and were treated with a single, open-label, intravenous dose of BI 655130, a monoclonal antibody against the interleukin-36 receptor, at 10 mg per kilogram of body weight (ClinicalTrials.gov number, NCT02978690).

Several syndromes manifest as recurrent daily fevers, skin lesions, and multisystem inflammation. We describe 4 patients with early-onset recurrent fevers, annular violaceous plaques, persistent violaceous eyelid swelling, low weight and height, lipodystrophy, hepatomegaly, and a range of visceral inflammatory manifestations. Laboratory abnormalities included chronic anemia, elevated acute-phase reactants, and raised liver enzymes. Histopathologic examination of lesional skin showed atypical mononuclear infiltrates of myeloid lineage and mature neutrophils. Our patients have a distinctive early-onset, chronic inflammatory condition with atypical or immature myeloid infiltrates in the skin. We propose the acronym CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome for this newly described disorder, which is probably genetic in origin. (J Am Acad Dermatol 2010;62:489-95.)
Disease course and treatment effects of a JAK inhibitor in a patient with CANDLE syndrome

M. Boyadzhieva, L. Maneva, V. Boyadzhiev, V. Iotova, I. Aladzhev, and S. Hamberton

Abstract

Background: CANDLE syndrome (an acronym for Chronic Atypical Neurotrophic Dermatosis with Lipodystrophy and Endocrine abnormalities) is a recently described rare autosomal recessive disorder characterized by systemic autoinflammation. Clinical manifestations include premature in the first year of life, episodes of fever accompanied by erythematous skin lesions, progressive lipodystrophy, vasculitis, peripheral swelling and failure to thrive. This syndrome is caused by loss of function mutations and malfunction of the immunoproteasome complex.

Most patients have bi-allelic mutations in the PSMB8 gene that encodes the β2-microglobulin subunit of the immunoproteasome. Examples of digenic inheritance have been also described in CANDLE. CANDLE patients have strong type I interferon gene expression signature and they are responsive to treatments with JAK inhibitors. However, possible serious side-effects remain a concern. Here, we report another patient with CANDLE whose disease activity was well controlled by the treatment with baricitinib.

Case presentation: We report a Bulgarian patient of the Turkish ancestry who carries bi-allelic mutations in the PSMB8 gene: p.Ala274Val and p.Lys112Gln. The pathogenic variant p.Ala274Val has not been previously described in patients with CANDLE. We also comment on the unusual feature in this patient, nephrolithiasis, that has not been described in other patients, however, it might be related to the positive family history for kidney stones. We have treated the patient with the JAK inhibitor baricitinib for the past year and we observed a significant amelioration of his inflammatory episodes, skin and joint manifestations, and improvements in physical activity and growth. The treatment with glucocorticoids (GC) was completely discontinued. No side effects have been observed, however.

49 months

30 months
Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond.
Karoline Krause

Neutrophilic Urticarial Dermatosis
A Variant of Neutrophilic Urticaria Strongly Associated With Systemic Disease. Report of 9 New Cases and Review of the Literature
Carine Kieffer, MD, Bernard Cribier, MD, PhD, and Dan Lipsker, MD, PhD

1. Clinically, the inclusion criteria were as follows:
   1.1. Patients with a recurrent or chronic cutaneous eruption consisting of macules, papules, or plaques,
   1.2. Individual lesions had to resolve within 48 hours,
   1.3. They could be pruritic or not.

2. Histopathologically, the following criteria had to be present:
   2.1. A diffuse neutrophilic infiltrate in the dermis, with interstitial involvement,
   2.2. Absence of significant vessel wall alteration (especially parietal necrosis),
   2.3. Absence of significant dermal edema.

→ mainly found to be associated with Still's disease, Schnitzler's syndrome and systemic lupus erythematosus
Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond.
Karoline Krause
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Histology: Neutrophil-dominated infiltrate

Schnitzler's syndrome

Urticaria
Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond.

Karoline Krause
Appearance of urticarial lesions

Common acute or chronic spontaneous urticaria

Wheal and flare

CAPS

Flat wheals, erythematous patches
Neutrophilic urticarial dermatosis: an entity bridging monogenic and polygenic autoinflammatory disorders, and beyond. 
Karoline Krause

**Autoinflammation: Clinical clues**

**Spontaneous wheals...**

+ No or little pruritus
+ Absence of angioedema
+ Diurnal pattern
+ Systemic symptoms and high inflammatory markers
+ No response to antihistamines or anti-IgE
Pyoderma gangrenosum and other rarer neutrophilic dermatoses as paradigm of autoinflammation
Angelo Valerio Marzano

TABLE II.—Classification of neutrophilic dermatoses.

<table>
<thead>
<tr>
<th>Epidermal</th>
<th>Dermal</th>
<th>Hypodermal</th>
<th>Epidermal/dermal/hypodermal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcorneal pustulosis (Sneddon-Wilkinson’s disease)</td>
<td>Sweet’s syndrome</td>
<td>Pyoderma gangrenosum</td>
<td>Overlapping forms</td>
</tr>
<tr>
<td>Amicrobial pustulosis of the folds</td>
<td>Erythema elevatum diutinum</td>
<td>Hidradenitis suppurativa</td>
<td>PAPA/PASH/SAPHO syndrome</td>
</tr>
<tr>
<td>Amicrobial pustulosis of the scalp/leg</td>
<td>Rheumatoid neutrophilic dermatosis</td>
<td>Behçet’s disease</td>
<td>Bowel-bypass syndrome</td>
</tr>
<tr>
<td>Acute exanthematic generalized pustulosis (AGEP)</td>
<td>Acneiform eruption due to EGFRIs</td>
<td>Neutrophilic panniculitis</td>
<td></td>
</tr>
<tr>
<td>Pustular psoriasis</td>
<td></td>
<td>Aseptic abscesses syndrome</td>
<td></td>
</tr>
</tbody>
</table>

IgA pemphigus

IgA: immunoglobulin A; EGFRIs: epidermal growth factor receptor inhibitors; PAPA: pyogenic arthritis, pyoderma gangrenosum and acne; PASH: pyoderma gangrenosum, acne and hidradenitis suppurativa; SAPHO: synovitis, acne, palmoplantar pustulosis, hyperostosis, osteitis.
Neutrophilic dermatoses

A Comprehensive Review of Neutrophilic Diseases

Authors

Angelo V. Marzano, Alessandro Borghi, Daniel Wallach, Massimo Cugno

## Pyoderma gangrenosum

### Table 1: Diagnostic criteria for pyoderma gangrenosum

<table>
<thead>
<tr>
<th>Major</th>
<th>Clinical:</th>
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<tbody>
<tr>
<td></td>
<td>Ulcer with violaceous and undermined borders or nodular, pustular, bullous, or vegetating lesions</td>
</tr>
<tr>
<td>Histological:</td>
<td>Neutrophil infiltrate of the dermis and hypodermis with a variable number of lymphocytes and macrophages and ulceration necrosis of the epidermis</td>
</tr>
<tr>
<td>Microbiological:</td>
<td>Negative cultures from intact or recent-onset lesions</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence of hematologic or solid neoplasia or inflammatory bowel diseases or rheumatological diseases</td>
</tr>
<tr>
<td></td>
<td>Absence of diabetes mellitus and chronic venous disease</td>
</tr>
<tr>
<td>Laboratory:</td>
<td>Presence of various circulating autoantibodies</td>
</tr>
</tbody>
</table>

The diagnosis requires three major criteria and at least one minor criterion.

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Diagnostic Criteria of Ulcerative Pyoderma Gangrenosum
A Delphi Consensus of International Experts

Figure 1. Diagnostic Criteria for Classic Ulcerative Pyoderma Gangrenosum

- Biopsy of ulcer edge demonstrating a neutrophilic infiltrate
- History
  - Exclusion of infection
  - Personal history of inflammatory bowel disease or inflammatory arthritis
  - History of papule, pustule, or vesicle that rapidly ulcerated
- Clinical examination (or photographic evidence)
  - Peripherally erythema, undermining border, and tenderness at site of ulceration
  - Multiple ulcerations (at least 1 occurring on an anterior lower leg)
  - Cribiform or "wrinkled paper" scar(s) at sites of healed ulcers
- Treatment
  - Decrease in ulcer size within 1 mo of initiating immunosuppressive medication(s)

In addition to a biopsy demonstrating a neutrophilic infiltrate, patients must have at least 4 minor criteria to meet diagnostic criteria.

a Including histologically indicated stains and tissue cultures.

b Ulcer should extend past area of trauma.
Plenary Sessions
How Autoantigens Drive Cutaneous Autoimmune Disorders
Michell Gilliet

Autoimmune diseases

• A clinical syndrome caused by:
  • Activated T cells +/-B cells
  • In absence of an ongoing infection
  • Recognizing host-derived autoantigens
How Autoantigens Drive Cutaneous Autoimmune Disorders
Michell Gilliet
How Autoantigens Drive Cutaneous Autoimmune Disorders
Michell Gilliet
Anti-PD1-induced rash | LL37-driven autoimmunity?

- Lichenoid skin rash associates with clinical responses
- Shared T cell clones in lung and skin specific for LL37, maspin, desmocollin, keratin 14
- Th1/Tc1 phenotype

*er et al. JAMA Oncology. 207:2921 (2019)*
How Autoantigens Drive Cutaneous Autoimmune Disorders
Michell Gilliet

• LL-37 is an autoantigen that induces potent virus-like immune activation
  • Forms DNA complexes that trigger intracellular nucleic acid receptors
  • Unleashes IFN-mediated CD4 and CD8 T cell responses (autoimmunity)

• Early unspecific driver of autoimmunity T cell polarization depends on genetic predisposition/tissue microenvironment:
  • Th17 for psoriasis, fTh antibodies for lupus, TH1 for cancer/anti-PD1
Clinical relevance | Early therapeutic targeting

Inhibitors of AMP production:
- NET inhibitors (PAD4 antagonists)

Targeting AMPs:
- Structural AMP Competitors (anionic, spacing)
- AMP inhibitors?

Targeting nucleic acids:
- Dnase/Rnase-Fc

pDC inhibition:
- Anti-ILT-7
- Anti-BDCA2

TLR/STING antagonists:
- TLR7/9 inhibitors
- TLR7/9 antagonists
- STING antagonists

Neutralization of IFN IFNAR signalling:
- Anti-IFN-α Ab
- Anti-IFNAR Ab
- JAK-1 Inhibitors

LL37-specific T cells

AutoAg specific T cell control
- Tolerogenic vaccines
- CAR-T cells targeting the AutoAg

DNA-LL37

Type 1 IFNs