Chronic Mucocutaneous Candidiasis (CMC)

By

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CMC does not represent a specific disease, but rather a phenotypic presentation of a spectrum of *Immunologic, Endocrinologic, Autoimmune* disorders.

The unifying feature of these heterogeneous disorders is impaired cell-mediated immunity against *Candida* species.
Candida is an opportunistic yeast. Normal flora of skin, mucous membranes, GIT.

**Immunity to candida:**
1. Normal barrier.
3. Humoral immunity.
Structure of Yeast Cell Wall

Yeast Cell Wall

- Mannoprotein
- β-Glucan
- β-Glucan + Chitin
- Mannoprotein
- Membrane
Gazendam RP et al, 2014

Humoral immunity and candida Oxidative Burst dysfunction (CGD) and candida

Two independent methods for candidal clearance

Neutrophil Phagocytosis of Candida albicans

1. Unopsonized C. albicans

2. Serum-opsonized C. albicans

CR3

FcγR

SYK

kindlin3

PI3K

CARD9

NADPH oxidase

PKC

Killing
NF-κB activation and cytokine production

APC use different receptors to identify different part of fungus (candida)

Activating transcription factors; CARD9, MyD88, TRAF6

NF-κB activation and cytokine production

Activation of T cells with Th17 development

Production of IL17/IL22 from Th17 cells

Binding to IL17 and IL22 R on epithelial cells/Neutrophils leading to fungal phagocytosis

Wang et al, 2016
CMC

- Syndromic
  - STAT1 GOF
  - APECED, Thymoma, Stat3 LOF, DOCK8

- Disease
  - 4 genes:
    - IL17F, IL17 RA, IL17 RC, ACT1
Case 1

- 35-year-old Male.
- Persistent oral candidiasis; dating since infancy.
- Candida esophagaitis
- Onychomycosis at 36 months of age.
- No pneumonia, sinusitis, otitis media and other serious infections.
- No endocrinopathy and autoimmune disorders.
- Family history was negative for similar illness.
- Laboratory test: normal skin test to tetanus and tuberculin. No response to candida antigens and decrease in vitro lymphocyte proliferation to candida antigens. Thyroid, parathyroid, and adrenal functions were normal.
Case 2

- 14-year-old girl.
- Persistent Oral thrush from late childhood.
- At age 11y, progressive muscle weakness, ptosis (Myasthenia Gravis). TTT plasmaphresis. Currently on low dose steroid on alternate days.
- At age 13y, macrocytic anemia due to B12 deficiency (pernicious anemia) and was treated successfully with B12 supplement.
- FH: negative.
- Delayed -type hypersensitivity skin test to candida was negative.
**Case 3**
- 27-year-old girl.
- Persistent oral candidiasis and onychomycosis during infancy.
- At ages 9 and 20 years she developed hypocalcemic seizure and severe weakness with skin hyper pigmentation.
- Hypoparathyroidism and adrenal insufficiency.
- No serious infections.
- FH: negative.
- Laboratory tests showed normal skin test to tetanus antigen but negative response to candida antigen. In vitro lymphocyte proliferation to candida was subnormal. She did not develop serious infections.

Fazlollahi et al, 2005
Diagnosis

All 3 cases have Autoimmune polyendocrinopathy, Candidiasis, Ectodermal Dystrophy (APECED).
Autoimmune regulator (AIRE) is a transcription element in the thymus that allows expression of self antigens and regulates their identification by self-reactive T cells leading to negative selection.
Why are patients with APECED susceptible to candidal infection?

The presence of high levels of anti-IL7 A and IL7F and anti-IL22 are responsible for susceptibility of these patients to candidal infection.
STAT1 GOF mutation

- STAT1 GOF mutation represents the most common form of CMC.

- 274 patients from 167 kindreds originating from 40 countries from 5 continents are being described in literature.

- The median age of the GOF STAT1 patients is 22 years (range, 1-71 years).

Tobiana et al, 2016
STAT1 GOF mutations identified to date
## Clinical presentation of STAT1 GOF

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
<tr>
<td><strong>CMC</strong></td>
<td>98%</td>
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<tr>
<td>Invasive fungal infection (candida/others)</td>
<td>10%</td>
</tr>
<tr>
<td>Invasive bacterial infection</td>
<td>74%</td>
</tr>
<tr>
<td>Viral disease</td>
<td>30%</td>
</tr>
<tr>
<td>Mycobacterial infection</td>
<td>6%</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>43%</td>
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<tr>
<td>Cerebral aneurysm</td>
<td>6%</td>
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<tr>
<td>Carcinoma mainly squamous cell carcinoma of the oesophagus</td>
<td>5.8%</td>
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STAT1 is a transcription factor in the downstream of both type I and II INF. GOF mutations might lead to Autoimmunity through activation of INF stimulated genes.
Most of the cases develop CMC as early as the first 5 years of life
Low IL17+ T cells are responsible for CMC in patients with STAT1 GOF.
Complications of STAT1 GOF mutations include:

1) Invasive infections.
2) Cerebral aneurysm.
3) Malignant transformation; carcinoma in oesophagus seen post chronic oesophageal candidiasis.
Survival is guarded in the presence of complications.
Management

1) Conservative; using antifungals and antibiotic prophylaxis.
2) HSCT; to date 6 cases were transplanted with 50% survival.
3) Management of complications.
Potential therapies

1) Recombinant IL-17A or IL-17F.
2) Inhibitors of STAT1 activity for specific use in patients with GOF STAT1 mutations may prove more useful.
3) Jak1 inhibitor; Ruxolitinib.
3) IFN-α/β-blocking antibodies might also alleviate autoimmune features and may be considered in the future.
Thank You