CHRONIC SPONTANEOUS URTICARIA (CSU) AS AUTO-IMMUNE FEATURE IN COMMON VARIABLE IMMUNODEFICIENCY (CVID)

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CVID

- Common variable immunodeficiency (CVID) is one of the most common primary humoral immunodeficiencies among adults

- Characterized by increased risk of infections, auto-immunity, auto-inflammation, malignancy
Chronic spontaneous urticaria (CSU)

- CSU is characterized by the presence of wheals and angioedema for at least six consecutive weeks
- Common disorder
- Auto-allergic condition
- Associated with various auto-immune diseases including auto-immune thyroiditis and systemic lupus erythematosus (SLE)
- The association between CSU and CVID is rare
Patient 1, male, 42 years old

- Unremarkable medical history
- Since 6 months episodes of CSU and angioedema
- Medical examination: no abnormalities except small lymph nodes neck and groins
- Lab: total IgE < 2 kU/L
Patient 1, male, 42 years old

Multiple weakly FDG-avid lymph nodes neck, axilla, mediastinum, lung hili, para-iliacal region, groins. Weakly increased uptake spleen. Patchy uptake right lung (CT: no nodules or bronchiectasis).
Additional diagnostics

- Bone marrow exam: no lymphoma, no mastocytosis

- Lymph node excision: reactive pattern

- Additional lab:
  - Low IgG (420 mg/dl = 4.2 g/L) and IgA (37 mg/dl = 0.37 g/L), normal IgM (96 mg/gl = g/L)
  - Low total memory B-cells
  - Disturbed response to immunization with polysaccharide pneumococcal vaccination
Conclusion

- **CVID**

- With chronic spontaneous urticaria

- **Treatment**
  - Omalizumab
    - Excellent response despite nondetectable IgE!
    - Effect started 1 month after 2nd injection.
  - No treatment for CVID (no infections and no bronchiectasis)
Patient 2, female, 52 years old

- Medical history:
  - thyroiditis
  - auto-immune hemolytic anemia
  - thrombocytopenia
  - recurrent respiratory tract infections
  - bronchiectasis on CT-scan

- CSU with moderate response to antihistamines
Diagnostics

- Slightly decreased number of total thrombocytes
- Undetectable levels of IgG, IgA, IgM and IgE
- CT-scan: consolidative nodule and bronchiectasis
Conclusion

- CVID with auto-immune features and GL-ILD

- With chronic spontaneous urticaria

- Treatment
  - Immunoglobulin replacement therapy (IVIG)
  - Initially prednisone, but because of progression of GL-ILD mycophenolate mofetil and rituximab
  - Response: currently free of infections, remission of ILD and remission of CSU
Chronic spontaneous urticaria

- Frequent urticaria, sometimes with angioedema, ≥ 6 weeks

- Association with auto-immune diseases
  - Up to 50% is ANA positive
Pathophysiology of CSU in CVID

- Auto-immune
  - Antibodies against the high affinity IgE receptors (FcεRIα)
  - Antibodies against IgE molecules

Bracken et al. Frontiers Immunology 2019
-Pelaia et al. J Asthma Allergy 2011
Omalizumab could be an effective treatment option

- Omalizumab is a humanized monoclonal IgG1 anti-IgE antibody, which binds to free IgE and inhibits their interaction with the FcεRI receptors on mast cells and basophils, leading to a downregulation of such receptors.

![Diagram showing the mechanism of action of Omalizumab in CSU in CVID.](image-url)
Previous reports on CSU and CVID

- Aimee Altschul et al. JACI. 2002.
  - 6 cases of CSU associated with CVID
  - A child with CSU associated with CVID
  - A woman with CSU and hypogammaglobulinemia
  - 3 cases of CSU and CVID
- Comberiati P et al. Front Immunol 2019
  - 1 patient with CSU and CVID treated with Omalizumab
CSU: another skin condition in CVID?
Conclusion and discussion

- CSU may be associated with CVID
- CSU as an auto-immune (auto-allergic) feature of CVID?
- Should all patients with CSU be screened for immunodeficiency?
  - Absolute prevalence probably low
  - CSU on itself is common (5% of Dutch population gets CSU at least for a short period of time)
  - Only if total IgE is undetectable?
  - Ask for infections