Inflammatory complications in CVID—what is new and what can be done?

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PID-patient care: an area in rapid transition
What is a PID-patient?
Diagnosis and clinical work-up

Neurology

Infectious diseases

Gastro

PID-patients

Hematology

Microbiology

Reuma

Lung

Immunology

Clinical genetics
Case: Robert, 35 years

- Normal childhood, bi-linear Evan’s syndrome diagnosed at age 17 (Tpk, RBC), increased susceptibility to infections around age 25, referred from hematology to us at age 31
- IgG: 2.2 g/L, IgA: 0, IgM: 0
- No vaccine response, low memory B-cells, splenomegaly, Evan’s syndrome
- CVID diagnosis was given and scIG was started
- Few infections, occasional findings of *H. Influenzae* in sputum

- Last 6 months: Gradual deterioration of general appearance
- Very tired, nightly chills, bad physical performance
- Difficult to work and to take care of his family with a newborn baby
Main problem for Robert: the lungs

- **Spirometry:** Static lung volumes: 63% of expected; Dynamic spirometry: 60%, Diff capacity: 74%
- **Pulmonary X-ray:** ”diffuse infiltrations bilaterally of unspecific nature”.
- **PET-CT:** ”several multiple hyper-metabolic nodules in the gut, along the aorta, inguinal, axillar, spleen and in the lung”
- **BAL:** no malignant cells, no TB, fungi, virus or bacteria, hyperinflammatory and mixed cellular pool
- **Needle punction of a lung infiltrate:** mixed lymfocytic infiltration, no malignant cells, no granuloma

- How should this patient be handled?
How is CVID defined?

- **Main criteria:**
  - Clinical symptoms: infections, autoimmunity or lymphoproliferation (at least one)
  - Hypogammaglobulinemia (at least 2 measurements, 3 weeks apart)
  - Low IgA or IgM
  - Low or absent response to polysaccarides or protein antigens
  - Other causes to hypogammaglobulinemia should be excluded

- **Supporting:** reduced memory B cell subsets and/or increased CD21-low subsets by flow cytometry
Facts about CVID

- Unknown cause
- Prevalence is around 1:20,000-1:30,000
- Onset can occur in children or adults
- Usually long time from onset of symptoms to diagnosis
- Not directly inherited, i.e. not mendelian genetics

- **A Danish study (2017)**
  - Prevalence 1:26,000
  - Median age onset of symptoms = 29 years
  - Median age at diagnosis = 40 years
  - Median diagnostic delay = 7 years

Westh et al, 2017
Infections

- S. pneumoniae
- H. influenzae
- S. aureus
- M. catarrhalis
- P. aeruginosa in BE

Inflammatory and Autoimmune

Lung

- LIP (Lymphocytic Interstitial Pneumonia)
- GLILD (Lymphadenopathy, Nodules/Opacities)

Liver

- Splenomegaly
- Nodular regenerative hyperplasia
- Granulomatous hepatitis

Intestine

- Diarrhoea
- Malabsorption
- Inflammatory bowel disease
- Nodular lymphoid hyperplasia
- Idiopathic enteropathy

Autoimmune

- Immune thrombocytopenic purpura
- Autoimmune Hemolytic anaemia
- Evans syndrome
- Rheumatoid Arthritis
- Anti-IgA antibodies
- Alopecia & Other

Jolles et al, 2013
Clinical phenotypes in CVID

CVID

No Disease Related Complications (62% - 78%)

Disease Related Complications (22% - 38%)

Cytopenias (6% - 15%)
p < 0.0005

Lymphoproliferation (6% - 15%)
p < 0.0001

Enteropathy (1% - 4%)
p < 0.0005

Jolles et al, 2013
Intestinal problems in CVID

A recent study where this question was addressed:

- GI symptoms in 103 CVID-patients and GI histopathological findings in 53 CVID-patients

- **Symptoms:** bloating (34%), pain (30%), and diarrhea (26%).

- **Histopathology:**
  - increased intraepithelial lymphocytes in the descending part of the duodenum, i.e., “celiac-like disease” (46% of patients),
  - decreased numbers of plasma cells in GI tract mucosa (62%)
  - lymphoid hyperplasia (38%),

- Reduced plasma cells in GI mucosa were associated with B-cell phenotypic characteristics of CVID, and increased serum levels of sCD14 (P =0.025), sCD25 (P =0.01), and sCD163 (P =0.04).

- Norovirus infection was not found as a cause of CVID enteropathy (none)

Almost 50% of CVID-patients had inflammation as shown with PAD Around 30% had GI-symptoms

Jorgensen et al, 2016
Inflammation in CVID

Small intestine (lymphocytic infiltrates)

Colon (fewer plasma-cells)

Small intestine (lymphoid aggregates)

CVID

Normal

Jorgensen et al, 2016
Intestinal problems are common in CVID

- Medical history
- Monitoring with fecal calprotectin
- Gastroscopy
- Colonoscopy

- Discussion with gastroenterologists
## Liver disease in CVID

### Table 2: Clinical manifestations, laboratory tests/examinations for liver involvement of CVID, and possible causes of liver abnormalities

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Abnormalities in laboratory tests</th>
<th>Abnormalities in liver examinations</th>
<th>Possible causes of liver abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Asymptomatic</td>
<td>A: Liver function tests</td>
<td>A: Imaging examinations</td>
<td>Infections (bacterium, parasite, hepatitis virus (A-G), Epstein-Barr virus, cytomegalovirus, human acquired immunodeficiency virus, etc)</td>
</tr>
<tr>
<td>B: Symptomatic</td>
<td>• Increased level of ALP, r-GT</td>
<td>• Structural alterations on ultrasonography, CT scan, or MRI</td>
<td>• Autoimmunity</td>
</tr>
<tr>
<td></td>
<td>• Increased level of ALT, AST and bilirubin</td>
<td>• Esophageal varices on endoscopy B: Histology</td>
<td>• Lymphoproliferation</td>
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<td></td>
<td>• Decreased level of albumin B: Coagulation markers</td>
<td>• Non-specific inflammation</td>
<td>• Malignancies</td>
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<td></td>
<td>• Increased PT, APTT</td>
<td>• NRH</td>
<td>• Dysfunction of metabolism (deposition of copper, iron, fat, etc.)</td>
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<td></td>
<td>• Decreased level of fibrinogen</td>
<td>• Granuloma</td>
<td>• Drugs</td>
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<td></td>
<td></td>
<td>• Portal hypertension</td>
<td>• Toxins</td>
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<td></td>
<td></td>
<td>• Liver cirrhosis</td>
<td>• Alcohol</td>
</tr>
</tbody>
</table>

**ALP** alkaline phosphatase, r-**GT** gamma glutamyl transpeptidase, **ALT** alanine transaminase, **AST** aspartate transaminase, **PT** prothrombin time, **APTT** activated partial thromboplastin time, **CT** computed tomography, **MRI** magnetic resonance imaging; **NRH** nodular regenerative hyperplasia

*Song et al., 2017*
Liver disease in CVID can occur – but is less common than GI-problems

- We follow our patients with liver enzymes, GT, ALP
- Regular ultrasound to monitor potential hepatomegaly / splenomegaly
- If pathological findings – discussion with hepatologists
Lung disease in CVID: Bronchiectasis

- 10-20 % of CVID-patients
- Likely a consequence of frequent infections
- A marker for lung-damage
- Could lead to chronic colonisation by opportunistic bacteria
Bronchiectasis is not associated with other CVID-related co-morbidities

**TABLE III. Summary of statistically significant relationships (univariate analysis)**

<table>
<thead>
<tr>
<th></th>
<th>Autoimmunity</th>
<th>Granulomas</th>
<th>Bronchiectasis</th>
<th>Splenomegaly</th>
<th>Splenectomy</th>
<th>Pneumonia</th>
<th>Lobectomy</th>
<th>Lymphoma</th>
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<tbody>
<tr>
<td>Enteropathy</td>
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<td>IgG trough</td>
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<td>IgG change</td>
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<td>Male sex</td>
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<td>Age at onset</td>
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</tbody>
</table>

+, Positive association, $P < .05$; ++, positive association, $P < .01$; ++++, positive association, $P < .001$; -, negative association, $P < .05$; --, negative association, $P < .01$; ---, negative association, $P < .001$; empty cells, $P \geq .05$.

N=2212 patients from the ESID-registry

Gathmann et al, 2014
GLILD: granulomatous lymphocytic interstitial lung disease

- **Clinical:** dyspnea, fatigue, low-grade fever
- **Physiology:** static, dynamic and diff cap
- **Radiology:** HRCT, ground-glass appearance, nodules
- **Nuclear medicine:** PET/CT, hypermetabolic nodules
- **Fibroscopy, BAL:** inflammatory cells only, no malignant cells, no infection
- **PAD, Histology:** lymphocytic infiltrations, nodular aggregates

- Other causes should be excluded (TB, lymphoma and sarcoidosis)
GLILD is sign of immundysregulation

- Approximately 10–20 % of patients with CVID develop GLILD
- Splenomegaly and adenopathy
- Cytopenias and evidence of immune dysregulation, with T cells skewed toward a memory phenotype
- Histologic evaluation of pulmonary and lymphatic tissue is most consistent with dysregulated lymphoproliferation (T- and B-cells).
- GLILD appears to be the pulmonary manifestation of a generalized, multi-systemic lymphoproliferative disease.
GLILD requires immunosuppressive therapy

- Steroids can work, but not always
- **Rituximab** (weekly doses of IV rituximab (375 mg/m²/infusion) for 4 weeks
- **Azathioprine** (oral, 1.0–2.0 mg/kg/day, 18 months duration).
- Rituximab infusions were repeated at 4–6 month intervals, for 3 or 4 total courses (12–16 infusions).
- Evaluation together with pulmonologists
- No consensus on the optimal protocol or if other treatments can be better.

Chase et al, 2013
Rituximab and mycophenolate mofetil, 3 months treatment

Improvement measured by PET-CT (FDG-uptake)

Improved lung-function and physical performance

Jolles et al, 2016
Laboratory biomarkers of GLILD and Lymphoproliferation

- Elevated IgM
- Suboptimal IGRT
- Inversely related to IgA
- Episodes of thrombocytopenia
- Elevated β-2 microglobulin (>3mg/ml)
  (sIL-2R is a similar marker)

**B cell biomarkers**
- Low smB- <2%
- IgD⁺IgM⁺CD27⁺ of CD19⁺ B cells
- Expansion of transitional B cells
  (Trhl >9% CD38⁺IgM⁺)
- CD21low B cells (> 10% of B cells)

**T cell biomarkers**
- CD4 T cells < 200 x 10⁶ cells/l*  
- Reduced naive CD4 T cells*
- Reduced Regulatory T cells

Clinical and Radiological Features of Lymphoproliferation

- GLILD
- Splenomegaly
- Widespread lymphadenopathy
  - Granulomatous Hepatitis
  - Enteropathy
  - Granulomas at other sites

Polyarthritus

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Jolles et al, 2016
GLILD is connected to a bad prognosis

**TABLE I.** Noninfectious pulmonary disorders complicating CVID

<table>
<thead>
<tr>
<th>Group 1</th>
<th>No pulmonary disease (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Bronchiectasis (n = 15)</td>
</tr>
<tr>
<td></td>
<td>Asthma (n = 8)</td>
</tr>
<tr>
<td>Group 3A (GLILD)</td>
<td>Granulomatous disease (n = 5)</td>
</tr>
<tr>
<td></td>
<td>LIP (n = 4)</td>
</tr>
<tr>
<td></td>
<td>Lymphoid hyperplasia (n = 2)</td>
</tr>
<tr>
<td></td>
<td>Follicular bronchiolitis (n = 1)</td>
</tr>
<tr>
<td></td>
<td>B-cell lymphoma (n = 1)</td>
</tr>
<tr>
<td>Group 3B (other ILDs)</td>
<td>BOOP (n = 3)</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity pneumonitis (n = 1)</td>
</tr>
<tr>
<td></td>
<td>Metastatic gastric carcinoma (n = 1)</td>
</tr>
</tbody>
</table>

*BOOP,* Bronchiolitis obliterans organizing pneumonia.

**FIG 2.** Kaplan-Meier survival plot demonstrating differences between the 2 groups of patients (GLILD vs non-GLILD). The median survival of 28.8 years in groups 1, 2, and 3B (solid line) is compared with the median survival of 13.7 years in group 3A (dashed line; P < .001). There is no statistical difference in survival between groups 1, 2, and 3B. Time is from the date of CVID diagnosis.

Bates et al, 2004
GLILD: how bad is it?

Table 4: Association between comorbidities and all-cause mortality. Results of Cox proportional hazard model with comorbidities as time-dependent covariate (N = 972)

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>HR (95% CI)(^a)</th>
<th>P-Value</th>
<th>HR (95% CI)(^b)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis</td>
<td>0.84 (0.44; 1.62)</td>
<td>0.612</td>
<td>0.83 (0.40; 1.86)</td>
<td>0.633</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>2.11 (1.17; 3.82)</td>
<td>0.013</td>
<td>1.67 (0.82; 3.39)</td>
<td>0.155</td>
</tr>
<tr>
<td>Autoimmunity (organ/ systemic)</td>
<td>1.61 (0.79; 3.27)</td>
<td>0.187</td>
<td>1.52 (0.67; 3.43)</td>
<td>0.311</td>
</tr>
<tr>
<td>Autoimmune cytopenia</td>
<td>0.72 (0.22; 2.35)</td>
<td>0.591</td>
<td>1.08 (0.33; 3.57)</td>
<td>0.897</td>
</tr>
<tr>
<td>Enteropathy</td>
<td>1.39 (0.54; 3.56)</td>
<td>0.493</td>
<td>0.97 (0.28; 3.41)</td>
<td>0.962</td>
</tr>
<tr>
<td><strong>Solid tumor</strong></td>
<td>3.19 (1.55; 6.57)</td>
<td>0.002</td>
<td>2.69 (1.10; 6.57)</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>Lymphoma</strong></td>
<td>3.95 (1.81; 8.66)</td>
<td>0.001</td>
<td>5.48 (2.36; 12.71)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>GLILD</strong></td>
<td>3.80 (1.47; 9.85)</td>
<td>0.006</td>
<td>4.85 (1.63; 14.39)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

\(^a\) Univariable analysis
\(^b\) Adjusted for age of CVID symptoms onset

Odnoletkova et al, 2018
GLILD management: recommendations

**First line: corticosteroids 30-70 mg/day**

**TABLE IV. Consensus on second-line drug therapy in GLILD**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No. of respondents</th>
<th>% Agree</th>
<th>% Disagree</th>
<th>Mean ± SD score *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus</td>
<td>Azathioprine</td>
<td>21</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>21</td>
<td>90</td>
<td>5</td>
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<tr>
<td></td>
<td>Mycophenolate</td>
<td>21</td>
<td>81</td>
<td>5</td>
</tr>
</tbody>
</table>

No consensus

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No. of respondents</th>
<th>% Agree</th>
<th>% Disagree</th>
<th>Mean ± SD score *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abatacept</td>
<td>18</td>
<td>33</td>
<td>28</td>
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<tr>
<td></td>
<td>Anti-TNF agents</td>
<td>17</td>
<td>29</td>
<td>47</td>
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<tr>
<td></td>
<td>Ciclosporin</td>
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<tr>
<td></td>
<td>Hydroxychloroquine</td>
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<td>42</td>
<td>32</td>
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<tr>
<td></td>
<td>Methotrexate</td>
<td>17</td>
<td>35</td>
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<td></td>
<td>Sirolimus</td>
<td>18</td>
<td>28</td>
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<td></td>
<td>Tacrolimus</td>
<td>18</td>
<td>22</td>
<td>33</td>
</tr>
</tbody>
</table>

**Inflammation in CVID**

Hurst et al, 2017
Increase in serum IgM is a marker for progressive lung disease

- Monocytes produce BAFF, which stimulate B-cells to proliferate and produce IgM
- Rituximab reverse this process and improve symptoms
What about whole genome sequencing and CVID?

- < 5% genetic causes to CVID-like syndromes
- CVID is likely to be a polygenic disease with multiple novel susceptibility loci implicated (Orange et al, 2011)
- Application of whole genome sequencing has revealed several key genes for CVID
  - TACI
  - CD19
  - CD81
  - CD21
  - NFKB
  - And more

It is likely that CVID will be divided in many different subgroups or separate diagnostic entities in the future

Ameratunga et al, 2018
Complex genetic network in CVID

- TACI
- NLRP12
- BAFF-R
- SKIV2L

34 CVID-patients
WGS + RNAseq

< 5% of CVID-patients have a known genetic cause to their disease and >95% do not have a known disease gene implicated

Van Schouwenburg et al, 2015
Back to our patient: what happened?

- We decided to start with immunosuppression:
- Important to **rule out lymphoma** (a lymph-node should be examined)
- Check **latent HBV** (HBsAg, HBV DNA, anti-HBc, can be positive due to IgG-substitution)
- Check **latent TB** (PPD + IGRA-test)
- Rule out **Sarcoidosis** (ACE, can be high due to inflammation)
- Prednisolone (Sarcoidosis-protocol, start 40 mg/day, down to 10-15 mg/day)
- New PET-CT after 3 months showed almost complete remission of hypermetabolic nodules
- Clear improvement of general appearance and physical condition – but for how long?
Final reflections and take home messages

- CVID-patients are out there: please find them and refer them!
- CVID with inflammatory complications is connected with high morbidity and mortality.
- CVID is most likely several different disorders from a genetic perspective
- We lack information about underlying mechanisms
- We lack prognostic markers
- PID is definitely more than infections – we need to think ”immunodysregulation”.
- Immunosuppression should be used more often in CVID-patients with inflammation.
- Multidisciplinary work is necessary!
The Team at Karolinska Univ Hospital

- **Our Doctors:**
  - Dr. Anna-Carin Norlin, MD, PhD
  - Dr. Peter Bergman, MD, PhD, Assoc Prof.
  - Dr. Emelie Wahren-Borgström, MD, PhD
  - Prof Edvard Smith, MD, PhD
  - Dr. Rolf Gustavsson, MD, PhD

- **Our nurses:**
  - Susanne Hansen
  - Kristina Johansson
  - Maria Lindén

- **Research network**
  - Petter Brodin
  - Yenan Bryceson
  - Kristian Riesbeck
  - Fredrik Kahn

- **Our aim is to develop a ”National Competence Center” within the area of Primary Immunodeficiency in adults. Please, contact us for referrals.**
Thank’s for your attention!

If you have further questions or comments, please contact me at: peter.bergman@ki.se