Refractory celiac disease (RCD)

KASSEM BARADA
LEBANESE SOCIETY OF GASTROENTEROLOGY
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A 49 year woman presents with intermittent watery diarrhea and bloating of two years duration. PMH and PE are negative. Labs reveal a Hct of 33% with an MCV of 71. TFTs and stool studies are negative. Anti-endomysial antibody is positive and anti-tTG is strongly positive. Duodenal biopsy revealed mild villous atrophy and increased IEL at 50/100 epithelial cells. You diagnose CD and prescribe a GFD. Six months later she comes back to you with persistent symptoms and says “your diet” is not working. Repeat serology and histopathology are unchanged. Which of the following best characterizes this patient’s condition:

- She does not have CD
- She has primary non-responsive CD
- She has secondary non-responsive CD
- She has refractory CD type I (RCD I)
- She has refractory CD type II (RCDII)
What is celiac disease (CD)?

- An immune mediated small intestinal enteropathy that is triggered by exposure to dietary gluten in genetically predisposed individuals
- It affects about 1% of people in the Western World
Clinical characteristics of CD

- Small intestinal pathology in all patients
  - Increase in intraepithelial lymphocytes
  - Crypt hyperplasia and villous atrophy
- Positive serology in > 95% of patients
  - Anti-endomysial antibodies
  - Anti-tissue transglutaminase antibodies
  - Anti-deamidated gliadin peptide antibodies
- HLA-DQ2 and/or HLA-DQ8 in > 99% of patients
CD is common in low risk populations in the developing world

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle East</td>
<td>0.5-1.8%</td>
</tr>
<tr>
<td>South and East Asia</td>
<td>0.48-1.44%</td>
</tr>
<tr>
<td>Africa</td>
<td>0.3-5.6%</td>
</tr>
<tr>
<td>Latin America</td>
<td>0.15-2.7%</td>
</tr>
</tbody>
</table>

Barada et al; Gastrointestinal Endoscopy Clinics of North America, 2012
CD is very common in high risk populations in the developing world.

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<tr>
<th>Region</th>
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<tbody>
<tr>
<td>Middle East</td>
<td>1.3-33.6%</td>
</tr>
<tr>
<td>South and East Asia</td>
<td>6.5-54.6%</td>
</tr>
<tr>
<td>Africa</td>
<td>3.4-31.6%</td>
</tr>
<tr>
<td>Latin America</td>
<td>1.2-10.7%</td>
</tr>
</tbody>
</table>

Barada et al; Gastrointestinal Endoscopy Clinics of North America, 2012
Prevalence of CD among 1000 patients presenting for UGI endoscopy at AUBMC

- 1.4-1.8%

- Majority responded to a GFD

  - Barada et al; Endoscopy, 2014
How often do patients respond to a GFD?

- 70-93% of patients with CD
- Primary non-responsive CD (NRCD)
  - Initial failure to respond to GFD
- Secondary non-responsive CD (NRCD)
  - Re-emergence of symptoms after initial normalization while maintaining GFD

- Leffler et al., CGH, 2007
What is non responsive CD (NRCD)?

- Persistent symptoms in patients prescribed GFD
- Occurs in 7-30% of patients
- The most common cause is continued intentional or inadvertent exposure to gluten
- All patients with NRCD need re-biopsy
Most patients with non-responsive CD do not have RCD
Woodward J et al, 2013

- Poor adherence to GFD (in 45% of patients)
- Differential sensitivity to gluten
- Symptoms unrelated to gluten
  - IBS
  - Bile salt mal-absorption
  - Colon cancer
- Lactose intolerance
- Pancreatic insufficiency
- Bacterial overgrowth
- Lymphocytic colitis
A 49 year woman presents with intermittent watery diarrhea and bloating of two years duration. PMH and PE are negative. Labs reveal a Hct of 33% with an MCV of 71. TFTs and stool studies are negative. Anti-endomysial antibody is positive and anti-tTG is strongly positive. Duodenal biopsy revealed mild villous atrophy and increased IEL at 50/100 epithelial cells. You diagnose CD and prescribe a GFD. Six months later she comes back to you with persistent symptoms and says “your diet” is not working. Repeat serology and histopathology are unchanged. Which of the following best characterizes this patient’s condition:

- She does not have CD
- **She has primary non-responsive CD**
- She has secondary non-responsive CD
- She has refractory CD type I (RCD I)
- She has refractory CD type II (RCDII)
RCD: definition

- **Persistent mal-absorption, malnutrition, and villous atrophy despite adherence to a gluten free diet (GFD) under the supervision of a professional dietitian for at least 12 months**

- **Diagnosis is made after excluding other causes of villous atrophy, and after excluding malignancies complicating CD**
Diagnosis of RCD requires exclusion of other causes of villous atrophy

- Tropical sprue
- Autoimmune enteropathy
- Common variable immunodeficiency
Clinical profiles of other causes of villous atrophy?
Malamut G et al, GECNA, 2012

- **Autoimmune enteropathy**
  - Rare
  - Chronic diarrhea and weight loss
  - Negative CD serology and HLA genotypes
  - Positive anti-enterocyte and anti-goblet cell antibodies
  - No response to GFD
  - Requires immunosuppressive therapy (steroids, ...)

- **Tropical sprue**
  - Living in or coming from tropics
  - Diarrhea, weight loss, megaloblastic anemia
  - Villous atrophy, but negative CD serology and HLA genotypes
  - Responds to antibiotics (tetracycline) plus folic acid

- **Common variable immunodeficiency**
  - Chronic diarreha and malabsorption
  - Villous atrophy
  - Depletion of plasma cells, and lymphoid hyperplasia
  - Responds to steroids and Ig
    - Malamut G et al, Am J Gastroenterol., 2010
Prevalence of RCD among CD patients in various countries
APT, 2014

<table>
<thead>
<tr>
<th>Country</th>
<th>CD number</th>
<th>RCD, n</th>
<th>RCD prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>ND</td>
<td>ND</td>
<td>5 %</td>
</tr>
<tr>
<td>Netherlands</td>
<td>158</td>
<td>11</td>
<td>7 %</td>
</tr>
<tr>
<td>US</td>
<td>603</td>
<td>10</td>
<td>1.7 %</td>
</tr>
<tr>
<td>UK</td>
<td>713</td>
<td>ND</td>
<td>0.7 % (RCD II)</td>
</tr>
<tr>
<td>US</td>
<td>204</td>
<td>3</td>
<td>1.5 %</td>
</tr>
<tr>
<td>US</td>
<td>844</td>
<td>34</td>
<td>4 %</td>
</tr>
<tr>
<td>US</td>
<td>700</td>
<td>73</td>
<td>10 %</td>
</tr>
<tr>
<td>Finland</td>
<td>12240</td>
<td>38</td>
<td>0.3 %</td>
</tr>
</tbody>
</table>
### Two types of RCD

<table>
<thead>
<tr>
<th>RCD I</th>
<th>RCD II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractoriness to GFD</td>
<td>Refractoriness to a GFD</td>
</tr>
<tr>
<td>Normal phenotype of IELs</td>
<td>Abnormal phenotype of IELs</td>
</tr>
<tr>
<td>Similar to active CD</td>
<td>Ulcerative jejunitis in 70% of patients</td>
</tr>
<tr>
<td>Autonomy towards gluten exposure</td>
<td>A low grade lymphoma</td>
</tr>
<tr>
<td>malnutrition</td>
<td>Risk of EATL 50% at 5 years</td>
</tr>
<tr>
<td>Risk of EATL 14% at 5 years</td>
<td>Severe malnutrition</td>
</tr>
<tr>
<td>Risk of collagenous sprue</td>
<td>Risk of collagenous sprue</td>
</tr>
<tr>
<td>Fair to good prognosis</td>
<td>Poor prognosis</td>
</tr>
</tbody>
</table>
What are risk factors for RCD?
Cellier et al, 2012

- Generally not known
- Homozygosity for HLA-DQ2
  - In 21% of patients with uncomplicated CD
  - In 44% of patients with RCD I
  - In 53% of patients with RCD II
- Poor adherence to a GFD
RCD: poor outcome is common

- High risk of developing enteropathy associated T cell lymphoma (EATL)
- Malnutrition that may be severe
- High morbidity and mortality
# Clinical characteristics of RCD patients: a large study from Finland (APT, 2014)

<table>
<thead>
<tr>
<th></th>
<th>RCD I, n=44</th>
<th>RCD II (n=10)</th>
<th>Regular CD, n=866</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>59%</td>
<td>50%</td>
<td>76%</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean age</td>
<td>56</td>
<td>59</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seronegativity</td>
<td>30%</td>
<td>20%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight loss</td>
<td>36%</td>
<td>70%</td>
<td>16%</td>
<td>0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54%</td>
<td>90%</td>
<td>38%</td>
<td>0.05</td>
</tr>
<tr>
<td>Family history of CD</td>
<td>28%</td>
<td>10%</td>
<td>66%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of GFD</td>
<td>13 y</td>
<td>10 y</td>
<td>10 y</td>
<td>0.017</td>
</tr>
<tr>
<td>% of pts. on strict GFD</td>
<td>80%</td>
<td>60%</td>
<td>96%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancies</td>
<td>16%</td>
<td>20%</td>
<td>5%</td>
<td>0.002</td>
</tr>
</tbody>
</table>
The same patient presents 18 months later with worsening diarrhea & progressive weight loss. She had been on a strict GFD under the supervision of a dietitian. Duodenal biopsies revealed villous atrophy and 55 IELs/100 epithelial cells. Work-up for causes of NRCD and other causes of villous atrophy is (-). You suspect she has RCD. The best thing to do is:

- Begin systemic steroids
- Begin systemic chemotherapy
- Do CT enterography and determine phenotype of IELs on intestinal biopsies
- Refer for stem cell transplantation
Diagnosis of RCD: is it type I or type II?

- Image the small intestines: are there strictures, ulcers or masses?
  - CT/MR enterography
  - Capsule endoscopy
  - Balloon enteroscopy
- Obtain adequate biopsies for histopathology
- Determine phenotype of IELs
  - Flow cytometry
  - Immunohistochemistry
  - T cell receptor chains clonal rearrangement by PCR
Video capsule endoscopic images of CD and RCD I & II
Strictures in RCDII by capsule endoscopy
Stricture in RCDII by balloon enteroscopy
EATL in a 65 y old man with RCD II on MRE
What are IELs and what do they do?

- Normal people have IELs (less than 25/100 epithelial cells)
- IELs maintain integrity of epithelium
- IELs normally comprise:
  - NK cells
  - αβ T-cell receptor (TCR) CD4+ T cells
  - αβ T-cell receptor (TCR) CD8+ T cells
  - γδ TCR T cells
- Patients with uncomplicated CD have > 25-30 normal IELs /100 epithelial cells
# Intraepithelial lymphocytes in RCD

<table>
<thead>
<tr>
<th>RCDI</th>
<th>RCDII</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Increased</td>
<td>- Increased</td>
</tr>
<tr>
<td>- Normal</td>
<td>- Abnormal &amp; monoclonal</td>
</tr>
<tr>
<td>- Express surface CD3</td>
<td>- Don’t express surface CD3</td>
</tr>
<tr>
<td>- Express surface CD8</td>
<td>- Don’t express surface CD8</td>
</tr>
<tr>
<td>- Express surface CD 103</td>
<td>- Don’t express T cell receptor</td>
</tr>
<tr>
<td></td>
<td>- Express <em>intracellular</em> CD3</td>
</tr>
<tr>
<td></td>
<td>- Decrease in γδ TCR expressing IELs</td>
</tr>
</tbody>
</table>
How do you find out if intraepithelial lymphocytes are abnormal?

- Flow cytometry
- Immunohistochemistry
- Genetic analysis of T-cell receptor clonality (also called T cell receptor (TCR) rearrangement studies)
  - Two modalities are generally needed
What are the specific criteria to diagnose RCDII?

- > 25% of CD103+ or CD45+ IELs lack surface CD3- T-cell receptors (TCR) on flow cytometry done on fresh frozen intestinal tissue OR

- > 50% of IELs expressing intracytoplasmic CD3, but not CD8 in formalin fixed tissue sections AND/OR

- Clonal rearrangement of the gamma chain of the T cell receptor (TCR) by PCR on duodenal biopsies
Lack of surface CD3 on flow cytometry in RCDII
Malamut et al, GECNA, 2012

Abnormal population of IEL
Celiac disease nonresponsive to a gluten free diet

Validation by a dietitian

Celiac Ab present at CD diagnosis
HLA DQ2/DQ8

Other causes of villous atrophy:
- Tropical sprue (breath test +)
- Primitive hypogammaglobulinemia (low IgA, IgG, IgM)
- Autoimmune enteropathy (anti-enterocytes Ab; anti-AIE 75 KD Ab)
- Others

Small bowel MRI/CT-scan
PET-Scan
Capsule endoscopy
Upper Endoscopy/Enteroscopy

Fresh Biopsy Isolation + FACs
CD3S- CD8- IEL>25%

Paraffin Biopsy Histochemistry CD3i+
CD8- IEL>50%

Frozen Biopsy Multiplex PCR
Clonal rearrangement of TCR

RCDI

RCDII
The same patient presents 18 months later with worsening diarrhea & progressive weight loss. She had been on a strict GFD under the supervision of a dietitian. Duodenal biopsies revealed villous atrophy and 55 IELs/100 epithelial cells. Work-up for causes of NRCD and other causes of villous atrophy is (-). You suspect she has RCD. The best thing to do is:

- Begin systemic steroids
- Begin systemic chemotherapy
- Do CT enterography and determine phenotype of IELs on intestinal biopsies
- Refer for stem cell transplantation
Case scenario (3)

- You diagnose the same patient with RCDII. She does not have EATL at this time. She wants to know what effective therapy she can get based on RCTs. She is mainly interested in decreasing her risk of EATL and improving her nutritional status. The best answer is:
  - Systemic steroids
  - Budesonide
  - Azathioprine
  - Cladribine
  - Stem cell transplantation
  - None of the above
Management of RCD I

- Make sure the patient is on a GFD
- Correct nutritional deficiencies
- Symptomatic anti-diarrheal agents
- No published RCTs!
- Drugs
  - Systemic steroids
  - Budesonide
  - Mesalamine
  - Azathioprine
Management of RCDII

- Similar to RCDI but less likely to succeed
- Severe malnutrition: consider TPN
- No published RCTs!
- Drug therapy
  - Cyclosporine?
  - Cladribine (a purine analogue)?
  - High dose chemotherapy with stem cell support (autologous stem cell transplantation)?
  - Anti-IL15? IL 15 is produced in excess and has anti-apoptotic effects!
You diagnose the same patient with RCDII. She does not have EATL at this time. She wants to know what effective therapy she can get based on RCTs. She is mainly interested in decreasing her risk of EATL and improving her nutritional status. The best answer is:

- Systemic steroids
- Budesonide
- Azathioprine
- Cladribine
- Stem cell transplantation
- None of the above
Case scenario (4)

- One year later, the patient is diagnosed with EATL in an ulcerated stricture in the proximal jejunum. She wants to know the best therapeutic regimen. The best answer is:
  - Chemotherapy
  - Surgical reduction
  - Chemotherapy and surgical reduction
  - Radiotherapy
Predictors of worse prognosis in EATL

**Analysis**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio [95 CI]</td>
<td>P</td>
</tr>
<tr>
<td>Stage (IV vs I/IIE)</td>
<td>1.6 [0.7-3.5]</td>
<td>0.237</td>
</tr>
<tr>
<td>Enteropathy (clonal vs non clonal)</td>
<td>4.2 [1.7-10]</td>
<td>0.0007</td>
</tr>
<tr>
<td>Serum albumin level (&lt;21.6 g/L vs &gt;21.6 g/L)</td>
<td>8.5 [3.2-22.4]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chemotherapy (- vs +)</td>
<td>14 [3.8-51]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reductive Surgery (- vs +)</td>
<td>5.1 [2.1-12.5]</td>
<td>&lt;0.0001</td>
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One year later, the patient is diagnosed with EATL in an ulcerated stricture in the proximal jejunum. She wants to know the best therapeutic regimen for her condition. The best answer is:

- Chemotherapy
- Surgical reduction
- **Chemotherapy and surgical reduction**
- Radiotherapy
Summary

* RCD is rare
* RCD is different from NRCD
* RCDII is differentiated from RCDI by the presence of abnormal IELs
* RCDII has a poor prognosis due to:
  - Malnutrition
  - High risk of EATL
Thank you
Approach to NRCD
BSG guidelines, GUT, 2014

NRCD

- Review diagnosis – review biopsy, serology and HLA status
  - Not CD on review

  Diagnosis confirmed

  - Not adherent, consult dietician

  Review dietary adherence

  Adherent

  Repeat upper GI endoscopy, biopsy, aspirate
  Colonoscopy and biopsy
  Stool culture
  Faecal elastase
  Thyroid function

  Exclude Giardia/ pathogen
  Microscopic colitis
  Exocrine pancreatic insufficiency
  Hyperthyroidism
  SIBO

  Consider wheat free gluten free diet
  Fructose intolerance
  Lactose intolerance
  Consider FODMAPs
How do you demonstrate the presence of aberrant IELs?
Schematic representation of IL-15 lymphomagenic action leading to the emergence of EATL in CD. In active CD mucosa, IL-15, mainly produced by epithelial cells and dendritic cells (DCs), which present tissue transglutaminase (tTG)-deamidated gluten peptides ...