Diagnostic approach to Refractory Coeliac Disease & its complications

Prof Kieran Sheahan
Pathology Dept,
Centre for Colorectal Disease
St Vincent’s University Hospital
Dublin Academic Medical Centre & UCD
What is Refractory coeliac disease?

Refractory sprue or refractory coeliac disease (RCD) is defined by:

Â Persistent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for at least 6 -12 months

Â Absent are other causes of non-responsive coeliac disease and overt malignancy

Â ‘Unclassified sprue’ - the underlying malabsorptive disorder is not adequately defined
Prevalence of refractory sprue among patients with coeliac disease

- The real prevalence of RCD is unknown but is probably rare
- 0.7% - 1.5% of patients with Coeliac Disease (non-referral population-based cohorts)
- More common in women
- Most cases diagnosed after age 50

West J. Celiac Disease and Its Complications: A Time Traveller’s Perspective Gastroenterology 2009 136: 32-4
Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease
Gut 2010 59: 547-557
Coeliac Disease

- Coeliac disease (CD) is a gluten-sensitive enteropathy characterized by villous atrophy, which is reversed by gluten withdrawal
- Genetically susceptible individuals (99% HLA-DQ2 or HLA-DQ8)
- Classical presentation: Steatorrhea, weight loss or other signs of nutrient or vitamin deficiency
- Coeliac disease may be clinically occult and may not be detected until late adulthood
Coeliac Disease in Ireland

- Coeliac disease is common in the Irish and in those of Irish descent.
- Approx. 1% of population
- Genetic gradients, largely determined by the advance of agriculture, and historical patterns of cereal ingestion.

Cronin, C, Shanahan, Fergus. Why is Celiac Disease So Common in Ireland? Perspectives in Biology and Medicine, 2001;44,342-352
Coeliac Disease

- NOT a histological diagnosis
- BUT histology is the gold standard and is required to support other features
  - anti-gliadin antibodies
  - anti-endomysial antibodies (EMA)
  - anti-tissue transglutaminase antibodies (TTG)
  - HLA-DQ2 and/or DQ8
  - response to gluten exclusion
  - gluten challenge
Response to GFD

- Clinically - a marked symptomatic improvement may occur within several days of starting GFD
- Mucosal improvement may continue for up to 2 years
Recurrent Symptoms May Occur In Established Coeliac Disease

Å Poor compliance with a strict GFD
  (may be unintentional)
Å Wrong initial diagnosis
Å (consider other causes of villous atrophy)
Å Associated or second cause of symptoms
  e.g. microscopic colitis
Å Superimposed complication
  e.g. collagenous sprue
Presentation of Refractory Sprue/Refractory Coeliac Disease

- Persistent diarrhoea, abdominal pain, and involuntary weight loss
- Multiple vitamin deficiencies
- Anaemia, fatigue, malaise
Refactory Coeliac Disease Patients

- The majority of patients with RCD experience initial clinical improvement on a GFD, but, after a period of remission, develop disease refractory to gluten abstinence (‘secondary RCD’)

- Patients who have no initial response to a GFD (‘primary RCD’ or ‘unclassified sprue’)
The first step in the diagnosis of RCD is to confirm the initial diagnosis of CD.

Confirm gluten abstinence.

Rule out other causes of villous atrophy.
Causes of Villous Atrophy

- Coeliac disease
- Tropical sprue
- Giardiasis
- Infectious enteritis
- Small bowel bacterial overgrowth
- Microscopic colitis
- Eosinophilic gastroenteritis
- Graft-versus-host disease
- Cow's milk and soy protein enteropathy
- Abetalipoproteinaemia
- Small bowel ischaemia
- Intestinal lymphoma
- Tuberculosis
- Crohn's disease
- Parasitic infestation
- Severe malnutrition
- Adult onset autoimmune enteropathy
- Common Variable Immunodeficiency
- HIV enteropathy
- Chemotherapy and radiation enteritis
Pathological investigation of RCD
Abnormal Intraepithelial Lymphocyte Detection

- Double CD3/CD8 immunohistochemistry
- T cell receptor clonal rearrangement by PCR
- Immunophenotyping using flow cytometry
Refractory Coeliac Disease

Clonal intraepithelial T-lymphocytes?
- >50% IELs with abnormal immunophenotype (CD3+ CD8-) by IHC
- > 20% ‘aberrant’ IELS (express cytoplasmic CD3ε, but lack surface expression CD3, CD4 and CD8) by flow cytometry
- Clonal T cell receptor gene rearrangement by molecular analysis

No

Refractory Coeliac Disease Type 1

Yes

Refractory Coeliac Disease Type 2
• Five-year survival higher in the type 1 group (96 vs 58 %).
• Most deaths (half) were due to development of T-cell lymphoma
• No patient with type 1 disease developed type 2 disease
Reliable identification of RCD type 2 patients can be difficult

Continual monitoring of both immunophenotype and clonality of IELs may be more accurate than once-off analysis for establishing RCD subtype and prediction of risk of lymphoma

Liu H, Brais R, Lavergne-Slove A et al. Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease. Gut 2010;59:452-460
Investigation of molecular markers in the diagnosis of refractory coeliac disease in a large patient cohort

U O'Shea, M Abuzakouk, C O'Morain, D O'Donoghue, K Sheahan, P Watson, S O'Brien, D Alexander, M Gatherwood, J Jackson, J Kelly and C Feighery

*J. Clin. Pathol.*, 2008;61;1200-1202

Table 1  Demographic and clinical details of patients with refractory coeliac disease

<table>
<thead>
<tr>
<th></th>
<th>Abnormal IEL ratio (n = 20)</th>
<th>Normal IEL ratio (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M</td>
<td>12/8</td>
<td>12/6</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>53 (35–72)</td>
<td>58 (27–84)</td>
</tr>
<tr>
<td>TCR clonality</td>
<td>5 (7 tested)</td>
<td>2 (7 tested)</td>
</tr>
<tr>
<td>IEL ratio &lt;25%</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>IEL ratio &lt;50%</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Marsh III lesion</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EATL</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Ulcerative jejunitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Died</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>
Treatment Options

Å RCD type 1 - prednisone, budesonide or combination of prednisone and azathioprine are beneficial
Å No established treatments for RCD type 2
Å Chemotherapeutic drugs alone or high-dose chemo followed by autologous stem cell transplantation for selected patients with RCD type 2
Å Future novel therapies, such as interleukin 15 blockade?

### WHO classification EATL, 2008

<table>
<thead>
<tr>
<th></th>
<th>Type I EATL</th>
<th>Type II EATL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>80-90%</td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td>Variable</td>
<td>Monomorphic; small to medium</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8</td>
<td>Mostly negative (20%+)</td>
<td>Mostly positive (80%)</td>
</tr>
<tr>
<td>CD56</td>
<td>Negative (&gt;90%)</td>
<td>Positive (&gt;90%)</td>
</tr>
</tbody>
</table>

Type II EATL may occur sporadically, without risk factors for coeliac disease. It has a distinct immunophenotype: CD3+, CD4-, CD8+, CD56+ and TCRβ+.
DIFFERENTIAL DIAGNOSES:
Common Variable Immune Deficiency

- CVID can display features similar to those of coeliac disease
- Villous atrophy in 24% to 53% of duodenal samples from patients
- Increased IELs (53%).
- CVID patients often show markedly decreased or absent plasma cells

Autoimmune Enteropathy

Autoimmune enteropathy is a rare cause of intractable diarrhoea associated with circulating gut autoantibodies and a predisposition to autoimmunity.

Adults and children

Histologically similar to coeliac disease

IgA and IgG anti-enterocyte antibodies

Other organ-specific autoantibodies

No coeliac-related autoantibodies

Steroid responsive
Figure 1. Anti-enterocyte antibodies. Indirect immunofluorescence with the patient’s serum on frozen section of normal human small bowel shows a linear fluorescence pattern along the brush border of the enterocytes (original magnification, 300×).
Collagenous sprue

- Rare form of small bowel enteropathy.
- Pathologic lesion consists of subepithelial collagen deposition associated with variable alterations in villous architecture.
- Characterised clinically by chronic diarrhoea and progressive malabsorption.
- It has traditionally been associated with significant morbidity
- 5 new cases of collagenous sprue and extensive literature review

- 13/30 patients died from complications of disease

- 7 cases of collagenous sprue.

- Clonal TCR gamma configurations were found in 5/6

- 3 of these patients died from malnutrition.
12 cases (8 females), 41-84 yrs

6 patients improved clinically with combination of GFD and immunosuppressant drugs; histologic improvement in 3/6.

1 patient died of another illness, 2 died of collagenous sprue complications

Only 4 had coeliac disease
Varying degrees of villous atrophy
Lamina propria cells and capillaries entrapped in collagen
Epithelial detachment
# TABLE 2. Histologic Features

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Villous Morphology</th>
<th>Subepithelial Collagen Band [Maximum Thickness (µm)]</th>
<th>Intraepithelial Lymphocytes (Per 100 Enterocytes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Total villous atrophy</td>
<td>110</td>
<td>53</td>
</tr>
<tr>
<td>Case 2</td>
<td>Subtotal villous atrophy</td>
<td>95</td>
<td>7</td>
</tr>
<tr>
<td>Case 3</td>
<td>Partial villous atrophy</td>
<td>140</td>
<td>9</td>
</tr>
<tr>
<td>Case 4</td>
<td>Partial villous atrophy</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Case 5</td>
<td>Partial villous atrophy</td>
<td>190</td>
<td>15</td>
</tr>
<tr>
<td>Case 6</td>
<td>Subtotal villous atrophy</td>
<td>120</td>
<td>40</td>
</tr>
<tr>
<td>Case 7</td>
<td>Subtotal villous atrophy</td>
<td>260</td>
<td>12</td>
</tr>
<tr>
<td>Case 8</td>
<td>Partial villous atrophy</td>
<td>170</td>
<td>9</td>
</tr>
<tr>
<td>Case 9</td>
<td>Partial villous atrophy</td>
<td>90</td>
<td>7</td>
</tr>
<tr>
<td>Case 10</td>
<td>Subtotal villous atrophy</td>
<td>120</td>
<td>7</td>
</tr>
<tr>
<td>Case 11</td>
<td>Partial villous atrophy</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Case 12</td>
<td>Partial villous atrophy</td>
<td>150</td>
<td>53</td>
</tr>
</tbody>
</table>
# IMPORTANT TO BIOPSY COLON & STOMACH

<table>
<thead>
<tr>
<th>Small bowel histology</th>
<th>Gastric histology (4/7 bx)</th>
<th>Colonic histology (7/9 bx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagenous sprue</td>
<td>Collagenous gastritis</td>
<td>Collagenous colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphocytic colitis</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>Chronic gastritis</td>
<td>No biopsy</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td><strong>Lymphocytic gastritis</strong></td>
<td>Normal colonic biopsy</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>No biopsy</td>
<td>Normal colonic biopsy</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td><strong>Collagenous gastritis</strong></td>
<td>Collagenous colitis</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>Normal antral biopsy</td>
<td>No biopsy</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>No biopsy</td>
<td><strong>Collagenous colitis</strong></td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>No biopsy</td>
<td>Collagenous colitis</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>No biopsy</td>
<td>Collagenous colitis</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td><strong>Collagenous gastritis</strong></td>
<td>Collagenous colitis</td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>Reactive gastropathy</td>
<td><strong>Collagenous colitis</strong></td>
</tr>
<tr>
<td>Collagenous sprue</td>
<td>No biopsy</td>
<td>No biopsy</td>
</tr>
<tr>
<td>Ulcerative jejuno-ileitis</td>
<td>No biopsy</td>
<td>No biopsy</td>
</tr>
</tbody>
</table>
No patient has developed lymphoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sample</th>
<th>Method</th>
<th>Result</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Jejunum, ileum, right and left colon</td>
<td>PCR</td>
<td>Monoclonal T-cell population (left colon only)</td>
<td>Clinical improvement with steroids</td>
</tr>
<tr>
<td>Case 3</td>
<td>1. Duodenum</td>
<td>PCR</td>
<td>Polyclonal T-cell population in duodenum.</td>
<td>Clinical improvement with GFD and steroids</td>
</tr>
<tr>
<td></td>
<td>2. Peripheral blood</td>
<td></td>
<td>Monoclonal T-cell population in peripheral blood.</td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>Duodenum</td>
<td>PCR</td>
<td>Monoclonal T-cell population</td>
<td>Died from complications of malnutrition</td>
</tr>
<tr>
<td>Case 6</td>
<td>Duodenum</td>
<td>PCR</td>
<td>Bi-clonal T-cell population</td>
<td>Clinical improvement with steroids and azathioprine</td>
</tr>
<tr>
<td>Case 7</td>
<td>Small bowel</td>
<td>PCR</td>
<td>Polyclonal T-cell population</td>
<td>Died from <em>Aspergillus</em> peritonitis after insertion of PEG tube</td>
</tr>
<tr>
<td>Case 12</td>
<td>1. Small bowel</td>
<td>PCR</td>
<td>Polyclonal T-cell population in duodenum.</td>
<td>Clinical improvement after partial small bowel resection and Continued GFD.</td>
</tr>
<tr>
<td></td>
<td>2. Peripheral blood</td>
<td>PCR</td>
<td>Monoclonal T-cell population in peripheral blood.</td>
<td></td>
</tr>
</tbody>
</table>

GFD indicates gluten-free diet; PCR, polymerase chain reaction; PEG, percutaneous enterogastrostomy.
Collagenous sprue is not always associated with dismal outcomes: a clinicopathological study of 19 patients

Efsevia Vakiani¹, Carolina Arguelles-Grande², Mahesh M Mansukhani³, Suzanne K Lewis², Heidrun Rotterdam³, Peter H Green² and Govind Bhagat³

Â 8 /19 (42%) responded to GFD, and 10 responded to immunosuppressive therapy.
Â One patient with type 2 RCD died
Â Patients who did not respond to GFD were more likely to have moderate (10-20μm) or marked (20μm) fibrosis
Clinical response to GFD and immunosuppression in 24/30 (80%). Histologic improvement in 9/30 patients.

1 patient died of CS complications

Sub-epithelial collagen deposition in colon or stomach in 25% patients

Thickness of collagen band did not correlate with response to treatment

Thickness >20μm correlated with a severe clinical syndrome.
Gluten-Free Diet and Steroid Treatment Are Effective Therapy for Most Patients With Collagenous Sprue

ALBERTO RUBIO-TAPIA, NICHOLAS J. TALLEY, SURRAKANIT R. SURUDU, TSUNG-TEH WU,* and JOSEPH A. MURRAY

Triggers
- Celiac disease
- Autoimmune enteropathy
- Hypogammaglobulinemic sprue
- Tropical sprue
- Other stimuli (?)

Environmental factors (?)
- Drug
- Infection
- Gluten or other food antigens

Gut inflammation
- Epithelial damage

Susceptible host
- Genetic susceptibility (?)

Stimulation of gut myofibroblast
- ↑ Collagen synthesis
- ↓ Degradation (?)

Fibrogenic response

Outcomes
- Persistent inflammation and fibrosis
- Complete remission
- Reversion of fibrosis with persistent inflammation
- Progression to lymphoma
- Death

Management
- Specific treatment (if available)
- Anti-inflammatory therapy

Figure 3. Possible mechanisms of the pathogenesis of CS.
Conclusions
Malabsorption

When patients fail to respond to GFD:

- Revisit and confirm initial diagnosis of CD
- Confirm adherence to GFD
- Exclude rare causes of villous atrophy
Conclusions
Refractory coeliac disease

- Discrimination between RCD type 1 and 2 is important for prognosis and treatment.
- Type 1 RCD is a treatable condition, and responds well to steroids.
- Type 2 RCD is associated with a poor prognosis and a high risk of lymphoma.
Conclusions

Collagenous sprue

- May be a histological pattern associated with several immune-mediated GI diseases, most commonly coeliac disease
- May be associated with collagen deposition in other parts of the GIT
- Most patients respond to a combination of GFD and immunosuppressive drugs
ACKNOWLEDGEMENTS

DR AOIFE MAGUIRE

PROF D O’DONOGHUE

SVUH