Management of Patients with Refractory Coeliac Disease

Paul J. Ciclitira and Alastair Forbes

Abstract

Coeliac disease (CD) is an immune-mediated disorder affecting the small intestine. The condition represents an intolerance to gluten. Removal of dietary gluten permits recovery, with a full recovery for the majority of affected subjects. A percentage of affected subjects who do not improve with a gluten-free diet are considered to have refractory coeliac disease (RCD). Refractory coeliac disease is subdivided into type 1, characterised by a polyclonal expansion of intraepithelial lymphocytes (IELs) that have a normal phenotype, and type 2 (RCD2) which exhibits IELs with a monoclonal phenotype. Subjects with RCD carry a high risk of complications, including ulcerative jejunitis and lymphoma affecting the small intestine, the latter termed enteropathy-associated T-cell lymphoma (EATL).

Keywords: coeliac disease, refractory coeliac disease, presentation, diagnosis and treatment

1. Introduction

Coeliac disease (CD) represents an enteropathy affecting the small intestine that is exacerbated by gluten in wheat, rye and barley. The condition occurs in genetically susceptible individuals who carry either the HLA DQ2 or DQ8 genotype. [1] The prevalence of the condition, of which there is increasing awareness, is 1–2% in the US and Northern Europe. [2, 3]. Treatment of the condition comprises a gluten-free approach that involves removal of wheat, rye and barley from the diet. However, between 5 and 30% of affected subjects do not fully respond to a gluten-free diet, [2–6] and are considered to have refractory coeliac disease (RCD).

The precise diagnosis of RCD presents challenges, but is important in the development of new therapeutic strategies. [7–9]

2. Pathogenesis of RCD

Gluten proteins from wheat, rye and barley are divided into different groups. Wheat gluten comprises gliadin and glutenin. There are α, β, γ and ω gliadin fractions, and glutenin is composed of low and high molecular weight glutenins (HMWG). All these components of wheat gluten have been shown to be toxic to subjects with CD. [9]

In CD there is increased permeability of the small intestine associated with an increase in zonulin, a protein found between enterocytes that has been reported
to be a modulator of tight junction permeability. [10, 11] It has been hypothesised that zonulin release induces increased absorption, into the lamina propria below the epithelium, of CD-toxic gluten fractions. The resultant gluten peptides in the lamina propria "stimulate aberrant adaptive and innate responses resulting in damage to the enterocytes, with infiltration of the mucosa by both intra-epithelial lymphocytes (IELs) and CD4 +ve lamina propria lymphocytes". Most of the increased number of IELs are CD3 + ve/CD8 + ve cells that express the α/β T-cell receptor (TCR), and a minority are γ/δ +ve (TCR)-expressing lymphocytes.

The adaptive response involves binding of the CD toxic peptides to HLA-DQ2 or HLA-DQ8. These reactive CD4 T-cells in the lamina propria recognise toxic gluten peptides and proteins. [12, 13] There is recognition of the gluten peptides bound to HLA-DQ2/DQ3, and to antigen presenting cells (APCs); this is enhanced by the enzyme tissue transglutaminase (tTg) that deamidates glutamine residues to glutamic acid [12]. Following activation of the T-cells, pro-inflammatory cytokines, including interferon-γ, are released. This in turn results in an inflammatory cascade, particularly affecting the proximal small intestine, that causes the observed villous atrophy [13].

The innate immune response appears to be mediated by IELs, enterocytes and dendritic cells, and is centred on increased secretion of the cytokine interleukin-15 (IL–15) [14]. It is possible that IL–15 production by enterocytes and dendritic cells is induced directly by gluten peptides. IL–15 stimulates the expression of MICA (a stress molecule) on enterocytes, and NKG2D (a natural killer receptor) on IELs. The IEL–induced NKG2D expression serves as an activating receptor with many ligands, including MICA [15]. In combination there may then be substantial cytotoxicity to enterocytes and thus the intestinal damage that is typical of CD.

It seems likely that RCD and uncomplicated CD have similar aetiopathogenic pathways. [14, 16] Most patients with RCD have increased levels of antigliadin and endomysial antibodies, although in RCD2 coeliac serology may become negative. Differentiation between RCD1 and RCD2 is based on evidence of either the polyclonal expansion of T-cells expression that occurs in RCD1, or the monoclonal expansion of T-cells in small intestinal biopsies or separated T-lymphocytes that can be demonstrated using double CD3/CD8 immuno-histochemistry in RCD2. An investigation of T-cell receptor clonal arrangements can be investigated by polymerase chain reaction on fresh tissue or by flow cytometry. [17–20]

The mechanisms behind the clonal expansion of T-cells in RCD2 are not well understood but there are several possibilities under active consideration. Genetic variation in the myosin IXB gene (MY09B) located on chromosome 19, has been proposed as a possible aetiopathological factor. [21] There is increased repairing of MICA and c-myc by the enterocytes [21–26]. An increase in IgM, Charcot-Leyden crystal proteins and apolipoprotein are observed and thought to be damaging in RCD2. [25] APO C3 apolipoprotein is also known to affect immunosurveillance cells, such as natural killer (NK) cells, and was singled out as potentially important in sustaining T-cell proliferation. [27]

IL–15 is overexpressed in untreated CD, and it is thought to play a pivotal role in the regulation of the IELs that characterise the disease and hence in in the pathogenesis of RCD. IELs show increased expression of IL–15Ra, elevated proliferation cytokine production and a reduction in apoptosis. [19]. It has been suggested also that IL–15 may induce the emergence of a clonal expression [19]. This multistep transformation may generate the pre-lymphomatous state and then progress to overt T-cell lymphoma [27]. Inhibition of IL–15 may have therapeutic value in RCD2 (see below) adding further weight to its suspected pathogenic importance.
3. Clinical features of RCD

3.1 Type 1 refractory coeliac disease

Patients with RCD1 may present with any combination of steatorrhoea, altered bowel habit (with both constipation and diarrhoea), abdominal pain, nausea, fatigue and weight loss [28]. RCD1 is also associated with thromboembolic infectious complications and autoimmune diseases. The radiological features on CT or MR scanning are similar to those of untreated CD, with increased ileal folds and decreased jejunal folds [29].

Patients with RCD1 exhibit Marsh type II or III appearances. [30] Both of these pathological gradings include villous atrophy. There is a moderate lymphoplasmacytic infiltrate in the lamina propria. [26] Collagen deposition (collagenous sprue) has been reported in 40% of patients with RCD1 [31]; this can be confirmed with a trichrome stain. Mucosal thinning with villous atrophy and crypt hyperplasia was reported in 30% of these patients.

The RCD1 IEL phenotype is equivalent to uncomplicated CD, with the majority of cells expressing CD3, CD7, CD8, CD103, and TCRβ. TCR gene rearrangement studies confirm that RCD1 cells constitute a polyclonal population. [28–32]

3.2 Type 2 refractory coeliac disease

RCD2 patients present with similar symptoms to those with RCD1, including malabsorption, weight loss, abdominal pain and diarrhoea. Most patients are aged 50–60. [28] The CT/MR appearances are similar to those in RCD1, but frequently also include lymphadenopathy, intussusception and hyposplenism. [29]

The standard histology of RCD2 mirrors RCD1, with the majority of patients demonstrating a degree of villous atrophy [30]. The cytological appearances of the IELs are normal. Cellier et al. [14] proposed that RCD2 (their refractory sprue) was associated with an abnormal subset of IELs that, on frozen section, were positive for CD103, CD7, and cytoplasmic CD3, but not for surface CD3, CD4, CD8, or TCRβ. This difference from RCD1 has contributed to the concept that RCD2 represents an early stage in the development of lymphoma. Aberrant IELs may also be found in gastric and colonic mucosa, and in the blood of RCD2 patients, implying that this is a diffuse gastrointestinal disease. The IELs in RCD2 patients rarely exhibit a normal CD3 + ve, CD8 + ve phenotype, and the majority have a CD3 + ve CD8 -ve pattern. However Goerres et al. [22] reported only a low frequency of loss of CD8 expression, and it is advocated that flow cytometry should be used to diagnose the condition.

Although a polyclonal IEL population has been reported in a very small proportion of RCD2 cases, it is usual to find monoclonality with a restricted rearrangement of the TCRβ gene when clonality studies are performed in RCD2.

4. Complications of RCD

4.1 Ulcerative Jejunitis

Most cases of ulcerative jejunitis (UJ) are preceded by problematic CD, such that UJ can be said to evolve from RCD. The mean age at onset of UJ is 50 years. The defining features are ulcerative lesions that are usually multifocal and which can involve the ileum as well as the jejunum. Presenting features include diarrhoea,
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steatorrhoea, abdominal pain and weight loss. There may be low grade fever, clubbing and nutritional deficiencies.

Mills et al. reported that the ulceration can extend through the full thickness of the mucosa, with secondary vascular changes [31] as well as submucosal oedema. There may also be fibrosis, leading to stricture formation. Complications can thus include haemorrhage, perforation and obstruction.

In some patients there is gastric metaplasia, and it is postulated that this contributes to ulcer formation. Most IELs in UJ have a phenotype identical to that of RCD2. The ulcers tend to show a mixed CD4 + ve/CD8 + ve and CD4-ve/CD8-ve phenotype. T-cell rearrangement studies identify clonality in the ulcers, the adjacent mucosa, or in both.

4.2 Enteropathy-type T-cell lymphoma

There is an increased risk of B- and T-cell lymphoma in coeliac disease. Enteropathy-associated T-cell lymphoma (EATL) is particularly linked to CD [29]. EATL usually presents with abdominal pain or overt intestinal perforation in adults with a background of RCD2 or UJ [33]. The strong association of EATL with HLA-DQB1 strengthens the inferred causal linkage between CD and EATL [33–36].

There are two main histological types of EATL. Type 1 is characterised by an infiltrate of medium sized cells containing round or angular nuclei with prominent nucleoli and a moderate amount of eosinophilic cytoplasm [33]. There may be marked pleomorphism with appearances like those of large-cell lymphoma or Hodgkin’s lymphoma. The second, rarer type of EATL exhibits a monomorphic population of small, densely staining cells with hyperchromatic nuclei and minimal cytoplasm.

The malignant cells of both forms of EATL demonstrate monoclonality, with the same TCR\(\gamma\) gene rearrangement as seen in IELs in intestinal mucosa affected by the CD but which is uninvolved in the malignancy.

4.3 Other types of lymphoma

In addition to EATL, other types of non-Hodgkin’s lymphoma are over-represented in patients with CD. Subtypes observed include B-cell neoplasms, follicular lymphoma, extranodal marginal zone lymphoma, and T-cell neoplasms.

4.4 Carcinoma of the GI tract

CD has an association with small bowel adenocarcinoma, which usually presents after the age of 45, with abdominal pain, weight loss, and/or anaemia. There is also an increased risk of squamous cell carcinoma of the upper digestive tract, including the oesophagus and oropharynx. There are minimally increased risks of primary liver cancer and of colorectal cancer.

5. Diagnostic approach to RCD

There are many reasons for patients with CD to fail to respond to a gluten-free diet, of which an underlying diagnosis of RCD is only one. [34] Poor dietary compliance and potential confusion of CD with other conditions should be excluded. It has been suggested that a minimum of three properly orientated crypt to villous units are necessary for reliable interpretation of villous atrophy [34]. Helicobacter pylori, giardia, tuberculosis, tropical sprue, Whipple’s disease, viral
enteritis, AIDS, autoimmune enteritis, food protein intolerance, Crohn’s disease, common variable immunodeficiency, collagenous sprue and eosinophilic gastroenteritis may all mimic CD [34]. Their exclusion from the differential diagnosis is not always straightforward when histological criteria are ambivalent or when multiple conditions co-exist (e.g., CD and infection).

The diagnosis of RCD runs in parallel with that of an initial comprehensive diagnosis of CD, which will therefore be briefly reprised. Coeliac serology should be obtained, with IgA and IgG antibodies to tissue transglutaminase and endomysium. Gliadin antibodies are unhelpful as IgG gliadin antibodies are raised in 5% of normal subjects, and in many of the conditions documented above, particularly Crohn’s disease. HLA DQ2/DQ8 studies should be undertaken. A set of intestinal biopsies should be obtained for histological assessment. These endoscopic biopsies should be repeated after 4–6 months to confirm the diagnosis, and when RCD is suspected. [15]

In addition to evidence of villous atrophy, the biopsies will be examined for increased intraepithelial lymphocytes. The suggested normal upper limit for the small intestinal mucosa is 25 IELs per 100 enterocytes, with 25–29 considered borderline, and ≥30 IELs regarded as pathological lymphocytosis. In the normal small intestine, there is a gradual reduction in the density of IELs between the bases and tips of the villi [37, 38]; a more even distribution of IELs along the lengths of the villi is strongly suggestive of underlying active CD [38, 39]. There is however a wide range of other conditions which cause intra-epithelial lymphocytosis, including *H. pylori* infection, enteric infarction, and autoimmune disease, and this may also occur with non-steroidal anti-inflammatory or other drugs.

According to the ESPGHAN diagnostic algorithm, the combination of a typical history, HLA-DQ2/8 positivity and coeliac serology at >10 x normal levels constitutes a diagnosis of coeliac disease in children [35]. Consequent to the COVID pandemic, the same diagnostic algorithm is now proposed for adults with symptoms of CD so long as they are ≤55 years of age, have no red flag symptoms, have a normal total IgA level, have an IgA tTG ≥10 times upper limit of normal, and a second positive antibody test such as anti-endomysial antibodies. However, most gastroenterologists feel this approach should only be temporary, as there is frequently discrepancy between the results of serology and small intestinal morphology [36, 40].

RCD will be considered in the patient who remains symptomatic or with persistently abnormal laboratory markers after apparent compliance with a gluten-free diet. Clinico-pathological correlation should first be undertaken to ensure that the initial diagnosis of CD was fully supported, including HLA DQ2/8 status, anti-endomysial and tissue transglutaminase antibodies, together with the presence of small bowel lesions, with particular attention to any history of a previous response to a gluten-free diet. RCD is however a histological diagnosis. Histological assessment will be particularly important where the initial diagnosis was made without a biopsy.

Appraisal of the gluten-free diet is crucial when contemplating RCD, as gluten contamination is the commonest cause of failure to respond to a gluten-free diet. Contamination can be asymptomatic with minimal quantities, and can occur in patients who have received poor advice or are unaware of the broad range of products that can contain gluten [28].

In the absence of an aberrant IEL immunophenotype, the main differential diagnosis of CD-like histological lesions is limited to uncomplicated but inadequately treated CD, and RCD1. If there was no prior histology giving a diagnosis of CD, then a history of a previous response to a gluten-free diet is naturally highly supportive [28–36]. Both CD and RCD1 exhibit a polyclonal increase in IELs, mostly a CD3+ve/CD8+ve IEL population. Persistence or recurrence of small bowel lesions of this type, despite strict adherence to a gluten-free diet for at least one year, fulfills most observers’ criteria for a diagnosis of RCD1.
The demonstration of a predominant CD3+ve/CD8-ve aberrant IEL phenotype leads to the consideration of RCD2 and its complications, including EATL. Polymerase chain reaction assessment of IELs and flow cytometry are now widely used to complement immunohistochemistry in the diagnosis of RCD2. These studies illustrate the importance of immune regulation in the likely pathogenesis of RCD and of RCD2 in particular.

Focal neoplasia (EATL and other forms) may be difficult to identify within the diffusely abnormal small intestine found in RCD2. Video capsule endoscopy, and PET-CT tomography scanning have been shown to be more effective in pinpointing EATL than CT alone. Video capsule endoscopy and subsequent enteroscopy are particularly useful in detecting the more subtle lesions that may be the only macroscopic evidence of an underlying lymphoma. Elwenspoel et al propose to undertake an assessment of the accuracy of all potential diagnostic routes for coeliac disease and its complications involving a systematic review, the results of which are awaited [41].

6. Treatment of RCD

6.1 RCD1

All RCD patients should be reviewed by an expert dietitian in order to help them maximise their ability to adhere to a strict gluten-free diet.

In RCD1 the addition of systemic steroids has proven useful in some patients. The anti-TNFα biologic infliximab has also been proposed for the treatment of resistant coeliac disease [42]. Subsequent proposals have suggested a regimen of prednisolone and azathioprine that led to histological and clinical improvement in the majority of RCD1 patients following treatment for one year [22]. Dosages need some personalisation, but a tapering schedule of prednisolone (from 40 mg/day to less than 10 mg) with azathioprine at 2 mg/kg seem appropriate for most patients.

Use of an elemental diet not only provided clinical and histological improvement, but also reduced epithelial expression of the cytokine IL-15.

The specific defect in permeability associated with zonulin excess appears to be improved on treatment with larazotide acetate. [11]

6.2 RCD2

Prednisolone/azathioprine has been found to be helpful in some patients with RCD2 [8, 22].

Chemotherapy agents, such as the anti T-cell nucleoside analogues including pentostatin and cladribine have also been used with some success. [43]

Recently, IAMG 714, a monoclonal antibody to IL-15, has been studied in a randomised, double-blind, placebo-controlled, parallel-group trial in patients with type 2 refractory coeliac disease [44, 45].

Stem cell transplantation has been proposed as a therapeutic option, but this invasive approach is not generally accepted.

Overt lymphoma will be treated on standard oncological criteria and will normally fall outside the responsibility of the gastroenterologist.

7. Conclusions

In conclusion, the diagnosis of RCD is not straightforward. This interpretation of the clinical picture may have been incorrect, and the original diagnosis should
always be reviewed, incorporating a re-assessment of the histology of small intestinal biopsies. Assessment of the gluten-free diet and correlation with the results of serology should be undertaken. PCR evaluation of biopsies or separated lymphocytes can be used to differentiate between RCD1 and RCD2, the former resembling severe but uncomplicated CD, while the latter typically has monoclonality and potentially premalignant features.

Treatment options have included steroids, azathioprine, infliximab, cladribine, stem cell transplantation and humanised monoclonal antibody to IL-15, (IAMG 714). There is to date no established standard intervention.

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Acronyms and non-standard abbreviations

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<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>APC</td>
<td>Anti-Presenting Cells</td>
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<td>APO</td>
<td>Apolipoprotein</td>
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<td>CD</td>
<td>Coeliac Disease</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>EATL</td>
<td>Enteropathy-associated T-cell lymphoma</td>
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<td>IELs</td>
<td>Intraepithelial lymphocytes</td>
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<td>(Ig)A and (Ig)G</td>
<td>Immunoglobulins</td>
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<td>IL</td>
<td>Interleukin</td>
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<td>iNK</td>
<td>Invariant natural killer cells</td>
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<tr>
<td>MR</td>
<td>Magnetic resonance</td>
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<td>NHL</td>
<td>Non-Hodgkin's lymphoma</td>
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<td>NK</td>
<td>Natural killer</td>
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<td>RCD</td>
<td>Refractory coeliac disease</td>
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<tr>
<td>TCR</td>
<td>T-cell receptor</td>
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<tr>
<td>tTG</td>
<td>Tissue transglutaminase</td>
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<td>UJ</td>
<td>Ulcerative jejunitis</td>
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References


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