Chapter 16
Refractory Celiac Disease

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Introduction

Celiac disease (CD) is a small-intestinal enteropathy induced by gluten in genetically predisposed individuals with HLA DQ2/DQ8 genotype. Its prevalence is 1 % in Europe and the USA. Its clinical presentation is hypervariable, and diagnosis relies on the detection of specific serum antibodies and on the demonstration of intestinal villous atrophy. Treatment relies on a lifelong gluten-free diet (GFD), which prevents bone, autoimmune, and malignant complications. Resistance to a GFD is mainly due to bad observance. Nevertheless, a small subgroup of CD patients may be primarily or secondarily resistant to a GFD due to an authentic refractory celiac disease (RCD).

Poor adherence to a GFD needs to be first excluded accordingly with the fact that less than 50 % of patients are compliant [1]. Persistent symptoms of malabsorption and intestinal villous atrophy after at least 12 months of a strict GFD define RCD. Diagnosis of this condition is made after exclusion of other small bowel diseases such as autoimmune enteropathy [2], tropical sprue [3], or common variable immunodeficiency [4].

RCD has been subdivided into two subgroups:

1. Type 1 RCD (RCDI) is defined by persisting villous atrophy despite a strict GFD associated with an increased number of intraepithelial lymphocytes (IEL) bearing a normal phenotype with surface CD3 and CD8 expression.
2. Type II RCD (RCDII) is characterized by clonal expansion of abnormal IEL lacking surface markers CD3, CD8, and T-cell receptor (TCR) (CD3s-, CD8s-, TCR-) and preserved expression of intracellular CD3 [5, 6].

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S.D. Rampertab and G.E. Mullin (eds.), *Celiac Disease*, Clinical Gastroenterology,
DOI 10.1007/978-1-4614-8560-5_16,

Frequency of RCDI and RCDII remains unknown. In the Derby cohort, West and Holmes report approximately 0.7 % of RCDII patients in a series of 713 celiac patients [7]. In this latest study, diagnosis of RCDII patients was made solely on the basis of ulcerative jejunitis [7], causing possible errors leading to underestimates of RCDII and overestimation of RCDI. A second recent study in a single North American referral center suggests a cumulative incidence of 1.5 % for both RCDI and RCDII among CD patients initially diagnosed in this center [8]. In this study, over 80 % of RCD patients were classified as type 1. A higher frequency of cases of RCDI than of RCDII was also observed in two other studies from the USA [9] and from Germany [10]. In contrast, a higher frequency of RCDII over RCDI was reported in two studies from Holland [11] and from France [12].

Diagnosis

Diagnosis of RCD relies on persistent malabsorption and villous atrophy after 1 year of strict GFD ascertained by a dietitian. Endoscopic assessment includes upper gastrointestinal endoscopy with biopsy. Double-balloon enteroscopy is required in suspicion of RCDII for a better assessment of ulcers, particularly for evidence of ulcerative jejunitis found in roughly 70 % of patients [12, 13].

Capsule endoscopy is useful by giving the extent of lesions. Capsule endoscopy has a superior accuracy in predicting villous atrophy than optical endoscopy [14, 15]. Furthermore, besides the diagnosis of persistent villous atrophy, capsule endoscopy allows the visualization of ulcers all along the intestinal tract, which may suggest RCDII before diagnostic confirmation [16]. Moreover, we experienced three cases of overt lymphoma revealed by capsule endoscopy, which presented with very suspicious intestinal strictures and jejunal ulcers [17]. Double-balloon enteroscopy, reaching the distal small bowel in the three cases, confirmed the capsule findings [15, 17].

Thus, the limitation of capsule endoscopy is the risk of retention, particularly in RCDII patients who are particularly at risk for strictures. It requires preliminary radiological imaging of the small bowel in order to rule out stricturing disease. The second limitation is the need of biopsy during endoscopy for definitive diagnosis.

In RCDI, histological examination is similar to that found in active celiac disease with villous atrophy and increased normal IEL. No other diagnostic criteria have been yet defined for RCDI. In contrast, the hallmark abnormal population, detected by three combined techniques, makes the diagnosis of RCDII more specific: over 25 % of the CD103+ or CD45+ IEL lacking surface CD3-T-cell receptor complexes on flow cytometry or more than 50 % IEL expressing intracellular CD3ε but no CD8 in formalin-fixed sections and/or the presence of a detectable clonal rearrangement of the gamma chain of the TCR in duodenal biopsies [12]. Similar features allow detecting lymphocytic gastritis and colitis containing the same abnormal population in around 50 % and 30 % of RCDII patients, respectively [12] (Table 16.1).

Table 16.1 Main criteria to differentiate RCDI and RCDII

Criteria	RCDI	RCDII
Ulcerative jejunitis	–	+
Abnormal phenotype of intraepithelial lymphocytes	–	+
Clonal rearrangement of TCR	–	+
Very increased risk of EATL	–	+
Poor prognosis (5-year survival of 50 %)	–	+

RCDII may be misdiagnosed when flow cytometry analysis of freshly isolated IEL is lacking. Discrepancies in diagnosis tools are probably involved in differences observed between European and North American countries [8, 9, 18]. Indeed, flow cytometry is commonly used in Europe for the diagnosis of aberrant IEL and is a technique that is more sensitive and more precise than immunohistochemistry [18]. Heterogeneity in detection of the clonal TCR rearrangement may also explain diagnostic differences, and specificity of the PCR product needs to be attested by formation of homoduplexes [12].

Clinical Forms and Prognosis

Primary resistance to a GFD is seen in roughly one-third to one-half of patients with RCDI and RCDII, respectively [12]. Besides the abnormal phenotype of IEL, RCDII has a more severe clinical presentation and is frequently associated with endoscopic ulcerative jejunitis responsible for severe protein loss enteropathy. Symptoms are notably less severe in RCDI, and endoscopic and histological features are similar to those found in active CD [12]. RCDII is associated with poor prognosis with 5-year survival rates of 44–58 % [9, 11, 12]. The more severe malnutrition combined with the higher risk of developing overt lymphoma explains the higher mortality in RCDII when compared to RCDI [12]. Even if the prognosis of RCDI is much better than RCDII, the mortality rate appears higher than in uncomplicated CD [9, 10].

There is as yet no curative treatment for RCD. Immunosuppressive drugs have only a poor effect on the histological response and may predispose to overt lymphoma [19]. Indeed, 33–52 % of RCDII patients develop enteropathy-associated T-cell lymphoma (EATL) within 5 years after diagnosis of RCDII is made [11, 12]. Onset of EATL in RCDI is much lower than in RCDII, with a 5-year rate of 14 % in the more conservative studies [12]. The higher risk of transformation into overt lymphoma in RCDII is due to its state of low-grade intraepithelial lymphoma [6]. Indeed, at this stage, clonal IEL are already engaged in malignant transformation as attested by their clonality, the presence of their chromosomal abnormalities, the recurrent partial trisomy 1q22-q44, and their tendency to disseminate in and outside the intestine [12, 20].

Abnormal IEL may be found in mesenteric lymph nodes, blood, bone marrow, and in different epitheliums such as lung and skin [12]. A high percentage of abnormal cells (up to 92 %) is predictive of abnormal circulating cells in peripheral blood [21]. Diagnosis of extraintestinal RCDII lesions can be performed by evidence of the same clonal TCR γ/δ chain rearrangement that is present in duodenum but also by immunohistochemistry.

EATL may develop in intestinal but also in cutaneous lesions of RCDII, with expression of the same IEL-specific integrin CD103. The clonal filiation between RCDII IEL and EATL is demonstrated by presence of the same TCRγ chain rearrangement [6]. In practice, regular follow-up, including control enteroscopy, computed tomography scan (CT-scan) or MRI small bowel follow-through, and positron emission tomography (PET) scan, is necessary to screen EATL as early as possible. No established interval has been yet defined. Specialized investigations can be reasonably performed every year and 6 months in RCDI and RCDII patients, respectively [12]. PET scan is of particular interest because high intensity is correlated with location of proliferating overt lymphoma cells [22] contrasting with the low intensity of nonproliferating RCDII cells [23]. It can further guide realization of radiological guided biopsy or explorative laparoscopy.

Pathogenesis

It is still debated whether RCD patients have a particular genetic background differentiating them from patients with uncomplicated CD. The small numbers of patients are the main limitations of genetic investigations. It has been reported that severity of celiac disease was correlated with the number of HLA-DQ2 copies: homozygosity for HLA-DQ2 was observed in 25.5 % of RCD I, 44.1 % of RCD II, and 53.3 % of EATL patients versus 20.7 % of uncomplicated CD patients and 2.1 % of controls [24]. Other genes involved in lymphocyte signaling (genes: *SH2B3* (12q34), *PTPN2* (18q11), *RGS1* (1q31)) and associated with celiac disease may be involved in the risk of developing lymphoma [25]. Studies are in progress, and ongoing genome-wide association studies suggest that the known celiac susceptibility variants may be not found in RCDII [26].

Exposure to gluten appears to be an important environmental factor as it increases the risk of autoimmune diseases and malignancies [27]. Risk of lymphomatous complications was reported to be four times higher in patients without observance to a GFD than compliant patients [28]. The amount of gluten consumption could be responsible for the differences in terms of severity of CD. A recent study reports a more severe outcome of CD in South compared to North Europe in relationship to a higher gluten intake [29]. The scientific rationale may rely on more intense production, under gluten exposure, of the cytokine IL-15, now known to play a key role in the progression of lymphoma associated with CD [30].

Infections, particularly viral infections, may constitute another environmental factor favoring emergence of RCD. Epidemiological factors argue that viral

infections such as rotavirus infection may increase the risk of CD in genetically predisposed individuals [31]. We can hypothesize that viral infection triggers inflammation and autoimmunity by hyperproduction of IL-15. Indeed, IL-15 is induced by a variety of intracellular pathogens [32]. We observed hepatitis B or C at onset of refractoriness in 20 % and 10 % of RCDI and RCDII patients, respectively [12].

The role of viruses in the pathogenesis of chronic inflammatory and autoimmune diseases is a popular hypothesis supported by a large number of studies. More than a specific virus, it is rather suspected that components of the antiviral responses and notably type 1 interferons might promote the onset of chronic inflammatory disorders (reviewed in [33]). Type 1 interferon may notably stimulate the survival and proliferation of CD8+ T cells and NK cells [34] either directly or via the induction of IL-15 [35]. We can hypothesize that such a mechanism may occur in RCDI, helping the immunological reaction initiated by gluten to evolve toward autoimmunity. Accordingly, symptoms improve under immunosuppressive treatments [11, 12]. However, mechanisms of RCDI are largely unknown and remain to be substantiated.

More progress has been performed recently in the understanding of the pathogenesis of RCDII. The phenotype is now well defined with accumulation of small clonal IEL without proliferation but with apoptosis defect [30]. In active CD and RCDII, IL-15 is produced in excess by enterocytes and lamina propria mononuclear cells. IELs are, in CD and RCD, enriched in cytolytic proteins (perforin, granzymes, Fas ligand) and produce large amounts of interferon gamma (IFN-γ), indicating their likely contribution to the prominent apoptosis observed in the flattened-surface epithelium [30, 36, 37]. The granzyme-perforin cytotoxicity accounts for the severe epithelial lesions observed in RCDII. Moreover, IL-15 exerts potent antiapoptotic effects that prevent the elimination of activated IELs and promote their massive accumulation [30]. Survival signal delivered by IL-15 requires, through the receptor of IL-15, IL-15Rβγ, activation of Jak3, STAT5, and the antiapoptotic factor Bcl-xL. Human anti-IL-15 antibodies inhibit ex vivo the IL-15-driven signaling pathway in intestinal organotypic cultures of RCDII patients. In vivo, treatment of mice overexpressing human IL-15 in the small bowel with this antibody wiped out the IEL hyperplasia observed in these mice [38].

Treatments

It has not yet been possible to design an effective treatment for RCD I or II. Steroids improved clinical symptoms in most patients with either type of RCD. Yet a histological response was observed only in 30–40 % of cases [12]. Steroid dependence and/or resistance requires trials of immunosuppressive agents such as azathioprine, cyclosporine, or anti-TNF-α with transient clinical response but rare mucosal improvement [12]. In RCDI, no scientific rationale has yet been established to treat specifically RCDI patients with targeted therapy.

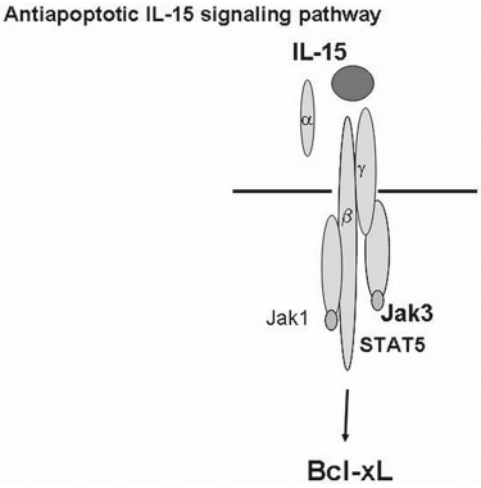

Fig. 16.1 Antiapoptotic IL-15 signaling pathway

In RCDII immunosuppressive drugs have, as could be expected, no impact on the abnormal clonal IEL population and could enhance the risk of overt lymphoma as observed with azathioprine and anti-CD52 [12, 19]. The bad prognosis of RCDII led to more aggressive treatments such as chemotherapy. Contrary to EATL which expressed Ki67, RCDII is characterized by onset of IEL with abnormal phenotype which massively accumulated without in situ detectable proliferation [30]. The non-proliferative RCDII cells are thus difficult to eradicate by regular chemotherapy [12] and may represent a reservoir of cells susceptible to more aggressive transformation.

Purine analogues such as pentostatine or cladribine (2CDA) showed moderate clinical, histological, and hematological efficacies [39, 40]. In our retrospective study of RCDII patients [12], 2CDA induced clinical and histological response. However, explosive onset of overt lymphoma was observed in the two treated patients within 3–8 weeks after treatment, precluding further use of these drugs inasmuch as enhanced risk of transformation into overt lymphoma has been previously observed in a series of 17 RCDII patients treated with 2CDA [40].

One possible alternative strategy is the use of the autologous hematopoietic stem cell transplantation which induced clinical and histological response, but no sustained reduction of abnormal IEL in the 13 treated patients [41, 42]. The use of chemotherapy before autologous hematopoietic stem cell transplantation may probably increase hematological response, and we are currently evaluating this strategy in a prospective phase II trial. Setting up targeted strategy appears necessary to complete the therapeutic armory to treat RCDII and to prevent overt lymphoma, whose prognosis is even worse than RCDII. Only 20 % of patients are alive 5 years after the diagnosis of lymphoma [43–45].

Targeted therapy blocking IL-15 signalling appears the treatment of choice in RCDII but needs to be tested in clinical trials [38] (Fig. 16.1). The recent development of a humanized anti-IL-15 antibody which has already been used without any

major side effects in a phase I–II trial in rheumatoid arthritis suggests the feasibility of this therapeutic approach [46]. Another possibility is to block the downstream molecules activated by IL-15. JAK3 inhibitor, currently used in treating rheumatoid arthritis [47], is another interesting drug to treat RCDII [48]. Treatment of RCDII will probably combine, in the near future, conventional chemotherapy agents and targeted therapy by anti-IL-15 antibodies or inhibitors of downstream activated molecules.

Conclusion

In conclusion, RCD refers to two distinct entities. On one hand, RCDI is indistinguishable from uncomplicated active CD except its autonomy toward gluten exposure, which probably relies on self-perpetuated autoimmune mechanisms. On the other hand, RCDII is a low-grade lymphoma characterized by clonal expansion of small aberrant IEL. Small bowel investigations (enteroscopy, videocapsule endoscopy) and specialized techniques of IEL analyses (immunohistochemistry, molecular biology, flow cytometry) are necessary for diagnosis of both forms of RCD. Prognosis of RCDII is very poor due to incurable malnutrition and very high risk of overt lymphoma. Survival of RCDI is better than in RCDII but inferior to CD survival [9, 12]. Recent advances in dissecting the pathogenesis of CD and RCD intend to hope next efficient treatments for these rare but severe diseases.

Acknowledgments We thank Nadine Cerf-Bensussan and Bertrand Meresse (Inserm U989, Université Paris Descartes) for collaboration for the figure.

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