Chapter 17

Refractory Celiac Disease

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Abstract

The main cause of failure to respond to a gluten-free diet (GFD) is persistent gluten ingestion, generally unnoticed. The refractory celiac disease (RCD) diagnosis is established after excluding other diseases, given the persistence of malabsorption and villous atrophy. This situation may appear initially after the disease diagnosis (primary) or after the initial response, when symptoms relapse despite strict adherence to a GFD (secondary).

RCD comprises a heterogeneous group of patients, usually in adults, which share a fortunately uncommon cause of non-responsiveness to the GFD (<5% of the celiac population). The detection changes in the intraepithelial lymphocyte population of the duodenal mucosa is of fundamental importance. When these lymphocytes appear in a population that does not express the surface T-cell receptor (CD3 and CD8), this is a potentially aggressive form of CD with a higher percentage of progression towards lymphoma (type II RCD).

Therapy is based on an adequate nutritional support and the use of corticosteroids or immunosuppressants (azathioprine and infliximab). The high risk of progression towards T cell lymphoma in type II RCD demands the use of different therapeutic regimens. Although currently no treatment has clearly shown to be effective in the long term, cladribine, immunotherapy with anti-CD52 (or similar treatments) and autologous stem cell transplantation are options to consider in the management of type II RCD. Antibodies that block interleukin-15 epithelial secretion, which is a key molecule in the pathogenesis, may have potential as new therapies.

1. Introduction

Removal of gluten in celiac disease (CD) is associated with clinical and histological recovery in most patients. Days or weeks after starting the GFD, a significant clinical improvement is observed, while histological lesions recover more slowly and, mostly in adults, they may persist for several months or even, in the absence of symptoms, for years in more than a third of the cases.[1,2]

However, a small percentage of celiac patients does not respond to a strict gluten-free diet; their intestinal villous atrophy persists, constituting the thus named[3] refractory celiac disease (RCD). RCD is a relatively rare entity, which appears in the adult form of CD and may progress with high morbidity and mortality. In recent years there has been an important advance in the understanding of its pathogenesis and various treatment options have emerged.[4] Since it appears in adult celiac disease, the rest of this chapter focuses only on adult disease forms.

2. Initial Management of the Lack of Response to the Gluten-Free Diet

The first step before reaching the RCD diagnosis is the initial management of the patients who do not respond to gluten withdrawal from the diet. This can happen in up to 20 % of the patients once the diagnosis is made.[2] Furthermore, in CD diagnosed in adulthood, over 30 % of the patients fail to recover from atrophy of the duodenal mucosa.[2] In cases of lack of clinical response, with or without mucosal recovery, after an initial diagnosis review many causes of lack of response to diet and of intestinal damage must be discarded (Table 1).

Continuous gluten intake, usually inadvertent and regular, is the leading cause of symptom persistence. Other drugs or substances containing gluten as an excipient must be ruled out. The persistence of high antibody titers (transglutaminase and endomysium) is a good indicator of ongoing contact with gluten.[5,6] However, the possibility has been put forward that these antibodies could lose the sensitivity to detect minor dietary transgressions in both children and in adults.[6,7] Overall, a thorough interrogation should be performed in conjunction with a dietary log and the help of a dietitian or nutritionist should be enlisted.

Intolerance to other foods, especially carbohydrates, is generally associated with CD, especially at the beginning.[8,9] Conducting tests based on breath hydrogen measuring may be useful for carbohydrate malabsorption evaluation, and in turn, to rule out intestinal bacterial overgrowth. Both carbohydrate intolerance and bacterial overgrowth may be responsible for the persistence of symptoms after excluding gluten from the diet.[10]

Exocrine pancreatic insufficiency may occur associated with villous atrophy, both in children and in adults.[9,11] Fecal chymotrypsin and elastase determination can help diagnose and establish the indication for initiating enzyme supplements. These patients should receive special attention in order to determine if pancreatic insufficiency reverses after initiating the GFD or if it otherwise remains as a primary insufficiency. A recent epidemiological study made in Sweden has found that patients with CD have a risk of developing chronic pancreatitis three times greater than the general population, and that they have five times the risk of needing pancreatic enzymes.[12]

Lack of adherence to diet (latent o unknown)
Intolerance to other foods (lactose, fructose)
Bacterial overgrowth
Pancreatic insufficiency
Microscopic or collagenous colitis
Inflammatory bowel disease
Collagenous sprue
Giardiasis
Ulcerative jejunitis
Infectious diarrhea
Autoinmune enteropathy
Common variable immunodeficiency syndrome
Intestinal lymphoma
Other tumors
Refractory celiac disease

Table 1. Causes of non-responsiveness to the gluten-free diet.

Microscopic colitis is an entity that shares CD's HLA genetic predisposition, which favors the association between these two diseases.[13,14] This occurs more frequently in females and when symptoms are primarily associated with persistent diarrhea.[14] In these cases, the performance of a colonoscopy with colon biopsies and proper treatment are imperative. A higher prevalence of inflammatory bowel disease among celiac disease patients than among the general population has been described[15] as well as a possible association of shared risk genes among CD, ulcerative colitis and Crohn's disease.[16] Therefore, the association between these diseases should be investigated when there is no response to the GFD.

CD is frequently associated with autoimmune conditions.[17] Thus it is that ulcerative jejunitis[18] or autoimmune enteropathy[19] can be observed as a cause of persistent symptoms. The common variable immunodeficiency syndrome may also occur in CD patients or else generate CD-like cases with villous atrophy but no response to the gluten-free diet, which require specific management.[20]

As always, malignancies should be ruled out, especially intestinal T-cell lymphoma, as a complication of CD. Weight loss, abdominal pain and night sweats are common symptoms when this kind of tumor is present.[21] Video capsule endoscopy[22,23] and double-balloon enteroscopy[24] are the two current techniques that have proven to be of great help for locating these tumors.

3. Definition and Epidemiology of Refractory Celiac Disease

Finally, once these causes have been ruled out, RCD will be diagnosed by exclusion. RCD was originally described in 1978 by Trier et al.[25] to define patients with villous atrophy and persistent diarrhea, unresponsive to GFD for at least 6 months. The American Gastroenterological Association (AGA),[26] has recently defined it as the persistence of villous atrophy and clinical malabsorption, unresponsive to the GFD. This situation may initially appear without actually responding to the GFD from its (primary) diagnosis or in patients already diagnosed with CD who, after a variable period, cease to respond to the GFD (secondary).[27] For some authors, the lack of initial response to gluten would lead to suspect that it is not really CD and therefore call it *non-celiac refractory sprue*.[28] Generally speaking, when there is no initial response to the GFD, the CD diagnosis should be revised. The existence of compatible data such as typical serology, HLA-DQ2 (+) or a family history support the RCD diagnosis. The absence of any of these parameters forces us to make a differential diagnosis with other pathologies.

Its frequency is of less than 5% of all CD patients. A Boston CD referral center recently reported an RCD prevalence of 4%.[29] In other studies, however, the prevalence does not exceed 1 % of the adult celiac population.[30] Its appearance in ages below 30 years is exceptional and most cases occur over the age of 50, with a higher prevalence in females.[31]

4. Pathogenesis and Classification

In recent years, knowledge of the pathogenic mechanisms involved in CD development has progressed. The adaptive immune response to the gluten level in the lamina propria has been well described. The lamina propria lymphocytes react to gliadin peptides once deaminated by the enzyme tissue transglutaminase. The presentation of these peptides is mediated by DQ2 and DQ8. Once the gliadin peptides have been recognized by these T lymphocytes (CD4+), they become active and secrete interferon-γ, which triggers the inflammatory response and is directly related to villous atrophy.[32]

However, less progress has been made in explaining the intraepithelial lymphocyte (IEL) increase since these already appear in the early stages of the disease and do not decrease after the GFD.[33] These T cells differ phenotypically from those present in the lamina propria, as these are mostly CD8+ with an increased expression of the γδ-type antigen receptor.[34] They are currently being the subject of special attention for their involvement in major CD complications: RCD and intestinal type T-cell lymphoma.[35,36] Interleukin 15 (IL-15) produced by enterocytes, in close contact with these IELs, appears to play a key role in the homeostasis of this lymphocyte population and in their potential transformation in RCD and lymphoma development.[37,38] An increase in the monocytic and enterocytic IL-15 transcriptional regulation appears to be the basis for the development of RCD and especially for type II RCD.[39]

In healthy subjects and uncomplicated celiac patients, IELs express the CD103 surface marker, which differentiates them from the lamina propria lymphocytes. Furthermore, they mostly have a lymphocyte T CD3+ CD8+ phenotype which can express the αβ or γδ T cell receptor (TCR).[34] Depending on the characteristics of this IEL population, two types of RCD can be differentiated, with different therapeutic approaches and prognosis.[35,39]

- Type I RCD: Here the IEL population presents phenotype surface markers similar to those of patients with active CD who have not started the GFD. Furthermore when, by means of molecular biology techniques, the T cell receptor gene arrangement is analyzed, it is seen to be polyclonal.
- Type II RCD: In this case the IEL phenotype is altered, constituting an "aberrant" population. This lymphocyte population has lost surface markers (CD3, CD8 and TCR), retaining the CD103 which characterizes it as intraepithelial, as well as CD3 intracytoplasmic expression. Furthermore, this population exhibits an oligo- or monoclonal TCR rearrangement. Due to these characteristics, type II RCD is also called *T cell cryptic intestinal lymphoma*, and considered to be a latent T lymphoma.[40]

5. Symptoms and Diagnosis

Clinical malabsorption associated with diarrhea is common to both RCD types. The type I usually appears in younger patients and its symptoms are less marked. Other autoimmune disorders, infections or thromboembolic phenomena can often be associated[41] with RCD. In type II, the average age is higher (50-60 years) and symptoms are usually more marked, with severe malabsorption and weight loss. Some patients may experience skin lesions mainly in limbs, similar to gangrenous pyoderma, as well as infections or fever with no known cause.[35] Weight loss and persistent diarrhea caused by malabsorption occur in up to 80 % of the cases and require discarding RCD in celiac patients.[29]

Endoscopy allows the observation of duodenal fold atrophy as well as of ulcerations which can lead to suspect ulcerative jejunitis. These ulcers, can also be seen in the stomach and the colon in RCD-II.[42] In order to view the entire small intestine and rule out the presence of lesions at different levels, capsule endoscopy can be helpful.[23] Lesions visualized by the capsule can be categorized by a biopsy taken by means of a push or a double balloon enteroscopy (it reaches distal sections with greater ease).[43]

Radiological tests, especially Computerized Axial Tomography (CAT) help rule out the presence of tumors, particularly intestinal lymphoma. Sometimes it is possible to observe an increase in the size and number of the mesenteric ganglia without a lymphoma or a diffuse thickening of the intestinal wall.[44]

The histology of duodenal mucosa exhibits an increased villous atrophy similar to those found in CD cases that have not yet started a GFD. Standard staining cannot differentiate between the both RCD types, being necessary to perform immunohistochemical staining on CD3 and CD8. As it can be seen in Figure 1, in both RCD types there is an IEL increase which are stained with CD3 (at a cytoplasmic level). But the first datum that steers us towards type II RCD is that, unlike type I and non-refractory celiac disease, these IELs cannot be stained with CD8.[45]

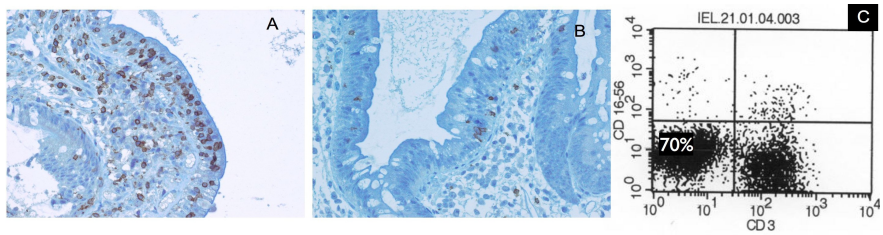

Figure 1. Aberrant lymphocyte population in type II RCD. (A) Immunohistochemistry of duodenal biopsy, where an increase in intraepithelial lymphocytes, whose cytoplasm is stained with CD3 marker, can be observed. However, this population is not stained with the CD8 marker (B). In panel C, by means of flow cytometry, it is confirmed that this aberrant population does not express surface CD3 in nearly 70% of intraepithelial lymphocytes.

More useful and informative is performing flow cytometry on biopsy samples, not only to categorize lymphocyte populations, but also to quantify this IEL "aberrant population" (Figure 1c). Thus RCD-II is identified in a population that mostly expresses surface CD103 (typical of IELs and unlike lamina propria lymphocytes), but that expresses neither surface CD3 (it does express intracytoplasmatic CD3 which can be observed in immunohistochemistry) nor surface CD8.[46]

When faced with type II RCD, a possible clonal TCR rearrangement must be sought by means of molecular techniques. The presence of oligo- or monoclonality is usually associated with RCD-II, but it is not essential for diagnosis.[41]

The aberrant RCD-II lymphocyte population can be found not only in duodenal biopsies, but also in those from the stomach, colon and peripheral blood.[42] This suggests that RCD-II is a disease that is not limited to the small intestine, but that it expands to the whole gastrointestinal tract and can spread through the blood. A datum of a high aberrant cell percentage (>80%) together with a clonal TCR rearrangement is highly predictive of developing an enteropathy-associated intestinal T lymphoma (EATL).[47,48]

Figure 2 offers an approach to celiac patients unresponsive to the gluten-free diet. This approach groups, on one hand, the initial focus on the lack of response to the diet and, on the other, diagnosis and management of suspected RCD.

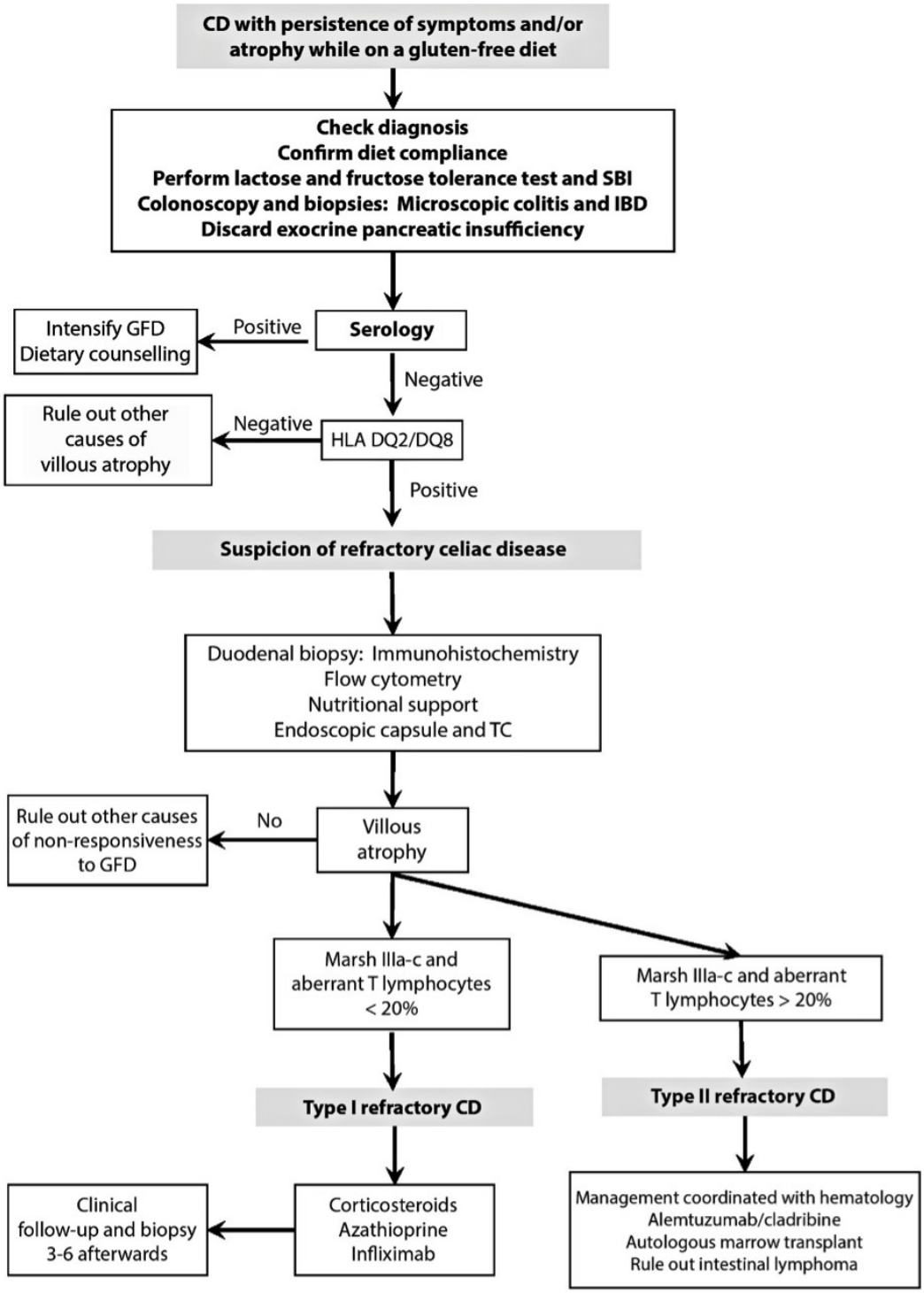

Figure 2. Approach for celiac patients unresponsive to the gluten-free diet.

6. Evolution and Prognosis

In general, RCD has a poor prognosis, with less than a 50% survival rate 5 years after diagnosis, for type II.[31,49] Although RCD is a heterogeneous group of entities, RCD-I may be an earlier stage of the disease than RCD-II, with a possibly less aggressive progression. The prognosis is linked to the presence and size of the population of aberrant IELs, which influences the risk of developing intestinal lymphoma.[50]

The presence of TCR clonality observed in RCD-II is also observed in intestinal lymphoma samples. This suggests a transformation of the aberrant lymphocytic cells we see in RCD in a high degree T lymphoma.[36]

It is currently not clear how to monitor patients with RCD in order to make an early lymphoma detection. Capsule endoscopy may reveal the presence of early tumor lesions in the small intestine. Positron Emission Tomography (PET) could also differentiate between RCD and an already developed lymphoma.[51] In general, a close clinical monitoring should be undertaken to search for the appearance of neoplasias upon deterioration of the patient or the appearance of alarming symptoms. Biopsies for histological, immunohistochemical and flow cytometry studies should be performed at least every 6 months until refractoriness is resolved. Faced with a type II RCD, we should identify biopsies and shorten the interval for monitoring the aberrant lymphocyte population, for an early detection of a progression towards a lymphoma[48] (Figure 2).

7. Treatment

The first step is a mainly nutritional support treatment, parenterally if necessary. Hydroelectrolytic disorders and mineral (iron, zinc, magnesium and calcium) and vitamin (B12, folic acid, K and D) deficiencies must be corrected. Of course, a strict gluten-free diet must be followed.

Current evidence regarding treatment is based on case series and expert opinions, without the benefit of controlled clinical trials. This is due to the low prevalence of this complication and to the differentiation of both RCD types.[4]

7.1. Treatment of Type I RCD

Besides the usual nutritional support, an elemental diet, based on amino acids, has been tested on these patients. The results showed clinical and histological improvements, coupled with a mucous interleukin 15 and interferon-γ secretion decrease in an RCD-I group of the patients.[52] The results observed using the elemental diet are short-term; it is necessary to progress further in the therapeutic scale.

Although there are no randomized studies, the most commonly used drugs are corticosteroids.[41] These are used intravenously or orally, depending on the clinical severity, a prednisone or prednisolone dose of 1 mg/kg. Local-action corticosteroids like budesonide have also been employed, with a similar clinical efficacy.[53] Overall clinical response to corticosteroids is good on

the short term, although histological improvement is not observed in a large percentage of cases. Furthermore, clinical recurrence is common upon their suspension.[41]

Cases with relapse after corticosteroid suspension or those in clinical remission who have had RCD-I, could be candidates for long-term immunosuppressive therapy. Azathioprine, has been the most tested drug, with a high rate of clinical and histological response.[54] Treatment dose and duration are not well established and it is generally recommended to follow the same guidelines as in inflammatory bowel disease.

Cyclosporine A, *infliximab*, tacrolimus and methotrexate have obtained variable results in isolated clinical cases.[55] Perhaps *infliximab* has been the most evaluated and it is the one with the best results in several cases. Its use could be reserved for situations involving azathioprine intolerance or lack of response to it.

7.2. Treating Type II RCD

There is no established treatment for this aggressive RCD form. It is recognized however, that in an aberrant and clonal lymphocyte population, the therapeutic approach should be more aggressive.[56] Here corticosteroids or *infliximab* may favor a transient clinical improvement, but with no effect on clonal proliferation. Immunosuppressants such as azathioprine may even promote lymphoma progression and its use is not recommended.[56] Recombinant human interleukin-10 (IL10-hr), has been employed to inhibit Th1 immune response to gliadin. However, it has not proved effective in reported a series of 10 RCD-II cases.[57]

Antineoplastic agents used in the management of leukemias and lymphomas, have been recently tested. Cladribine (2-clorodeoxyadenosine) is a synthetic purine analog, used in hairy cell leukemia (a rare *T lymphoma* type). Its use in a number of RCD-II cases caused clinical and histological improvement but with aberrant lymphocyte population persistence and progression to lymphoma in 40% of the cases.[58]

Alemtuzumab is an anti-CD52 monoclonal antibody used in the treatment of chronic lymphocytic leukemia. Its use in an RCD-II case resulted in a clinical and histological improvement, together with a progressive decline in the aberrant clonal lymphocyte population of clonal and remission maintenance for more than 36 months.[50] The response has been variable in other cases, perhaps associated with different stages of disease.

Autologous bone marrow transplantation, after intensive chemotherapy, has been used in both in an established lymphoma[59] as well as in an RCD-II series, with good clinical and histological outcomes and reduced clonal lymphocyte populations.[60]

Nevertheless, there is no current ideal treatment for this RCD-II clonal population, which is the reason why novel therapies that act more specifically are being sought. In this regard, interleukin-15 blockage may be a promising approach. The production of these cytokines is increased by the epithelium of RCD-II patients.[38] Additionally it has been described that, when overexpressed, it can induce lymphoma in transgenic mice[61] and that it directs IEL expansion and activity in relation to enterocytes.[37,38,62,63] Thus, blocking its activity, the elimination of the aberrant IEL population can not only be achieved, but also the prevention of epithelial destruction.

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