Refractory Coeliac Disease (About 05 Cases)

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Abstract

Refractory coeliac disease (RCD) is defined by persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for at least 6 - 12 months in the absence of other causes of non-responsive treated coeliac disease and overt malignancy. Symptoms are often severe and require additional therapeutic intervention besides a GFD. RCD can be classified as type 1 which usually improves after treatment with a combination of aggressive nutritional support, adherence to a GFD, and alternative pharmacological therapies. By contrast, clinical response to alternative therapies in RCD type 2 is less certain and the prognosis is poor. Severe complications such as ulcerative jejunitis and enteropathy-associated T cell lymphoma may occur in a subgroup of patients with RCD. The aim of this article is to describe the profile of patients with RCD, their management and their evolution in a series of 284 patients with celiac disease.

Keywords: Refractory Coeliac Disease; Gluten-Free Diet; Therapeutic Management

Introduction

Refractory coeliac disease (RCD) is a rare complication of Celiac Disease (CD), defined by persistent malabsorption symptoms and villous atrophy despite adherence to a strict gluten-free diet for at least 6 to 12 months. RCD is classified as type I or type II (lymphoma in situ) based on the absence or presence of an aberrant intra-epithelial lymphocyte (IEL) population.

Materials and Methods

We report 5 cases of RCD collected within our practice over a period of 24 years (1995 - 2018). All our patients benefit from a specialized consultation of celiac disease and a gluten-free diet analysis by a well-informed dietician. Our goal is to describe the profile of patients with RCD, their management and their evolution.

Result

Out of 284 cases of celiac disease, 5 cases were complicated by RCD (1.17%), including 4 men and 1 woman (sex ratio = 4), the mean age was 43.2 years with extremes between 21 and 72 years old. Initially the diagnosis of CD was posed on an array of clinical, biological,
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histologic, and serologic evidence. IEL rate varied between 35% to 70%, and villous atrophy (AV) varied between partial and total. Serology was positive in 3 out of 5 cases.

The diet was initiated immediately after confirmation of the diagnosis of CD, and the evolution was marked by a clinical and biological improvement that lasted between 12 and 18 months.

Our 5 patients with RCD have the following symptoms: severe chronic diarrhea, weight loss with significant malnutrition, edema and leg paraesthesia.

The pathological result was: 4 patients had RCD type I sprue and 1 patient had RCD type II with ulcerative jejunitis.

As to the therapeutic management of these patients, three of them were put on budesonide and parenteral nutrition, one patient was lost of view and the last one is under investigation.

The evolution of patients on budesonide was marked by clinical and biological improvement in two patients, and death of the third by multiple location lymphoma.

Discussion

A small subgroup of patients with CD may be primarily or secondarily resistant to a well observed GFD due to an authentic refractory CD (RCD).

Refractory celiac disease (RCD) refers to 2 distinct entities according to the normal (RCDI) or abnormal (RCDII) phenotype of intestinal intraepithelial lymphocytes [1]. Diagnosis requires specialized small bowel investigations (enteroscopy, small bowel imaging) and techniques (immunohistochemistry, molecular analysis, flow cytometry).

The real prevalence of RCD is unknown but probably rare because of the low number from major CD referral centers of RCD cases reported in the literature [2,3].

The incidence of CD complicated by RCD found in our series is 1.17% (5 of 284) which is close to the result found in the literature for example: A North American referral center suggests a cumulative incidence of 1.5% for both RCDI and RCDII among patients with CD diagnosed in this center [4]. In the Derby cohort, J. West and G. Holmes report approximately 0.7% of patients with RCD with ulcerative jejunitis in series of 713 patients with CD [5].

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CD affects two times as many women than men [6] consistent with the predominance of diagnosed CD in adult women. The predominance of disease in women diminishes somewhat in those patients with both RCD and EATL [7]. Unlike the result of our study where the predominance of RCD belongs to men 4 men against 1 woman.

The age of diagnosis of RCD is often around 50 years old and rarely before 30 years of age [8]. In our study, the mean age was 43.2 years with extremes between 21 and 72 years old.

Diarrhea, gastrointestinal disorders, anemia, fatigue, and malaise are common [9]. The majority of patients with RCD are diagnosed because of the development of new symptoms or recurrence of diarrhea. In our group patients with RCD have the following symptoms: severe chronic diarrhea, weight loss with significant malnutrition, edema and leg paraesthesia.

Hospitalization to monitor adherence to GFD and for parenteral nutrition was necessary for one patient with RCD because of severe weight loss, malnutrition, multiple nutritional deficiencies, and severe hypoproteinemia. Udesonide (9 mg/day), Prednisone (0.5 - 1 mg/kg/day), or a combination of prednisone and azathioprine (2 mg/kg/day) are clinically effective to induce clinical remission and mucosal recovery in most patients with RCD type 1 [10,11]. Clinical response to steroids is observed in the majority of patients with RCD type 2, Other immunosuppressive drugs or biological modifiers have been used with some clinical benefit in steroid-dependent or steroid-refractory patients including cyclosporin, infliximab (5 mg/kg/day) and alemtuzumab [12].

As to the therapeutic management of our patients, three of them were put on budesonide and parenteral nutrition, one patient was lost of view and the last one is under investigation.

Steroids improved clinical symptoms in most patients with either type of RCD with various histologic responses from 30% to 40% of cases to nearly 90% in a recent study using open capsule budesonide [13].

Prognosis of RCDII is worse than RCDI because of more severe malnutrition and an elevated risk of overt lymphoma [14].

Molecular analysis showed a polyclonal repertoire for RCDI. In contrast, the abnormal population characteristic of RCD type II is sought by 3 combined techniques in duodenal biopsies; The pathological result in our study was: 4 patients had RCD type I sprue and 1 patient had RCD type II with ulcerative jejunitis which is an entity often associated with this pathology [15].

Prognosis of refractory coeliac disease type II is poor because therapies are less effective and high risk of progression to enteropathy-type T-cell lymphoma [16].

Risk of lymphomatous complications was reported 4 times higher in patients without adherence to a GFD than compliant patients [17].
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In our study, the evolution of patients on budesonide was marked by clinical and biological improvement in two patients and death of the third by multiple location lymphoma.

Conclusion

RCD is a rare complication of CD, RCD type I is well managed by a nutritional and pharmacological support, unlike RCD type II which is of poor prognosis.

Bibliography


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