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CLINICAL STAGING AND SURVIVAL IN REFRACTORY CELIAC DISEASE: A SINGLE CENTER EXPERIENCE

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Abstract

Background & Aims—Refractory celiac disease (RCD) occurs when both symptoms and intestinal damage persist or recur despite strict adherence to a gluten-free diet. In RCD, the immunophenotype of intraepithelial lymphocytes may be normal and polyclonal (RCD I) or abnormal and monoclonal (RCD II). The aim is to describe the clinical characteristics, treatment, and long-term outcome in a large single-center cohort of patients with RCD.

Methods—We compared the clinical characteristics and outcome in 57 patients with RCD: 42 with RCD I and 15 with RCD II.

Results—The overall 5-year cumulative survival is 70, 80 and 45 percent in the entire cohort, RCD I, and RCD II respectively ($p = 0.07$, among subtypes). The drop in survival was more evident during the first two years after the diagnosis. Fifteen (26%) patients died ($n=8$ with RCD I and $n=7$ with RCD II). The refractory state itself and enteropathy-associated T-cell lymphoma (EATL) were the most common causes of death, respectively. A new staging system is proposed based on the cumulative effect of five prognostic factors investigated at the time of the refractory state diagnosis: for patients in stages I, II, and III, the 5-year cumulative survival rate was 96, 71, and 19 percent, respectively ($p<0.0001$).

Conclusions—RCD is associated with high mortality with RCD II having an especially poor prognosis because of the development of EATL. A new staging model is proposed that may improve the precision of prognosis in patients with RCD.

Keywords

refractory sprue; corticosteroids; lymphoma; intraepithelial lymphocyte; capsule endoscopy; body imaging

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INTRODUCTION

Celiac disease (CD) is characterized by intestinal damage induced by the ingestion of gluten in susceptible individuals, with clinical and mucosal recovery in most patients after gluten withdrawal.¹ Nonresponsive CD can be described by the lack of initial response to a gluten-free diet (GFD), or the recurrence of gastrointestinal symptoms despite maintenance of GFD in a patient who responded initially to the GFD.² Gluten contamination is the most common cause of nonresponsive CD, but others need to be considered such as microscopic colitides, exocrine pancreatic insufficiency, lactose intolerance, small-intestine bacterial overgrowth, irritable bowel syndrome, and refractory celiac disease (RCD).^{2, 3}

RCD is characterized by persistent symptoms, severe malabsorption, and intestinal damage despite strict adherence to a GFD. RCD is a diagnosis of exclusion as all other causes of non-response in treated CD must be systematically eliminated before a diagnosis of RCD is made.^{2, 3} The true prevalence of RCD is unknown, but the syndrome may affect ~5% of patients with CD and it was the cause of nonresponsive CD in 18% of referrals to a tertiary level center in the United States.^{2, 4} Patients with RCD are classified as having either primary RCD if they never responded to a GFD or secondary if their relapsed despite adherence to the GFD.^{4, 5} An alternate classification for RCD is based on the immunophenotype of intraepithelial lymphocytes as RCD I (or polyclonal), in which the intraepithelial lymphocyte phenotype is normal, or RCD II (or monoclonal), in which there is a clonal aberrant phenotype of the intraepithelial lymphocyte.^{6, 7}

The monoclonal phenotype (RCD II) is supported by: i) the presence of an aberrant intraepithelial lymphocyte population containing intracytoplasmic CD3 (CD3e) without surface expression of CD3 and CD8 by immunohistochemical or flow cytometric studies and ii) clonally-restricted rearrangement of the T-cell receptor- γ chain by polymerase chain reaction and/or southern blot.⁶⁻⁸

RCD I usually improves after treatment with a combination of aggressive nutritional support, adherence to a GFD, and alternative pharmacologic therapies.^{1, 6} Corticosteroids, either alone or in combination with other immunosuppressive drugs, may suppress clinical manifestations of RCD I.^{1, 9} Azathioprine is not useful for induction of response because of a delayed onset of action but may be beneficial as steroid-sparing drug in those patients who have side effects or are dependent on high-dose of steroids.^{6, 10, 11} Recently, budesonide was found to induce clinical improvement but not necessarily mucosal recovery in most patients with RCD without the side effects associated with systemic active steroids.¹² By contrast, RCD II is usually resistant to any known therapy, and the coexistence of enteropathy-associated T-cell lymphoma (EATL) must be rigorously investigated.^{1, 6, 13, 14} High dose chemotherapy followed by autologous hematopoietic stem-cell transplantation (ASCT) has been successful and is a promising though invasive alternative therapy for the treatment of RCD II in a single center.¹⁵ RCD II does not respond to conventional therapy, thus, it has been associated with a poor prognosis (5-year survival rate: ~50%) mainly because the development of overt EATL.^{11, 16} However, as RCD is rare, systematic information on the long-term outcome in patients with RCD is scarce and reports are quite anecdotal.

In the present study, we sought to describe the clinical features, treatment, and long-term outcome of patients with rigorously defined RCD evaluated at a single referral center.

METHODS

Patients

The study group included patients with RCD treated at the Mayo Clinic Rochester between June 1998, when the first patient was included, and October 2007, the cutoff date for entry into this report. Most patients (>96%) were evaluated and treated in the Celiac Clinic (by J.A.M.).

Diagnostic Criteria for Refractory Celiac Disease

The internationally accepted criteria for classification of the RCD (and subtypes) were used to maximize the correct allocation of patients by categories.^{4–6, 11} The operational definition of RCD case required:

Major criteria—

1. Recurrence or persistence of symptoms (diarrhea, involuntary loss of weight, and/or abdominal pain) and intestinal damage (at least partial villous atrophy) after gluten exclusion for at least 6–12 months
2. Exclusion of other causes of nonresponsive CD including expert dietary inquiry to exclude intentional or inadvertent gluten contamination
3. Need of alternative therapy because of lack of response to GFD
4. Absence of overt intestinal or systemic lymphoma
5. Previous diagnosis of biopsy-proven CD with history of clinical response to the GFD. Positive serologic celiac tests, the presence of human leukocyte antigen (HLA) alleles at-risk for CD DQ2 or DQ8, and a family history of CD were considered supportive for the diagnosis of CD, especially in patients with primary non-response to GFD.^{1, 17}
6. Subtypes were determined by the absence (RCD I) or presence (RCD II) of an aberrant [monoclonal] phenotype of intraepithelial lymphocytes determined by immunohistochemical and/or T-cell clonality analyses.

Minor criteria—

1. Endomysial (EMA) or tissue transglutaminase (tTGA) autoantibodies (positive to support CD diagnosis and negative to support GFD compliance and the refractory state)
2. Absence of anti-enterocyte antibodies

A “definite” case required the presence of all six major criteria. Patients with EATL diagnosed prior to CD were not included here because the outcome is determined by the neoplasm but not by the refractory state itself.¹⁸ Patients with other refractory sprue-like conditions, such as adult autoimmune enteropathy, hypogammaglobulinemic sprue, collagenous sprue, and tropical sprue, were excluded.^{19, 20} In the collection of data, the date of the first medical examination at Mayo Clinic Rochester at which a patient 1) met the diagnostic criteria for RCD, or 2) required the initiation of an alternative therapy (e.g. parenteral nutrition or steroids) due to lack of response to a GFD was defined as “zero time”. Finally, before categorizing patients as RCD, all other causes of nonresponsive CD were systematically investigated and eliminated as previously reported by our group.² Some patients with positive serology (either EMA or tTGA) that suggested gluten contamination were classified as RCD after a period of close dietary surveillance and/or after these patients required additional therapy to control their symptoms.^{5, 16}

Data Collection

Clinical and laboratory data were collected from the medical record and listed according to the patient “zero time”. Additionally, the results of small-bowel follow-through, contrast abdominopelvic computerized tomography (CT) scan, upper-endoscopy, CT-enterography, capsule endoscopy, and celiac serology were reviewed. Only data that reflected conditions that existed before any specific therapy were included. Histological findings were classified according to the modified Marsh classification.²¹ Immunohistochemical and T-cell clonality studies used to identify clonal expansion of aberrant intraepithelial lymphocytes in the intestinal biopsy were reviewed.

Response to Treatment

The primary goal of this study is to describe the clinical characteristics and outcome in a cohort of patients with RCD; however, to clearly describe the clinical course of the disease after the time when the specific therapy was initiated, some arbitrary definitions were used. “Clinical response” was defined by disappearance of diarrhea, and at least 2 of the following criteria: an increase of body mass index greater than 1 point, increase in albumin greater than 10% of the baseline level, increase of hemoglobin greater than 1 point, and/or reversion 1 stage in the modified Marsh classification after treatment.²² “Remission” required both clinical response and normal intestinal biopsy (healing) during the follow-up.

Detection of Clonal Expansion of Aberrant Intraepithelial Lymphocytes

The presence of aberrant intraepithelial lymphocytes was evaluated in fixed or fresh frozen intestinal tissue by the following methods: i) immunohistochemical -an aberrant clone was defined by the lack of expression of the β -chain of T-cell receptor and the surface markers CD3 and CD8, with preserved expression of the intracytoplasmic CD3 (CD3 ϵ) in >50% of intraepithelial lymphocytes as previously described,⁷ and ii) detection of T-cell receptor- γ rearrangement by polymerase chain reaction or southern blot.²³

Statistical Analysis

Data were summarized using descriptive statistics. The chi-square or 2 sample t- test were used to test for an association between clinical factors and groups (RCD I vs RCD II). Survival was summarized by the Kaplan-Meier method. The log-rank test was used to assess the association of survival with particular variables at refractory state diagnosis and with disease subgroups. The regression coefficient (β) and hazard ratio (HR) with 95% confidence interval (CI) were estimated for each prognostic factor using univariate Cox proportional hazards regression. A p value <0.05 was considered statistically significant.

Ethical Issues

This study was approved by the Institutional Review Board of the Mayo Foundation.

RESULTS

Patients

Patients (n=57, 67% female) with a median age at refractory state diagnosis of 59 years (range, 30–76) were included. Forty-two (74%, 29 female) and 15 (26%, 9 female) had RCD I and RCD II, respectively. Fifty-two (91%) were Caucasians, three Hispanic, and two African American. Forty-eight (84%) were evaluated for RCD because of persistent villous atrophy and the development of new symptoms or recurrence of diarrhea after initial clinical response to a GFD with a median time on GFD of 18 months (range, 12–276) before the diagnosis of the refractory state. A positive serologic test (either EMA or tTGA), supportive of the diagnosis of CD, was found before the onset of GFD or sometime during follow-up in

29 (60.4%) of those 48 patients. The HLA DQ2 or DQ8 alleles at-risk for celiac disease were present in all 32 (67%) patients investigated. A family history of celiac disease was found in 6 (12%) patients. In 9 (16%) patients requiring early intervention to control their symptoms after 6 months of non-response to a GFD (primary non-response), the diagnosis of CD was supported by a positive serologic test (either EMA or tTGA) before the onset of GFD in 6 patients, the presence of the HLA DQ2 or DQ8 alleles at-risk for CD in all 9 patients (8 were DQ2+ and 1 DQ8+), and the exclusion of other sprue-like conditions by a combination of endoscopic features, serology, imaging or histologic findings. All patients had both persistent diarrhea and loss of weight at the time of RCD diagnosis. Abdominal pain was more frequent in RCD II (93% vs 45%, $p = 0.002$). The mean stool output, estimated at the time of the refractory state diagnosis in 21 (37%) patients was 999.2 g/day, with an average fecal fat content of 27.9 g/day on a high fat diet (> 100 g/d). Associated diseases were: microscopic colitis in 19 (33%) patients (17 with RCD I), ulcerative jejunoileitis in 4 (4 with RCD II), and cavitating mesenteric lymphadenopathy in 3 (all with RCD II). Quantitative culture of intestinal fluid was performed in 33 (58%) patients; of whom 5 (3 with RCD I) had small-intestine bacterial overgrowth (defined by $>10^5$ colony forming units). In those patients, the diagnosis of RCD was considered only after the lack of clinical response to oral antibiotics. HLA-class II genotyping was available in 41 (72%); all tested patients had the HLA alleles at-risk for CD (33 DQ2+ [3 homozygous for DQ2], 4 DQ2+/DQ8+, and 4 only DQ8+) (Table 1).

Endoscopic and Imaging Findings

The mucosa of the small-bowel was visually reported as abnormal [showing scalloping, fissuring, loss of folds, or the mosaic pattern] by the endoscopist in 33 (65%) of 51 patients in whom the description of the intestinal mucosa was available in the endoscopic report. In the 18 patients where the endoscopist didn't identify macroscopic features of atrophy, the degree of villous atrophy on histology was stage 3a ($n=13$), 3b ($n=1$), and 3c ($n=3$). Standard upper-endoscopy had an overall sensitivity of 64.7% compared to histology for detection of villous atrophy.

Capsule enteroscopy was performed in 27 (47%) patients (19 with RCD I). Capsule failed to leave the stomach in 3 patients (2 with RCD I). Extensive enteropathy [features of atrophy located in duodenum and jejunum] was found in 16 (6/8 [75%] RCD II vs 10/19 [53%] RCD I), proximal enteropathy in 5 (RCD I = 4). No features of atrophy were observed in 3 (RCD I = 3; partial villous atrophy (stage 3a) was observed on histology in the 3 patients). The extent of involvement was patchy in 22 (92%) of the 24 with complete examination and continuous in only 2. Multiple erosions or villi nodularity with thickening in the jejunum was observed in 4 patients (RCD I = 3). Capsule enteroscopy had an overall sensitivity of 87.5% compared to histology for detection of villous atrophy.

A total of 73 radiologic studies (abdominopelvic CT [$n=26$], CT-enterography [$n=28$], and/or small-bowel follow-through [$n=19$]) were performed at Mayo in 51 (89%) patients with RCD during the evaluation of the refractory state. Multiple studies were done in 24 (47%) patients. Intestinal abnormalities or lymphadenopathy were detected by at least one radiologic study in 29 (57%) patients (*Supplemental Table 1*).

Histological Spectrum in Refractory Celiac Disease

All patients had persistent villous atrophy and intraepithelial lymphocytosis despite the GFD: stage 3a in 32 (56%) patients (RCD I = 26), 3b in 7 (12%) patients (RCD I = 4), and 3c in 18 (32%) patients (RCD I = 12). Fixed or fresh frozen intestinal tissue of all the patients was investigated to detect clonality or aberrant intraepithelial lymphocytes. The methods used were immunohistochemistry alone in 8 (14%) patients, and both

immunohistochemistry and molecular studies for T-cell receptor- γ gene rearrangement in 49 (86%) patients.

Medical Treatment

All patients were instructed to follow a strict GFD and by definition required alternative therapies (dosage at the time of the refractory state diagnosis): prednisone (0.5 to 1 mg/kg body weight) was used in 30 (53%) patients (21 RCD I, and 9 RCD II), prednisone (0.5 to 1 mg/kg body weight) was used in combination with azathioprine (1–2 mg/kg day, range 50–150 mg/day) in 7 (12%) patients with RCD I, budesonide 9 mg/day in 15 (26%) patients (14 RCD I), 2-chlorodeoxyadenosine [2-CDA] (5 mg/m²/day, days 1 to 5 q28 days per 2 cycles) in 2 patients with RCD II, and high dose chemotherapy followed by ASCT in 1 patient with RCD II. Two patients with RCD II were reluctant to receive any drug therapy and were treated with total parenteral nutrition alone. Total parenteral nutrition was used in a total of 16 (28%) patients (12 with RCD I), 4 required long-term home parenteral nutrition. Pancreatic enzyme supplementation was used as ancillary therapy in 6 (10%) patients (5 with RCD I). No patient received alemtuzumab, infliximab, or cyclosporine.

Clinical and Histologic Response

After treatment, “clinical response” was observed in 44 (77%) patients. Follow-up biopsies were available in 26 (47%) patients, with median time from the RCD diagnosis to the follow-up biopsy of 23.5 months (range, 6–54). Healing (“clinical remission”) of the intestinal mucosa was achieved in 9 (35%) patients: 6/18 (33%) with RCD I versus 3/8 (37%) with RCD II ($p = 0.7$). Healing of the intestinal mucosa was observed in 2/11 patients treated with prednisone, 1/2 with prednisone and azathioprine, 4/9 with budesonide, 1/1 with ASCT, and 1/2 with total parenteral nutrition alone.

Eight patients with RCD II had follow-up biopsies after a median time of 15 months (range, 7–41); the aberrant clone of intraepithelial lymphocytes was not further detected in 3 patients after treatment with strict GFD plus ASCT, high-dose prednisone, and 2-CDA respectively (the histology was Marsh 0 and Marsh 3a [$n=2$] respectively), but in 5 patients (all treated with high-dose prednisone and strict GFD) the aberrant clone was still present at follow-up (the histology was Marsh 0 [$n=2$], Marsh 3a [$n=2$], and Marsh 3c respectively). Two of five patients with persistent clone despite treatment, developed overt EATL during follow-up (18 and 34 months after T-cell clone detection, respectively). The 3 patients with persistent clone but no overt EATL had a clinical follow-up (since the first detection of the T-cell clone) of 15, 29, and 40 months, respectively. One of three RCD II patients without aberrant clone at follow-up developed overt EATL, 11 months after treatment with 2-CDA. One patient of 18 with RCD I and follow-up biopsy, switched to RCD II (clone was detected in the follow-up biopsy) despite good clinical response and so far, has not developed EATL (follow-up = 132 months).

Progression to EATL in RCD II and Treatment

Ten (67%) patients with RCD II developed EATL after a median time from RCD II diagnosis to EATL diagnosis of 18 months (range, 9–34). After EATL diagnosis, systemic chemotherapy was the primary treatment in 6 patients and high-dose chemotherapy followed by ASCT in 3. One patient received only supportive therapy because of rapid disease progression. Partial resection of the jejunum was necessary in 5 (50%) patients. The planned chemotherapy courses were completed in 7 patients. A response to initial chemotherapy was observed in 7 (complete response, $n=4$; partial response, $n=3$). Relapses occurred 4–23 months from diagnosis in 4 of those who responded to initial treatment. Of the total 10 patients, 7 (70%) have died, 6 from progressive disease (*Supplemental Table 2*).

Survival Analysis

Five-year cumulative survival rate was 80% in RCD I vs 45% in RCD II ($p = 0.07$). No association between subgroup and survival was observed after adjusting for age ($p=0.35$). Drop in survival was more evident during the first two years after diagnoses of the refractory state in both RCD I and RCD II (Figure 1). Fifteen (26%) patients died ($n=8$ with RCD I and $n=7$ with RCD II). The refractory state with emaciation and EATL were the most common causes of death in RCD I and RCD II respectively (Table 2).

Formation of the Staging System

Five factors were found to be associated with mortality if present at the time of the refractory state diagnosis (in order of significance from strong to borderline): albumin 3.2 g per deciliter, hemoglobin 11 g per deciliter, age 65 years, the presence of aberrant intraepithelial lymphocytes (T-cell clone), and total villous atrophy (stage 3c) on the intestinal biopsy (Table 3). The presence of each prognostic factor in an individual patient have a cumulative negative effect on survival ($p<0.0001$) (Table 4).

To create the staging system, a point score was assigned to the prognostic factors based on their relative weight determined by their regression coefficient (β) from univariate Cox regression. In particular, a point score of 1 or 2 for presence of the factor was defined as the rounded β value and summed over all 5 factors. Among patients with a total point score of 0 ($n=15$) and 1 ($n=12$), the 5-year cumulative survival rates were 93% and 100 % respectively. Among patients with a score of 2 ($n=7$) and 3 ($n=9$), the 5-year cumulative survival rates were 80% and 65% respectively. Among patients with a score of 4 ($n=10$) and 5 ($n=4$), the 5-year cumulative survival rates were 25% and 0% respectively.

Stages were then defined and numbered with Roman numerals customary in ordinal staging systems. Stage I combined patients with a point score of 0 or 1 ($n=27$), stage II patients with a point score of 2 or 3 ($n=16$), and stage III patients with a point score of 4 or more ($n=14$). The survival curves for patients in the three stages are shown in Figure 2, indicating distinctive prognostic gradients ($p<0.0001$).

DISCUSSION

The principal findings are: 1) RCD I and RCD II are associated with high mortality especially during the first 2 years after the diagnosis of the refractory state (5-year cumulative survival for the entire cohort = 70%) and 2) a new staging system for RCD is proposed based on the cumulative effect on survival from five prognostic factors scored at the time of the refractory state diagnosis: albumin 3.2 g per deciliter, hemoglobin 11 g per deciliter, age 65 years, the presence of aberrant intraepithelial lymphocytes, and severe degree of histological damage (stage 3c).

The strict diagnostic criteria for RCD in our cohort required of the systematic exclusion of both other causes of nonresponsive CD and refractory sprue.^{1, 2, 5, 17} While gross gluten contamination was investigated by expert dietary inquiry and most patients (81%) had a negative serologic test at the time of RCD diagnosis suggesting strictness of the GFD, a minority (19%) of patients had persistently positive celiac serology (either tTGA or EMA) despite GFD, consistent with other previous reports.^{3, 5, 12} Reasons for persistent positive serologic tests in RCD are unknown but maybe related to: 1) induction of tissue transglutaminase up-regulation by severe inflammation and the destructive lesion associated with RCD, 2) celiac autoantibodies kinetics, and 3) low-grade gluten contamination by a hidden source.^{24, 25}

Although open-label and purely observational, our experience suggest that patients with RCD I may have a good clinical response and sometimes complete histologic healing after treatment with prednisone (with or without azathioprine) or budesonide, consistent with previous reports.^{9, 10, 12, 26} Diarrhea and general status may improve in patients with RCD II after treatment with corticosteroids but histologic healing is rare, and more importantly, progression to the highly-lethal EATL was not prevented in most patients. Other more effective therapeutic options with the aberrant intraepithelial lymphocyte as target and healing of the intestine as well as avoid progression to EATL as primary outcomes are clearly needed for patients with RCD II.^{13, 14}

In our study, accuracy of the classification of RCD into subtypes was supported by the use of the current available methodology of immunostaining of intraepithelial lymphocytes and T-cell clonality analysis.^{7, 23} Previous studies demonstrated that the risk of EATL development is closely correlated to the presence of T-cell clones.^{6, 11} Our data are consistent with this observation, as only patients in whom a clone of aberrant intraepithelial lymphocytes was previously detected, developed EATL during follow-up. Thus, immunohistochemical and T-cell clonality analyses may help to predict EATL development and outcome. Interestingly, the aberrant clone was not further detected after treatment in the intestinal tissue of 3 patients with RCD II. The lack of detection of the aberrant clone of intraepithelial lymphocytes may be explained by complete suppression or significant decrease in aberrant T-cells induced by treatment that render the clone undetectable by conventional methods.^{15, 22} The effect of drug-induced T-cell clone suppression on lymphomagenesis is less clear, as one of our RCD II patients developed EATL during follow-up in the absence of detectable T-cell clone. The use of novel and more accurate methods to detect aberrant T-cells such as flow cytometry may have an important role in EATL risk stratification.²⁷

The refractory state and EATL were the most frequent causes of death in RCD I and RCD II, respectively. The drop in survival is particularly significant within the first 2 years after the diagnosis of the refractory state; thus, an early diagnosis and aggressive treatment are mandatory, especially because in our series, the mean time to progression from RCD II to EATL was only 17 months. It is possible that the older age at diagnosis of the refractory state or referral bias might explain the short time to progression from RCD to EATL in our patients.

As previously reported, in our population, RCD II had a poor prognosis despite treatment, especially after the development of EATL.^{11, 16, 18} Seventy percent of our patients with EATL have died and the clinical follow-up in 2 survivors treated with a complete course of CHOP regimen is limited to less than 24 months; thus, their risk of relapse is still high.¹⁸ The longest disease-free survival was achieved in one patient who received high-dose chemotherapy followed by ASCT (up to 6 years) but 2 other patients died because relapse or disease progression despite adequate ASCT engraftment, consistent with a recent study.²⁸

While the presence of aberrant intraepithelial lymphocytes defining RCD II was observed as a negative prognostic factor, we identified other prognostic factors with a cumulative effect for predicting poor outcome. Based on the presence or absence of these factors at the time of the RCD diagnosis, we developed a new staging system in which each category has a distinctive prognostic gradient in our cohort. For patients in stages I, II, and III, the 5-year cumulative survival rate (95% CI) was 96% (89%, 100%), 71% (47%, 95%), and 19% (0%, 41%), respectively. Thus, patients in stage II and stage III might require a more aggressive treatment and close follow-up, specially for RCD II, because the high-risk of EATL development and mortality (Figure 3). If responsive patients with RCD II will need rapid progression to ASCT or just continuation of less invasive therapies remains to be

demonstrated by prospective randomized trials, but novel or invasive interventions might be appropriate for stage II or stage III patients because their poor prognosis with conventional therapies.

A major advantage of our proposed staging system is that the information it required can be easily obtained as part of the initial systematic evaluation in patients with persistent symptoms despite gluten withdrawal. Although the new proposed clinical staging model will need further validation in a prospective cohort and in other populations (likely a multinational cohort), we believe it will be useful to improve the precision of prognosis in patients with RCD. The new staging system may be especially useful to assess outcome after treatment of RCD with experimental drugs.

Study limitations include the retrospective evaluation of data, the heterogeneous length of follow-up, and the single center referral with a potential of referral bias. Finally, multivariate analysis was not performed because the relative low number of patients and cumulative events in this cohort makes this tool underpowered.

In conclusion, RCD is associated with high mortality with RCD II having a poor prognosis because the development of EATL. Corticosteroids are highly effective to control symptoms in the majority of patients with RCD and may induce histologic healing in a small number of patients with RCD I. A new staging system is proposed that may improve the precision of prognosis in patients with RCD.

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Abbreviations

ASCT	autologous hematopoietic stem-cell transplantation
CD	celiac disease
EATL	enteropathy-associated T-cell lymphoma
EMA	endomysial antibodies
GFD	gluten-free diet
HLA	human leukocyte antigens
RCD	refractory celiac disease
tTGA	tissue transglutaminase antibodies

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(A)

(B)

FIGURE 1.
5-year survival by Kaplan-Meier method for the entire cohort (A) and according to the subtype of refractory celiac disease (B)
+ = censored

FIGURE 2.

5-year survival of patients with refractory celiac disease in the three prognostic stages: stage I = point score 0 or 1, stage II = point score 2 or 3, and stage III = point score 4.

+ = censored

FIGURE 3.

Proposed protocol for diagnosis and treatment in refractory celiac disease

TABLE 1

Demographic and clinical characteristics in patients with refractory celiac disease

Patient Characteristics	Refractory Celiac Disease Type I (n=42)	Refractory Celiac Disease Type II (n=15)
Median age at diagnosis of celiac disease (range), years	54 (22–77)	61 (46–75)
Median age at diagnosis of the refractory state (range), years	57.5 (30–76)	70 (47–76)
Median time from diagnosis of celiac disease to diagnosis of refractory state (range), months	16 (6–276)	12 (6–252)
Female, n (%)	29 (69%)	9 (60%)
Median follow-up (range), months	26.5 (1–156)	22 (2–84)
Positive endomysial or tissue transglutaminase at diagnosis of the refractory state, n (%)	9 (21%)	2 (13%)
Diarrhea, n (%)	42 (100%)	15 (100%)
Involuntary loss of weight, n (%)	42 (100%)	15 (100%)
Abdominal pain, n (%)	19 (45%)	14 (93%)
Body mass index, mean (standard deviation), kg/m ²	22.0 (±4.7)	19.2 (±2.7)
Hemoglobin, mean (standard deviation), g/dl	12.4 (±1.8)	11.3 (±1.2)
Albumin, mean (standard deviation), g/dl	3.1 (±0.7)	3.2 (±0.7)

TABLE 2

Cause of death in patients with refractory celiac disease

Cause of death	Refractory Celiac Disease Type I (n=8)	Refractory Celiac Disease Type II (n=7)
Refractory state itself	5	0
Enteropathy-associated T-cell lymphoma	0	6
Other celiac disease-related	0	0
Other celiac disease-unrelated	3 *	1 **

* Giant cell myocarditis, progressive Creutzfeldt-Jacob disease-like neurologic disorder, invasive aspergillosis

** Unexplained multiple organ failure

TABLE 3

Survival of patients with refractory celiac disease according to the presence of prognostic factors

Characteristic	No. of patients	5-year cumulative survival % (95 percent CI) *	Hazard Ratio (95 percent CI) [p-value] **
Age: 65 years	19	53 (29, 77)	4.5 (1.0, 21.4) [0.06]
50-64	21	74 (54, 94)	2.3 (0.4, 11.6) [0.33]
<50	17	84 (64, 100)	1 (reference)
Hemoglobin: 11 g/dl	17	46 (21, 71)	3.4 (1.2, 9.5) [0.02]
>11	40	79 (65, 93)	1 (reference)
Albumin: 3.2 g/dl	22	40 (19, 61)	9.1 (2.6, 32.4) [0.001]
> 3.2	35	88 (75, 100)	1 (reference)
T-cell clone: yes	15	45 (17, 73)	2.5 (0.9, 6.8) [0.08]
no	42	80 (68, 92)	1 (reference)
Total villous atrophy: yes	18	50 (22, 78)	2.4 (0.9, 6.8) [0.09]
no	39	77 (63, 91)	1 (reference)

* Kaplan-Meier method

** Univariate Cox regression analysis

TABLE 4

Survival result according to the number of prognostic factors

No. of prognostic Factors *	No. of patients (# of deaths)	5-year cumulative survival rate % (95% CI)
0	15 (1)	93 (81,100)
1	12 (0)	100
2	15 (3)	78 (55, 100)
3	11 (8)	22 (0, 48)
4	4 (3)	0
Total	57 (15)	70 (57, 83)

* No patient in this series had the 5 prognostic factors