Clinical Staging and Survival in Refractory Celiac Disease: A Single Center Experience

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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:*** **Fifteen of 57 patients died during follow-up (n = 8 with RCD I and n = 7 with RCD II), each within the first 2 years after RCD diagnosis. The overall 5-year cumulative survival is 70%, 80%, and 45% for the entire cohort, RCD I, and RCD II, respectively. 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 5 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%, respectively ($P < .0001$).** ***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.**

Celiac disease (CD) is characterized by intestinal damage induced by the ingestion of gluten in susceptible persons, 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 a 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 because all other causes of nonresponse 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 (1) the presence of an aberrant intraepithelial lymphocyte population containing intracytoplasmic CD3 (CD3ϵ) without surface expression of CD3 and CD8 by immunohistochemical or flow cytometric studies and (2) clonally restricted rearrangement of the T-cell receptor-γ chain by polymerase chain reaction, Southern blot, or both.[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

Abbreviations used in this paper: 2-CDA, 2-chlorodeoxyadenosine; ASCT, autologous hematopoietic stem-cell transplantation; CD, celiac disease; CI, confidence interval; CT, computerized tomography; EATL, enteropathy-associated T-cell lymphoma; EMA, endomysial antibodies; GFD, gluten-free diet; HLA, human leukocyte antigen; RCD, refractory celiac disease; tTGA, tissue transglutaminase antibodies.

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action but may be beneficial as a steroid-sparing drug in those patients who have side effects or are dependent on high-dose 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, although 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 of the development of overt EATL.[11,16] However, because 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.

Materials and 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 RCD

The internationally accepted criteria for classification of 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 and minor criteria. The major criteria included the following:

(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 nonresponse 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, T-cell clonality, or both analyses.

Minor criteria included the following:

(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 antienterocyte antibodies

A "definite" case required the presence of all 6 major criteria. Patients with EATL diagnosed before 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 spruelike 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 start of an alternative therapy (eg, parenteral nutrition or steroids) because of the 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 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. In addition, 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.

Histologic 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 was 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