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Celiac Disease and Persistent Symptoms

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CLINICAL SCENARIO

A 52-year-old male is referred for persistent diarrhea, bloating, weight loss, and iron deficiency anemia following a diagnosis of celiac disease one year ago. At the time of his original diagnosis, serology was notable for a high IgA tissue transglutaminase titer >250 (normal less than 20), intraepithelial lymphocytosis and partial villous atrophy on small intestinal biopsy, and significant steatorrhea.

He reports being compliant with a gluten-free diet, though clinically his symptoms have only marginally improved. Recent laboratories (within a month from referral) show a normal IgA tissue transglutaminase titer, microcytic anemia, low ferritin, and elevated fecal fat (12 grams/24 hours on 100gram daily fat intake). Repeat upper endoscopy shows mucosal scalloping on gross exam and partial villous atrophy on small bowel histology.

What would be the next step in further evaluation of the ongoing symptoms and additional potential etiologies?

THE PROBLEM

This vignette illustrates a case of nonresponsive celiac disease (NRCD). NRCD is defined by a lack of initial response to a prescribed gluten-free diet (GFD), or the recurrence of symptoms despite maintenance of GFD in a patient who responded initially to GFD. The exact prevalence of NRCD is unknown but the presence of symptoms after treatment with a GFD is common in patients with celiac disease (CD). This clinical problem requires a systematic diagnostic and therapeutic approach because of the many distinct underlying etiologies. What are the expected clinical, serological, and histological responses after treatment with a GFD? The amount of time to fell better on a GFD is different for every person but clinical improvement is usually evident within weeks after treatment with a GFD. CD-specific serology, which is gluten-dependent, normalizes by 6-12 months in most patients with strict adherence to GFD. Mucosal recovery after GFD may take longer than 1 year despite strict adherence to the GFD and may be incomplete, especially in adult-onset CD.

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MANAGEMENT STRATEGIES AND SUPPORTING EVIDENCE

Does this patient have celiac disease?

The clinical case discussed here concerns a middle-aged man with a clinical diagnosis of CD well supported by typical symptoms (malabsorption), high titers of IgA tissue transglutaminase antibody (overall specificity >95%) and by the presence of partial villous atrophy in the duodenal biopsy. Thus, although the first step when faced to patients with NRCD is to evaluate the certainty of the original diagnosis, an alternative original diagnosis in this case seems unlikely. When the original diagnosis of CD is uncertain, we strongly recommend that the quality of the studies and not just the results should be reviewed. Patients that are self diagnosed or whose initial diagnosis did not follow the usual diagnostic recommendations often do not have CD even if they have clinical improvement after gluten exclusion. Inquiry about the type of serological test(s) that was used to support the diagnosis as well as any dietetic restrictions (e.g., self-prescribed GFD) at the time of initial evaluation may be relevant to refute (or support) the diagnosis of CD because the diagnostic accuracy of serology vary among tests (and centers) and may be affected by a GFD. Anti-gliadin antibodies have a poor specificity for CD and should not be regarded as strong evidence to support CD diagnosis. A positive family history may be supportive evidence for CD, especially if a first-degree family member has biopsy-confirmed CD. A history of biopsy-proven dermatitis herpetiformis confirms CD as the underlying cause of villous atrophy. Re-review of the original intestinal biopsy slides by an expert pathologist may reveal an alternative diagnosis. The use of small-bowel mucosa tissue transglutaminase 2-specific IgA autoantibody deposits may help to distinguish NRCD from other types of enteropathy, especially when the original CD diagnosis is uncertain or for seronegative patients. This method is not widely available, require frozen specimens and experience for the interpretation of results. Finally, the absence of human leukocyte antigens (HLA)-DQ2 or DQ8 alleles may be extremely useful to rule out CD when biopsy results are inconsistent with serology.

What is the differential diagnosis when the original diagnosis of CD is uncertain?

The differential is extensive and should include all other many causes of villous atrophy besides CD. Other causes of villous atrophy with characteristic histology such as Whipple's disease, collagenous sprue, and eosinophilic enteritis may be excluded by re-review of the intestinal biopsy.

A recent travel or residence history to tropical areas including Southeast Asia, tropical Africa, Central and South America, or the Caribbean islands would increase suspicion of tropical sprue being the underlying cause of persistent symptoms. If additional diseases have been excluded and tropical sprue is a strong consideration, empiric treatment with antibiotics and folate would be indicated.

Autoimmune enteropathy (AIE), collagenous sprue, and Whipple's disease could be additional potential etiologies, though these diseases are less common. A recent case series on AIE characterized the overlapping clinical and histological features of AIE and CD. The distinguishing features of positive gut epithelial cell antibodies (anti-enterocyte and/or anti-goblet cell antibody) and persistent villous atrophy with associated malabsorption despite gluten restriction are suggestive of AIE. Intraepithelial lymphocytosis could be observed in patients with AIE. Gut epithelial cell antibodies are not specific for AIE but support the diagnosis when other clinical criteria for AIE are present. Anti-goblet cell antibodies may be especially nonspecific and should be interpreted cautiously. There is a need for rigorous studies regarding sensitivity and specificity of gut epithelial cell antibodies. Collagenous sprue is characterized by villous atrophy, severe symptoms, and a thick subepithelial

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collagen band. Collagenous sprue is a heterogeneous disorder that may or may not be associated with CD. The mainstay of treatment for both starts with either systemic or topical steroids, though experience is limited due to the rarity of these diseases. Immunosuppressive drugs and total parenteral nutrition are often necessary in patients with either AIE or collagenous sprue. The GFD can be dispensed with those patients who do not carry the at-risk HLA alleles associated with CD.

Causes of Nonresponsive Celiac Disease

Intentional or inadvertent gluten contamination is the most common cause of NRCD (Figure 1). Deliberate ingestion of gluten is not often acknowledged but most commonly patients are unknowingly ingesting gluten, highlighting the importance of expert dietary instruction with the initial diagnosis of CD and a detailed dietary review when patients present with a less than adequate response to a GFD. While serological follow-up tests are not especially sensitive to low level gluten intake, a persistently positive test after 1 year of a GFD suggests a high level of gluten ingestion. A normal follow-up serology doesn't guarantee either adherence to GFD or mucosal recovery of the intestine. The discovery of gluten contamination by dietary review or by inference from serological testing should be broached tactfully with the patients providing them with information and support to assist in identifying and eliminating gluten sources. Membership of a CD support group could be useful for some patients to remain gluten free. If gluten contamination has been reasonably excluded, other additional disorders associated with NRCD must be actively investigated (Table 1). Repeat upper endoscopy with intestinal biopsy may help to differentiate causes of NRCD associated with persistent mucosal damage from those usually associated with normal duodenal mucosa.

Small intestinal bacterial overgrowth and exocrine pancreatic insufficiency are two causes of persistent steatorrhea despite treatment with a GFD. Quantitative cultures of duodenal aspirates or a positive breath test (e.g., lactulose) are characteristic of bacterial overgrowth but clinical response to antibiotics confirms the diagnosis. Low fecal elastase (or other indirect pancreatic function tests) is a common finding in NRCD and may suffice to evaluate for exocrine pancreatic insufficiency, though an empiric trial of pancreatic enzymes supplementation is a useful approach when steatorrhea persists.

The risk for microscopic colitis is increased up to 70-fold in the celiac disease population as compared to the general population. Microscopic colitis is a frequent cause of persistent or more often recurrent watery diarrhea though is less likely in patients with steatorrhea. If other etiologies are excluded, colonic biopsies taken proximal to the rectosigmoid junction are indicated. There is currently no consensus on whether flexible sigmoidoscopy or colonoscopy is the best approach for endoscopic biopsy in microscopic colitis. Most patients with abnormal histology may have evidence of disease in the left colon but colonoscopy may be necessary to unmask patients with isolated right-side disease (~10%).

A subgroup of patients with NRCD may have more than one disorder associated with persistent symptoms (e.g., concurrent microscopic colitis and bacterial overgrowth). Thus, for these patients, specific treatment for all associated disorders is necessary to alleviate symptoms.

Finally, after exclusion of other more frequent causes, refractory celiac disease should be considered in patients with severe symptoms and NRCD.

Does this patient have refractory celiac disease?

Refractory CD (RCD) is a rare complication of CD defined by "persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a GFD for at least

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6–12 months in the absence of other causes of NRCD and overt malignancy." These patients are at higher risk for T-cell lymphoma than celiacs in remission and a careful search for the complication of lymphoma is necessary. RCD type 1 is characterized by polyclonal T-cell expansion in the mucosa. The presence of abnormal (clonal) expansion of the intraepithelial lymphocytes is the hallmark of RCD type 2. The abnormal intraepithelial lymphocyte phenotype is supported by the loss of normal surface markers CD3, CD4 and CD8 with preserved expression of intracytoplasmic CD3 (e.g., ≥40–50% by immunohistochemistry or >20–25% by flow cytometry) and by T-cell receptor clonal rearrangement by polymerase chain reaction. Interval monitoring of intraepithelial lymphocyte immunophenotype and clonality may be more accurate than a single snapshot evaluation to classify RCD subtype and to predict risk of lymphomagenesis. The abnormal T-cells (clone) may serve as a source of the devastating enteropathy-associated T cell lymphoma. Both RCD type 1 and type 2 RCD can be associated with excess mortality. Mortality in RCD type 1 is more often due to severe malnutrition and/or secondary infection especially early in the course of the disease. RCD type 2 is associated with increased mortality due to an especially high risk of progression to enteropathy-associated T-cell lymphoma. Novel techniques are available to accurately examine either the whole small-bowel or extraintestinal tissues (e.g., wireless capsule endoscopy, balloon enteroscopy, CT- and MRI-enterography, PET scan). A combination of these techniques could be very useful to distinguish between severe CD and complicated CD and to exclude malignancy in RCD. Management of RCD requires careful attention to correcting the fluid and nutritional deficiencies that are common in these patients. Bone disease may be severe and parenteral nutrition may be necessary. The mainstay of treatment for RCD type 1 is steroid therapy with prednisone or more recently, budesonide. Azathioprine either alone or in combination with steroids can be used in those with RCD type 1. Oral cyclosporine may be effective for RCD type 1 but severe side effects require consideration. There is no established treatment for RCD type 2. (Figure 2) Although clinical response can be observed in most patients with RCD type 2 after treatment with steroids, the risk of progression to lymphoma is not affected. Intravenous cladribine can be useful for some patients with RCD type 2 but lymphomagenesis still a concern. Potent chemotherapy followed by autologous hematopoietic stem cell rescue has been explored for treatment of RCD type 2 in a pilot study from a single center. In the near future, interleukin-15 blockade may be a potential therapeutic target for RCD type 2. Long term prognosis of RCD depends in large part on the presence or absence of these aberrant T-cell populations and progression to lymphoma although other clinical factors may be relevant such as older age, low hemoglobin, hypoalbuminemia, and degree of villous atrophy at diagnosis of the refractory state.

AREAS OF UNCERTAINTY

The prevalence and causes of NRCD in the community are not known yet. The most cost-effective approach for NRCD remains to be determined. The long-term outcomes after intervention in patients with NRCD are incompletely understood. The best therapeutic approach for asymptomatic subjects with persistently abnormal mucosa after GFD is unknown.

PUBLISHED GUIDELINES

The AGA Institute technical review on the diagnosis and management of CD published in 2006 outlines the key aspects of evaluating a celiac patient with persistent symptoms: verification of the original diagnosis and compliance with a GFD, and consideration of either other causes of NRCD or severe complications (e.g., RCD and malignancies).

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RECOMMENDATIONS FOR THIS PATIENT

In the patient described in the vignette, an empiric trial with pancreatic enzymes led to complete resolution of his symptoms. Gluten contamination was ruled out by an expert dietitian but adherence to GFD was reinforced. One year later, the patient remains asymptomatic two months after stopping pancreatic enzyme supplementation with both normal serology and histology.

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Abbreviations used in this paper

AIE	autoimmune enteropathy
CD	celiac disease
GFD	gluten-free diet
NRCD	nonresponsive celiac disease
RCD	refractory celiac disease

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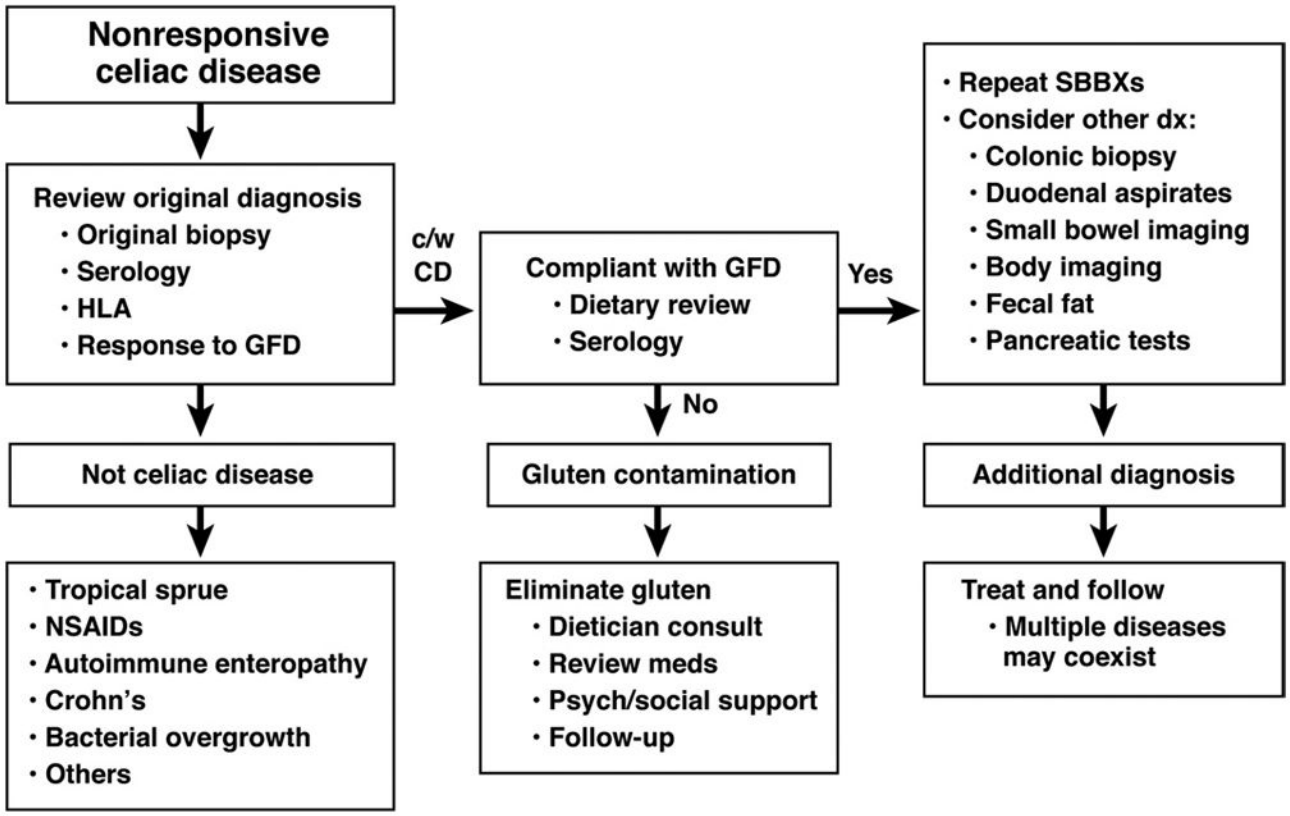

Figure 1.
Diagnostic approach in non-responsive celiac disease.

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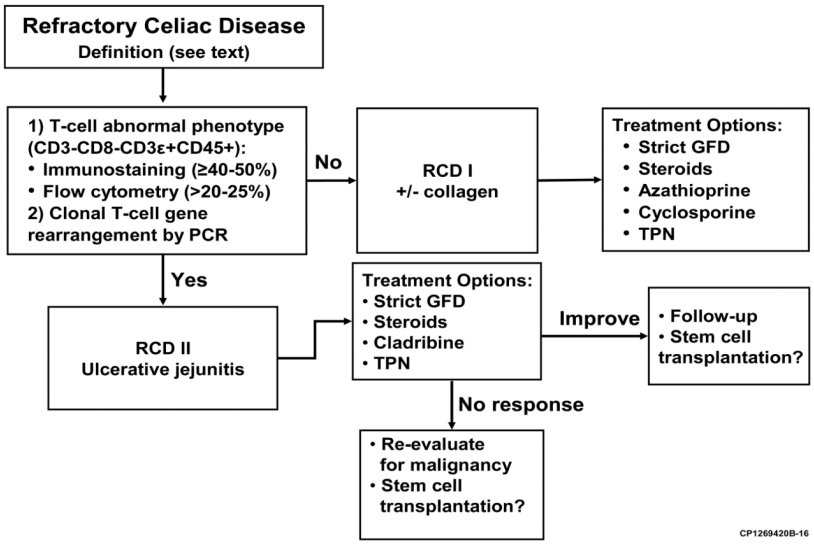

Figure 2.
Diagnostic and therapeutic approach in refractory celiac disease

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Table 1

Differential diagnosis of nonresponsive celiac disease

Etiology	Diagnostic approach	Comments
Gluten contamination *	Dietary review, celiac serology, intestinal biopsy	Most frequent cause of nonresponsive celiac disease
Small intestine bacterial overgrowth *	Breath tests, culture of intestinal fluid, empiric trial with antibiotics	Frequent
Exocrine pancreatic insufficiency	Fecal elastase or other indirect pancreatic function tests, empiric trial with pancreatic enzymes	Low fecal elastase observed in up to 30% treated celiacs with diarrhea
Microscopic colitis	Colonic biopsies	Frequent, suspect if recurrent watery diarrhea
Refractory celiac disease *	Detection of abnormal (clonal) intraepithelial lymphocytes, extensive endoscopic and imaging evaluation	Rare, diagnosis of exclusion that may be supported by positive findings
Functional bowel disorders	Clinical criteria	Common, diagnosis should be strongly suspected in patients with normal histology and prominent symptoms
Protein-losing enteropathy	Fecal α-1 antitrypsin	Rare, suspect if severe hypoalbuminemia or lymphopenia
Lactose and fructose intolerance	Breath tests, food exclusion trial	Prevalence in nonresponsive CD unknown
Giardiasis *	Microscopic analysis of stool or intestinal fluid, Giardia antigen in stool	Frequent cause of chronic symptoms and malabsorption. Prevalence of giardiasis in nonresponsive CD unknown
Malignancies	Bowel & body imaging, deep- enteroscopy with biopsies	Rare but important especially in old adults

* Disorders associated with abnormal duodenal biopsy on follow-up