Online Submissions: wjg.wjgnet.com
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2008 February 14; 14(6): 828-830
World Journal of Gastroenterology ISSN 1007-9327

OBSERVER

Refractory celiac disease and sprue-like intestinal disease

Hugh James Freeman

Hugh James Freeman, Department of Medicine (Gastroenterology), University of British Columbia, Vancouver, BC, Canada
Correspondence to: Hugh James Freeman, MD, FRCPC, FACP, Department of Gastroenterology, University of British Columbia, Hospital, 2211 Wesbrook Mall, Vancouver, BC V6T1W5, Canada. hugfree@shaw.ca
Telephone: +1-604-8227216 Fax: +1-604-8227236
Received: November 10, 2007 Revised: January 1, 2008

Abstract

Celiac disease is a gluten-dependent small intestinal mucosal disorder that causes malabsorption, often with diarrhea and weight loss. Diagnosis is based on detection of typical biopsy changes in the proximal small bowel, followed by evidence for an unequivocal response to a gluten-free diet. Refractoriness in celiac disease may be due to poor diet compliance, sometimes intentional, or consumption of ubiquitous sources of gluten. Alternatively, the original diagnosis may not be correct (eg., duodenal Crohn's disease), or a second cause for symptoms may be present (eg., collagenous colitis, functional bowel disorder). In some with recurrent symptoms, a complication may be present (eg., collagenous sprue, small bowel carcinoma, lymphoma). In some, a response to a gluten-free diet can not be unequivocally defined, and more precise historical terms have been used including "sprue-like intestinal disease" or "unclassified sprue". Although a "wastebasket diagnosis", these likely represent a heterogeneous group, and some, but not all, may develop lymphoma. Precise definition will be critical in the future as an array of new treatments, including biological agents, may emerge.

Key words: Refractory celiac disease; Refractory sprue; Unclassified sprue; Celiac disease; Intestinal lymphoma; T-cell enteropathy

Peer reviewer: William Dickey, Altnagelvin Hospital, Londonderry, BT47 6SB, Northern Ireland, United Kingdom

Freeman HJ. Refractory celiac disease and sprue-like intestinal disease. *World J Gastroenterol* 2008; 14(6): 828-830 Available from: URL: http://www.wjgnet.com/1007-9327/14/828.asp DOI: http://dx.doi.org/10.3748/wjg.14.828

INTRODUCTION

Celiac disease is a gluten-dependent malabsorption disorder that involves the small bowel and can cause diarrhea and weight loss. Diagnosis is based on two criteria: first, proximal small intestinal mucosal biopsies that show typical biopsy abnormalities; and second, evidence for an unequivocal response to a gluten-free diet. Severe ("flat") or variably severe small bowel mucosal architectural abnormalities are present with crypt epithelial cell hyperplasia and villous atrophy. Lymphoid cell changes also occur, including intraepithelial lymphocytosis. Alterations are most severe in duodenum and proximal jejunum, and less severe, or absent, in ileum. Although characteristic, these findings are not specific or diagnostic alone as several disorders can produce similar, but not necessarily, identical histopathological changes (Table 1). Some serological assays (eg., tissue transglutaminase antibodies, or tTG) are useful screening tools in adults, but these alone do not permit a definitive diagnosis. The most critical step in the diagnosis of celiac disease is definition of a gluten-free diet response. Usually, with a gluten-free diet, diarrhea resolves and weight gain occurs. Histopathologic changes in the small bowel normalize, initially in distal intestinal sites of involvement, and later, sometimes only after prolonged periods (even months to years), in the proximal duodenum[1,2]. Recent studies have also shown that normalization of duodenal biopsies may take even longer in the elderly[3].

REFRACTORINESS IN CELIAC DISEASE

Recurrent symptoms may occur in established celiac disease (Table 2). Most often, this appears to be due to poor compliance with a strict gluten-free diet, although compliance is sometimes very difficult to define or fully ascertain. Intentional dietary indiscretion may be obvious, or, alternatively, there may be limited awareness of gluten-containing food sources. Gluten is so ubiquitous, known to be present in pill capsules and communion wafers, as well as in a host of processed food products. Gluten-free foods may be quite expensive, limited in their palatability, and, especially in some developing countries, difficult to obtain. Moreover, professionals, including physicians and dietitians, support groups and the internet, all represent potential sources of inaccurate information. Motivation to follow a strict diet may be limited if symptoms are minimal or absent when "cheating" occurs. Finally, social or peer pressure, especially during adolescence or early adulthood may also hinder efforts to maintain compliance.

In some with recurrent symptoms, however, other causes may be responsible. It is possible that the original

Table 1 Some causes of biopsy changes similar to celiac disease

Causes	Diseases
Sprue syndromes	Collagenous sprue
	Mesenteric lymph node cavitation syndrome
	Oats-induced villous atrophy
	Other protein injury (soy, milk)
	Unclassified or refractory sprue
Infectious causes	Infectious gastroenteritis
	Specific infections (eg., parasite: strongyloidiasis, Protozoan: giardia, mycobacteria)
	Tropical sprue
	Stasis syndrome (contaminated small bowel syndrome)
	Whipple's disease
Deficiency causes	Nutrients (zinc, vitamin B12, folic acid)
	Kwashiorkor
	Immunodeficiency syndromes
Others	Intestinal lymphangiectasia
	Crohn's disease (duodenum)
	Graft-versus-host disease
	Immunoproliferative disease (lymphoma)
	Macroglobulinemia
	Zollinger-Ellison syndrome
	Drug-induced small bowel injury (eg. NSAIDs)

diagnosis was incorrect, especially if there was only limited attention to defining the response to a gluten-free diet. And, there are many conditions that may cause a virtually identical histopathological small bowel lesion[4]. In addition, a second cause for symptoms may have developed. These may include other associated or linked disorders, like collagenous colitis[5] or even a functional bowel disorder. Alternatively, in those that appear to have "refractory" symptoms, a complication may have developed (eg., collagenous sprue, small intestinal carcinoma, lymphoma)[6]. In some with persistent symptoms and architecturally abnormal biopsies, clonal expansion of an aberrant intra-epithelial lymphocyte population has been reported (so-called type 2 disease versus type 1 disease with apparently normal intraepithelial lymphocyte phenotype). This condition has been labeled "cryptic T-cell lymphoma" as there appears to be a higher risk of overt T-cell lymphoma[2,7].

UNCLASSIFIED SPRUE OR "SPRUE-LIKE INTESTINAL DISEASE"

Sometimes, the small bowel biopsy changes do not appear to improve despite apparently good compliance on a gluten-free diet. Persistent symptoms and changes in the small bowel biopsies are present. Although a relatively treatment-resistant form of celiac disease could be present, possibly with a distal small bowel diet response, it is more likely that celiac disease is not present at all. Rather than labeling these patients with refractory celiac disease, more precise terms have been historically used including "sprue-like intestinal disease" or "unclassified sprue"[8].

In these, persistent symptoms and ongoing pathological changes are present despite a strict gluten-free diet. In some reports, persistent pathological abnormalities refer to results of repeated endoscopic biopsies from the proximal small bowel during an arbitrary time period of 6 mo to up to one year. Rarely, there is a rapidly progressing disease course that makes it difficult to show a convincing response to a gluten-free diet. While clinical and pathological changes are reminiscent of celiac disease in some of these patients, there is usually no convincing evidence that a gluten-free diet response ever occurred. "Sprue-like intestinal disease" or unclassified sprue is a "wastebasket" disease diagnosis that appears to represent a heterogeneous group of different disorders. Some eventually develop lymphoma, but some do not. A few are reported to have epithelial cell antibodies, specificially anti-enterocyte and anti-goblet cell antibodies. These have been reported in both children or adults with persistent diarrhea and severe biopsy changes, similar to untreated celiac disease. In these, no response to a gluten-free diet or any dietary exclusion occurs. Some believe that these represent a distinct autoimmune enteropathic disorder[10].

Table 2 Recurrent or refractory symptoms in celiac disease

Dietary non-compliance
Ubiquitous gluten source (eg., pill capsules)
Wrong initial diagnosis
Associated or second cause (eg., collagenous colitis)
Superimposed complication (eg., collagenous sprue, lymphoma)

FUTURE DEVELOPMENTS

Refractory disease represents a complex array of difficult clinical problems, in part, because definitions are evolving and there is no clear consensus for treatment, unless a lymphoma has already been detected. In case reports of refractory disease with clonally expanded T-cell populations, use of infliximab[11] and cladribine[12] were described, but progression to overt lymphoma occurred. In addition, use of autologous hematopoietic stem-cell transplantation has also been done, but with mixed results, especially if overt T-cell lymphoma is present[13-15]. Better refinements in the definition of refractory diseases are needed, possibly using genetic markers to identify risk[16]. These may eventually aid in treatment, especially with emergence of an array of new biological agents for treatment of immune-mediated and malignant disorders.

REFERENCES

1 **Freeman HJ**. Adult celiac disease and the severe "flat" small bowel lesion. *Dig Dis Sci* 2004; **49**: 535-545
2 **Green PH**, Cellier C. Celiac disease. *N Engl J Med* 2007; **357**: 1731-1743
3 **Tursi A**, Brandimarte G, Giorgetti GM, Elisei W, Inchingolo CD, Monardo E, Aiello F. Endoscopic and histologic findings in the duodenum of adults with celiac disease before and after changing to a gluten-free diet: a 2-year prospective study. *Endoscopy* 2006; **38**: 702-707
4 **Freeman HJ**. Small intestinal mucosal biopsy for investigation of diarrhea and malabsorption in adults. *Gastrointestinal Endoscopy Clin North Am* 2000; **10**: 739-753
5 **Freeman HJ**. Collagenous colitis as the presenting feature of biopsy-defined celiac disease. *J Clin Gastroenterol* 2004; **38**: 664-668
6 **Freeman HJ**. Lymphoproliferative and intestinal malignancies

in 214 patients with biopsy-defined celiac disease. *J Clin Gastroenterol* 2004: **38**: 429-434

7 **Cellier C**, Patey N, Mauviex L, Jabri B, Delabesse E, Cervoni J-P, Burtin M-L, Guy-Grand D, Bouhnik Y, Modigliani R, Barbier J-P, Macintyre E, Brousse N, Cerf-Bensussan N. Abnormal intestinal intraepithelial lymphocytes in refractory sprue. *Gastroenterology* 1998; **114**: 471-481

8 **Rubin CE**, Eidelman A, Weinstein WM. Sprue by any other name. *Gastroenterology* 1970; **58**: 409-413

9 **Gillett HR**, Arnott ID, McIntyre M, Campbell S, Dahele A, Priest M, Jackson R, Ghosh S. Successful infliximab treatment for steroid-refractory celiac disease: a case report. *Gastroenterology* 2002; **122**: 800-805

10 **Akram S**, Murray JA, Pardi DS, Alexander GL, Schaffner JA, Russo PA, Abraham SC. Adult autoimmune enteropathy: Mayo Clinic Rochester experience. *Clin Gastroenterol Hepatol* 2007; **5**: 1282-1290

11 **Vivas S**, Ruiz de Morales JM, Ramos F, Suarez-Vilela D. Alemtuzumab for refractory celiac disease in a patient at risk for enteropathy-associated T-cell lymphoma. *N Engl J Med* 2006; **354**: 2514-2415

12 **Al-toma A**, Goerres MS, Meijer JW, von Blomberg BM, Wahab PJ, Kerkhaert JA, Mulder CJ. Cladribine therapy in refractory celiac disease with aberrant T cells. *Clin Gastroenterol Hepatol* 2006; **4**: 1322-1327

13 **Al-toma A**, Visser OJ, van Roessel HM, von Blomberg BM, Verbeek WH, Scholten PE, Ossenkoppele GJ, Huijgens PC, Mulder CJ. Autologous hematopoietic stem cell transplantation in refractory celiac disease with aberrant T cells. *Blood* 2007; **1098**: 2243-2249

14 **Al-toma A**, Verbeek WH, Visser OJ, Kuijpers KC, Oudenjans JJ, Kluin-Nelemans HC, Mulder CJ, Huijgens PC. Disappointing outcome of autologous stem cell transplantation for enteropathy-associated T-cell lymphoma. *Dig Liver Dis* 2007; **39**: 639-641

15 **Bishton JM**, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T-cell lymphoma. *Br J Haematol* 2007; **136**: 111-113

16 **Wolters VM**, Verbeek WH, Zhernakova A, Onland-Moret C, Schreurs MW, Monsuur AJ, Verduijn W, Wijmenga C, Mulder CJ. The MYO9B gene is a strong risk factor for developing refractory celiac disease. *Clin Gastroenterol Hepatol* 2007; **5**: 1399-1405, 1405. e1-e2

S- Editor Li DL **L- Editor** Alpini GD **E- Editor** Wang HF