

WRITING REQUIREMENTS OF OBSERVATION



1 Title: Title should be less than 12 words.

2 Running Title: A short running title of less than 6 words should be provided.

3 Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

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5 Abstract: An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/...; MATERIALS AND METHODS (no more than 140 words); RESULTS(no more than 294 words): You should present *P* value where necessary and must provide relevant data to illustrate how it is obtained, e.g. 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$; CONCLUSION(no more than 26 words).**6 Keywords:** Please list 5-10 key words for each manuscript, selected mainly from Index Medicus, which reflect the content of the study. [Each key word is separated by](#) a semicolon.

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8 Tables and illustrations: Each table or illustration should be made on a separate sheet and should be “self-explanatory” (sufficient to be intelligible without reference to the text). Avoid repetitions of data in the text, tables, and illustration. Explain tersely the symbols, letters, or number used. Indicate the number and character of observations and subjects. Identify statistical significance by superscripts in front of the probabilities (P), e.g. ^a $P < 0.05$, ^b $P < 0.01$ vs A; ^c $P < 0.05$, ^d $P < 0.01$ vs B; etc.

8.1 Figures: You should provide decomposable figures with a size of 5 : 7 (height : width) in general. The curves or straight lines should be clear. Freehand or typewritten lettering is unacceptable. Units can not be omitted. Combine related curves in a single figure when possible. A composite of curves will save space and convey more information. Standard symbols (e.g. ○, ●, ×, □, ■, △, ▲) should be used when there are multiple curves.

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8.2.2 Images submitted should be those which uniquely display the data. Figures are not limited, but must be thoroughly justified. For figures that have multiple panels, the labels should be set in uppercase Helvetica or Arial letters and should not contain periods or parentheses. Please be sure to embed all fonts. Micrographs should be provided with a scale bar, if appropriate, instead of magnification. Figures should be should be either Photoshop or Illustrator files (in tiff, psd, eps, ai, pdf, or JPEG formats) at 300 dpi resolution (for a figure no smaller than 50 mm in height and 86 mm in width). Our professional in-house illustrator will work with authors to ensure the highest quality and clarity of published figures. Please provide only one legend for

each photo or figure that contains all the pertinent information. Figures or photos should be grouped according to their themes. For example, Figure 1 Pathological changes of atrophic gastritis tissue before and after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: Explain the symbols, arrows, numbers, or letters in the illustrations. Identify the method of staining and magnification of the photomicrographs (eg, HE stain, ×900). For those including methodology, the legend should be no more than 100 words (no more than 500 words in total). For those not including methodology, the legend should be no more than 300 words (no more than 800 words in total). Letters in photos or figures should be lowercased while the first one be capitalized. An interval should be inserted between numbers and units. Photos or figures that are obtained at different time or places must not be grouped into one, unless those photos or figures are arranged in a time order. There are intervals between photos or figures of the same group. Photographs or figures should be put in an independent file.

8.2.3 Authors should list the names of tools they use to obtain and edit the image file. Images must be edited equally and contrast must be reasonable. Editing that is far beyond the contents is forbidden. It is not allowed to over-emphasize the difference between experiment data and control data, or over-emphasize a certain part of the photos by ignoring some other parts. (A) Electrophoresis and blotting images: must include negative, positive controls and molecular Marker; provide the reference of the identified antibodies; explain the specificity and active spectrum of the agents not identified; band should be clear; important bands must not be deleted; leave six-band space around the blotting bands; we suggest not use high-contrast blotting, for over-display may conceal the other bands. Authors should try to exhibit the bands on the gray background. Black frame may be used if the background is weak. (B) Microscopic or endoscopic images: cells from different field must not be put in the same field; images should be adjusted at a whole; avoid

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Format for OBSERVATION

OBSERVATION

Hugh James Freeman, MD, FRCPC, FACP, *Series Editor*

Refractory celiac disease and sprue-like intestinal disease

Freeman HJ. Refractory or unclassified celiac disease

Hugh James Freeman

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Author contributions: Freeman HJ solely contributed to this paper.

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Abstract (256 words)

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.

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

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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 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, specifically 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].

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.

ACKNOWLEDGMENTS

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S-Editor L-Editor E-Editor

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)

Table 2 Recurrent or refractory symptoms in celiac disease

Dietary non-compliance

Ubiquitous gluten source (e.g. pill capsules)

Wrong initial diagnosis

Associated or second cause (e.g. collagenous colitis)

Superimposed complication (e.g. collagenous sprue, lymphoma)