REVIEW ARTICLE

MEDICAL PROGRESS

Celiac Disease

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Celiac disease is a unique autoimmune disorder, unique because the environmental precipitant is known. The disorder was previously called celiac sprue, based on the Dutch word *sprue*, which was used to describe a disease similar to tropical sprue that is characterized by diarrhea, emaciation, aphthous stomatitis, and malabsorption.[1,2] Celiac disease is precipitated, in genetically predisposed persons, by the ingestion of gluten, the major storage protein of wheat and similar grains.[3] Originally considered a rare malabsorption syndrome of childhood, celiac disease is now recognized as a common condition that may be diagnosed at any age and that affects many organ systems. The therapy for the disease is a gluten-free diet; however, the response to therapy is poor in up to 30% of patients, and dietary nonadherence is the chief cause of persistent or recurrent symptoms. Small intestinal adenocarcinoma, refractory sprue, and enteropathy-associated T-cell lymphoma are complications of celiac disease that must be ruled out when alarming symptoms such as abdominal pain, diarrhea, and weight loss develop despite a strict gluten-free diet.

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PATHOGENESIS

Celiac disease results from the interaction between gluten and immune, genetic, and environmental factors (Fig. 1).

THE ROLE OF GLUTEN

Celiac disease is induced by the ingestion of gluten, which is derived from wheat, barley, and rye. The gluten protein is enriched in glutamine and proline and is poorly digested in the human upper gastrointestinal tract. The term "gluten" refers to the entire protein component of wheat; gliadin is the alcohol-soluble fraction of gluten that contains the bulk of the toxic components. Undigested molecules of gliadin, such as a peptide from an α-gliadin fraction made up of 33 amino acids, are resistant to degradation by gastric, pancreatic, and intestinal brush-border membrane proteases in the human intestine and thus remain in the intestinal lumen after gluten ingestion.[4] These peptides pass through the epithelial barrier of the intestine, possibly during intestinal infections or when there is an increase in intestinal permeability, and interact with antigen-presenting cells in the lamina propria.

MUCOSAL IMMUNE RESPONSES

In patients with celiac disease, immune responses to gliadin fractions promote an inflammatory reaction, primarily in the upper small intestine, characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy (Fig. 1). This response is mediated by both the innate and the adaptive immune systems. The adaptive response is mediated by gliadin-reactive CD4+ T cells in the lamina propria that recognize gliadin peptides, which are bound

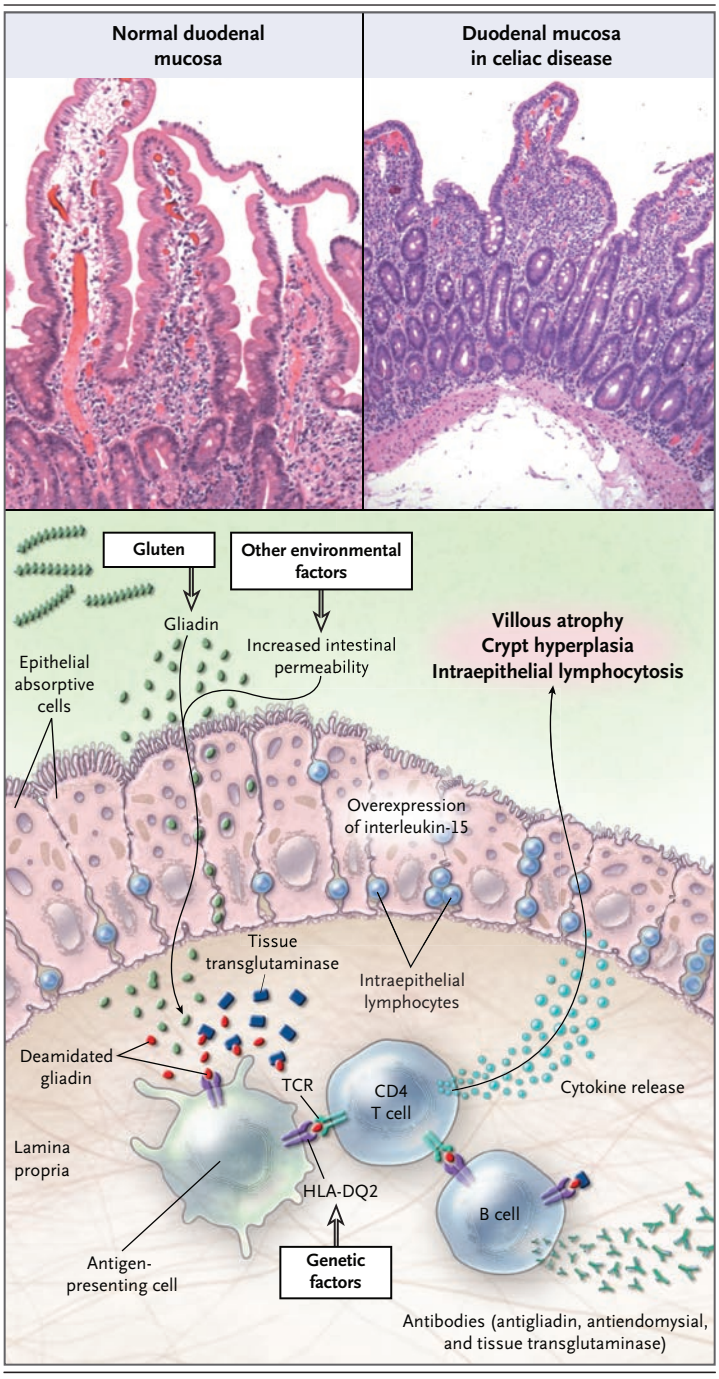

Figure 1. Interaction of Gluten with Environmental, Immune, and Genetic Factors in Celiac Disease.

Gluten is digested by luminal and brush-border enzymes into amino acids and peptides. The gliadin peptides induce changes in the epithelium through the innate immune system and, in the lamina propria, through the adaptive immune system. In the epithelium, gliadin damages epithelial cells, resulting in increased expression of interleukin-15, which in turn activates intraepithelial lymphocytes. These lymphocytes become cytotoxic and kill enterocytes that express MIC-A (a stress protein) on their surface. During infections or as the result of permeability changes, gliadin enters the lamina propria, where it is deamidated by tissue transglutaminase, allowing interaction with HLA-DQ2 (or HLA-DQ8) on the surface of antigen-presenting cells. Gliadin is presented to gliadin-reactive CD4+ T cells through a T-cell receptor, resulting in the production of cytokines that cause tissue damage. This leads to villous atrophy and crypt hyperplasia, as well as the activation and expansion of B cells that produce antibodies. Images of mucosa courtesy of Govind Bhagat, M.D.

to HLA class II molecules DQ2 or DQ8 on antigen-presenting cells; the T cells subsequently produce proinflammatory cytokines,[5] particularly interferon-γ.[6] Tissue transglutaminase is an enzyme in the intestine that deamidates gliadin peptides, increasing their immunogenicity.[7] The ensuing inflammatory cascade releases metalloproteinases and other tissue-damaging mediators that induce crypt hyperplasia and villous injury.[8] Gliadin peptides also activate an innate immune response in the intestinal epithelium that is characterized by increased expression of interleukin-15 by enterocytes, resulting in the activation of intraepithelial lymphocytes expressing the activating receptor NK-G2D, a natural-killer-cell marker.[9] These activated cells become cytotoxic and kill enterocytes with surface expression of major-histocompatibility-complex class I chain-related A (MIC-A), a cell-surface antigen induced by stress, such as an infection.[10,11] The mechanism of the interaction between the processes in the epithelium and lamina propria has not been elucidated.

GENETIC FACTORS

The genetic influence in the pathogenesis of celiac disease is indicated by its familial occurrence.[12] Celiac disease does not develop unless a person has alleles that encode for HLA-DQ2 or HLA-DQ8 proteins, products of two of the HLA genes.[13] However, many people, most of whom do not have celiac disease, carry these alleles; thus, their presence is necessary but not sufficient for the development of the disease. Studies in siblings and identical twins suggest that the contribution of HLA genes to the genetic component of celiac disease is less than 50%.[14] Several non-HLA genes that may influence susceptibility to the disease

have been identified, but their influence has not been confirmed.

ENVIRONMENTAL FACTORS

Environmental factors that have an important role in the development of celiac disease have been suggested by epidemiologic studies. These include a protective effect of breast-feeding[15] and the introduction of gluten in relation to weaning.[16-18] The initial administration of gluten before 4 months of age is associated with an increased risk of disease development,[18] and the introduction of gluten after 7 months is associated with a marginal risk.[18] However, the overlap of gluten introduction with breast-feeding may be a more important protective factor in minimizing the risk of celiac disease.[16] The occurrence of certain gastrointestinal infections, such as rotaviral infection, also increases the risk of celiac disease in infancy.[19] Further study of environmental factors might facilitate the development of strategies for primary prevention of celiac disease.[20]

EPIDEMIOLOGY

Celiac disease occurs in adults and children at rates approaching 1% of the population.[21-25] The disease is recognized not only throughout Europe and in countries populated by persons of European ancestry but also in the Middle East,[23,26] Asia,[27] South America.[28] and North Africa.[29] In most affected people, celiac disease remains undiagnosed,[21] although the rate of diagnosis is increasing.[30]

CLINICAL MANIFESTATIONS

Clinical manifestations of celiac disease vary greatly according to age group. Infants and young children generally present with diarrhea, abdominal distention, and failure to thrive. However, vomiting, irritability, anorexia, and even constipation are also common. Older children and adolescents often present with extraintestinal manifestations, such as short stature, neurologic symptoms, or anemia.[31]

Among adults, two to three times as many women have the disease as men, for unknown reasons. In general, the prevalence of autoimmune diseases is higher in women than in men, and iron deficiency and osteoporosis, each of which prompts an assessment for celiac disease, are more often diagnosed in women. The predominance of the disease in women diminishes somewhat after the age of 65 years.[32] The classic presentation in adults is diarrhea, which may be accompanied by abdominal pain or discomfort. However, diarrhea has been the main presenting symptom in less than 50% of cases in the past decade.[33] Other, silent presentations in adults include iron-deficiency anemia, osteoporosis, and incidental recognition at endoscopy performed for other reasons, such as symptoms of gastroesophageal reflux.[34] Less common presentations include abdominal pain, constipation, weight loss, neurologic symptoms, dermatitis herpetiformis, hypoproteinemia, hypocalcemia, and elevated liver enzyme levels.[35] Substantial proportions of patients have received a previous diagnosis of the irritable bowel syndrome[32,36] and are overweight.[37] Patients often have symptoms for a long time and undergo multiple hospitalizations and surgical procedures before celiac disease is diagnosed.[32,38,39]

Some cases are diagnosed because of increased surveillance for celiac disease among people who have a family history of the disease[24] and among those with Down syndrome, Turner's syndrome,[40,41] or type 1 diabetes, all of which are associated with celiac disease.[42] Persons with celiac disease have an increased risk of autoimmune disorders as compared with the general population.[43-45]

A case-finding study performed in multiple primary care practices in North America reported a 43-fold increase in the rate of diagnosis of celiac disease over the 2 years of the study.[46] The indications for screening in those who received the diagnosis included bloating, the irritable bowel syndrome, thyroid disease, chronic unexplained diarrhea, chronic fatigue, and constipation. The case-finding study shows that many patients with celiac disease are seeking health care for a great variety of common symptoms and that the more frequent use of screening is uncovering more cases of the disease.

DIAGNOSIS

The diagnosis of celiac disease requires both a duodenal biopsy that shows the characteristic findings of intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy and a positive response to a gluten-free diet. The diagnostic criteria developed by the European Society for Pediatric Gastro-

enterology and Nutrition require only clinical improvement with the diet,[47] although histologic improvement on a gluten-free diet is frequently sought and is recommended in adults because villous atrophy may persist despite a clinical response to the diet. In most patients, the diagnosis is easily established. However, roughly 10% of cases are difficult to diagnose because of a lack of concordance among serologic, clinical, and histologic findings.

SEROLOGIC TESTING

Typical indications for serologic testing include unexplained bloating or abdominal distress; chronic diarrhea, with or without malabsorption or the irritable bowel syndrome; abnormalities on laboratory tests that might be caused by malabsorption (e.g., folate deficiency and iron-deficiency anemia); first-degree relatives with celiac disease; and autoimmune diseases and other conditions known to be associated with celiac disease (for more information on indications for serologic testing, see the table in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

The most sensitive antibody tests for the diagnosis of celiac disease are of the IgA class. The available tests include those for antigliadin antibodies, connective-tissue antibodies (antireticulin and antiendomysial antibodies), and antibodies directed against tissue transglutaminase, the enzyme responsible for the deamidation of gliadin in the lamina propria. The antigliadin antibodies are no longer considered sensitive enough or specific enough to be used for the detection of celiac disease, except in children younger than 18 months of age,[48] although new-generation antibodies to deamidated gliadin peptides appear to be promising.[49] Antireticulin antibodies are also rarely measured, having been surpassed in use by endomysial and anti–tissue transglutaminase antibodies.

The diagnostic standard in celiac serologies remains the endomysial IgA antibodies; they are highly specific markers for celiac disease, approaching 100% accuracy. The recognition that the enzyme tissue transglutaminase is the autoantigen for the development of endomysial antibodies[50] allowed development of automated enzyme-linked immunoassays that are less expensive than the endomysial antibody test. Overall, the sensitivity of the tests for both endomysial antibodies and anti–tissue transglutaminase antibodies is greater than 90%,[48] and a test for either marker is considered the best means of screening for celiac disease.[48] The titers of endomysial antibodies and anti–tissue transglutaminase antibodies correlate with the degree of mucosal damage[51,52]; as a result, the sensitivity of these antibody tests declines when a greater number of patients with lesser degrees of villous atrophy are included in studies.[53,54] The various commercially available assays for anti–tissue transglutaminase antibodies have different characteristics and resultant sensitivities and specificities.[55]

Selective IgA deficiency is more common in patients with celiac disease than in the general population — 1 case in 40 as compared with 1 in 400. Consequently, patients with celiac disease and selective IgA deficiency lack IgA endomysial antibodies and IgA antitissue antibodies against tissue transglutaminase. It is recommended that the test for anti–tissue transglutaminase antibodies be used as a single screening test for celiac disease.[48,56] If the levels of this marker are within the normal range (or if it is absent) and there is a high suspicion of celiac disease, selective IgA deficiency needs to be ruled by measuring total IgA levels. In such cases, a test for IgG antibodies against tissue transglutaminase should be performed.[57]

These antibody tests fare less well in the clinical-practice setting than in the research setting.[58,59] A recently developed rapid test for anti–tissue transglutaminase antibodies that uses a sample of fingertip blood may be a convenient point-of-care test for the purpose of both case finding and dietary monitoring.[60]

THE ROLE OF *HLA-DQ2* AND *HLA-DQ8* ASSESSMENT

The *HLA-DQ2* allele is identified in 90 to 95% of patients with celiac disease, and *HLA-DQ8* is identified in most of the remaining patients.[61] Because these alleles occur in 30 to 40% of the general population (with *HLA-DQ2* more common than *HLA-DQ8*), the absence of these alleles is important for its high negative predictive value.[62] Thus, the presence or absence of *HLA-DQ2* and *HLA-DQ8*

is important for determining which family members should be screened with serologic testing and is useful for ruling out the disease in patients already on a gluten-free diet or for patients in whom the diagnosis is unclear.

BIOPSY AND HISTOLOGIC ASSESSMENT

Biopsy of the small intestine remains the standard for diagnosing celiac disease, and it should always be performed when clinical suspicion is high, irrespective of the results of serologic testing. Biopsy confirmation is crucial, given the lifelong nature of the disease and the attendant need for an expensive and socially inconvenient diet. Although no studies have examined the number of biopsies required for diagnosis, we believe that at least four to six endoscopic-biopsy specimens should be obtained from the duodenum, given the patchy nature of the disease and the difficulty of orienting the small pieces of tissue taken during biopsy for assessment of villous morphology.[63,64]

Who should undergo endoscopic biopsy? In addition to patients whose serologic tests are positive, any patient who has chronic diarrhea, iron deficiency, or weight loss should undergo duodenal biopsy, irrespective of whether serologic testing for celiac disease has been performed. The recognition of endoscopic signs of villous atrophy, such as scalloping of mucosal folds, absent or reduced duodenal folds, or a mosaic pattern of the mucosa, should prompt biopsy.[65] However, because these abnormalities are not sensitive markers of the presence of celiac disease,[66] biopsy should be performed even if they are absent.

The spectrum of pathologic changes in celiac disease ranges from near-normal villous architecture with a prominent intraepithelial lymphocytosis to total villous atrophy.[67] Pitfalls in the pathological diagnosis include overinterpretation of villous atrophy in poorly oriented biopsy specimens and inadequate biopsy sampling in patients with patchy villous atrophy.[63,64] The histologic findings in celiac disease are characteristic but not specific[68]; their presence permits a presumptive diagnosis of celiac disease and initiation of a gluten-free diet. Indeed, celiac disease is not the only cause of villous atrophy (Table 1). The diagnosis is confirmed when there is a favorable response to the diet.

Table 1. Causes of Villous Atrophy Other Than Celiac Disease.

Giardiasis
Collagenous sprue
Common-variable immunodeficiency
Autoimmune enteropathy
Radiation enteritis
Whipple's disease
Tuberculosis
Tropical sprue
Eosinophilic gastroenteritis
Human immunodeficiency virus enteropathy
Intestinal lymphoma
Zollinger–Ellison syndrome
Crohn's disease
Intolerance of foods other than gluten (e.g., milk, soy, chicken, tuna)

Table 2. Fundamentals of the Gluten-free Diet.

Grains that should be avoided
Wheat (includes spelt, kamut, semolina, triticale), rye, barley (including malt)
Safe grains (gluten-free)
Rice, amaranth, buckwheat, corn, millet, quinoa, sorghum, teff (an Ethiopian cereal grain), oats
Sources of gluten-free starches that can be used as flour alternatives
Cereal grains: amaranth, buckwheat, corn (polenta), millet, quinoa, sorghum, teff, rice (white, brown, wild, basmati, jasmine), montina (Indian rice grass)
Tubers: arrowroot, jicama, taro, potato, tapioca (cassava, manioc, yucca)
Legumes: chickpeas, lentils, kidney beans, navy beans, pea beans, peanuts, soybeans
Nuts: almonds, walnuts, chestnuts, hazelnuts, cashews
Seeds: sunflower, flax, pumpkin

TREATMENT

Nutritional therapy, the only accepted treatment for celiac disease, involves the lifelong elimination of wheat, rye, and barley from the diet. Clinical studies suggest that oats are tolerated by most patients with celiac disease and may improve the nutritional content of the diet and overall quality of life.[69] However, oats are not uniformly recommended, because most commercially available oats are contaminated with gluten-containing grains during the growing, transportation, and milling processes.[70]

Although wheat, rye, and barley should be avoided, there are other grains that can serve as substitutes as well as other sources of starch that can provide flours for cooking and baking (Table 2). Because the substitute flours are not fortified with B vitamins, vitamin deficiencies may occur; they have been detected in patients who are on the diet for a long time (more than 10 years).[71] Therefore, vitamin supplementation is advised. Meats, dairy products, and fruits and vegetables are naturally gluten-free and help to make for a more nutritious and varied diet.

After the diagnosis of celiac disease has been established, the patient should be assessed for deficiencies of vitamins and minerals, including folic acid, B_{12}, fat-soluble vitamins, iron, and calcium, and any such deficiencies should be treated. All patients with celiac disease should undergo screening for osteoporosis, which has a high prevalence in this population.[72,73] The health care team should include a skilled dietitian who monitors the patient's nutritional status and dietary adherence on a regular basis. In children, ongoing evaluation includes monitoring of growth and development.

The elimination of gluten usually induces clinical improvement within days or weeks, though histologic recovery takes months or even years, especially in adults, in whom mucosal recovery may be incomplete.[74] In rare cases, children tolerate the reintroduction of a normal diet after a long-term clinical and histologic response.[75]

Patient-support organizations are a valuable source of information about the disease and the diet. Most countries have national support groups that are easily accessed on the Internet. The cost of the gluten-free products varies by country, but the diet is usually expensive, making dietary treatment problematic for patients with limited financial resources. Gluten-free products are particularly expensive and hard to find in developing countries, whereas in other countries (including the Netherlands, the United Kingdom, New Zealand, Italy, Sweden, and Finland), the government subsidizes these products.

There is considerable interest in the development of nondietary therapies that might either replace or supplement the rigorous gluten-free diet. Currently, the most attractive alternative involves the use of recombinant enzymes that digest the toxic gliadin fractions in the stomach or the upper small intestine.[76,77] Therapies that interfere with the immune response — by blocking the binding of deaminated gliadin to HLA-DQ2 or HLA-DQ8, for example, or by blocking the action of tissue transglutaminase — are unlikely to be without side effects.

ASSESSMENT OF CASES WITH A POOR RESPONSE TO THERAPY

A gluten-free diet fails to induce clinical or histologic improvement in 7 to 30% of patients,[78] and such lack of response should trigger a systematic evaluation (Fig. 2). The first step is to reassess the initial diagnosis, since villous atrophy with associated crypt hyperplasia is not exclusive to celiac disease (Table 1). Rare causes should at least be considered in people who do not have the expected response to the diet. In patients with a questionable diagnosis, *HLA-DQ2* or *HLA-DQ8* typing may be useful, since the negative predictive value of this test is almost 100%.[62]

The second step is to address the likelihood of dietary nonadherence, the most common cause of unresponsive celiac disease. An experienced dietitian is required to assess the degree of adherence and possible reasons for nonadherence (Table 3). The highest rates of adherence are reported among patients with a diagnosis in childhood and those with severe symptoms at presentation. In France and Belgium, less than half of adults with celiac disease who were studied adhered strictly to the diet for more than a year after diagnosis.[79] In a study in the United Kingdom, the rate of adherence was low for both teenagers and adults,[80] and in a study in Italy, adolescents in whom the diagnosis was established on the basis of mass serologic screening had poor adherence.[81] In another study, many people in whom the disease was diagnosed in childhood became nonadherent to a strict gluten-free diet as adults.[82] The persistence of endomysial antibodies or anti–tissue transglutaminase antibodies in patients on a gluten-free diet for a year or more is suggestive of poor dietary adherence.[79] Other causes of persistent symptoms in patients on a strict gluten-free diet are listed in Table 3.

COMPLICATIONS OF CELIAC DISEASE

Although the majority of patients who have recurrent or new symptoms when on a supposedly gluten-free diet are in fact ingesting gluten, either

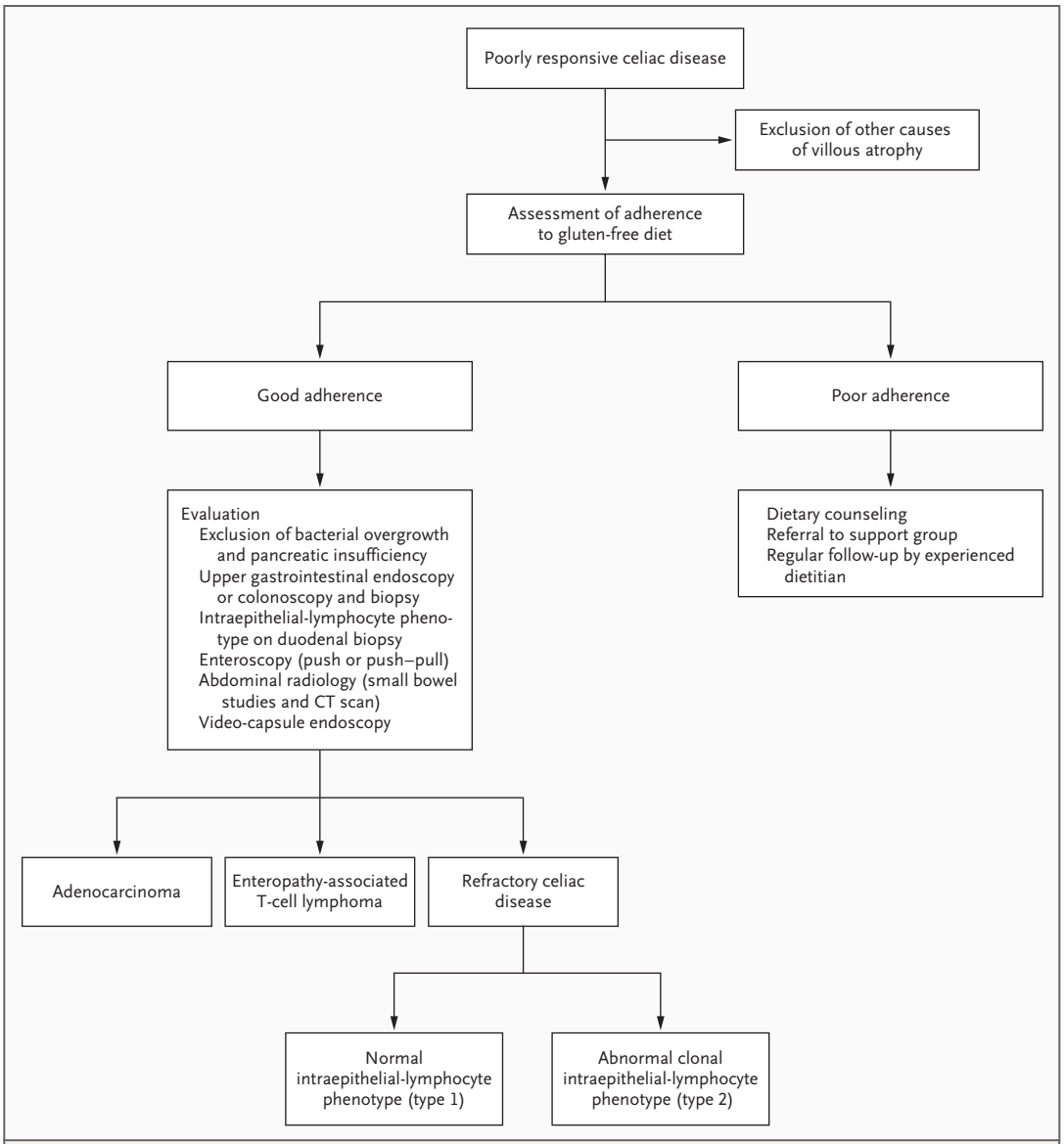

Figure 2. An Assessment Plan for a Patient with Poorly Responsive Celiac Disease.

intentionally or unintentionally, a substantial proportion may have a serious complication of celiac disease: intestinal adenocarcinoma, enteropathy-associated T-cell lymphoma, or refractory sprue.[83,84]

ADENOCARCINOMA OF THE SMALL INTESTINE

Patients with celiac disease have an overall risk of cancer that is almost twice that in the general population. New population-based studies demonstrate that the risk is not as great as once considered.[85] Reported cancers include both T-cell and B-cell non-Hodgkin's lymphoma that may be either intestinal or extraintestinal; oropharyngeal and esophageal adenocarcinoma; and cancers of the small and large intestine, hepatobiliary system, and pancreas.[86,87] The risk of breast cancer, however, appears to be reduced.[85,86]

In patients with celiac disease, the risk of adenocarcinoma of the small intestine, generally a rare cancer, is increased manyfold as compared with the risk in the general population[88]; still, the overall risk is very low given the rarity of this cancer. These carcinomas are most often located in the jejunum and are more likely to develop as an

Table 3. Problems of Dietary Adherence and Poor Response in Celiac Disease.

Reasons for poor adherence to a gluten-free diet
High cost
Poor availability of gluten-free products (in developing countries)
Poor palatability
Absence of symptoms when dietary restrictions not observed
Inadequate information on gluten content of food or drugs
Inadequate dietary counseling
Inadequate initial information supplied by diagnosing physician
Inadequate medical or nutritional follow-up
Lack of participation in a support group
Inaccurate information from physicians, dietitians, support groups, or Internet
Dining out of the home
Social, cultural, or peer pressures
Transition to adolescence
Inadequate medical follow-up after childhood
Causes of poorly responsive celiac disease
Incorrect diagnosis
Gluten ingestion (intentional or unintentional)
Microscopical colitis
Lactose intolerance
Pancreatic insufficiency
Bacterial overgrowth
Intolerance of foods other than gluten (e.g., fructose, milk, soy)
Inflammatory bowel disease
Irritable bowel syndrome
Anal incontinence
Collagenous sprue
Autoimmune enteropathy
Refractory celiac disease (with or without clonal T cells)
Enteropathy-associated T-cell lymphoma

adenoma–carcinoma sequence than as dysplasia in flat mucosa.[89] Intuitively, video-capsule endoscopy, which allows for visualization of the entire small intestinal mucosal surface, would seem to be ideal in screening for cancers, but as yet no data support this approach. At present, video-capsule endoscopy plays a role in the evaluation of celiac disease that is complicated by the development of abdominal pain or occult bleeding.[90]

ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA

Enteropathy-associated T-cell lymphoma occurs in adults, with the incidence peaking in the sixth decade of life, and is usually at an advanced stage at diagnosis. Symptoms may include malaise, anorexia, weight loss, diarrhea, abdominal pain, and unexplained fever. The development of lymphoma is usually indicated by clinical relapse of symptoms of celiac disease after a period of good response to gluten withdrawal. Enteropathy-associated T-cell lymphoma usually develops in the jejunum but may also be found in the ileum or in extraintestinal sites (e.g., liver, brain, chest, and bone) and is often multifocal. The prognosis is poor; less than 20% of patients survive for 30 months.[91] The phenotype of enteropathy-associated T-cell lymphoma is consistent with a tumor that derives from a clonal proliferation of intraepithelial lymphocytes. Immunohistochemical phenotyping indicates that this lesion is most commonly CD3+, CD4−, CD8−, CD30+, and CD103+.[92] The treatment of this tumor is chemotherapy based, although there is a role for surgery in the treatment of localized or complicated tumors.[93] Successful autologous stem-cell transplantation has been reported.[94]

REFRACTORY CELIAC DISEASE

Approximately 5% of patients may have refractory celiac disease, defined as persistent symptoms and villous atrophy despite scrupulous adherence to a gluten-free diet.[95] The symptoms that usually develop in these patients include diarrhea, weight loss, recurrence of malabsorption, abdominal pain, bleeding, and anemia, and ulcerative jejunitis often arises as well. This syndrome is also known as refractory sprue. The term was originally coined because it was unclear whether patients with diarrhea and villous atrophy whose condition did not improve with a gluten-free diet actually had celiac disease.[2]

Refractory celiac disease may be classified as type 1, in which there is a normal intraepithelial lymphocyte phenotype, or type 2, in which there is a clonal expansion of an aberrant intraepithelial lymphocyte population. The identification of an aberrant clonal population is primarily prognostic, since it is associated with a high risk of ulcerative jejunitis and frank enteropathy-associated T-cell lymphoma; the risk is so high that this condition has been described as a cryptic T-cell lymphoma.[83,96,97] The intraepithelial lymphocyte expansion may be driven by overexpression of interleukin-15 by the epithelium.[9-11] Specific immunophenotypic changes in the intraepithelial lymphocytes are seen in type 2 refractory celiac disease. Intraepithelial lymphocytes in active celiac disease exhibit surface expression of CD3, CD8, T-cell receptor (TCR) $\alpha\beta$, and TCR$\gamma\delta$, where-

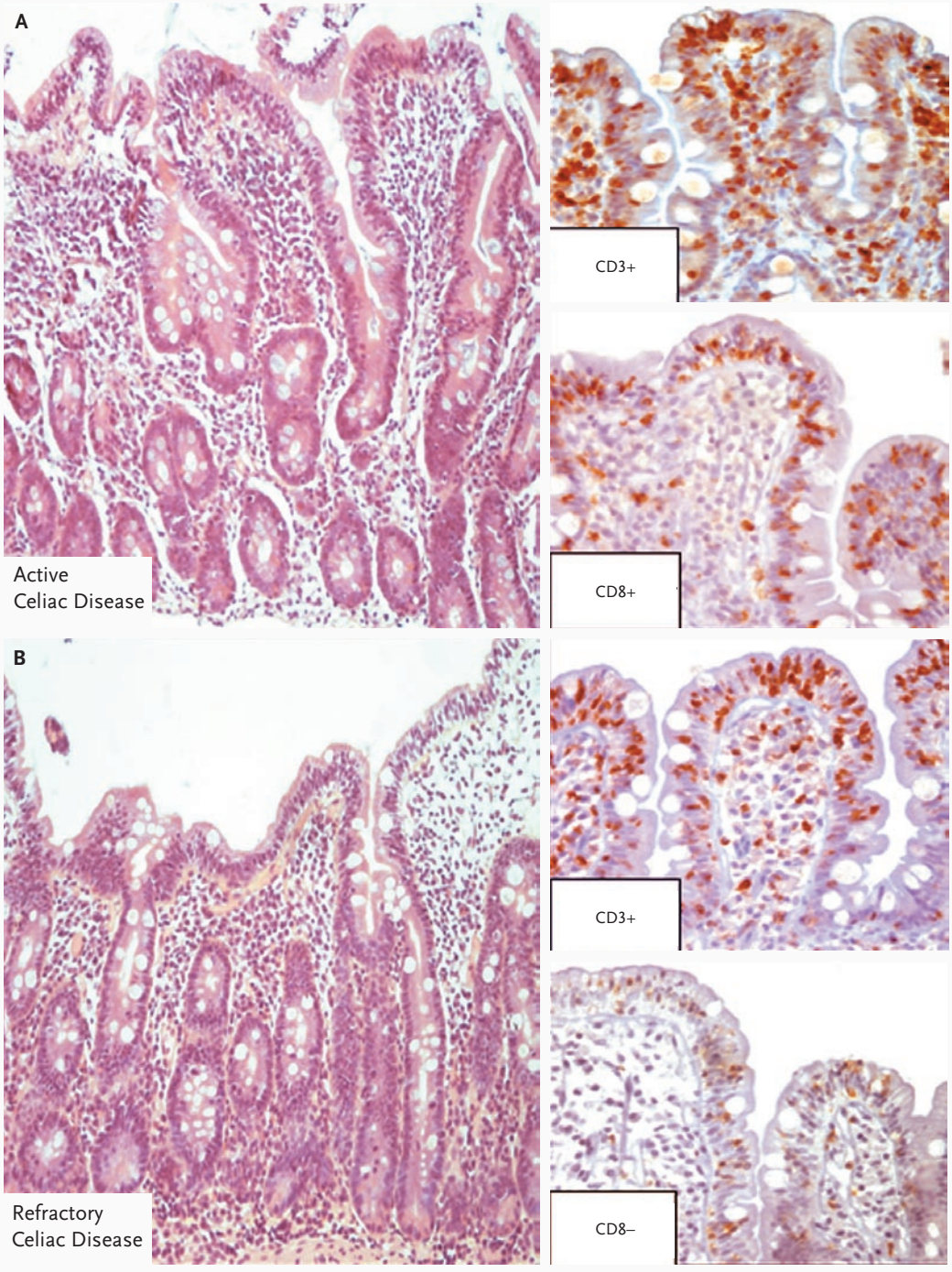

Figure 3. Phenotyping Intraepithelial Lymphocytes in Active versus Refractory Celiac Disease.

In active celiac disease (Panel A, hematoxylin and eosin), most intraepithelial lymphocytes express CD3 and CD8 (CD3+,CD8+) receptors, whereas in refractory celiac disease (Panel B, hematoxylin and eosin), most of these lymphocytes express CD3 but not CD8 (CD3+,CD8–). In insets, brown color denotes positive immunostaining. Images provided by Dr. Diane Damotte, Department of Pathology, European Georges Pompidou Hospital.

as intraepithelial lymphocytes in type 2 (clonal) refractory sprue continue to express CD3 in the cytoplasm but lack surface expression of CD8, CD3, TCR$\alpha\beta$, and TCR$\gamma\delta$.[92,96,98,99] Immunohistochemical studies demonstrating the presence of these cell-surface markers can be performed on formalin-fixed biopsy specimens in most clinical pathology laboratories. They allow for differentiation of type 2 refractory celiac disease, in which an abnormal phenotype of the intraepithelial lymphocytes (CD3+,CD8–), from type 1, in which there is a normal phenotype (CD3+,CD8+). Patients who are not adherent to the diet will also express this normal phenotype (Fig. 3).[100]

The development of new symptoms (e.g., weight loss, abdominal pain, or fever) or the recurrence of diarrhea in patients who are on a strict gluten-free diet often requires extensive investigation, including the use of contrast radiology or computed tomographic (CT) enteroclysis (in which CT imaging is performed after infusion of a large volume of contrast material — often 2 liters — into the small intestine), video-capsule endoscopy, positron-emission tomographic scanning, extended upper endoscopy (so-called push or push–pull enteroscopy), and laparoscopy.[90,101]

Treatment of refractory celiac disease involves nutritional support and repletion of vitamins and minerals, together with a strict gluten-free diet. In most cases, corticosteroids induce clinical improvement.[83] Immunosuppressive drugs may be beneficial[102,103] but should be used with caution, since they may promote the progression to lymphoma.[104]

The successful use of infliximab,[105] an anti-CD52 monoclonal antibody, and cladribine (2-clorodeoxyadenosine) has been reported, although the persistence of clonally expanded, aberrant intraepithelial lymphocytes and progression to an overt lymphoma have been reported in some treated patients, indicating that these drugs do not cure the disease.[106,107] Autologous hematopoietic stem-cell transplantation has been successful.[108]

New therapeutic strategies, such as blocking interleukin-15, should be aggressively investigated, since the prognosis for patients with clonal refractory disease is poor, with a 5-year survival rate of less than 50%.[83]

SUMMARY

Celiac disease occurs in nearly 1% of the population in many countries. The diagnosis, which is straightforward in most cases, is usually established on the basis of serologic testing, duodenal biopsy, and observation of the response to a gluten-free diet. A poor response to the diet is common and requires extensive evaluation to rule out intestinal lymphoma and refractory sprue, complications that arise as the result of clonal expansion of intraepithelial lymphocytes.

Increasing awareness of the epidemiology and diverse manifestations of the disease, as well as the availability of sensitive and specific serologic tests, especially among primary care physicians, will lead to more widespread screening and diagnosis, which in turn will lead to greater availability of gluten-free foods and efforts to develop drug therapies that relieve patients of the burden of a gluten-free diet. In addition, earlier diagnosis may lead to a reduction in the complications of the disease.

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