Diagnosis and Management of Gluten-Associated Disorders

A Clinical Casebook

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Preface

You are the place
where language fails
and I am the translator
of no language

–Morani Kornberg, *Dear Darwish*

The field of gluten-associated disorders (GADs), or gluten-related disorders, has grown tremendously in recent years. These disorders represent a spectrum of immune-mediated reactions to wheat or gluten, once believed to be rare, but currently affecting approximately 5% of the US population. Gluten is present in wheat, rye, and barley and has viscoelastic properties, helps dough rise, and adds flavor. For these reasons, it is widely used in different food products (including non-cereal), leading to an increase in the total amount of gluten in a typical western diet.

Based on pathogenesis, these disorders may be classified into three categories. The first, GADs of autoimmune origin, includes celiac disease (CeD), dermatitis herpetiformis (DH), and gluten ataxia (GA). The second, disorders of allergic origin, includes wheat allergy (WA) and eosinophilic gastroenteritis (EGE). The last group is comprised of conditions that are neither of autoimmune nor allergic origin, including non-celiac gluten sensitivity (NCGS), or non-celiac wheat sensitivity, and fructan intolerance (FI). Each disorder exhibits a unique pathophysiological response to gluten or wheat inges-

tion, but the overlap in clinical presentation results in diagnostic challenges, which this casebook aims to resolve.

The first chapter presents the main GAD, CeD, a multiorgan immune-mediated enteropathy affecting nearly 1% of the US population, caused by gluten ingestion in a subset of genetically predisposed individuals, who carry either or both HLA-DQ2/DQ8. The prevalence of CeD has increased over the last five decades, yet over 80% of patients remain undiagnosed. Most patients are diagnosed during adulthood with a female predominance. Gliadin is one of the main proteins in gluten, enhancing intestinal permeability in CeD and stimulating intestinal epithelial cells and intestinal epithelial lymphocytes to produce proinflammatory cytokines. Along with deamidated gluten, these lead to further recruitment of antigen presenting cells, natural killer cells, and lymphocytes, which then mediate antibody production and villous damage. Classical CeD presents with signs and symptoms of malabsorption (such as diarrhea, weight loss, and growth failure) while non-classical CeD manifests with non-malabsorptive symptoms (such as constipation, abdominal pain, dyspepsia, and bloating). Subclinical CeD presents with extraintestinal symptoms or clinical or laboratory signs (such as iron deficiency anemia, osteoporosis, and enamel defects) without gastrointestinal (GI) symptoms, and symptomatic CeD is characterized by GI and/or extraintestinal symptoms associated with gluten ingestion. CeD diagnosis is based on a combination of clinical, serological, and histopathological findings, and treatment is primarily a gluten-free diet (GFD), which requires patient education, adherence, and monitoring.

Chapters 2 and 3 present the dermatological and hepatic manifestations of CeD, respectively. DH is a gluten-responsive cutaneous manifestation of CeD, associated with herpetiform clusters of pruritic vesicles and urticated papules, typically on the elbows, knees, and buttocks, and characterized by granular immunoglobulin (Ig)A deposits in the dermal papillae. Although intestinal biopsies are unnecessary for diagnosis, if obtained, the majority of patients have enteropathy. Likewise, liver inflammation in CeD is not an uncommon phenomenon, with associated transaminitis seen in 10% of patients.

Chapters 4, 5, 6, and 7 attend to four unique subgroups with CeD: children, females, self-diagnosed individuals, and seronegative patients, respectively. Chapter 4 outlines the accepted approach to screening and diagnosing pediatric CeD, including specific criteria for non-histological diagnosis. The next chapter discusses the specific manifestations of CeD in women and the potential reproductive complications. Chapter 6 presents the role of a gluten challenge, mainly in undiagnosed individuals on a GFD with a positive CeD genotyping. The latter test has a high negative predictive value, and a negative result effectively rules out CeD. The last chapter in this section summarizes the pathogenesis, clinical course, and treatment options in seronegative CeD (SNCD).

The fourth section (Chaps. 8, 9, 10, 11, 12, and 13) focuses on non-responsive CeD (NRCD), or the newly termed "slow-responsive CeD", defined as the persistence (primary) or recurrence (secondary) of symptoms or signs of CeD after 6 to 12 months of being on a GFD. This umbrella term encompasses multiple underlying etiologies, the most common of which is inadvertent gluten exposure. Refractory CeD (RCD) is another important cause of non-responsiveness which affects over 1% of patients with CeD. Type I RCD is differentiated from type II RCD by the absence of aberrant or clonal intraepithelial lymphocytes (IELs), and subsequently improved prognosis. The book discusses the challenging diagnosis and management of RCD, which consists of immunosuppressive and experimental therapies, along with the risk of progression to enteropathy-associated T-cell lymphoma (EATL). The two last chapters in this part present the rare entity of celiac crisis, which may be associated with hemodynamic instability, electrolyte imbalance, hypoalbuminemia, and acidosis, followed by the role of wireless capsule endoscopy (WCE) in suspected or known CeD, including NRCD due to ulcerative jejunitis and EATL.

Chapter 14 discusses the association between functional GI disorders (FGID) and CeD and the role of low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet in overlap irritable bowel syndrome (IBS). The following chapter describes the role of the special-

ized GI dietitian in the management and monitoring of CeD along with evaluating and supplementing relevant vitamin and mineral deficiencies. Methods for monitoring gluten content of food are also addressed.

The final part focuses on NCGS and FI. NCGS is a poorly defined syndrome in patients without CeD and WA, characterized by IBS-like and extraintestinal symptoms, typically occurring soon after ingestion of gluten-containing foods and disappearing quickly upon their withdrawal. In Western countries, the prevalence of NCGS is estimated to be as high as 3%. Currently, there are no reliable biomarkers to detect NCGS. The book also outlines this challenging clinical diagnosis and current treatment with an individualized GFD. Finally, the clinical response to fructans in patients with FI is discussed, possibly due to colonic distension and gaseous byproducts of these undigested carbohydrates breakdown, along with the role of the GI dietitian in the differentiation between NCGS and FI.

In conclusion, this casebook offers a comprehensive review of the variety of GADs, exploring real clinical vignettes accompanied by easy-to-digest discussions and key points from world-renowned experts. The clinical variability in GADs explains why the vast majority of CeD patients are undiagnosed or misdiagnosed. Raising awareness and education are pivotal in improving screening rates and accurate diagnosis and management. The presented cases serve as a valuable resource for adult and pediatric gastroenterologists, hepatologists, primary care physicians, registered dietitians, nurses, and basic-science and translational researchers with an interest in GADs, both for trainees as well as those already in clinical practice or established research. This book can be useful for rheumatologists, neuropsychiatrists, dermatologists, obstetrician-gynecologists, and oncologists, who often encounter patients with extraintestinal manifestations of CeD and other GADs.

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Abbreviations

Ab	antibody
ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
AGAb	anti-gliadin antibody
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CBC	complete blood count
CD	Crohn's disease
CeD	celiac disease
CRP	C-reactive protein
CT	computerized tomography
DGP	deamidated gliadin peptide antibody
DH	dermatitis herpetiformis
DM	diabetes mellitus
EATL	enteropathy-associated T-cell lymphoma
EGE	eosinophilic gastroenteritis
EMA	anti-endomysial antibody
EoE	eosinophilic esophagitis
ESR	erythrocyte sedimentation rate
FGID	functional gastrointestinal disorders
FI	fructan intolerance
FODMAP	fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
GAD	gluten-associated disorder
GERD	gastroesophageal reflux disease
GI	gastrointestinal

HLA	human leukocyte antigen
IBD	inflammatory bowel diseases
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with predominant constipation
IBS-D	irritable bowel syndrome with predominant diarrhea
IBS-M	irritable bowel syndrome with mixed bowel habits
IDA	iron deficiency anemia
IEL	intraepithelial lymphocyte
Ig	immunoglobulin
MRE	magnetic resonance enterography
NCGS	non-celiac gluten/wheat sensitivity
PCR	polymerase chain reaction
PET	positron emission tomography
PTCL	peripheral T-cell lymphoma
SCT	stem cell transplantation
SIBO	small intestinal bacterial overgrowth
SNCD	seronegative celiac disease
TCR	T-cell receptor
TSH	thyroid-stimulating hormone
tTG	tissue transglutaminase antibody
RCD	refractory celiac disease
US	United States
ULN	upper limit of normal
WA	wheat allergy
WBC	white blood cells
WCE	wireless capsule endoscopy

Chapter 1
From Classical to Non-classical Celiac Disease

Nir Bar, Dana Ben-Ami Shor, and Guy A. Weiss

Case Presentation

A 42-year-old woman was referred for evaluation of iron deficiency anemia (IDA). She denied overt gastrointestinal (GI) bleeding and reported normal menses. She had 1–2 regular bowel movements daily (Bristol stool scale type 4). Her weight has been stable, and she has been vegan for the last 15 years. Her past medical history included only Hashimoto's thyroiditis, for which she was on daily levothyroxine. Her family history was notable for small bowel cancer in her father, who died at age 65.

On examination, she had a body mass index (BMI) of 22 kg/m^2 and no pallor was noticed. Her heart rate and other vital signs were normal. Abdominal exam was unremarkable, and rectal exam showed brown-colored stool on the glove without blood.

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Labs were notable for microcytic anemia with hemoglobin of 10.7 g/dL, mean corpuscular volume (MCV) 79 fL, red cell distribution width (RDW) 16%. Iron was 30 mcg/dL, transferrin 380 mg/dL, and ferritin 10 mcg/L. Otherwise, platelets, white blood cells (WBC), alanine transaminase (ALT), aspartate transaminase (AST), and thyroid-stimulating hormone (TSH) were all within normal limits.

Prior gynecological evaluation was unremarkable without clinical evidence of menorrhagia. She was scheduled for upper endoscopy and colonoscopy to rule out peptic ulcer disease and neoplasm. Her colonoscopy revealed small internal hemorrhoids and two diminutive polyps. Her upper endoscopy demonstrated typical CeD findings (Fig. 1.1). Biopsies were obtained in accordance with the 2013 American College of Gastroenterology (ACG) guidelines, i.e., 1–2 biopsies from the duodenal bulb and at least 4 biopsies from the distal duodenum. Pathological review confirmed Marsh 3b lesions (Fig. 1.2). The patient was requested to complete serological testing for CeD, with the following results: tissue transglutaminase (tTG) immunoglobulin (Ig)A 140 U (normal < 20) and total IgA 235 mg/dl (normal range).

Diagnosis

Anemia is a common extraintestinal manifestation of untreated CeD in all age groups [1–3]. CeD is increasingly found in patients with unexplained anemia. Consequently, IDA is an indication for CeD screening in adults [4]. The presence of anemia seems to be associated with a more severe disease presentation [5]. Anemia usually is caused by impaired iron or folate absorption from the proximal small bowel; in severe disease with ileal involvement, vitamin B12 absorption may also be impaired [6]. Hypoprothrombinemia and clinically apparent bleeding can be caused by vitamin K deficiency in CeD [7]. Hyposplenism of unknown cause, with thrombocytosis, deformed erythrocytes, and splenic atrophy, occurs in up to 50% of adults with CeD but only rarely is seen

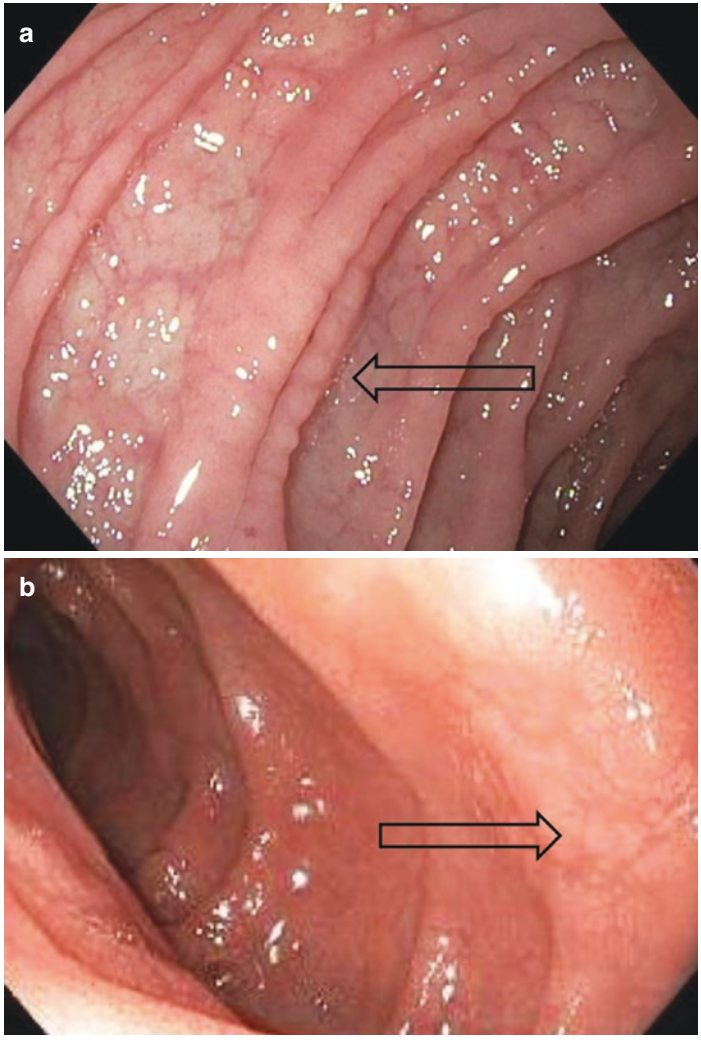

FIGURE 1.1 Endoscopic findings in CeD. (**a**) Scalloping in the third portion of the duodenum (arrow). (**b**) Nodularity and fissures in the second portion of the duodenum (arrow). (**c**) Loss of folds in the second portion of the duodenum

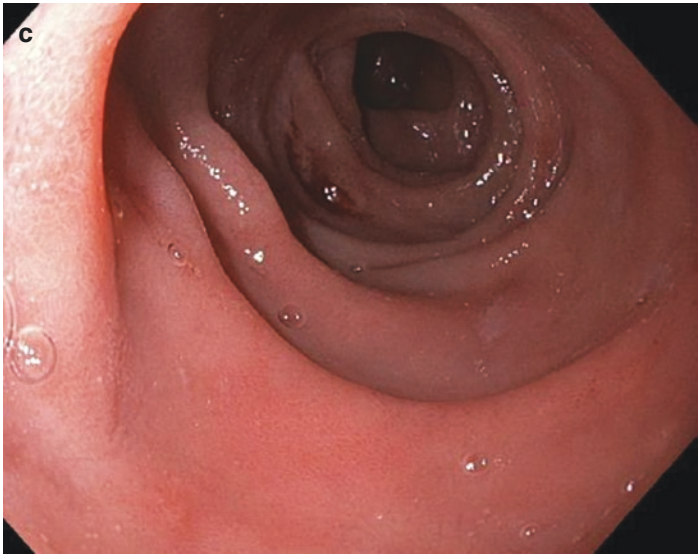

FIGURE 1.1 (continued)

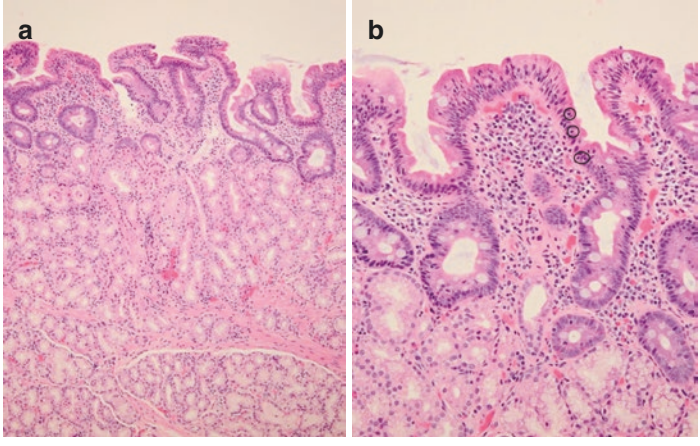

FIGURE 1.2 Histological findings in CeD. (**a**) Marsh 3b with subtotal villous atrophy along with intraepithelial lymphocytosis and crypt hyperplasia (10× magnification). (**b**) Marsh 3b lesion (20× magnification), black circles—intraepithelial lymphocytes

in children [8]. Evidence of hyposplenism may disappear with a gluten-free diet (GFD) [8]. Some reports have suggested that CeD can be associated with occult GI bleeding [9], but another study found that occult bleeding was no more common in patients with CeD compared with a control population [10]. Thus, occult GI bleeding is likely not a major contributor to iron deficiency. Anemia may be present in seropositive individuals even before the development of enteropathy (i.e., potential CeD). Therefore, the etiology of anemia in CeD seems to be more complex and multifactorial [11].

CeD has a wide range of manifestations. The 2013 Oslo multidisciplinary task force traded the traditional definitions—"typical," "atypical," "silent," and "latent"—and focused on "classical," "non-classical," and "potential," to reduce the variability in the use of gluten-associated disorders (GADs) terminology. Classical CeD presents with signs and symptoms of malabsorption, including diarrhea, steatorrhea, weight loss, or growth failure. Non-classical CeD manifests without malabsorption, but rather with symptoms such as constipation, abdominal pain, dyspepsia, and bloating. Subclinical CeD presents with extraintestinal symptoms or clinical or laboratory signs, such as IDA, osteoporosis, enamel defects, or transaminitis, without GI symptoms. Symptomatic CeD (rather than "overt CeD") is characterized by GI and/or extraintestinal symptoms associated with gluten ingestion [12].

Gastroesophageal reflux disease (GERD) has been inconsistently associated with undiagnosed CeD [13]. Dermatological manifestations or associations of CeD include dermatitis herpetiformis (DH; see Chap. 2), psoriasis, eczema, vitiligo, alopecia areata, atopic dermatitis, cutaneous vasculitis, and rashes due to micronutrient deficiencies [14]. More common in children, CeD is associated with dental enamel hypoplasia, likely related to nutritional deficiency and immune-mediated processes occurring during enamel formation (first 7 years of life). Aside for enamel defects, oral abnormalities include delayed eruption, recurrent aphthous ulcers, atrophic glossitis, cheilosis, xerostomia, and even squamous cell carcinoma of the oropharynx [15].

Bone mineralization disorders are also associated with CeD. Osteopenia and osteoporosis may be found in three fourth of patients with CeD, even in the absence of GI symptoms [16]. Moreover, persistent villous atrophy was shown to be associated with increased risk of hip fracture, and the degree of villous damage predicted bone density. The mechanism in which bone disease occurs in CeD is undetermined. Vitamin D and calcium malabsorption may play a role in the pathogenesis of bone disease, leading to bone resorption by inducing secondary hyperparathyroidism. In the past, rickets was found in children with CeD, though nowadays it is quite rare. Secretion of proinflammatory cytokines in CeD may also affect bone turnover, subsequently leading to reduced bone density [17]. Guidelines suggest testing CeD patients for osteoporosis [2], and according to some experts, bone density scans should be done one year after diagnosis and initiation of a GFD. Additional disorders aside for osteoporosis and osteopenia include potential infertility (see Chap. 5), delayed puberty, and hypocholesterolemia [18–20].

Several neuropsychiatric conditions are thought to be associated with CeD, though data are sometimes conflicting. Gluten encephalopathy includes a wide range of GFD-responsive symptoms. Headaches, usually migraine and tension headaches, are found more often in CeD compared to controls. GFD-nonresponsive white matter abnormalities on brain magnetic-resonance imaging (MRI) may be detected [36]. Gluten ataxia (GA), a rare neurological disturbance in CeD, is an otherwise idiopathic sporadic ataxia in association with positive CeD serology with or without enteropathy, likely to be induced by transglutaminase 6 autoantibodies directed against the cerebellum. However, these antibodies are also found in CeD patients without major neurological deficits. A third of GA patients have enteropathy, but less than a tenth of patients report GI symptoms. GFD may lead to clinical improvement [35].

Peripheral sensorimotor neuropathy is also more commonly found in CeD, even without accompanying nutritional deficiencies, such as B12 or copper [21]. Neuropathy may not be GFD-responsive. Epilepsy has also been described in association with CeD, with approximately 4% of CeD patients

suffering from epilepsy and up to 2.5% of epileptic patients having CeD [21]. In this context, it is important to mention CeD, epilepsy, and cerebral calcifications (CEC) syndrome, which is a rare clinical condition (see also Chap. 5). Depression is found in up to a third of patients, at times mediated by a deficiency in vitamin B6 and other micronutrients, or an accompanying autoimmune disease such as hypothyroidism. Anxiety is also commonly described [21], as similarly seen with other chronic conditions. While the latter improves with a GFD, the former is less responsive to the diet.

Pulmonary presentation includes the rare Lane-Hamilton syndrome or idiopathic pulmonary hemosiderosis with CeD [22]. Conflicting data exist about the association with coronary artery disease and cerebrovascular disease. Patients with CeD may have increased risk for atherosclerotic disease, mediated by persistent inflammation, nutritional deficiencies leading to hyperhomocysteinemia, or reduced intake of beneficial whole grains secondary to the GFD itself [23]. Hepatic disorders, mostly hepatocellular enzymes elevation, are discussed later in detail (see Chap. 3).

CeD is also known to be more prevalent in individuals with autoimmune disorders as Hashimoto's thyroiditis and type I diabetes mellitus (DM), allergic conditions as eosinophilic esophagitis (EoE), and genetic syndromes like Down and Turner. The link between thyroid disease and CeD likely relies on the common human leukocyte antigens (HLA) occurring with increased frequencies in both CeD, thyroid disease [24], and other autoimmune conditions [25]. CeD patients also have a higher likelihood of developing selective IgA deficiency and microscopic colitis [26]. CeD is also associated with autoimmune gastritis and lymphocytic gastritis and exocrine pancreatic insufficiency. As IgA is a mucosal immunoglobulin, unsurprisingly, CeD and glomerular IgA deposition often coexist (found in up to a third of patients with CeD). Gliadin-IgA immune complexes are formed and deposited in the glomeruli, but normally do not cause renal damage. Actual glomerulonephritis is uncommon, presumably because no complement activation occurs, so patients have no specific renal manifestations [27].

Screening

Based on the 2013 ACG Clinical Guidelines: Diagnosis and Management of CeD, patients with symptoms, signs, or laboratory evidence suggestive of malabsorption, such as chronic diarrhea with weight loss, steatorrhea, postprandial abdominal pain, and bloating, should be screened for CeD. The disease should be sought among the explanations for elevated serum aminotransferase levels when no other etiology is found. Patients with type I DM should be tested if they have any digestive symptoms, signs, or laboratory evidence suggestive of CeD. Patients with a first-degree family member who has a confirmed diagnosis of CeD should be tested if they show possible signs or symptoms or laboratory evidence of CeD. Although the United States Preventive Services Task Force (USPSTF) in 2017 concluded that current evidence is insufficient to assess screening for CeD in asymptomatic persons [28], testing of asymptomatic first-degree relatives of CeD patients should be considered [2].

The 2019 European Society for the Study of Coeliac Disease (ESsCD) guideline for CeD and other GADs advised to conduct serological screening (followed by duodenal biopsies if seropositive) for patients with IBS, unexplained transaminitis, chronic GI symptoms, microscopic colitis, Hashimoto's thyroiditis and Graves' disease, osteopenia/osteoporosis, unexplained ataxia or peripheral neuropathy, recurrent aphthous ulcerations, dental enamel defects, infertility, recurrent miscarriages, late menarche, early menopause, chronic fatigue syndrome, unexplained acute or chronic pancreatitis, epilepsy, headaches including migraines, mood disorders, attention-deficit disorder, cognitive impairment, hyposplenism or functional asplenia, psoriasis or other non-DH skin lesions, Down or Turner syndrome, pulmonary hemosiderosis, or IgA nephropathy [35]. The guideline also recommends genetically screening asymptomatic first-degree family members of CeD patients. Serology in those who carry the genes can be considered every 3–5 years, and upon seroconversion or with symptoms development, duodenal biopsies are advised.

Serologic tests for CeD provide an effective first step in identifying candidates for intestinal biopsy. Serologic tests look for three antibodies (Abs) common in CeD: tTG2, endomysial (EMA), and deamidated gliadin peptide (DGP) Abs (see Chap. 7 for sensitivities and specificities). To screen patients for CeD, measurement of tTG2 IgA is the preferred cost-effective test. Total serum IgA level should be measured as well to exclude selective IgA deficiency and avoid false-negative test results. IgG-based testing (IgG-DGP or IgG-TG2) should be used in people with IgA deficiency at diagnosis and follow-up [29]. Seronegative CeD (SNCD) is discussed in Chap. 7. All diagnostic serologic testing should be done while patients are consuming a gluten-containing diet [2].

Histology

Patients with positive serologic test results should undergo an upper endoscopy with small intestinal biopsies to confirm the diagnosis. Endoscopic features of CeD include bulb atrophy with visible submucosal vessels, mucosal fissuring, nodular mucosa (mosaicism), scalloping, and/or loss of folds. Enteropathy that is limited to the duodenal bulb is termed ultrashort CeD.

Since a third of CeD patients during their index endoscopy have normal mucosal appearance, multiple biopsies of the duodenum (as mentioned above: one or two biopsies of the bulb and at least four biopsies of the distal duodenum) are recommended to confirm the diagnosis [2]. Double-bite biopsies are discouraged, although commonly used. A diagnosis of CeD requires the demonstration of histological changes associated with the disease, which can be classified according to Marsh, modified Marsh (Marsh-Oberhuber) with the subtypes 3A–3C, or the simplified Corazza classifications [2]. The modified Marsh is the most widely used system.

The 2019 American Gastroenterological Association (AGA) Clinical Practice Update on Diagnosis and Monitoring of CeD [30] suggests that high level of tTG IgA (> ×10 upper normal limit) is a reliable and accurate test for diagnosing

active CeD. When such a strongly positive result is combined with a positive EMA in a second blood sample, the positive predictive value for CeD is virtually 100%. In adults, upper endoscopy and duodenal biopsies may then be performed for purposes of differential diagnoses. So far, the updated AGA recommendations have not been adopted in North America. Testing for HLA DQ2 and DQ8 can help exclude the diagnosis in select clinical situations [2] (see Chaps. 6, 7, and 8).

The utility of wireless capsule endoscopy is discussed in Chap. 13. Of note, several radiological findings that may suggest CeD include reduced jejunal folds, increased ileal folds, enteritis, intussusception, mesenteric lymphadenopathy, splenic atrophy, and vascular changes [35].

Management

The cornerstone of treatment in all patients with CeD is invariably a GFD. Dietary management is discussed at length in Chap. 15. Non-dietary therapeutic modalities are being developed and studied in clinical trials, including glutenases, tight junction modulators, tTG inhibitors, HLA-DQ2 blockers, and interleukin-15 inhibitors, but are not yet approved for use in practice. While some of these potential therapies appear promising, currently they may at best be used to supplement rather than eliminate the GFD.

The effect of a GFD on non-classical CeD varies. Confirming normalization of the abnormalities leading to CeD diagnosis is recommended by current guidelines [2]. Anemia in CeD patients would respond to a GFD. Bone disease is another manifestation which responds to a GFD. Bone density improves, and the risk for fracture declines, as patients adhere to a GFD [16]. Headaches seem to respond to GFD, and mood disorders are somewhat alleviated, though evidence is scarce and conflicting. Epilepsy is better controlled on a GFD, though antiepileptic treatment is usually still required. Unfortunately, the other mentioned neuropsychiatric manifestations are not as responsive. Ataxia may improve on a GFD, though long-standing cases are partially irreversible, and neuropathy may not regress [21, 31].

Oral aphthous ulcers improve when patients start a GFD, though the enamel defects do not [32]. With IgA nephropathy, GFD does not improve glomerular filtration rate, despite decreasing IgA-gliadin complexes [27]. Pulmonary symptoms and parameters improve when a GFD is instituted in Lane-Hamilton syndrome [22]. Histological remission on a strict GFD takes 6–24 months, with more than half of patients showing Marsh 1 lesion after a year on a GFD. More importantly, normalization of tTG during follow-up does not predict resolution of villous atrophy [35].

Monitoring

People with CeD should be monitored regularly for residual or new symptoms, assessment for complications, and compliance with or adherence to GFD. The latter factor is key in managing CeD in clinic, from primary care to tertiary centers, since adherence or compliance barriers are numerous (see Fig. 1.3). Monitoring of adherence to GFD should be based on a combination of history, dietitian evaluation, and annual serology. Other tests may include CBC, ALT, vitamins (A, D,

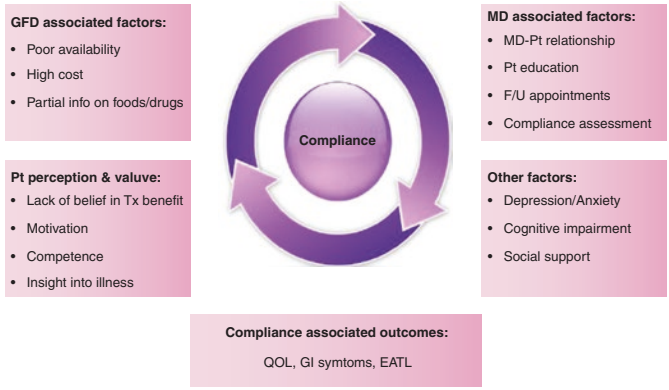

Figure 1.3 Compliance Barriers in CeD. (Adapted from Weiss, et al. [33, 34]). *Pt* patient, *Tx* treatment, *GFD* gluten-free diet, *MD* physician, *F/U* follow-up, *QOL* quality of life

E, B12), copper, zinc, carotene, folic acid, ferritin, iron, and carnitine, according to presentation (specific monitoring of mineral and vitamins is discussed in Chap. 15).

Patients with persistent or recurrent symptoms despite a GFD require additional work-up, including upper endoscopy with intestinal biopsies [2], as discussed in Chaps. 8, 9, and 10. Hyposplenic patients, but likely all CeD patients, should receive the pneumococcal vaccine every five years. All patients should also receive an annual influenza vaccination. Aside for progression to enteropathy-associated T-cell lymphoma (EATL) (see Chap. 11), CeD is also associated with small bowel adenocarcinoma and esophageal squamous cell carcinoma. After the first years of CeD diagnosis, there is a decrease in the overall incidence of non-Hodgkin lymphomas, solid cancers, and all GI cancers [35].

Case Outcome

The patient was diagnosed with non-classical CeD based on her enteropathy and positive celiac serology and was instructed to initiate a GFD. She was referred to a specialized GI dietitian (see Chap. 15). After a year on a GFD and oral iron supplements twice daily, her anemia resolved and her celiac serology normalized.

Clinical Pearls/Pitfalls

1. A wide range of non-classical presentations need to be carefully considered to avoid misdiagnosis of CeD.
2. Consideration of neuro-CeD should be made in patients with idiopathic ataxia, encephalopathy, or neuropathy.
3. Subclinical CeD presents with extraintestinal symptoms or clinical/laboratory signs, such as IDA, osteoporosis, enamel defects, and transaminitis, without GI symptoms.
4. IDA is an indication for CeD screening in adults.

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Chapter 2
Dermatitis Herpetiformis

Teea Salmi and Kaisa Hervonen

Case Presentation

A 44-year-old man presented to a dermatology clinic with a severely itching rash. He was otherwise healthy, but had been diagnosed with CeD 11 months earlier. Evaluation for CeD was initiated due to bloating and acid regurgitation, and at the time of the CeD diagnosis, a subtotal villous atrophy was detected on duodenal biopsies, compatible with Marsh 3b, along with markedly elevated tTG IgA and EMA titers (>1:500). After CeD was diagnosed, the patient was advised to adhere to a strict GFD. However, at the dermatology clinic, he admitted to having occasional dietary lapses. The itching rash had appeared 4 months earlier on his scalp and thereafter also on his elbows, knees, buttocks, and neck. He had noticed blisters on his skin and was suffer-

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ing from insomnia due to the severe pruritus. The patient had been treated with topical potent corticosteroids, which had not offered much relief. Aside from his rash, the patient was asymptomatic, with resolution of his bloating and acid regurgitation while on a GFD. On physical examination he was noted to have erythematous papules, crusting, erosions, and post-inflammatory hyperpigmented macules on his elbows, knees, buttocks, and scalp. No vesicles were detected (Fig. 2.1).

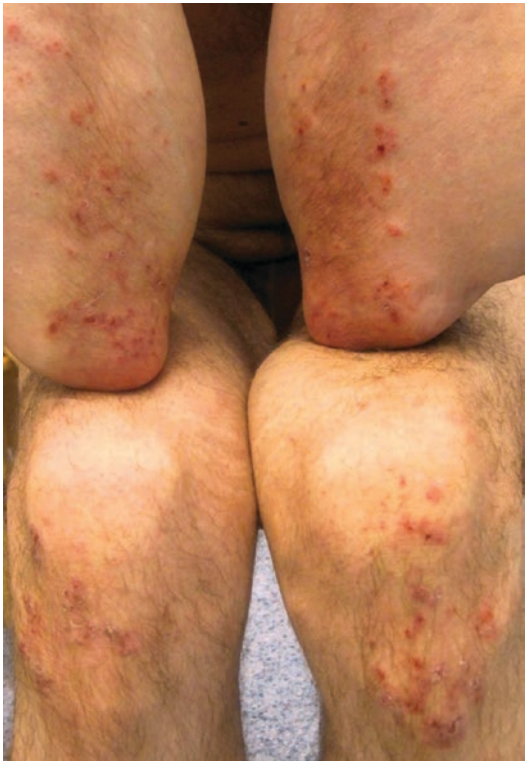

FIGURE 2.1 Dermatitis herpetiformis on the elbows and knees of our patient

Diagnosis

Due to the highly suggestive clinical picture and prior CeD diagnosis, the patient was evaluated for DH. In DH, dietary gluten induces an intensively pruritic vesicular rash in individuals with genetic predisposition, i.e., HLA DQ2 and/or DQ8 haplotypes. DH typically involves the elbows, knees, and buttocks but less often additional areas as well [1]. The rash in DH is polymorphic with vesicles, papules, and macules, but due to scratching the vesicles are often broken and excoriated to erosions and crusts. DH is slightly more common among males than females, and even though DH can appear at any age, the disease is mostly diagnosed during adulthood [2, 3].

DH is considered a specific form of CeD manifesting primarily in the skin. Currently approximately 13% of CeD patients are affected by DH [2, 3]. Obvious GI symptoms are rare in DH, despite the fact that most patients (75%) have small bowel villous atrophy (Marsh 3) and the remainder have mild enteropathy with increased intraepithelial lymphocytes (IEL), particularly γδ + IELs [4, 5]. tTG IgA are often present in the serum at the time of diagnosis, but they are less prevalent than in CeD, and their level correlates with the degree of small bowel mucosal damage [4]. Therefore, the presence of circulating tTG supports the diagnosis, but negative serology does not exclude DH.

In DH the clinical picture is often highly suggestive of the disease, but since the blisters are often eroded and crusted, other pruritic skin diseases such as urticaria, atopic dermatitis, scabies, and especially linear IgA bullous disease should be considered as differential diagnoses. In all patients, the diagnosis of DH should be confirmed with a skin biopsy taken from a healthy-appearing skin next to the rash, i.e., perilesional skin, and examined under direct immunofluorescence [6]. Pathognomonic finding for DH is granular IgA deposits in the papillary dermis (Fig. 2.2). Histopathological findings from lesional skin biopsies are not fully specific for DH. Interestingly, even though serum antibodies measured in clinical practice target tTG, the immune response in the skin

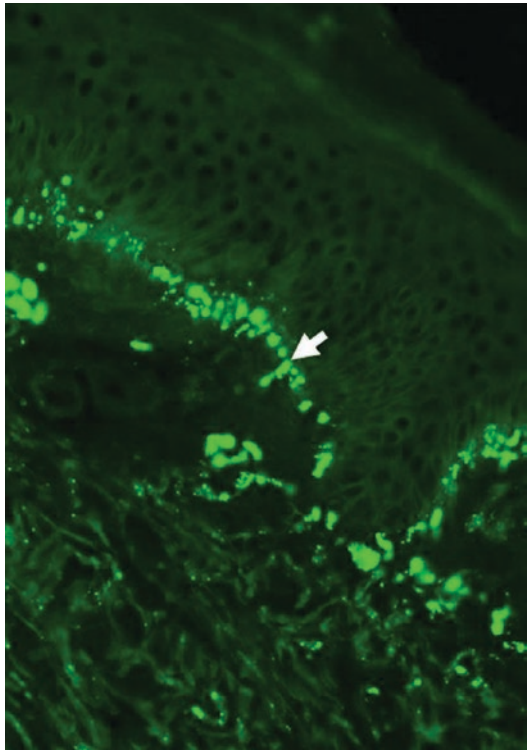

FIGURE 2.2 Direct immunofluorescence showing pathognomonic granular IgA deposits in the papillary dermis (arrow) in a perilesional skin biopsy of a DH patient

is directed against epidermal transglutaminase, not tissue transglutaminase [7].

The clinical picture of the rash in our case was highly typical of DH. Skin biopsy was taken from healthy elbow skin next to the rash and revealed strong IgA deposits in the dermis. Serum tTG IgA were only slightly elevated (17 IU) with borderline EMA (titer 1:5). The patient had previously been diagnosed with CeD due to GI symptoms without skin involvement. It is known that the phenotype of CeD can change over time from classical disease into DH [8], which

had occurred to our patient. The changing phenotype of CeD has been mostly associated with poor dietary compliance, which was also the case with him.

Upper endoscopy with small bowel biopsies is not necessary for the diagnosis of DH. Even though the severity of the small bowel mucosal damage in DH varies from inflammatory changes to severe villous atrophy, intestinal findings at diagnosis do not affect treatment outcome or long-term prognosis of DH [9, 10]. However, in this case the evaluation of the small bowel mucosa was warranted in light of gluten exposure and phenotype change, suggesting ongoing enteropathy, confirmed by his small bowel biopsies showing partial villous atrophy (Marsh 3a).

Management

Our patient developed DH following his CeD diagnosis, while on a GFD. In addition to a GFD, in this situation, the recommended treatment is initiation of oral dapsone (4,4′-diaminodiphenyl sulfone), which relieves both pruritus and the rash rapidly (Table 2.1). Moreover, since the patient admitted to having dietary lapses on GFD, a dietary consultation was recommended and strict GFD adherence advised, since lapses in the diet were likely the reason for the appearance of the DH rash during GFD treatment.

The treatment of choice for all patients with DH is a strict life-long GFD, since both rash and enteropathy are gluten-dependent [11, 12]. Similarly to CeD, in DH wheat, rye, and barley are excluded from the diet, and the majority of patients tolerate oats well [10, 13]. The rash in DH responds slowly to the diet, and it usually takes months until the rash totally disappears while on a GFD. Therefore, patients with widespread, active rash require additional treatment with dapsone.

Dapsone is a sulfone-derived antimicrobial medication, which also has potent anti-inflammatory properties. Dapsone is known to relieve the itch and the rash in DH

Table 2.1 Gluten-free diet and dapsone in dermatitis herpetiformis (DH)

Gluten-free diet	Dapsone
Necessary in all DH patients	**Necessary in 2/3 of the DH patients**
Effects	
Heals DH rash and enteropathy	Heals DH rash, but has no effect on the enteropathy
Has a slow effect on the rash (often months)	Effective for rash within a couple of days
Follow-up	
No routine tests[a]	Routine tests to assess for possible side effects (mostly hematological)
Life-long treatment	Discontinued within a couple of years

[a]Serum tissue transglutaminase antibodies should be followed up in seropositive subjects

within a few days, but it has no effect on the enteropathy. The initial dose of dapsone in DH is 25–50 mg/day, but the dose can be increased up to 100 mg/day if needed. When the rash is controlled, the dose of dapsone can gradually be tapered to a minimum maintenance level and finally discontinued when the rash is controlled with GFD alone after a mean duration of 2 years [12]. Dapsone is usually well tolerated, but has some hematological side effects, like hemolysis, methemoglobinemia, and agranulocytosis. Therefore, complete blood count (CBC) should be followed during treatment. Hemolytic anemia is the most common hematologic side effect, and it is dose-dependent and rare in daily doses of 50 mg or less. However, patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to dapsone-related hemolysis and therefore should be treated with lower doses.

GFD in DH offers, in addition to rash and enteropathy resolution, a good long-term prognosis. Lymphoma risk in DH is known to be increased up to six to ten-fold, but a GFD

for more than 5 years seems to protect against it [14, 15]. Interestingly, lymphomas observed in DH patients have been mainly B-cell lymphomas, not enteropathy-associated T-cell lymphomas (EATL) like in CeD [15]. In CeD the risk of bone fractures is known to be increased, but according to the only relevant study thus far, the fracture risk is likely not increased in GFD-treated DH [16]. Several studies have also reported a higher mortality rate in CeD compared to the general population, but on the contrary, in DH there are studies showing significantly lowered all-cause standardized mortality ratios [10, 17]. In these studies, over 95% of DH patients adhered to a GFD, which may explain the excellent prognosis.

DH may rarely be nonresponsive or refractory to a strict GFD. This has been examined in one study, which found that 1.7% of DH patients have persistent rash despite a strict GFD for a mean of 16 years [18]. The small bowel mucosa had recovered in all, indicating that refractory DH is different from refractory celiac disease (RCD). In cases of refractory DH, a close evaluation of the GFD should be completed by a specialized dietitian along with an upper endoscopy with duodenal biopsies to ensure the healing of enteropathy.

In addition, DH patients have increased risk of concomitant autoimmune disorders, which needs to be considered during long-term follow-up.

Case Outcome

After his DH diagnosis, our patient adhered to a strict GFD, and serum tTG normalized at 3-month follow-up. Dapsone was discontinued 2 years after the DH diagnosis due to temporary transaminitis of unknown etiology. Mild dermatological symptoms continued until the rash was controlled with a GFD alone 3 years after diagnosis. Therefore, the patient suffered from slightly prolonged symptoms, which, however, eventually responded to GFD, and refractory DH diagnosis was not made. After discontinuation of dapsone and clearance of all dermatological symptoms, annual physical examination and tTG assessment were advised.

Clinical Pearls/Pitfalls

1. In DH, blisters are often eroded and crusted due to severe itching and scratching, which hinders differential diagnoses of other itching skin diseases.
2. DH diagnosis should always be verified with perilesional skin biopsy and direct immunofluorescence examination showing granular IgA in the papillary dermis.
3. Negative serum tTG does not exclude DH.
4. Small bowel biopsies are not necessary in DH diagnosis, but if obtained, the majority of the patients have small bowel mucosal villous atrophy.
5. The treatment of choice in DH is a strict life-long adherence to a GFD.

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Chapter 3
Celiac Disease and the Liver

Beshoy Yanny, Jasleen K. Grewal, and Vijeta K. Vaswani

Case Presentation

A 58-year-old male presented to the emergency department with jaundice, ascites, and hepatic encephalopathy, which have been worsening over the previous 3 months. He was diagnosed with CeD at the age of 25 after developing abdominal cramping, diarrhea, and weight loss. At the time of diagnosis, the patient was noted to have a positive EMA and tTG. Upper endoscopy findings were confirmatory of CeD with Marsh 3a lesions on duodenal biopsies. He was also noted to have a mild elevation in transaminases. The patient's aspartate aminotransferase (AST) ranged from 85 to 201 IU and alanine aminotransferase (ALT) ranged from 48 to 108 IU. He was managed with a strict GFD with improvement in symptoms, however, without resolution of his hepatic abnormalities. Work-up also included viral hepatitis (hepatitis A, B, and C) serology, cytomegalovirus

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(CMV) PCR, Epstein-Barr virus (EBV) PCR, and herpes simplex virus (HSV) PCR, all of which returned negative. Liver ultrasound showed only evidence of hepatic steatosis. His hepatic function tests continued to worsen with transaminases increasing, with an AST peak of 520 IU, an ALT peak of 800 IU, and a total bilirubin of 8.5 mg/dL. Additional work-up also included a positive antinuclear antibody (ANA) with a titer of 1:160 and a positive anti-smooth muscle antibody (ASMA) with a titer of 1:80. A liver biopsy was subsequently performed, showing lymphocyte infiltration, increased plasma cells, and interface hepatitis, consistent with autoimmune hepatitis (AIH) (Fig. 3.1). The patient was started on oral prednisone 60 mg daily with initial normalization of the liver tests, followed by a corticosteroid taper with initiation of oral azathioprine 50 mg daily. His GI symptoms improved; however, he did have intermittent recurrences. Repeat celiac serology was positive, and a repeat upper endoscopy after a year with duodenal biopsies showed regression from Marsh 3c to Marsh 2.

At the age of 43, his abdominal pain, cramping, and diarrhea recurred despite being on a strict GFD and adherent to azathioprine. A repeat upper endoscopy with duodenal biopsies showed active CeD with Marsh 3c lesions, compatible with refractory CeD (RCD), without T-cell aberrancy on immunohistochemistry. His transaminases started increasing shortly after the recurrence of his abdominal symptoms. A repeat corticosteroid taper and mycophenolate mofetil (MMF) followed by the addition of tacrolimus were tried as second- and third-line agents for AIH with underlying type I RCD, unfortunately without benefit.

At the age of 58, he presented to the emergency department with decompensated liver cirrhosis and portal hypertension-associated ascites and hepatic encephalopathy. His Model for End-Stage Liver Disease (MELD) score on admission was 35. He was admitted to the liver floor for liver transplant evaluation and listing.

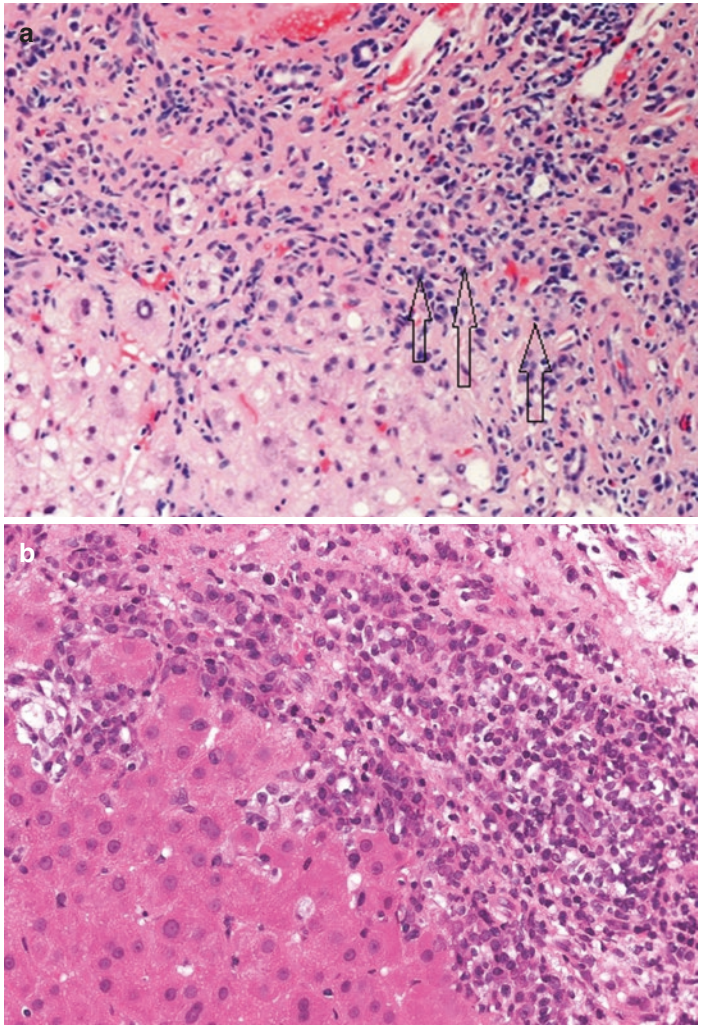

FIGURE 3.1 Liver biopsy suggesting AIH (at 100× magnification). (**a**) highlights interface hepatitis (long arrows), abundance of lymphocytes (white arrows), and rosette formation. (**b**) highlights the inflammatory cells of AIH including multiple plasma cells and lymphocyte infiltration

Diagnosis and Management

Our patient developed cirrhosis secondary to AIH in the setting of secondary type I RCD. This is not an uncommon scenario, as 6–9% of patients with CeD will develop elevated transaminases [1, 2]. In most cases, the transaminases normalize with a GFD. However, up to 2% of these patients will be diagnosed with AIH. The first report of the association between CeD and liver inflammation was made in 1977 by Hagander and colleagues, who reported that 30 out of 74 adults with known CeD developed elevated transaminases that would then normalize on a GFD within 6–12 months [3]. The following year, Lindberg and colleagues confirmed diet-dependent liver damage in patients with CeD in childhood by showing improvement in transaminases and histology via liver biopsy after maintaining a GFD [4]. Subsequently, an Italian study showed that 57% of children with active CeD had elevated transaminases [5]. With time, reports on the hepatic involvement in CeD have increased. Current U.S. data shows a rate of 40% of gluten-dependent elevated transaminases in patients with CeD, resonating Hagander's findings [6].

Two major categories of CeD-associated liver disorders have been described, cryptogenic and autoimmune. While both subcategories share some similar laboratory findings, from mild to severe elevations in transaminases, through mild to severe liver dysfunction, and up to decompensated cirrhosis with portal hypertension, they differ in histological findings and clinical response to a GFD [7–9]. In CeD-associated hepatitis, biopsies show preserved liver architecture with a mild mononuclear infiltrate of the portal tract and/or the lobular tract [7–9] and slight hyperplasia of the Kupffer cells [7–9]. After 12 months of a GFD, the above-mentioned histological findings usually normalize [7–9]. In cases of AIH in patients with CeD, along with elevated transaminases, laboratory findings include elevated ANA, ASMA, anti-liver kidney microsomal antibody (LKM), and/or anti-liver cytosol type 1 antibody [8, 9]. Liver biopsies for

the latter disorder often show both mononuclear and eosinophilic infiltration of the portal tract [8, 9]. Patients with AIH generally do not improve with gluten avoidance alone and will require additional immunosuppressive therapy [7–11]. Although these clinical differences exist between cryptogenic hepatitis and AIH in CeD, it is unknown if they are truly two separate diseases with a different pathogenesis or if they are varied expressions of the same disease [12–14]. It is hypothesized that patient factors, such as genetic predisposition, immunological factors such as F-actin antibody positivity, and cumulative exposure to gluten, can help determine the type and reversibility of the liver involvement CeD patients encounter [12–14]. Furthermore, patients with AIH tend to have a more pronounced hepatitis and are more likely to progress to cirrhosis despite a GFD and immunosuppression. While patients who are diagnosed with cryptogenic turned CeD-associated hepatitis usually improve with a GFD, the longer the gluten exposure, the more resistant the hepatitis becomes.

It is hypothesized that in the pathogenesis of AIH and CeD, a genetic link exists [15]. Both diseases tend to express specific combinations of genes located on chromosome 6 for class II HLA [15]. These findings are seen in both pediatric and adult populations [9, 18, 19].

AIH is further categorized as AIH-type 1 and AIH-type 2, based on the autoantibodies detected in the bloodstream [20]. AIH-type 1 is represented by a positive ANA and/or ASMA and in some cases elevation of the IgG levels [20]. In AIH-type 2, positive anti-LKM1 is seen [21]. It is often difficult to diagnose AIH in patients with active CeD, partly due to the fact that the positivity of ASMA is shared in both conditions. Thus, the discrimination between AIH and cryptogenic or CeD-associated hepatitis is a diagnostic challenge, often mitigated by a liver biopsy. Accordingly, a patient with CeD and severe villous atrophy but no apparent liver damage may have elevated ASMA of unclear significance. In such cases, treatment can be a difficult clinical decision between a GFD alone and additional immunosup-

pressive therapy. Currently the clinical impact of a GFD in patients with AIH is not well established [8, 9]. Interestingly, patients with AIH and diet-treated CeD have fewer hepatic relapses off immunosuppression, compared to patients with AIH without CeD [24]. Table 3.1 lists the liver diseases associated with CeD. The mechanism of liver injury in CeD is poorly understood; however, several theories have been proposed (Table 3.1).

Case Outcome

Management of decompensated cirrhosis was initiated on hospital admission. A paracentesis did not show evidence of spontaneous bacterial peritonitis. Blood cultures, urine culture, and chest x-ray were unremarkable. Abdominal ultrasound with Doppler showed patent vasculature without hepatic malignancy. The patient was symptomatically treated with lactulose, rifaximin, furosemide, and spironolactone. His immunosuppression regimen was discontinued given his decompensated cirrhosis. Due to the high MELD score on admission, an expedited liver transplant evaluation was initiated and completed during the same hospitalization, and he was listed for liver transplantation. During his admission, he developed hematemesis and was diagnosed with esophageal variceal bleeding, requiring endoscopic band ligation. A successful orthotopic liver transplant was completed approximately 2 weeks later.

Post-liver transplant, the patient recovered well and was discharged home 10 days later. He continues a strict GFD. His current chronic immunosuppression regimen includes tacrolimus and MMF. Currently, 5 years post-transplant, the patient is doing well and remains asymptomatic. His liver tests continue to be normal, and he has not experienced any bouts of rejection since the liver transplant.

Table 3.1 Prevalence, Mechanism of Liver Injury, and Outcomes of CeD-associated Hepatic Disorders

Liver disorder	Prevalence[a]	Proposed mechanism(s) of liver injury	Outcome	References
Cryptogenic or CeD-associated Hepatitis (transaminitis of unclear etiology)	4–24%	– Increased intestinal permeability causing an inflammatory reaction with cytokines traveling to the liver through the portal circulation – SIBO and development of endotoxemia – Chronic inflammation and tTG IgA deposits in the hepatocytes – Activated T-cells may home the liver	80–90% of patients have resolution of the elevated transaminases and histologic findings after 1 year on GFD	[2, 9, 25]
Autoimmune Hepatitis (AIH)	1.6%	– Association of HLA II gene on chromosome 6 in both CeD and AIH – F-actin antibody positivity in both diseases	– Unclear benefit of GFD – Relapse after withdrawal of immunosuppressive therapy often happens – Increased risk of progression to end-stage liver disease	[8, 9, 15–24]
Primary Sclerosing Cholangitis (PSC)	1.6%	Unknown	Increased progression to end-stage liver disease	[26–29]

(continued)

Table 3.1 (continued)

Liver disorder	Prevalence[a]	Proposed mechanism(s) of liver injury	Outcome	References
Primary Biliary Cholangitis (PBC)	3–6%	Unknown	– Increased progression to end-stage liver disease – Early detection and diagnosis may improve outcome	[9, 30–34]
NAFLD/NASH	Likely higher than in the general population (>25%)	Cytokine production and malabsorption	– Improvement with a combination of GFD and weight loss – Non-adherence is associated with increased risk for disease progression and end-stage liver disease	[35–45]
End-stage Liver Disease	Unknown	tTG and EMA levels decrease on immunosuppression post-liver transplantation	– Most require liver transplantation – CeD often remits with the high-dose immunosuppressive therapy used post-liver transplant	[46–70]

[a]Prevalence of liver disease in patients with CeD and not vice versa. CeD has a much higher prevalence in patients with primary liver disease like AIH and cryptogenic hepatitis

Clinical Pearls/Pitfalls

1. The presence of elevated transaminases is not an uncommon phenomenon in CeD.
2. Prompt evaluation by hepatology is warranted if the liver tests do not improve despite a GFD to assess for AIH, viral hepatitis, NAFLD, PBC, PSC, and cryptogenic liver disease.
3. Persistent transaminitis despite a negative hepatic serological work-up in a GFD-compliant patient with resolved GI symptoms may require a liver biopsy.
4. Persistent transaminitis after 1 year on a GFD with serology suggestive AIH warrants a trial of immunosuppressive therapy.
5. Early detection of reversible liver disorders is key in preventing progression to end-stage liver disease and transplantation.

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Chapter 4
Pediatric Celiac Disease

Hilary Jericho and Stefano Guandalini

Case Presentation

A 4-year-old girl presented to the pediatric gastroenterology outpatient clinic with abdominal distention and constipation. She was the product of a full-term pregnancy, delivered by uncomplicated cesarean section. She was provided a standard cow's milk-based formula at birth and tolerated this without difficulty. The child was developmentally appropriate and thrived through infancy with normal daily, soft bowel movements and no GI symptoms until 16 months of age when she developed fever, cough, and congestion. She was taken to the local ER and found to have a right-sided pneumonia on chest x-ray and was prescribed a course of amoxicillin/clavulanic acid. Her pneumonia resolved, but shortly thereafter she developed

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new-onset constipation with passage of infrequent large, hard stools that would often cause anal pain and bleeding with passage. A high-fiber diet with increased fluid intake was encouraged, but failed to relieve the constipation, prompting the initiation of polyethylene glycol, 17 grams daily. On the medication she was able to produce daily, soft stools, but with each attempted wean from the medication, the constipation would worsen, necessitating ongoing usage.

Roughly 6 months after the onset of constipation, the family noted a protuberance of her abdomen, exacerbated with eating, and alleviated with bowel movements. There were no complaints of abdominal pain, nausea, or vomiting. She was referred to pediatric gastroenterology at 4 years of age for chronic constipation and abdominal distention. At that time in addition to her constipation and abdominal distention, she was also noted to have hit a plateau in her weight and height growth, despite a robust appetite, being surpassed in height by her younger sister (Figs. 4.1, 4.2, and 4.3). She was noted to have a thin, short stature with a tympanic abdomen. She was otherwise well appearing on exam.

Given her history and exam, basic labs were sent with a normal basic metabolic panel (BMP); a slight elevation of her AST to 52 U/L (nl < 32); low total protein and albumin levels of 5.4 g/dL and 3.1 g/dL, respectively; normal inflammatory markers; a slightly low free thyroxine (T4) level of 0.82 ng/dL (nl 0.93–1.7), but a normal thyrotropin or thyroid-stimulating hormone) (TSH); a microcytic anemia with a hemoglobin of 7.0 g/dL (nl 11.3–13.2); a mean corpuscular volume (MCV) of 63.2 fL (nl 80–100); a total immunoglobulin (Ig)A of <50 mg/dL; elevated endomysial antibody (EMA) of 1:320; and a tissue transglutaminase (tTG) level of >100 units (nl < 4). Subsequent testing also revealed iron, vitamin D, and zinc deficiencies. She was started on vitamin supplementation and scheduled for an esophagogastroduodenoscopy (EGD) for further evaluation of celiac disease (CeD). A "cracked desert appearance" with scalloped folds was noted grossly on endos-

FIGURE 4.1 Our 4-year-old patient (left) with her 2-year-old sister (right)

copy (Figs. 4.4 and 4.5). A mildly active antral gastritis along with partial villous atrophy and increased intraepithelial lymphocytes in the duodenal bulb and the second portion of the duodenum consistent with Marsh 3a was found on histology (Fig. 4.6). The patient and family received detailed instruction from a trained dietitian on the gluten-free diet (GFD) which was initiated following the scope.

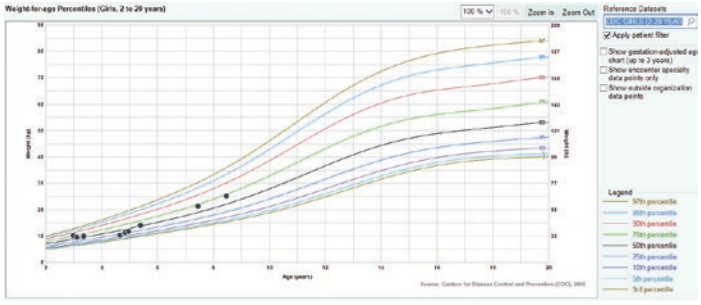

FIGURE 4.2 Weight-for-age Growth Chart

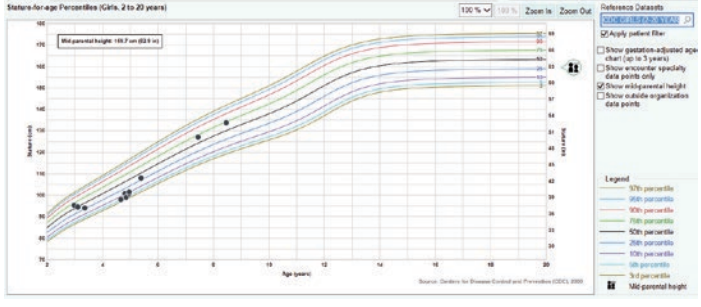

FIGURE 4.3 Height-for-age Growth Chart

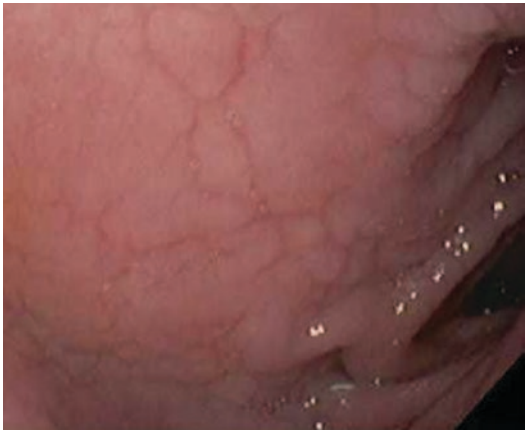

FIGURE 4.4 Duodenal bulb showing flattened villi and nodularity

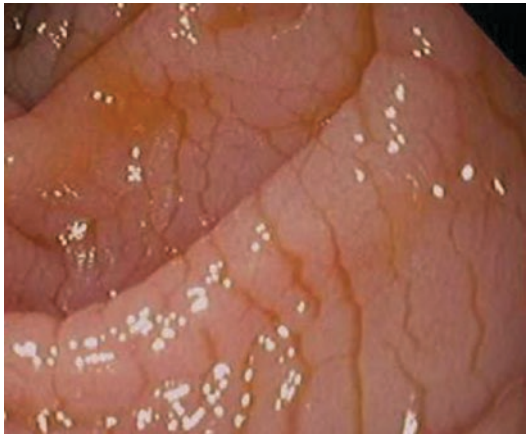

FIGURE 4.5 Second portion of duodenum showing fissured and scalloping

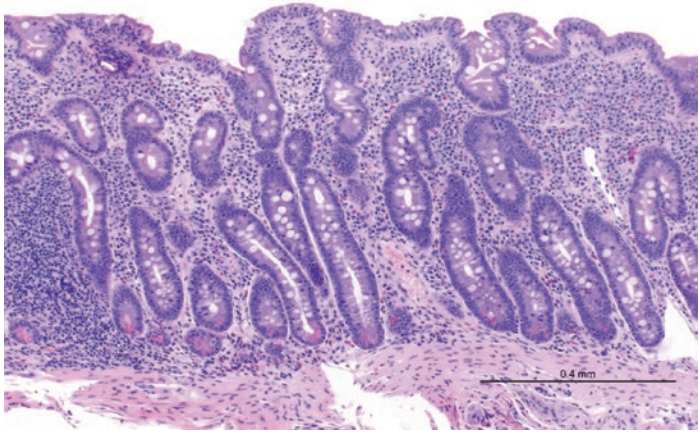

FIGURE 4.6 Duodenal histology showing villous atrophy with increased intraepithelial lymphocytes consistent with the diagnosis of CeD

Diagnosis and Management

Celiac Disease in Children, Not Just a Gastrointestinal Disorder

While diarrhea and abdominal pain are the two most common GI symptoms in children with CeD [1, 2], extraintestinal manifestations are becoming increasingly common in children as well. Among them, short stature is arguably the most common [3, 4].

It is important to pay special attention to CeD children with short stature. When related to malabsorption of nutrients, it should completely reverse once a child is strictly adherent to a GFD. In fact, within 24 months of starting a strict GFD, celiac children should attain appropriate catch-up growth and return to their expected height trajectory. If short stature in a prepuberal patient persists beyond 24 months on a strict GFD and celiac serologies have normalized, it is imperative to explore for other missed comorbidities, such as inflammatory bowel diseases (IBD), food aversion, Turner syndrome, or growth hormone deficiency, which may be accounting for the ongoing short stature.

Interestingly, children with extraintestinal manifestations of CeD as the main presenting symptom appear to have a more severe degree of villous atrophy than those presenting with GI manifestations or asymptomatic patients detected through screening [5].

Children have greater and faster rates of recovery for both GI and extraintestinal symptoms as compared to adults [16] (Figs. 4.7, 4.8, and 4.9). In addition, in both children and adults, GI symptom recovery appears to occur in a faster manner as compared to extraintestinal symptoms, likely secondary to a more complex mechanism leading to extraintestinal involvement, requiring more time for reversal [1, 2, 6, 7]. Factors that lead to worse rates of recovery include poor adherence to GFD, female sex, and a longer duration of symptoms prior to CeD diagnosis [2, 7–9].

FIGURE 4.7 Our 10-year-old patient (left) with her 8-year-old sister (right)

What Causes Celiac Disease?

Early childhood exposures to infections, especially of viral origin, increase the risk of later development of CeD in genetically predisposed children [10–12]. In fact, viral infections have been proposed to elicit pathological processes leading to the initiation of T-helper 1 (T_H1) immunity against dietary gluten and inducing CeD. Specifically, reovirus, an otherwise innocuous virus, has been noted to have the potential to trigger an inflammatory response to dietary antigens, especially to gluten, thus making it a likely major new environmental factor for the onset of CeD [13].

Additional factors, likely related to dysbiosis, may be at play: birth via cesarean section [14], exposure to antibiotics [15, 16], birth season [17], socioeconomic status [18, 19], and prior diagnosis of a cow's milk protein intolerance [20]. The role of feeding practices, previously thought to be prominent, has instead been down-sized by well-conducted multicenter studies [21, 22]. However, infants fed during the

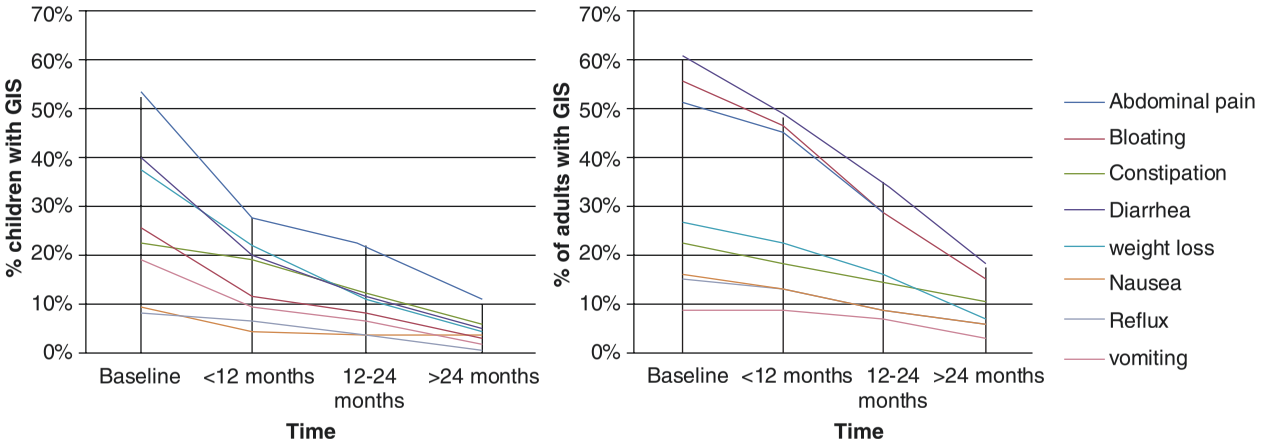

FIGURE 4.8 Improvement in GI symptoms over time in children versus adults on a GFD

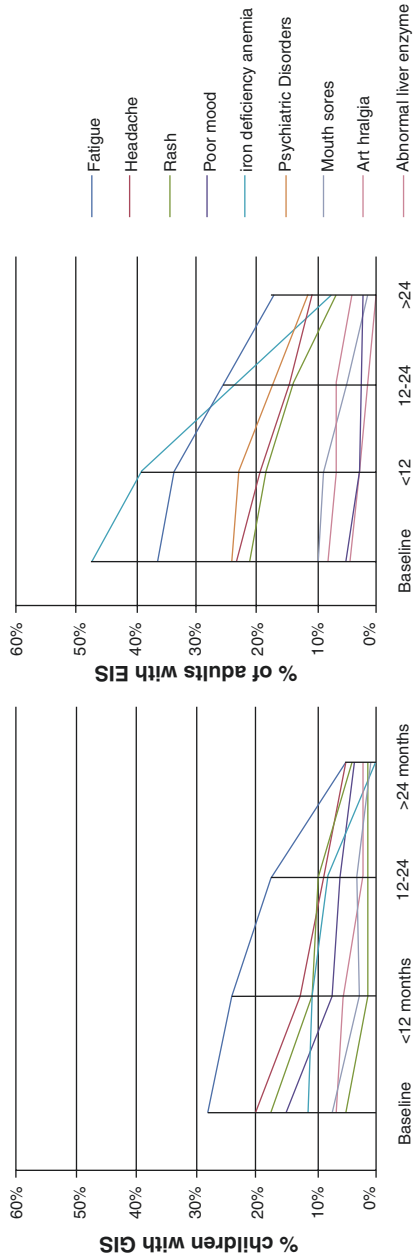

FIGURE 4.9 Improvement in extraintestinal symptoms over time in children versus adults on a GFD

first 2 years of life with a mostly "Mediterranean diet" appear to have decreased risk of later development of CeD [23]. In conclusion, neither the duration of breastfeeding nor the time of gluten introduction impacts the risk of developing CeD.

A Careful Diagnosis

Currently, it is universally recommended that tTG IgA be the first line of screening, given its very high sensitivity [24–26], similar to adults. Concurrent total serum IgA needs to be determined to guarantee that the patient is able to produce tTG IgA. In patients who are IgA deficient (<20 mg/dl), both tTG IgG [27–29] and DGP IgG [30] can be useful as markers of CeD.

In 2012, an ad hoc task force of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) published an evidence-based algorithm that allowed skipping the duodenal biopsy under certain circumstances including pediatric patients with a clinical history and genetic analysis compatible with CeD, tTG IgA levels more than ten times the upper limit of normal, and a positive titer of EMA [31]. A large, prospective, multicenter study later provided additional compelling evidence supporting the validity of this biopsy-skipping approach and showing that it is applicable in roughly 50% of all children suspected of CeD [32]. Of interest, these authors also demonstrated that genetic analysis (a requisite in the original guidelines) is not required for accurate diagnosis and can be skipped and this further simplified approach still holds a positive predictive value of virtually 100%. More recently, an expert review by the American Gastroenterological Association (AGA) Clinical Practice directed to adult as well as to pediatric patients supported the validity of such approach, although *allowing* for a diagnostic upper endoscopy in adults "for purposes of differential diagnosis" [33].

Screening Children/Siblings of Celiac Patients

The availability of a very sensitive blood test such as the tTG IgA has allowed a number of studies on individuals considered at risk for CeD, such as those with other autoimmune conditions (the most common example being type I DM) but also asymptomatic ones. In this regard, many investigations have disclosed the high prevalence of CeD in first-degree relatives of patients. A recent study in the US [34] reported a prevalence as high as 44%, while a previous large meta-analysis showed an overall prevalence of 7.5%, but varying considerably in terms of relationship with the index patient [35]. Thus, current consensus suggests screening all first-degree relatives of known patients.

Treatment and Follow-Up

Strict, lifelong adherence to a GFD remains the only available treatment for patients diagnosed with CeD and is expected to result in a complete return to health in the majority of cases, as already discussed.

However, being able to accurately assess a patient's adherence to the GFD and the diet's efficacy is not always an easy task. The recent availability of a sensitive and accurate test for the detection of minimal traces of gluten (in the form of gliadin immunogenic peptides) in stool or urine samples [36] may provide a very useful addition in our tools to monitor the diet of CeD patients, especially when dealing with nonresponsive CeD (NRCD) (see Chap. 15).

With appropriate instruction from a specialized dietitian, the GFD can be balanced and healthy. This would include a GFD containing a predominance of healthier, naturally occurring gluten-free foods and a limited amount of less healthy, certified processed gluten-free products [37].

Further recommendations for follow-up in children were recently provided by a task panel of experts [38]. The stron-

gest agreement was reached for the routine testing of tTG IgA at follow-up to assess dietary adherence, as well as a strong consideration to repeat a CBC, TSH, and an expert dietitian assessment [38].

Case Outcome

The patient returned for follow-up 1 month after initiation of a GFD with complete resolution of her constipation and abdominal distention. She remained on a gluten-free multivitamin with iron. She was noted to have had a rise in her weight from the 20th to the 33rd percentile and a rise in her height from the 5th to the 10th percentile. Hematologic testing was repeated 4 months from initiation of the GFD with complete normalization of her tTG IgA, hemoglobin, iron studies, and protein levels. She was also noted at that time to have improved energy levels and an additional rise in her weight to the 55th percentile and a rise in her height to the 31st percentile. The patient has remained clinically asymptomatic through present day with ongoing normalization of her labs and a stabilization of her weight and height at the 75th percentile (Figs. 4.2, 4.3 and 4.7).

Clinical Pearls

1. Could a child with chronic headaches, or joint pain, or unexplained high transaminases have just CeD? Yes, you bet! One needs to think way beyond the large belly and smelly stools when it comes to a pediatric CeD.
2. Testing first-degree relatives of a known celiac child is easy in clinical practice when addressing a sibling: but one needs to be more convincing when it comes to mothers, and the task reaches its highest level of difficulty when convincing a father! But it must be done: be persuasive and insistent!

3. Almost all celiac children do well on the gluten-free diet and achieve complete remission of labs too within a year; no need to re-biopsy for the vast majority. The most common cause of persistently elevated TTG? Ongoing gluten ingestion.

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Chapter 5
Celiac Disease and Women's Health

Carolina Ciacci and Fabiana Zingone

Case Presentation

A 42-year-old woman presented to an outpatient gastroenterology clinic with a recent weight loss. She reported a past medical history of menarche at the age of 15 years and 4 months (very late in Southern Italian standards), followed by regular menstrual cycles. At age 18 she developed temporal epilepsy. At age 26 she was placed on thyroid hormone replacement therapy for subclinical hypothyroidism. At the time, anti-thyroid antibodies were negative. At age 31 she had a first miscarriage at 13 weeks of gestation, followed by two other miscarriages. Following these events, she was placed on antidepressant therapy (citalopram) for 3 years. At age 37 she

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The greatest happiness is to know the source of unhappiness (Fyodor Dostoyevsky)

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delivered a low birthweight baby (2.1 kg) after assisted conception hormone treatment.

She also reported chronic constipation that she self-managed with fiber supplements. She denied a history of iron deficiency or abdominal pain. She reported infrequent episodes of GERD since turning 18, which was attributed to anticonvulsant therapy. Her epilepsy was poorly controlled with daily seizures after being switched from levetiracetam to carbamazepine.

She described a 7 kg weight loss in about 3 months, representing 17% of her baseline weight. She denied nausea, vomiting, anorexia, or reduced intake of calories. The patient also reported worsening fatigue.

Her hemoglobin levels were within the normal range (13.2 g/dL), ferritin low normal (32 mcg/L) with normal total serum protein level (7.2 g/dL). tTG IgA was 130 U/mL (normal value < 20) with positive EMA titers. Borderline low cholesterol (132 mg/dl) and subtherapeutic carbamazepine level suggested malabsorption. She underwent an upper endoscopy with duodenal biopsies. The upper endoscopy revealed cardial incontinence and biopsy-confirmed short-segment Barrett's esophagus, along with pale gastric mucosa and scalloping in the second portion of the duodenum (Fig. 5.1a, b). Histology showed subtotal villous blunting, crypt hyperplasia, and intraepithelial lymphocytosis (>45 IELs/100 enterocytes), compatible with Marsh 3b lesion.

She was placed on proton-pump inhibitor (PPI) therapy at double dosage for the Barrett's esophagus and started a GFD.

Diagnosis and Management

This clinical case is a complex one with GI and extraintestinal manifestations, but mainly due to gender-related complications of undiagnosed CeD with associated refractory epilepsy. Despite the absence of overt malabsorption, signs such as late menarche or adolescence onset of temporal epilepsy should have triggered an evaluation for CeD.

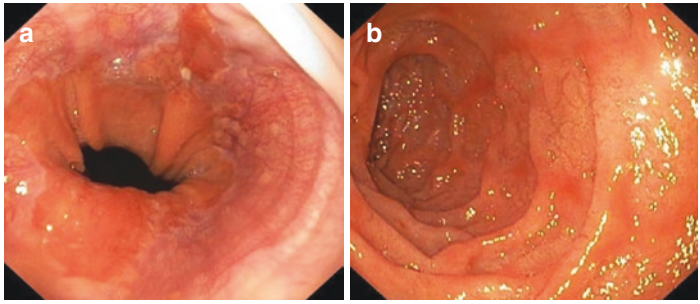

FIGURE 5.1 (**a**) Salmon-colored mucosa in the distal esophagus, biopsy-proven short-segment Barrett's esophagus. (**b**) Fissures and scalloping of the distal duodenum, suggestive of CeD. Histology of the duodenal mucosa showed Marsh 3b lesions

Like other autoimmune conditions, CeD is more frequent in women than in men [1–4]. It has a negative impact on women's health by decreasing bone mineral density and fertility, increasing the risk of concurrent autoimmune diseases, and poorly affecting their quality of life [5–8]. Previous reports suggest a difference in the clinical presentation between sexes. Women present more frequently with abdominal pain and iron deficiency anemia (IDA), and also after diagnosis, while on a GFD, they tend to report persistent symptoms and worse quality of life [7, 9, 10]. A recent population-based study showed that women were more likely to present with constipation, and also other symptoms/signs such as anemia, abdominal distention, and bloating were more common in women but without statistical significance [11]. So, even if constipation is a frequent condition in women, reported in up to 29% of the general population [12], it does not exclude the diagnosis of CeD [11]. Hypocholesterolemia is a significant finding in non-vegetarian adults and coupled with iron deficiency suggests the presence of undiagnosed CeD [13]. CeD is 1.5–2 times more prevalent in patients with epilepsy compared to the general population, while epilepsy is about two times more prevalent in patients with CeD compared to the general population [14, 15]. There is no statistically significant

difference in associated autoimmune diseases or depression between males and females [1].

Several studies have suggested that CeD might be associated with obstetric-gynecological problems such as delayed menarche, early menopause, infertility, endometriosis, recurrent miscarriages, intrauterine growth retardation, and low birth weight [16–18]. Morris and colleagues described for the first time in 1970 reversal of infertility on a GFD in three women with CeD [19]. However, subsequent studies reported contradictory results, and currently there are no recommendations to screen females with infertility for CeD. A 2014 epidemiological study on nearly 2.5 million British women concluded that women with CeD do not have a higher risk of clinically recorded fertility problems compared to healthy women, either before or after diagnosis [20]. Similarly, a cross-sectional study in men and women referred for fertility treatment did not find any increased risk of CeD [21]. However, a 2016 meta-analysis reported that women with "all causes" infertility (known and unknown) were 3.5 more likely of having CeD, compared to the control population. Similarly, women with "unexplained infertility" had a sixfold risk of having CeD. Of 884 women with infertility, 20 had CeD (prevalence of 2.3%), while of 623 women with "unexplained infertility," 20 had CeD (prevalence of 3.2%) [6]. A recent study reported only a single case of positive CeD serology among 197 women with unexplained infertility and 0 in 196 of those with an identifiable cause for their infertility [22].

Another meta-analysis reported a significantly higher risk for developing obstetric complications, including preterm birth, intrauterine growth restriction, stillbirth, low birthweight, and small for gestational age, in CeD patients compared to healthy women, noting also a significant decrease of preterm delivery once on a GFD [23]. A nationwide matched cohort study following 6319 women with CeD and 63,166 healthy women with reproductive events between the ages of 15 and 50 years reported that the rates of pregnancy, live birth, stillbirth, molar and ectopic pregnancy, spontane-

ous abortion, and abortion due to fetal disease were the same. However, prior to being diagnosed, women with CeD had a higher risk of spontaneous abortion, with 11 extra spontaneous abortions per 1000 pregnancies (adjusted odds ratio 1.12, 95% CI: 1.03–1.22) and 1.62 extra stillbirths per 1000 pregnancies (adjusted odds ratio 1.57, 95% CI: 1.05–2.33) compared with healthy women [24]. Other studies did not show increased risk of recurrent pregnancy loss in CeD compared to controls [25, 26].

Outcome

The patient arrived for her first 3-month follow-up visit. She insisted she was compliant with a strict GFD, associated with a modest weight gain. However, the seizures failed to reduce in frequency or intensity. Serum carbamazepine level increased but did not reach the expected therapeutic level.

At her 1-year follow-up, her tTG IgA levels improved but were still elevated (fivefold ULN) with positive EMA and low serum carbamazepine level. She complained of fatigue, daily epileptic episodes, dyspepsia, and acid regurgitation despite PPI therapy.

Dietitian consultation confirmed a strict adherence to GFD with recommendation to avoid processed food.

Eighteen months after the initiation of a GFD, her clinical picture did not change. The patient complained of a decreased quality of life because of her fatigue and frequent seizures. She gained only 2.1 kg. tTG levels were still four times above the ULN. Carbamazepine levels were still subtherapeutic. Urinary gliadin peptides were negative. The patient was asked to prepare a food journal for 1 week, which did not disclose gluten-containing products.

A repeat upper endoscopy revealed resolution of her Barrett's esophagus but unchanged duodenal micronodularity. Histology revealed persistent enteropathy, suggestive of refractory celiacdisease (RCD). No monoclonality of T-cells was present to suggest type II RCD (see Chap. 10).

About 2 years after being on a GFD, the patient did not improve. tTG IgA levels were threefold the ULN. However, this time the point-of-care urine test (GlutenDetect, Biomedal srl, Fig. 5.2) revealed the presence of gliadin peptides in the sample. A careful examination of food and drug intake revealed ingestion of two to three energy bars daily, which were not previously reported, meant to improve her fatigue. These bars contained a mix of ginseng, nuts, honey, and barley.

Three months after avoiding these gluten-containing energy bars, her tTG IgA levels dropped dramatically to a few units above the normal range. Her fatigue persisted but the epileptic episodes reduced in frequency. Carbamazepine level was finally within the therapeutic range. Plasma cholesterol levels also increased to 165 mg/dL. She also reported a notable improvement of dyspepsia and heartburn, and subsequently her PPI dose was decreased.

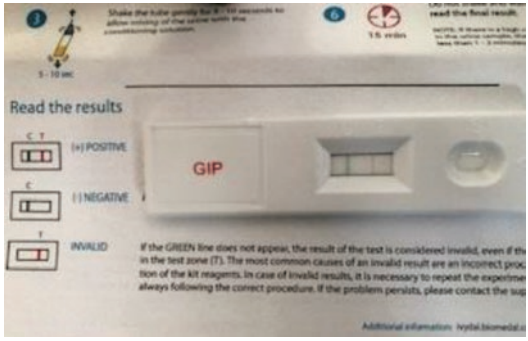

FIGURE 5.2 The detection of gluten peptide in urine is a useful point-of-care test (GlutenDetect, Biomedal Srl, similar to GlutenDetective, Glutenostics LLC). The central well in the image shows a second faint red line (positive test), indicating that gluten was ingested in the previous 24 hours

Clinical Pearls/Pitfalls

1. When treating women with CeD, focus should be placed on iron deficiency, fertility, osteoporosis, irritable bowel syndrome, anxiety, and depression. Although these symptoms/signs are quite frequent in women, they might be related to voluntary or inadvertent dietary gluten exposure
2. Despite the controversy, infertile women and women who underwent at least two miscarriages should be screened for CeD

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Chapter 6
Gluten Challenge in Gluten-Associated Disorders

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Case Presentation

A 29-year-old female with a past medical history of hypothyroidism has been referred to the gastroenterology clinic by her primary care physician for complaints of fatigue and multiple episodes of diarrhea alternating with constipation for the last 2 years. In the clinic, she revealed that she had noticed some improvement over the last 6 months after self-initiating a gluten-free diet (GFD), having read about its health benefits. Physical examination was unremarkable. She was on thyroxine supplements, and her thyroid function tests over the past 1 year were within normal limits. You suspect celiac disease (CeD) to be one of the differential diagnoses given its association with hypothyroidism, the patient's symptom profile, and her reported responsiveness to a GFD. How would you proceed? If a tTG and/or small intestinal biopsy were to be done while on her GFD, and results came back as normal, would they be reliable for ruling out CeD in this patient? Would HLA-DQ testing help?

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Diagnosis and Management

Traditional diagnostic tests for CeD like serologic tests and intestinal biopsy normalize on a long-term, strictly GFD, rendering them less informative for the diagnosis or exclusion of CeD in individuals following a GFD. Gluten challenge is a medically supervised process, whereby an individual already on a GFD receives a specified amount of dietary gluten, to evaluate response in their clinical course, celiac serology, intestinal histology, and/or other parameters for diagnostic or research purposes [1]. Challenging patients with possible non-celiac gluten sensitivity (NCGS) or CeD who are already on a GFD allows for diagnosis through exacerbation of symptoms (NCGS) and/or through the increase in celiac serologies and demonstration of small intestinal villous atrophy (CeD) [2, 3]. Therefore, in the patient described in this clinical vignette, a gluten challenge would guide further management. In addition to diagnostic purposes, gluten challenge may be used in both NCGS and CeD in research settings for studying their pathogenesis, discovery of relevant biomarkers, and testing of novel therapies.

Indications for Gluten Challenge in Different Populations

Gluten challenge is a helpful tool in managing a number of conditions that respond to a GFD. GFD is the mainstay of CeD treatment and is also recommended in certain other forms of gluten intolerance, namely, NCGS, wheat allergy (WA), gluten ataxia, and more [4] (see Chaps. 1, 15, 16, and 17). The proportion of people across the globe that currently follow the GFD (3.7–7%) therefore is much higher than the latest reported global prevalence of biopsy-proven CeD (0.7%) [5–11]. This difference is also explained by the significant number of individuals that have voluntarily adopted the GFD without any medical guidance, assuming that this diet has some health benefits, like ameliorating symptoms of

bloating, migraines, fatigue, and depression [5, 12]. Moreover, in recent times, active marketing of GFD as a healthy lifestyle choice has complicated the assessment of CeD and GADs in general [13, 14]. Responsiveness to a gluten challenge would therefore be highly useful to objectively diagnose/rule out a GAD in such individuals, prior to recommending a lifelong GFD.

The American College of Gastroenterology (ACG) recommends that HLA-DQ2/DQ8 testing should be done before subjecting any patient to a formal gluten challenge for a possible diagnosis of CeD [1]. This is because HLA-DQ2/DQ8 has a high negative predictive value; a negative result effectively rules out CeD. In a patient who has HLA-DQ2/DQ8 genotype and is on a GFD, the next step is to check celiac serological tests. If the serology tests are positive, the patient should undergo duodenal biopsy to confirm CeD diagnosis. However, in case of negative serology results, the patient should undergo a gluten challenge, which is the gold standard to confirm or exclude CeD/NCGS [1]. These individuals are typically those that are suspected to have CeD or NCGS (based on symptoms in the past that responded to GFD) but had started a GFD without undergoing complete serological and/or histological tests, or those whose past results of these tests are unknown.

After the gluten challenge, serological and histological tests should be performed to confirm the diagnosis. The ACG guidelines lay out an approach to gluten challenge as shown in Fig. 6.1. Patients who are unable or unwilling to undergo a gluten challenge and are already on the GFD with improved symptoms should be managed as CeD with a strict GFD until proven otherwise [1].

There are also certain individuals in whom gluten challenge is not appropriate. These include those who develop severe symptoms on gluten exposure, potentially gluten-related severe neurological symptoms (such as ataxia), children younger than 5 years old or at pubertal growth spurt, pregnant or breastfeeding women, and/or women trying to conceive [16, 17].

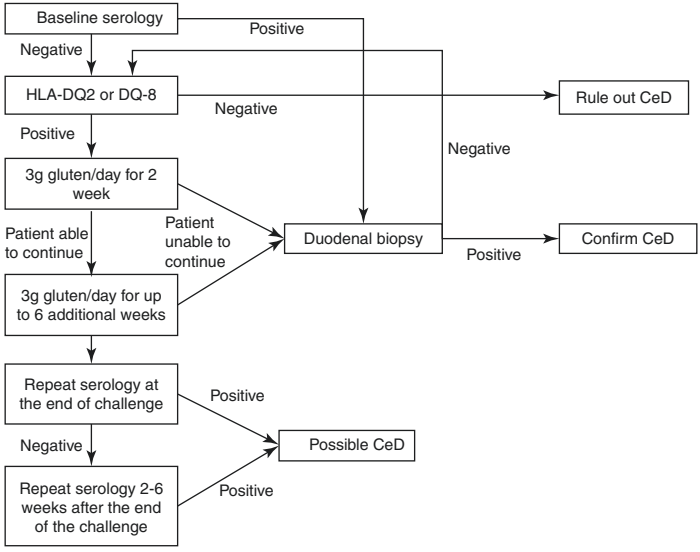


FIGURE 6.1 Approach to gluten challenge for CeD diagnosis. (Adapted from Rubio-Tapia et al. [1] revised based on 2019 AGA Clinical Practice [15])

Patients with a possible diagnosis of WA that report GI, skin, or respiratory symptoms after food ingestion but without positive specific skin or serological tests may benefit from a wheat challenge instead of a gluten challenge. There is no standardized protocol; however, it is recommended to consider consultation with an allergist and to begin the wheat challenge with an individualized dose while anticipating a variable amount of time before IgE-mediated symptoms occur [18].

Principles of Gluten Challenge

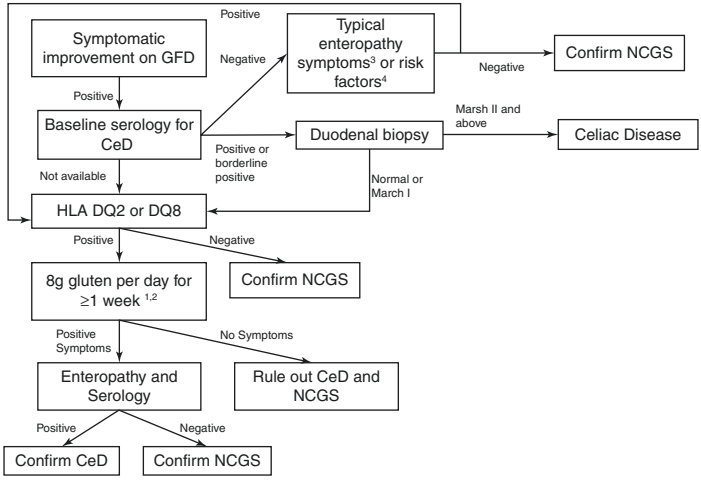
Setting

Although there is no formal evidence to suggest so, gluten challenge should be performed under the supervision of physicians. It is based on the logic that specialists in gastroenterology and nutrition may be required to oversee gluten

administration as well as to manage complications of gluten challenge if they ensue. As noted previously, an allergist may be additionally required to conduct a wheat challenge in WA patients [18].

Blinding

For the diagnosis of NCGS, it is highly recommended to perform the gluten challenge as a single- or double-blinded placebo-controlled (DBPC) crossover trial [1, 19, 20]. It is based on the fact that symptomatic outcomes in gluten challenge are very likely to be affected by placebo and nocebo effects. Blinding is therefore highly relevant for NCGS where the diagnosis is based on the improvement of symptoms after GFD, in the absence of any specific biomarkers [18, 20]. However, in CeD diagnosis, blinding is less critical due to the availability of objective serological tests, well-characterized histological endpoints and HLA-genotyping test (Fig. 6.2).



[1]Prior to the gluten challenge, the patient must follow a GFD at least for 3 weeks and 1 week washout period between crossover
[2]The crossover trial should be single- or double-blinded placebo-control to reduce the placebo effect.
[3]Typical enteropathy symptoms: Malabsorption symptoms (weight loss, diarrhea and nutrient deficiencies).
[4]Risk factors: Familiy history of CeD and/or personal history of autoimmune diseases.

FIGURE 6.2 Approach to gluten challenge for NCGS diagnosis. (Adapted from Kabbani et al. [2])

Similarly, in WA patients who present with objective signs and symptoms occurring after wheat exposure, even an open challenge may suffice. A negative result, in this case, would have a high negative predictive value. There is no formal recommendation on blinding in the wheat challenge [18].

In a blinded challenge, the gluten-containing foods used to challenge patients should be identical to the gluten-free placebo in gastronomic as well as mechanical characteristics like appearance, smell, taste, and texture. They should also have a similar nutritional composition [18, 21].

Gluten formulation

Wheat-based food products, commercially available pure gluten, gliadin, or its toxic oligomer fragments have been used in various studies which utilized a gluten challenge [18–20, 22]. Examples of wheat-based products include wheat bread or crumbs, cookies, udon noodles, and cereal bars, to state a few. Wheat gluten, on the other hand, has been used as is, or in the form of gastric soluble capsules, or added to a "vehicle" like cereal bars or muffins. However, there has been no standardized gluten formulation used across different studies.

Recommendations in the ACG guidelines regarding the gluten formulation to be used in gluten challenge in CeD are based on a study by Leffler and colleagues. In this study, gluten challenge was administered using two or five slices of wheat bread per day, which represent approximately 3 g and 7.5 g per day of gluten, respectively [1, 19]. Other studies have used biscuits, gluten powder, or purified gluten in capsules [18, 22, 23]. Additionally, it is known that the 33-mer peptide is the most immunotoxic fragment in gliadin and may be used for gluten challenge instead of whole gluten. This is because of its well-characterized cytotoxic effect on intestinal epithelial cells and also its capacity to activate gut-derived T-cell lines in CeD [18, 24].

Conversely, gluten formulation used in the diagnosis of NCGS should incorporate other components too. Alpha trypsin inhibitors (ATI) have also been implicated in NCGS, and

hence it is essential to know the amount of ATI in the gluten formulation used for the gluten challenge. At the same time, since irritable bowel syndrome (IBS) mimics NCGS in clinical presentation but may be caused by FODMAPs, it may be worth estimating the amount of FODMAPs in the gluten formulation of patients being tested for NCGS [25] See also Chaps. 14, 16, 17.

For testing WA, patients should similarly be challenged with wheat to ensure that they are exposed to all potential allergens that cause the hypersensitivity [18, 26]. Due to the sparse of literature on wheat challenge in WA, currently there is no consensus on what the appropriate protocols should be.

Hence, there is a need for standardization of the gluten challenge materials to provide safe, practically feasible, and comparable results for all patients; this need has been emphasized in the scientific community as well [27]. Additionally, the gluten preparation should also contain sufficient amounts of the immunoreactive substance. There have been some attempts to prepare such material, with a known, reproducible composition [20]; however, a broader consensus is yet to be reached.

Dose and Duration

The previous regimen of gluten challenge in CeD patients recommended by the ACG was that of >10 g of gluten per day administered orally for 8 weeks. However, this had been based on limited data [1, 3, 28, 29]. The disadvantages of this regimen included the inconvenience and lack of compliance of patients to such a prolonged period of gluten consumption due to accompanying symptoms. Also, given the fact that different patients respond differently to the same dose of gluten, the full 8 weeks of gluten challenge might not be needed in a considerable proportion of patients. As mentioned, 3 g gluten were found to be equally effective in inducing gluten-associated clinicopathological features in CeD patients when compared to 7.5 g of gluten daily (2 vs. 5 slices of bread) given for 14 days [19]. The response was measured by symptomatic,

serological and histological endpoints (see *Endpoints for Gluten Challenge*). The 2019 AGA Clinical Practice advised returning to a normal diet with three slices of wheat bread daily preferably for 1–3 months before repeat measurement of tTG IgA [15].

For NCGS patients, the Salerno Experts' Criteria lay out a standardized gluten challenge regimen, as a two-step process in which 8 g of gluten are given per day for a 1-week gluten challenge [20]. However, other researchers have used slightly different regimens. Di Sabatino and colleagues analyzed 59 adults without CeD or WA, who self-reported gluten sensitivity and were NCGS suspects [30]. At the time of the study, however, they had all been on gluten-containing diets. In this double-blind crossover RCT, 4.375 g/day of purified wheat gluten capsules (~2 slices of bread) given for 1 week caused a significant increase in symptoms like brain fog, aphthous stomatitis, as well as abdominal pain and bloating. In an earlier double-blind placebo-controlled study by Biesiekierski, 34 patients with self-reported gluten sensitivity were asked to consume 16 g of commercially prepared gluten (8 g in a muffin and 4 g in two slices of bread) for 6 weeks [31]. There was a significant difference in symptoms with gluten within a week of starting the gluten-containing diet compared to placebo, thereby showing that shorter periods of exposure may at least partially suffice to show improvement in clinicopathological features of these patients. Regardless, one of the merits of the study was that the exact chemical composition of the gluten used was documented, and effort was also made to ensure no FODMAP in the gluten. A few studies examining the effect of even shorter gluten challenges in NCGS patients using 16 g of gluten for 3 days found no worsening of abdominal symptoms or extraintestinal symptoms [20, 29, 32].

In summary, a minimum of 3.5 g of gluten has been used across all studies for testing NCGS patients. The challenge should be single- or double-blind placebo-controlled with crossover [20]. Since NCGS may be a transient condition, periodic, gluten challenges may be encouraged in this population,

especially with pediatric patients [33]. A suitable algorithm for gluten challenge to diagnose NCGS is suggested in Fig. 6.2.

Endpoints of Gluten Challenge

Symptomatic Endpoints of Gluten Challenge

Celiac Disease

Several tools have been used especially in research settings to assess the symptomatic response to gluten challenge in patients with suspected CeD already on a GFD. The commonly used tools include Celiac Symptom Index (CSI), Gastrointestinal Symptom Rating Scale (GSRS), and a modified version of GSRS for CeD (CeD-GSRS).

GSRS contains 15 questions to assess common GI symptoms. This questionnaire is organized into five sub-domains (reflux, abdominal pain, constipation, diarrhea, and indigestion) [34]. Due to the relative lack of reflux and constipation in CeD, a modified version of GSRS (CeD-GSRS) has been developed [35, 36]. However, neither of them assesses extraintestinal symptoms in CeD patients.

In an effort to develop a specific questionnaire for CD, Leffler and colleagues validated the CSI that contains 16 questions grouped into two sub-domains (specific symptoms and general health) and concluded that it is potentially useful for monitoring symptoms [37]. Other questionnaires to evaluate the overall health and quality of life that have been traditionally used in CeD include the Psychological General Well-Being Index (PGWBI) and the CeD-related quality of life (CD-QOL) questionnaire. PGWBI is a score derived from six domains: anxiety, depressed mood, self-control, positive well-being, general health, and vitality [38]. Meanwhile, CD-QOL is another tool that has 20 items grouped into four sub-domains (limitations, dysphoria, health concerns, and inadequate treatment). It has been validated as a quality of life measure for CeD patients [39]. These scales have been applied in research settings to assess the effect of dose and/or duration ranging of gluten [19]

and the protective effect of novel therapeutics [35, 40] on symptoms of celiac patients during gluten challenge.

A study that used these scales evaluated the effect of two different doses of gluten (3 g/day vs.7.5 g/day) administered over a 14-day period to celiac patients; symptoms were found to start worsening after 3 days of gluten challenge. These symptoms persisted for 14 days and returned to baseline levels (as assessed by CSI and GSRS) by day 28 after the beginning of gluten challenge.

A systematic review examined the effect of different doses and duration of gluten challenge on symptomatic endpoints in pediatric and adult populations [22]. The review included studies that had used doses of gluten varying from 0.2 to 30 g/day and durations in the range of 1 day–8 years. It found that 43%–80% of the adults with diagnosed or suspected CeD developed symptoms, and the percentage of symptoms and their severity increased throughout the gluten challenge. Meanwhile, in the pediatric population, symptomatic response was found in 4% of children with only 1–2 weeks of gluten administration, while 96% developed symptoms with 15 weeks of gluten challenge. Children were therefore found to have considerable variability in terms of the time to onset of symptoms. Overall, symptomatic endpoints were found to have a low positive predictive value.

Due to the considerable variability in the time to onset of symptoms and their low positive predictive value as an independent outcome measure in gluten challenge, they are best utilized as a complementary endpoint along with more objective biomarkers.

Non-celiac Gluten Sensitivity

NCGS remains a diagnosis of exclusion due to the lack of specific biomarkers and the overlap of symptoms with IBS and CeD. However, the development of Salerno Experts' Criteria has facilitated the clinical assessment for NCGS [20]. See also Chap. 16.

As per the Salerno Experts' Criteria, a confirmation of the diagnosis of NCGS requires a two-step evaluation. The first

step is an assessment of the clinical response of the patient on GFD. This is followed by the evaluation of the effect of reintroducing of gluten. As a prerequisite, CeD and WA must be ruled out before assessing the patient in step 1. Symptomatic responses are evaluated using a weekly, self-administered, modified version of GSRS (that includes extraintestinal manifestations in addition to GI symptoms) through a 6-week follow-up. Responders are defined as patients with a decrease of ≥30% in the baseline score (one to three main symptoms or ≥1 symptom without worsening of others) for ≥3 weeks during the follow-up.

After concluding the first step, it is mandatory to reintroduce gluten to the responders. The reintroduction of gluten should be performed by a single- or double-blinded placebo-controlled gluten challenge. This challenge consists of the administration of 1 week of 8 g/day gluten challenge followed by 1-week washout of strict GFD and by 1 week of placebo. The patients' symptomatic response would be evaluated daily by the self-administered modified GSRS during the whole challenge.

A meta-analysis showed that Salerno Experts' Criteria succeed in predicting a more accurate prevalence of confirmed NCGS [41]. Additionally, it found a causal relationship between gluten and symptomatic relapse in 40% of patients when a gluten challenge is performed according to Salerno Experts' Criteria. In conclusion, due to the lack of a definitive biomarker for NCGS, gluten challenge with symptom assessment remains a crucial step in the diagnosis of NCGS.

Serologic Tests Following a Gluten Challenge

Celiac Disease

Several serological tests help in the diagnosis of CeD, but they are generally insufficient to confirm the diagnosis. tTG IgA and DGP IgA/IgG have been found to be increased in a gluten challenge study with their highest levels on day 28 [19]. These findings are supported by a systematic review that found an increase of these antibody levels in adults and chil-

dren (tTG IgA: 0–25% vs. 35–59%, respectively) after a 14-day gluten challenge [22]. However, longer duration of gluten challenge (1.5–3 months) stimulates a higher rise in both serological tests (adults 30–43% vs. children 89%).

Other serological tests, such as AGA IgA and EMA IgA, show similar response, with variation proportionate to the dose and duration of gluten challenge. 15–78% of children and 0% of adults had increased antibody levels in both serological tests after a 2-week gluten challenge. However, 70–100% of children and 17–85% of adults showed increased levels in these serological tests after longer durations of gluten challenge (2–14 months) [22].

Hence, serological tests serve as a complementary endpoint for the diagnosis of CeD due to its broad variability depending on the dose and the duration of gluten challenge.

NCGS

Currently, there are no accepted serological tests for diagnosis of NCGS.

Evaluation of Small Intestinal Mucosa Following a Gluten Challenge

Celiac Disease

Characteristic mucosal findings identified on duodenal biopsy remain the gold standard for CeD. Histological endpoints are generally the best accepted measures in both clinical and research settings to detect the response to gluten challenge in celiac patients. For example, Leffler and colleagues used the villous height to crypt depth ratio (Vh:Cd) and intraepithelial lymphocyte (IEL) count to assess the response to two different doses of gluten challenge (3 g and 7.5 g/day of gluten). They found a decrease of Vh:Cd and an increase in the mean of IELs on day 14 of gluten challenge without any significant differences between the two tested doses [19].

Similarly, in a systematic review, increased count of IELs was observed in adults as early as the first or second day of gluten challenge; IEL count was found to be elevated in

100% of the adults by four-weeks of challenge [22]. Meanwhile, 91–100% of children reported an increase of IELs within 1–2 months. Likewise, the Marsh score when used as an endpoint for gluten challenge is also found to vary in proportion to the dose and length of gluten challenge [22].

NCGS

Currently, there are no specific tests to confirm the diagnosis of NCGS. NCGS patients have been reported to have a wide variety of histological findings ranging from normal histology to an increase in T-cells [42], redistribution of T-cells (without an increase) in small clusters in the superficial epithelium and linear distribution in deeper layers, increase of eosinophils in lamina propria, and an increase of IELs [43, 44]. Overall however, there is no histologic finding that has been established to be specific for NCGS; therefore effect of a gluten challenge cannot be evaluated in terms of histological parameters.

Emerging Biomarkers

In addition to the above-discussed serological and histological endpoints to detect response to gluten, other markers have been evaluated to monitor patients in the context of a gluten challenge or a GFD regimen. These markers have been developed in an attempt to supplant or supplement the use of mucosal biopsies, since the latter is invasive and not suitable for frequent monitoring. Furthermore, albeit being a highly useful test in the diagnostic panel for GAD, gluten challenge is a lengthy and cumbersome procedure. It is theoretically burdened by a significant reduction of patient compliance due to the onset of symptoms related to gluten ingestion. For this reason, there have been attempts to discover alternatives to gluten challenge.

Currently, much work is being done to discover novel biomarkers of CeD based on the immunological pathways involved in its pathogenesis. The well-characterized relationship of the major histocompatibility complex class II (MHC-II) molecule, HLA-DQ2.5, with the immune response

and the pathogenesis of CeD has facilitated the development of potential biomarkers for its diagnosis [45, 46].

Lactulose-to-Mannitol (LAMA) Ratio

It is an experimental biomarker that has been used to detect intestinal permeability [17, 19, 47]. In CeD patients, enteropathy results in a decrease in the transmembrane absorption of monosaccharides (e.g., mannitol) and an increase in the paracellular absorption of disaccharides (e.g., lactulose). This can be measured in the form of the LAMA ratio. The test is performed by administering a solution containing 7.5 g lactulose and 2 g mannitol in approximately 100 mL of water orally to a patient after a 4 h fasting period. Excretion of the sugars is measured in a 6 h urine collection. A LAMA ratio of more than 0.03 is considered to be a positive test [47].

In a study involving a 14-day gluten challenge, Leffler and colleagues found the LAMA ratio to rise, although non-significantly on day 14 of the gluten challenge. Furthermore, there was no significant correlation of LAMA with other endpoints [19]. Similarly, a study that tested the protective effect of larazotide (tight junction modulator) during a gluten challenge found no significant difference in LAMA ratios between the gluten challenge and gluten-free groups [17].

Serum Intestinal-Fatty Acid Binding Protein (Serum I-FABP)

Serum I-FABP is a cytosolic protein present in mature enterocytes. It is rapidly released into systemic circulation when intestinal epithelium is damaged [48]. Serum I-FABP has been shown to increase with active CeD and normalize on a strict GFD. It also correlates with the severity of villous atrophy in CeD patients at the time of diagnosis [49]. Based on this knowledge, serum I-FABP might be useful to detect non-adherence to GFD or inadvertent gluten ingestion, without having to rely on mucosal biopsies.

In a study that examined the effect of a 14-day gluten challenge in adult population, serum I-FABP increased at the end of the challenge and correlated with the IEL levels, which is known to detect early disease activity [50]. In children, increased serum I-FABP plus elevated celiac autoantibody, and HLA-DQ2 and/or DQ8 positivity has been suggested as an alternative to invasive testing to establish CeD diagnosis. With sensitivity, specificity, and positive predictive value of 92.1%, 87.7%, and 87.5% respectively, the optimal cutoff for serum I-FABP has been estimated to be 450 pg/mL [51].

Therefore, if established as a reliable biomarker, serum I-FABP may find utility in developing shorter gluten challenges. However, larger studies are required to validate serum I-FABP as a diagnostic test for CeD.

Gluten-Reactive T-Cells

The central pathogenesis of CeD is related to the presence of gluten responsive T-cells. These cells can now be detected using blood tests developed to assess gluten-specific T-cells, directly either by tetramer assay or by the assessment of IFN-γ ELISPOT (enzyme-linked immunospot) assay [52].

The IFN-γ ELISPOT was evaluated in patients with confirmed CeD diagnosis with HLA-DQ2.5 and compared with non-CeD patients (regardless of the HLA-DQ2.5 status), with both groups being on a strict GFD for at least 6 months. Their blood samples were taken on day 0 and day 6 of the 3-day gluten challenge [52].

The sensitivity and specificity were 85.1% and 100%, respectively, for IFN-γ measured by ELISA or ELISPOT. Meanwhile, IP-10 (IFN-γ-inducible protein-10) measured by ELISA had a sensitivity of 100% and specificity of 94.1%.

These results suggest that the detection of gluten-reactive T-cells allows earlier detection of an immune response specific for CeD after a 3-day gluten challenge. This test may allow for reduction in the length of the gluten challenge currently recommended.

HLA-DQ Gluten Tetramer

The HLA-DQ gluten tetramer test can be used to detect gluten-specific T-cells in the peripheral blood of celiac patients [53]. These tetramers are complexes of four soluble MHC molecules, linked with a single T-cell epitope derived from gluten (DQ2.5-glia-α1a or DQ2.5-glia-α2). These MHC molecules are bound to a streptavidin molecule that is coupled with a fluorescent marker [53, 54]. However, due to the extremely low levels of circulating gluten-responsive T-cells, it is necessary to enrich this cell population [54,55]. Multivalent engagement of MHC molecules leads to a stable binding of the tetramer to T-cell receptors (TCRs) on the T-cell surface, which allows direct visualization of the T-cells. Importantly, sufficient affinity between the TCR and peptide-MHC molecules appears to be achieved only by T-cells that express TCRs specific for the particular peptide-MHC complex.

Sarna and colleagues showed that HLA-DQ gluten tetramer was able to detect T-cell response to gluten in peripheral blood mononuclear cells (PBMCs) on day 6 of a 3-day gluten challenge [53]. Further research demonstrated that gluten-specific T-cells were detectable in the blood of CeD patient even without gluten challenge [56]. In a later study, HLA-DQ tetramers were confirmed to be sufficiently sensitive to detect gluten-reactive T-cells in peripheral blood in treated or untreated CeD patients without requiring gluten challenge [54]. In this study treated and untreated CeD patients had significantly higher T-cell levels compared to healthy subjects ($p < 0.0001$).

In another study, HLA-DQ gluten tetramer blood test was tested in patients with and without CeD in the absence of gluten consumption [57]. It was found to have a sensitivity and specificity of 97% and 95%, respectively, for subjects on GFD with or without CeD. Meanwhile, the sensitivity increased to a 100%, and the specificity decreased (90%) when the test was performed on untreated CeD patients compared with healthy subjects.

In summary, HLA-DQ gluten tetramer blood test may have a role in CeD diagnosis algorithm, particularly in HLA-DQ2.5 patients on self-instituted GFD. In this scenario,

this test could obviate the need of gluten challenge followed by duodenal biopsy because of the high negative predictive value of HLA-DQ gluten tetramer test [57]. Further research is needed to determine the role in the full spectrum of CeD patients.

Intraepithelial Lymphocyte Immunophenotyping

Intraepithelial lymphocytes (IELs) are a part of the intestinal mucosal defense barrier. In CeD patients on gluten-containing diet, IELs have been found to be increased, particularly the IELs with the TCR$\gamma\delta$ receptor, with a decrease in NK-like IELs [58]. Recent studies have further shown that these TCR$\gamma\delta$ and NK-like IELs remain altered in CeD, independent of gluten intake [59]. Hence IEL immunophenotyping could be a useful tool for the diagnosis of CeD, particularly in patients who are already on GFD. A retrospective study compared both IEL levels (TCR$\gamma\delta$ and NK-like IELs) in three different pediatric groups (CeD patients on GFD, CeD on a gluten diet, and a control group) [58]. This study found a significant increase in the number of IELs, decrease in NK-like IELs, and increase in TCR$\gamma\delta$ IELs in the epithelium of CeD patients on a gluten-containing diet compared to CeD patients on GFD. These trends were similar and even more pronounced on the comparison of the CeD with the control patients [58]. However, due to the size imbalance between the three studied groups and retrospective study limitations, larger prospective studies are needed to establish the role of this test in the diagnosis of CeD.

Potential NCGS Biomarkers

Specific serological tests or intestinal histopathological features that are diagnostic of NCGS are yet to be discovered. Recent studies have yielded mixed results on potential biomarkers. For example, the IgG anti-gliadin antibody (IgG AGA) has been found to occur more frequently in patients with NCGS compared to the general population, while other studies have found it to be a weak predictor of NCGS [60, 61].

Mucosal IFN-γ mRNA has also been explored as a potential marker. It was found to be increased after a 3-day gluten challenge in NCGS patients, which may indicate a possible role in the pathophysiology and diagnosis of NCGS [56]. Further research is still needed to definitively establish objective diagnostic markers for NCGS.

Case Outcome

Genetic testing in the patient revealed HLA-DQ2 genotype. tTG done at the same time was negative, although close to the upper limit of normal. The patient therefore underwent a gluten challenge with 3–5 g of gluten (2–4 slices of bread) per day for 2 weeks, beyond which time, the patient reported increased and intolerable GI symptoms and fatigue. Upper endoscopy with duodenal biopsy done at the end of this period revealed partial villous atrophy, and labs showed raised tTG titers. This unequivocally confirmed the diagnosis of CeD in this patient, in addition to providing a baseline value of tTG with which to follow up on adherence to a GFD. Hence the patient was started on a strictly GFD, in conjunction with dietitian consultation. During subsequent visits in the gastroenterology clinic, the patient was found to have a marked improvement in symptoms, along with a gradual normalization of tTG levels.

Clinical Pearls/Pitfalls

1. Gluten challenge is a relevant and useful diagnostic tool in the light of an increasing number of patients now self-reporting sensitivity to gluten.
2. Three to five grams of gluten challenge daily (2–4 slices of wheat bread) for a minimum of 2 weeks prior to endoscopy and a maximum of 8–12 weeks prior to serology, depending, on the symptom tolera-

bility, may be sufficient to diagnose CeD in patients already on a GFD.
3. Gluten challenge may also support the discovery of newer biomarkers of gluten sensitivity and new therapies in this area.
4. There is a need to use a standard approach to gluten challenge, including the formulation, dose, and duration as well the outcomes to be studied to measure response to the challenge.
5. The potential to aggravate symptoms make the gluten challenge difficult to be employed as a routine diagnostic tool in clinical settings.
6. New biomarkers like serum I-FABP and HLA-DQ tetramer test require further validation in larger prospective studies to determine their role in the diagnostic algorithm of CeD.

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Chapter 7
Seronegative Celiac Disease

Suneeta Krishnareddy and Benjamin Lebwohl

Case Presentation

A 38-year-old woman presented to her primary care physician with vague abdominal complaints of bloating and generalized food intolerances for several years, worsening over the past 6–8 months. She had a family history of CeD (her brother had biopsy-proven CeD), so her primary care physician checked her celiac serology, which was negative. She continued with her regular diet and continued to experience symptoms and 3–4 months later developed heartburn for which her primary care physician referred her to a gastroenterologist for evaluation. During that evaluation, she underwent an upper endoscopy which revealed scalloping of the second portion of the duodenum, and duodenal biopsies showed complete villous atrophy (Marsh 3c). At that time her gastroenterologist repeated celiac serologies which were again negative, but told her she likely had CeD and should initiate a GFD.

The patient was hesitant to change her entire lifestyle, given a busy family life and frequent work travel, and did not

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want to go on a GFD unless it was certain that she had CeD, so she sought a second opinion at the celiac clinic. She reported ongoing intermittent abdominal bloating, not associated with any particular food, and heartburn. Serum IgA was 140 (wnl), tTG IgA was 2 (normal < 4), tTG IgG was 7 (normal < 10), DGP IgA was 7 (normal < 20), and DGP IgG was 14 (normal < 20). Biopsy slides were reviewed by the GI pathologist and confirmed to be Marsh 3c. She had further workup including immunoglobulin (Ig) levels, fecal intestinal pathogens (including *giardia duodenalis* and *Escherichia coli*), as well as anti-enterocyte antibodies, all of which were negative. Her celiac genetic testing revealed DQ2 homozygous genes. Based on these data, she was diagnosed with SNCD, and she commenced on a GFD.

Diagnosis and Management

As previously mentioned, CeD is a chronic enteropathy characterized by a degree of villous atrophy and lymphocytic inflammation of the epithelial layer covering the mucosa. While there is a discrete grading system laid out by Marsh and Oberhuber ranging from increased intraepithelial lymphocytes (IEL) (Marsh 1) to total villous atrophy (Marsh 3c) [12], the diagnosis of CeD is not only based on pathological findings. The serological assessment of autoantibodies associated with this disease is essential to achieve an accurate diagnosis (antibodies against tTG, DGP, and/or EMA) while on a gluten-containing diet [7]. While used in the past, anti-gliadin antibodies (AGAb) are considered less relevant for their low sensitivity and specificity and have been replaced by DGP in the current practice [15]. While seronegative CeD is rare, it seems to represent the most common cause of serology-negative villous atrophy [6, 14].

Celiac antibodies are detected in the vast majority of patients with CeD (with an overall sensitivity ranging from 94% to 98%, Table 7.1), while a minority of CeD patients may test negative and thus termed SNCD, and in these cases

Table 7.1 Sensitivity and specificity of main autoantibodies used in clinical practice for the serological diagnosis of CeD [23]

Test	Sensitivity %, (range)	Specificity, % (range)
AGAb IgA	85 (57–100)	90 (47–94)
AGAb IgG	80 (42–100)	80 (50–94)
EMA IgA	95 (86–100)	99 (97–100)
EMA IgG	80 (70–90)	97 (95–100)
tTG IgA	98 (78–100)	98 (90–100)
tTG IgG	70 (45–95)	95 (94–100)
DGP IgA	88 (74–100)	90 (80–95)
DGP IgG	80 (70–95)	98 (95–100)

Adapted from Armstrong et al. [3]
AGAb anti-gliadin antibody, *DGP* deamidated gliadin peptide, *EMA* anti-endomysial antibody, *tTG* tissue transglutaminase

the diagnosis is strictly dependent on the demonstration of villous atrophy on pathology. The finding of villous atrophy with negative CeD serology is a clinical challenge as many conditions may cause severe small intestinal damage (see Chap. 8, Table 8.3). The cornerstone for the diagnosis of SNCD is represented by the histological response to a GFD, after having excluded other causes of gluten-independent villous atrophy. Diagnostic duodenal biopsies must be correctly oriented and performed while on a gluten-containing diet and in the absence of concomitant immunosuppressive therapy [18].

Pathogenesis

It has been speculated that SNCD may be due to lack of passage of autoantibodies produced in the intestine into the circulation. The production of antibodies in individuals with CeD occurs in the intestinal mucosa, as evidenced by the presence of immune complexes detectable by immunofluorescence. Autoantibodies cross the mucosa and enter into

blood vessels where they are detected by standard assay [8]. It is postulated that in SNCD, the antibodies are confined to the lamina propria. Some evidence does exist to confirm this hypothesis, showing deposits of tTG complexed with IgA anti-tTG in a pediatric population affected by SNCD, but in Marsh 1 lesions only [19], which is also termed "Marsh 1 CeD" or "mild enteropathy CeD." This study highlights the heterogeneity in work done thus far in this clinical entity. First reported in 2004, patients with Marsh 1 lesions and negative serologies were considered CeD patients, whereas nowadays, with current understanding of disease pathology and classification, these patients would no longer be classified as having active CeD. Another area of confusion includes patients with partial villous atrophy and weakly positive EMA who are labeled as seronegative because of negative tTG IgA. Finally, patients with villous atrophy and negative tTG IgA and tTG IgG but no histological recovery following GFD should also not be considered as SNCD. All this variability has led to inconsistencies in diagnosis and management of this SNCD. For future purposes, this entity should be defined as patients with villous atrophy without either EMA IgA/IgG or tTG IgA/IgG, who show response to GFD.

Another possible explanation for seronegativity in CeD could be immaturity of the immune system. Indeed, CeD is often associated with dysregulation of the immune system, in particular immunoglobulin deficiencies such as selective IgA deficiency or common variable immunodeficiency (CVID) [5]. In these immune disorders, it is presumed that a lack of maturation of plasma cells leads to the inefficient production of autoantibodies directed against tTG, thus explaining the seronegativity. Even in these cases, deposits of tTG may be retrieved in duodenal samples [13]. In this situation, CeD can still be a difficult diagnosis to make as villous atrophy can be observed unrelated to gluten due to immunodeficiency or infectious etiology. In these diagnostic dilemmas, it is paramount that histological recovery is demonstrated after initiation of the GFD.

Diagnosis

The diagnosis of SNCD can be difficult as many patients are on a GFD prior to testing, therefore making antibodies or lack thereof hard to interpret. The gold standard for CeD diagnosis still remains duodenal biopsy showing villous atrophy. As previously mentioned, this also can be difficult to interpret as biopsies can be oriented sub-optimally, pathologists have interobserver variability, and villous atrophy is not specific for CeD. The cornerstone for the diagnosis of SNCD is represented by a histological response to a GFD, after having excluded other causes of gluten-independent villous atrophy. The timing of histological response to GFD is somewhat vague and not well studied, but ideally should not be done sooner than 12–18 months post-initiation of the GFD [9]. Premature tissue sampling can falsely label a patient as non-responsive and preclude correct treatment.

The European Society for the Study of Coeliac Disease (ESsCD) advises to proceed with duodenal biopsies for seronegative patients with chronic diarrhea, diarrhea with malabsorption (mainly weight loss), unexplained IDA, GI symptoms with family history of CeD or personal history of autoimmune disease or IgA deficiency, pediatric failure to thrive, skin biopsy-proven DH, villous atrophy on WCE, or unexplained high ileo/colostomy output [23].

Other testing has been used to help confirm the diagnosis including HLA DQ2 and DQ8 haplotyping. As the absence of HLA DQ2 or DQ8 virtually excludes the likelihood of having CeD, a negative test is extremely helpful, while a positive test helps in risk stratifying patients who meet other criteria (as villous atrophy or family history) in determining a correct diagnosis. While a positive family history, in first-degree relative, can aid in the diagnosis of SNCD, it is not necessary if other criteria are met.

It is important to consider other causes of non-celiac villous atrophy and complete a workup to rule out these causes, including stool pathogen assay for infectious etiologies, quantitative immunoglobulins to rule out CVID, and extensive medi-

cation and travel history to rule out olmesartan-induced villous atrophy and tropical sprue, respectively. It is also often prudent to check anti-enterocyte antibody to rule out autoimmune enteropathy. Other conditions (as listed in Chap. 8, Table 8.3) can usually be ruled out with careful medical history, and further examination should be done based on the clinician's index of suspicion (e.g., colonoscopy, HIV testing, etc.).

Clinical Course and Natural History

The clinical course of SNCD is often difficult to ascertain as the literature describes a heterogeneous population, mostly due to inconsistent diagnostic criteria for SNCD. Usually, SNCD patients are older at age of diagnosis when compared with seropositive ones, and the classical presentation is more common [17, 21]. Studies have shown that patients with SNCD have classical symptoms, such as weight loss and diarrhea, as well as association with other autoimmune disorders suggesting an aggressive form of disease, and would benefit from the GFD [20, 22]. Results for sex predominance are discordant: in two studies there is a predominance of male sex [16, 17], while in two others, a predominance of SNCD in the females was noted [4, 21].

Recent publications on seronegative villous atrophy and SNCD describe diverse patient populations, and composite results seem to suggest a poor prognosis and a high risk of developing complications [4, 17, 21]. Mortality in seronegative villous atrophy including SNCD was reported to be 6 deaths per 100 person-years, where only 0.2 deaths per 100 person-years occurred in seropositive CeD. The cause of death in these patients was mainly related to the development of malignancy, including enteropathy-associated T-cell lymphoma (EATL) and B-cell lymphoma [17]. In another study, the mortality in SNCD was found to be 11.2% compared to 3.2% in seropositive CeD. It is tempting to speculate that in these patients with SNCD, delayed diagnosis leads to long-standing enteropathy, which may in turn increase the risk of complications, but more studies are needed to confirm this.

Treatment

The management of SNCD is still somewhat controversial. The treatment options for SNCD, similar to CeD, are lifelong adherence to the GFD. However, usefulness and appropriateness of the diet are often questioned, as correctly discriminating such patients from the heterogeneous differential diagnosis of seronegative villous atrophy is still the most important step. Once other forms of gluten-independent villous atrophy have been excluded, a GFD is often started. Reports have described severe nutritional deficiencies in SNCD [2], thus necessitating initiation of the GFD and monitoring for resolution of deficiencies.

Case Outcome

Six months after starting the GFD, the patient reported improvement in her heartburn and subsequent discontinuation of her daily H2 blocker and significant improvement in her abdominal pain and bloating. She noted that she was now able to eat many foods that previously caused her symptoms, and aside from gluten, her diet had a lot more variety than previously. She was doing well and felt her overall health was much improved.

Clinical Pearls/Pitfalls

1. SNCD is an elusive condition due to its challenging diagnosis. The only clear diagnostic criteria is histological response to the GFD; therefore, a trial of GFD is warranted, either as part of the workup or as long-term treatment.
2. SNCD might be considered as “immature” CeD (where the global expression of antibodies is lacking) versus “milder” CeD (due to weaker involvement of adaptive immunity and a minor activation of tissue transglutaminase).

3. SNCD is an uncommon condition. Suspected patients should not be placed on a GFD until extensively investigated for other causes of villous atrophy.
4. Approximately 30% of patients with seronegative villous atrophy will be diagnosed with SNCD.

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Chapter 8
Non-Responsive Celiac Disease

Isabel A. Hujoel and Alberto Rubio-Tapia

Case Presentation

A 19-year-old woman presented to a gastroenterology clinic with recently diagnosed CeD and persistent symptoms. A year prior to presentation, she was seen at an outside facility for diarrhea, upper abdominal pain, bloating, postprandial nausea, and early satiety, along with arthralgia, hair loss, menorrhagia, and Raynaud's phenomenon. She had undergone an upper endoscopy with duodenal biopsies which showed increased intraepithelial lymphocytosis and partial villous blunting, compatible with Marsh 3a lesion. Blood work demonstrated elevated tTG IgA (63.7 U/mL, normal <10 U/mL) and normal total IgA. DGP IgA was positive at 31.7 U (normal <20 U). She was subsequently seen by a dietitian and had been strictly complying with a GFD. Following the initiation of the diet, she noted complete resolution of her symptoms aside from persistent upper abdominal pain, postprandial nausea, and early satiety. At the time of her 1-year follow-up visit, she again confirmed a strict GFD for roughly 1 year, although she did note

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possible contamination while eating out and less control over her diet since recently starting college.

Given concern for gluten exposure, serology was obtained and she was referred back to a dietitian. The serology showed normal tTG IgA and DGP IgA. The dietitian's assessment for contamination was unremarkable. An upper endoscopy with biopsies of the duodenum and duodenal aspirates showed healed mucosal villi and negative cultures, respectively.

Diagnosis

Non-responsive celiac disease (NRCD) is defined as continued or a recurrence of symptoms or laboratory changes consistent with CeD despite a GFD for a period of 6–12 months [1]. Following initiation of a GFD, symptoms generally improve within weeks [2]. Mucosal recovery can be delayed, however, and in up to roughly 70% of individuals, there can be persistent mucosal abnormalities despite a strict GFD at 2 years [3]. Symptom resolution has not been found to be an accurate indicator of mucosal recovery.

Symptoms of NRCD commonly include abdominal pain, diarrhea, and weight loss [4]. This condition is common and can affect up to 30% of those with CeD on a GFD [5]. Primary NRCD is defined by an initial lack of response to GFD, while secondary NRCD is defined by an initial response to a GFD but then a return of symptoms later. NRCD can be due to several different causes, with the most common being inadvertent gluten exposure [6, 7]. The European Society for the Study of Coeliac Disease (ESsCD) advocates for the use of the term "slow responders" and recommends against the use of "NRCD," since most of these patients will improve over time on a strict GFD or have another remediable cause for their persistent symptoms [13]. Evaluation by a dietitian, therefore, is a helpful initial step in work-up. Other possible causes include incorrect initial diagnosis of CeD, slow mucosal recovery, inflammatory bowel disease (IBD) including microscopic colitis,

Helicobacter pylori infection, food intolerances (such as lactose and fructose), irritable bowel syndrome (IBS; see Chap. 14), small-intestinal bacterial overgrowth (SIBO), pancreatic insufficiency, and refractory celiac disease (RCD) (Table 8.1) [6, 7]. RCD, defined as persistent malabsorption and villous atrophy despite a GFD for a period of over 1 year, is rare, with prevalence estimates ranging from 0.7% to 1.5% of cases of CeD, although it is estimated to comprise up to nearly a fifth of those seen at referral centers for persistent symptoms [6]. Distinguishing NRCD from RCD is important, as the prognosis and management of the two entities are significantly different (see Chaps. 9 and 10).

The initial step in approaching NRCD is to confirm that the diagnosis of CeD was correct (Table 8.2). The basis for the original diagnosis of CeD should be investigated for the presence of positive celiac serology, villous atrophy, and permissive genotype. In this patient, her small bowel histology and elevated serologic markers support the diagnosis. If the diagnosis of CeD is in question, then alternative causes of their symptoms, or villous atrophy (if seen on histology), should be investigated. Absence of HLA-DQ2/DQ8 is helpful to rule out CeD in patients on a GFD. A gluten challenge may be necessary to definitively determine if CeD is present or not in selected cases [8] (see Chap. 6).

Once the diagnosis of CeD is confirmed, inadvertent gluten exposure needs to be excluded. Gluten exposure in NRCD is most commonly not deliberate and may be in part due to insufficient education on a GFD [6]. Persistently elevated tTG or EMA could suggest continued gluten exposure; however, it can also be seen in RCD. Additionally, normal serologies may be found despite clinically significant levels of gluten consumption. Therefore, the patient should undergo thorough evaluation with an experienced dietitian. In our case, the combination of negative serologies and a thorough dietary review with the dietitian made inadvertent gluten ingestion less likely (Fig. 8.1).

One study found that 82% of those who were on a strict GFD, as judged by experienced dietitians, had symptom

Table 8.1 Etiologies of Non-Responsive Celiac Disease

Frequency (%) [4, 6, 8]	Potential cause for continued symptoms	When to consider	Testing
36–51	Continued gluten exposure	Everyone	– Dietary review with dietitian – Celiac serologies
8–22	Functional disorders such as IBS	Those with supportive symptoms	Review of symptoms/ history
6–18	Microscopic colitis	Those with supportive history and diarrhea	Colonoscopy with random colonic biopsies (consider performing at time of EGD)
6–14	SIBO	Those with supportive history and symptoms (such as diarrhea)	Culture of small bowel aspirate (consider obtaining in everyone at time of EGD) or lactulose breath test
8–12	RCD	Everyone	Upper endoscopy with small intestinal biopsies; exclusion of other etiologies
0–12	Pancreatic insufficiency	Those with supportive history	– Pancreatic testing including fecal fat and elastase – Pancreatic enzyme trial
11	Incorrect diagnosis of CeD	Everyone	Review of initial diagnosis (including blood work, histology, response to a GFD, and genotyping)
2–7	Food intolerance (i.e., lactose/ fructose)	Those with supportive history	– Dietary review and history – Breath tests – Exclusion trial

Others: Eating disorders, autoimmune enteropathy, protein-losing enteropathy, malrotation of the gut, peptic ulcer disease, gastroparesis, IBD, food allergies (including wheat), common variable immune deficiency (CVID), duodenal adenocarcinoma, Whipple disease

Table 8.2 Factors to consider when evaluating initial diagnosis of celiac disease

Evaluating initial celiac disease diagnosis	
Was HLA genotyping done and were permissive gene pairs seen (HLA DQ2 and/or HLA DQ8)?	If these gene pairs are absent, CeD is highly unlikely, and an alternative diagnosis should be sought
Did they ever have biopsy-confirmed dermatitis herpetiformis?	If so, this confirms the presence of CeD
Were celiac serologies checked, and were IgA/IgG tTG and/or EMA checked and positive?	If positive (especially with high titers), this is highly suggestive of CeD; however, negative serologies cannot rule CeD out
Were small bowel biopsies consistent with CeD?	– If the diagnosis was based only on biopsy results, this is unreliable, as villous atrophy can be seen in many different conditions – Small bowel biopsies consistent with CeD in conjunction with positive serologies, family history, and/or response to a GFD are suggestive of CeD
Was diagnosis based only on response to a GFD?	If this is the case, then the diagnosis of CeD is not reliable, as response of symptoms to a GFD is not specific to CeD

reduction with a gluten contamination elimination diet, which is a diet focused on whole unprocessed foods with the goal of eliminating any possible source of gluten cross-contamination [9]. Therefore, in individuals who have positive serology or at least Marsh 2 histology, a gluten contamination elimination diet can be considered although more evidence is needed to support this recommendation.

If gluten exposure is unlikely, the next step is a follow-up upper endoscopy with small bowel biopsies. If diarrhea remains a predominant symptom (especially if not steatorrhea), a concurrent colonoscopy with random biopsies should

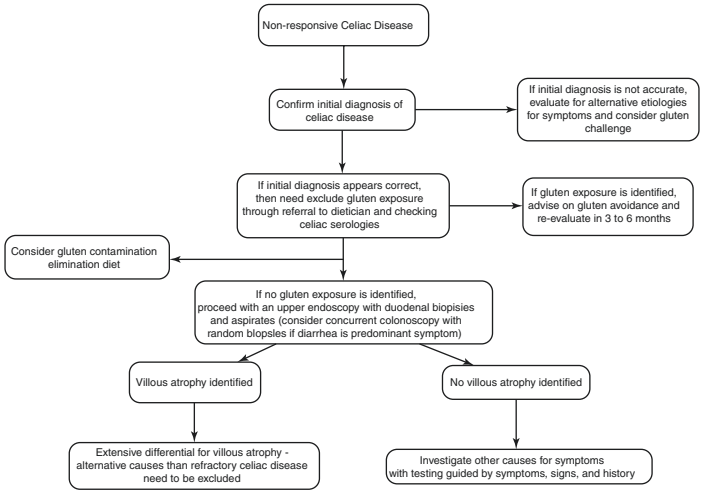

Figure 8.1 Suggested approach to NRCD

be considered to evaluate for microscopic colitis. If continued villous atrophy is found, the differential is broad and includes RCD, gluten exposure, and medications (Table 8.3). If normal or almost normal mucosa is seen, then alternative causes need to be investigated. These include functional bowel disorders such as IBS (see Chap. 14), microscopic colitis, food intolerances, and SIBO (although the latter can present with villous atrophy in roughly 30% of cases). *Lymphocytic duodenitis* only (without villous atrophy) can be seen in microscopic colitis, food hypersensitivity (cow's milk, soy, fish, eggs, etc.), peptic ulcer disease, *H. pylori*-associated duodenitis, drugs (NSAIDs, proton pump inhibitors), infections (viral enteritis/post-infectious syndrome, giardiasis, cryptosporidium), autoimmune disorders (rheumatoid arthritis, Hashimoto's thyroiditis, SLE, multiple sclerosis), and blind loop syndrome, IBS, and NCGS [13]. Further evaluation should be guided by the specific symptoms. In this case, given the nausea, a gastric emptying study was the best next test. An underlying etiology is generally found in 90% of cases [8].

Table 8.3 Alternative causes of villous atrophy

Alternative causes of villous atrophy	
Autoimmune	Crohn's disease, autoimmune enteropathy, CeD, RCD
Infectious	HIV enteropathy, tropical sprue, *Mycobacterium avium* complex (MAC), Whipple disease, giardiasis, tuberculosis, SIBO
Infiltrative	Amyloidosis, collagenous sprue, eosinophilic enteritis
Medications	Angiotensin-receptor blockers (olmesartan, losartan), NSAIDs (sulindac), alcohol, chemotherapy/immunosuppressive (azathioprine, mycophenolate mofetil, methotrexate, colchicine [14]), anti-CTLA4 antibody (ipilimumab), antibiotics (neomycin)
Neoplasm	Lymphoma
Others	Common variable immune deficiency, (CVID), abetalipoproteinemia, peptic duodenitis, Zollinger-Ellison syndrome, small bowel ischemia, malnutrition, radiation enteritis, graft-versus-host disease

Management

Management of NRCD is based on the underlying identified cause. If individuals have inadvertent gluten contamination, and the source of contamination is found, then patients should be advised on how to avoid future contamination. They should then return for re-evaluation in 3–6 months by both the physician and dietitian. Although controversial, some physicians recommend avoiding oats in those with NRCD [10]. This is due to the high frequency of cross-contamination with gluten in commercial oats.

If food intolerances are identified, then individuals should be instructed to avoid intake of those foods. Microscopic colitis should be treated with budesonide [11] and discontinuation of medications such as NSAIDs, PPI, and SSRI. SIBO

can be treated with antibiotic therapy (noting that relapse is common), such as rifaximin or metronidazole [12] with or without neomycin for methane-producing bacteria. Pancreatic insufficiency is treated with pancreatic enzyme replacement, and empiric treatment can be trialed. If a functional cause is identified, treatment should involve symptomatic management, reassurance, and possibly neuromodulators, as discussed in Chap. 14. If they have constipation, fiber supplementation should be tried first as the GFD may not be providing sufficient fiber, which can in turn exacerbate constipation. Osmotic laxatives may need to be added.

Case Outcome

In this patient's case, a 4-hour gastric emptying study was performed and was normal. Given this and her symptoms, it was thought that she likely had overlapping functional dyspepsia causing her persistent epigastric pain, postprandial nausea, and early satiety. She was therefore started on low-dose nortriptyline. When she was seen in follow-up 6 weeks later, she noted partial but not complete improvement in her symptoms with the nortriptyline. Subsequently her dose was increased with symptom resolution.

Clinical Pearls/Pitfalls

1. The accuracy of the initial diagnosis of CeD needs to be examined, as an incorrect diagnosis has been found in up to 11% of individuals with NRCD.
2. Gluten exposure is the most common cause of NRCD and should be evaluated with a careful dietary review by a dietitian.
3. All individuals presenting with NRCD should undergo an upper endoscopy with biopsies. Further testing should be guided by specific symptoms.

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Chapter 9
Type I Refractory Celiac Disease

Marjorie M. Walker and Michael D. Potter

Case Presentation

A 46-year-old woman presented to the gastroenterology clinic with diarrhea and fatigue. She was diagnosed with CeD 2 years ago. At the time of diagnosis, her tTG levels were elevated at over 200 IU/mL (per local laboratory cut-off value). As reference ranges may vary with different commercial tests, it is advised to confirm test cutoff values [1]. She had a permissive genotype for CeD (heterozygous HLA DQ2), and duodenal biopsies demonstrated total villous atrophy with increased IEL (70/100 enterocytes), compatible with Marsh 3c lesions. She commenced a GFD and received parenteral iron therapy for iron deficiency anemia (IDA). At a current 2-year follow-up visit, she reported ongoing diarrhea and fatigue, and laboratory test showed persistent IDA.

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Diagnosis

The patient has ongoing gastrointestinal (GI) symptoms and signs of malabsorption in the context of a previous definitive diagnosis of CeD, raising the possibility of NRCD or RCD. The former is defined by relapse or ongoing symptoms despite maintaining a strict GFD and occurs in 4–30% of CeD patients, with inadvertent or deliberate gluten ingestion as the most frequent cause [2, 3] (see Chap. 8). A detailed assessment by a specialized dietitian is most important in this scenario to identify inadvertent gluten intake with a follow-up duodenal biopsy [2]. Chronic GI symptoms may persist in CeD despite strict adherence to a GFD, even in those with mucosal healing, suggesting coexistent or overlapping pathology [4]. These include other food intolerances, small intestinal bacterial overgrowth (SIBO), microscopic colitis, and pancreatic insufficiency [5]. Irritable bowel syndrome (IBS) may also overlap with CeD, with a higher prevalence seen even in those strictly adherent to a GFD [6] (see Chap. 14). An algorithmic approach to diagnosis of RCD is presented in the following chapter (Chap. 10, Fig. 10.2).

RCD is defined by persistent malabsorptive symptoms (most expert opinion-based definitions will include persistence or recurrence of signs and symptoms of malabsorption) alongside enteropathy in a patient with confirmed CeD, despite strict adherence to a GFD for 12 months, in the absence of other causes of villous atrophy or malignant complications [2, 7]. This is therefore a clinicopathological diagnosis requiring a repeat duodenal biopsy, as symptoms and serology correlate poorly with histological findings [8]. This entity is rarer, believed to affect only 0.7–1.5% of celiac patients [7], usually after the age of 50. At the time of RCD diagnosis, most patients have normal celiac serology, including EMA and tTG [7]. However, the presence of persisting elevated titers of circulating EMA and/or tTG does not completely exclude RCD, but in this case adherence to a GFD should be questioned [3]. Splenic hypofunction, a risk factor for RCD, can be noted in a peripheral blood smear by Howell–Jolly bodies and pitted

RBC or on imaging by decreased spleen size. To confirm a diagnosis of RCD, a duodenal biopsy is mandatory. Multiple duodenal biopsies, one or two from the bulb and at least four from the second portion of the duodenum, are adequate for diagnosis [1]. The characteristic duodenal histology appearances in type I RCD are of villous atrophy, increased intraepithelial lymphocytes (IELs) >30/100 enterocytes, usually much greater in number (see Fig. 9.1), which are CD3- and CD8-positive on immunocytochemistry (IHC). Immunophenotyping of intraepithelial T cells allows differentiation of RCD into type I and type II RCD. Type I RCD shows a similar immunophenotype of IELs to that in untreated CeD, and these CD3-positive intraepithelial T cells do not lose CD8 cell surface differentiation markers. Type II RCD has aberrant immunophenotyping of IELs, defined by genetic analysis of T-cell receptor (TCR) clonality, IHC, and/or flow cytometry [1] (see Chap. 10).

Confusion in diagnosis can arise in patients with small intestinal damage, but without symptoms, as this may simply represent slow mucosal healing: Confirmed mucosal recovery occurs in only 34% of patients at 2 years, and therefore persisting villous atrophy may well be part of the natural history of treated CeD [9], or at least the "slow responders". Other

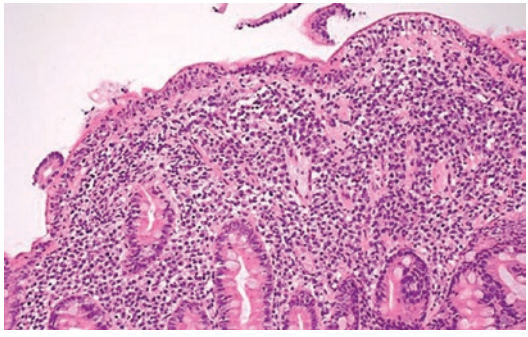

Figure 9.1 Duodenal biopsy in a patient with type I RCD with total villous atrophy and increased intraepithelial lymphocytes (70/100 enterocytes) (magnification ×20)

causes of villous atrophy must be excluded prior to making a diagnosis of RCD, for example, medications, malignancy, and Crohn's disease [7, 8] (see Chap. 8, Table 8.3 for differential diagnoses). Some CeD patients with Marsh 3b–3c on diagnosis may have clinical improvement with mild villous atrophy on follow-up biopsies (Marsh 3a) and should not be categorized as RCD, since their villi will likely regrow overtime [14].

Management

Management is based on prospective case series and expert opinion, with no randomized controlled trial evidence. Nutritional deficiencies should be corrected, which may require enteral or parenteral feeding [10], and the GFD should be continued under the supervision of a specialized dietitian. Corticosteroids are first-line pharmacological therapy, with prednisone (0.5–1 mg/kg/day) and budesonide (9 mg/day) commonly used and effective for the majority of patients with type I RCD [7]. Since most will be steroid-dependent, budesonide, which is extensively metabolized at first pass, may be the preferred option [7, 10]. Open-capsule budesonide protocol is discussed at length in Chap. 10. Steroid-sparing agents such as azathioprine (2 mg/kg/day), cyclosporine, infliximab, tacrolimus, and alemtuzumab have also been used with some success [7, 11]. Type I RCD has a much better prognosis than type II RCD, with a 5-year survival of 80–96% (compared with 44–58% in type II RCD) [10, 12, 13], with mortality related to either nutritional inadequacy or non-celiac-related causes (rather than the association with EATL with type II RCD).

Case Outcome

In this patient repeat celiac serology was negative, and a detailed nutritional review with a dietitian did not reveal any discernible or inadvertent gluten intake. Her endoscopy was repeated, and duodenal biopsies showed partial villous atro-

phy with increased intraepithelial lymphocytes (70/100 enterocytes) (Fig. 9.1). Immunostaining for CD3 and CD8 showed positivity for both T-cell subsets with no predominance or lack of staining. TCR gene rearrangement study was also performed revealing a (normal) polyclonal pattern. A diagnosis of type I RCD was made, and the patient was commenced on budesonide taper for 3 months (9 mg for 4 weeks, 6 mg for 4 weeks, and 3 mg for weeks) with resolution of symptoms.

Clinical Pearls/Pitfalls

1. Persistent symptoms in CeD despite GFD are common; NRCD is commonly due to partial/inadvertent nonadherence to a GFD, and a detailed assessment by a dietitian is key. Celiac serology is usually still elevated in this case.
2. Persistent symptoms, enteropathy, and malabsorption despite a strict GFD are rare; RCD requires repeat duodenal biopsies demonstrating persistent villous atrophy with increased intraepithelial lymphocytes (Marsh 3 lesions).
3. Type I and type II RCD can be differentiated based on the absence or presence of clonality in the T-cell populations observed in duodenal biopsies.
4. Type I RCD has a good prognosis, with the majority responding well to corticosteroid therapy, with low risk of EATL and ulcerative jejunoileitis.

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Chapter 10
Type II Refractory Celiac Disease

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Case Presentation

A 57-year-old man presented for evaluation for bloating, flatulence, and abdominal pain. His primary care physician obtained basic laboratory studies and noted iron deficiency anemia (IDA). He was referred to a gastroenterologist and underwent an upper endoscopy, and biopsies were taken from a normal-appearing duodenum. These returned showing total villous atrophy and increased intraepithelial lymphocytes. tTG IgA was 73 U/mL (normal <4 U/mL). Based on these findings, he was diagnosed with CeD and initiated a gluten-free diet (GFD).

One year after starting a GFD, he presented to a tertiary care facility for reassessment. He was having improved, but persistent, symptoms of bloating and abdominal pain. tTG IgA has normalized. Upper endoscopy was repeated with

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duodenal biopsies showing persistent total villous atrophy. T-cell receptor (TCR) gene rearrangement study was initially equivocal. However, repeat assessment demonstrated a clonal TCR gene rearrangement by polymerase chain reaction (PCR), and more than 50% of CD3+ intraepithelial lymphocytes (IEL) with loss of CD8 were detected by immunohistochemistry (IHC). Tissue flow cytometry was not completed. Computed tomography with enterography (CTE) showed mildly enlarged mesenteric lymph nodes. Wireless capsule endoscopy (WCE) revealed no small bowel malignancy. There was no peripheral blood T-cell clone by flow cytometry, and positron emission tomography (PET) was negative for evidence of lymphoma. Open-capsule budesonide therapy was initiated with clinical improvement. Duodenal histological improvement was noted over time (see Fig. 10.1).

Diagnosis

As discussed in Chap. 8, NRCD is defined by persistent symptoms and histologic small bowel villous damage despite 6–12 months on a GFD [1–3]. NRCD can be seen in up to 30% of patients with CeD, most often due to gluten contamination [1, 2, 4, 5]. Confirmation of the initial diagnosis of CeD is important as lymphoproliferative disorders can present like RCD. These disorders can demonstrate aberrant CD3+ T-cells, but express CD4+, CD8+, or even NK markers.

RCD is rare, affecting approximately 1–2% of patients with CeD [6]. Type II RCD involves an aberrant, clonal T-cell population of intraepithelial lymphocytes in the absence of lymphoma [7, 8], while type I RCD does not have this aberrant, clonal T-cell population (see Chap. 9).

When RCD is suspected, repeat duodenal biopsies should be evaluated for aberrant, clonal T-cell populations, and T-cell clone should be evaluated in the peripheral blood by flow cytometry. This analysis is complicated and should be completed by a pathologist familiar with the lymphocyte phenotypes and clonality associated with type II RCD and

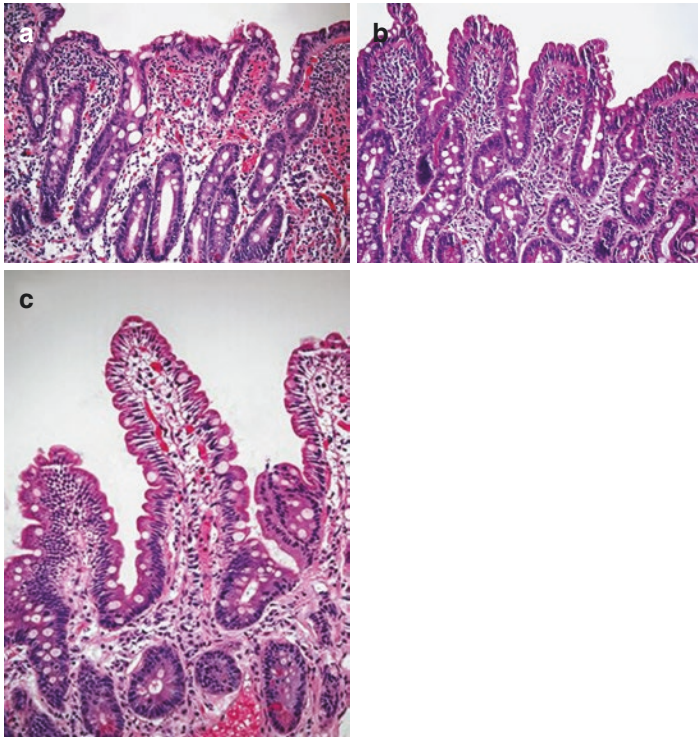

Figure 10.1 Duodenal histology in patient with type II refractory celiac disease. Panel **a** shows duodenal histology after 1 year on a GFD. This demonstrates total villous atrophy and increased intraepithelial lymphocytes, compatible with Marsh 3c lesions. Panel **b** shows duodenal histology after 6 months on open-capsule budesonide therapy, with partial villous atrophy and increased intraepithelial lymphocytes, compatible with Marsh 3a lesions. Panel **c** shows duodenal histology after 5 years of budesonide therapy with normal villous architecture, compatible with Marsh 0 histology

EATL. Traditionally, immunohistochemistry (IHC) and polymerase chain reaction (PCR) have been used for this evaluation [8, 9], with flow cytometry of duodenal lymphocytes becoming an alternative option with less inter-observer variability [10]. The abnormal T-cell population is suspected

when there is loss of normal T-cell surface markers (most specifically CD3 and CD8) but preserved intracellular expression of CD3 in >50% of T-lymphocytes by IHC or >20–25% by flow cytometry and a clonal rearrangement of a TCR by PCR [7, 9–11]. Clonal TCR gene rearrangements have been seen in up to 6% of those with treated CeD, in 17% with type I RCD, and in 67% of those with type II RCD [12]. Therefore, the presence of a clonal TCR gene rearrangement must be reinforced with the IEL phenotype and both the clinical picture of malabsorption and villous atrophy before making the diagnosis of type II RCD. Unfortunately, flow cytometry of the IELs derived from small bowel biopsies (submitted in saline) has been limited to a few research centers in the USA. The chapter includes an algorithmic approach to evaluation and diagnosis (Fig. 10.2).

Management

Once the diagnosis of type II RCD has been made, therapy is indicated, since this entity is regarded as pre- or low-grade lymphoma. Multiple therapies have been utilized for the treatment of RCD (both subtypes). These have included enteric and systemic glucocorticoids, azathioprine, cyclosporine, cladribine, anti-CD52 monoclonal antibodies (alemtuzumab), anti-interleukin (IL)-15 monoclonal antibodies (AMG 714), anti-tumor necrosis factor (TNF)-alpha monoclonal antibodies, and high-dose chemotherapy followed by autologous hematopoietic stem cell transplant [13–23]. Results of these therapies have been mixed, and a recent small phase 2a randomized double-blind placebo-controlled, parallel-group study on AMG714 showed no difference after 10 weeks of therapy (or placebo) in terms of primary endpoint of aberrant IEL reduction from baseline [34]. None of these therapies have been shown to prevent progression to lymphoma, and anecdotal reports suggest that immunosuppressive drugs may be associated with increased risk.

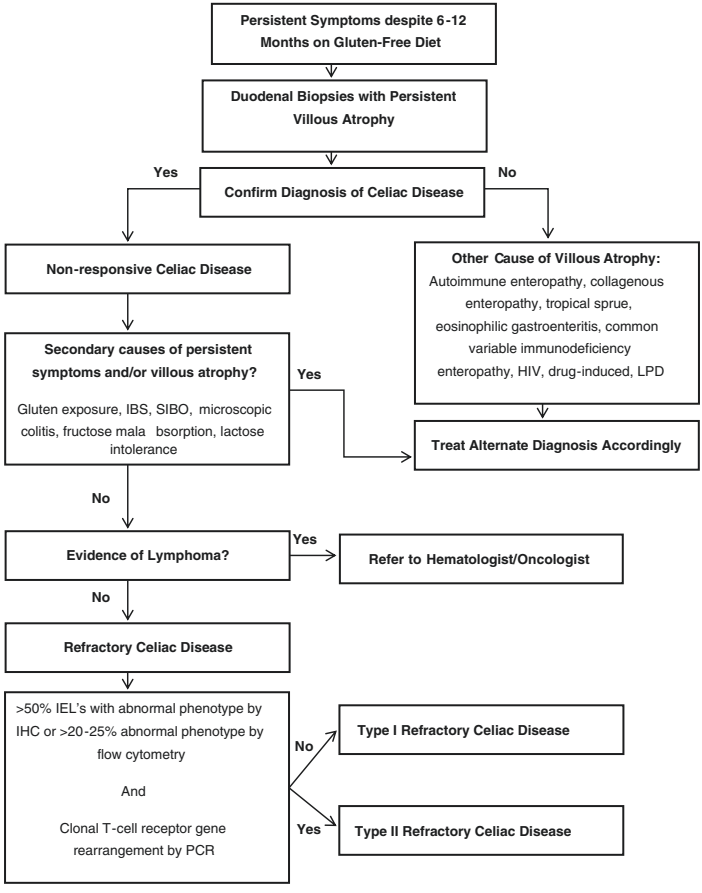

FIGURE 10.2 Algorithmic approach to diagnosis of NRCD and RCD. *IBS* irritable bowel syndrome, *HIV* human immunodeficiency virus, *IELs* intraepithelial lymphocytes, *IHC* immunohistochemistry, *LPD* lymphoproliferative disorder, *PCR* polymerase chain reaction, *SIBO* small intestinal bacterial overgrowth. (Modified from Rubio-Tapia et al. [7])

Open-capsule or compounded budesonide has been demonstrated as an alternative to systemic corticosteroids given decreased systemic effect due to the efficient first-pass inactivation in the liver by CYP3A4 [13]. The open-capsule regimen involves utilizing commercially prepared, enteric-coated budesonide (Entocort EC). The first 3 mg capsule of the day is opened, and the granules/enteric beads are mixed with applesauce or similar soft food, chewed, and swallowed. The second capsule is opened, mixed with applesauce, and swallowed without chewing. The third capsule is swallowed whole [13]. The rationale is that the chewed enteric beads would treat the proximal small bowel, opened capsule would treat the mid-small bowel, and the whole capsule would treat the distal small bowel. This regimen demonstrated improvement in both clinical and histological endpoints for both type I and type II RCD. In type I RCD, 92% had clinical improvement with 89% demonstrating histologic improvement after treatment with open-capsule budesonide, while in type II RCD only 53% had histologic improvement without detectable aberrant T-cell phenotype on follow-up biopsies [13]. Dose titration and withdrawal has not been evaluated systematically, but usually the dose is adjusted to the minimal dose to maintain both symptomatic and histologic improvement.

Cladribine, purine analogue, is another agent used for the treatment of type II RCD. One group evaluated a step-up approach where patients were treated with cladribine and if they did not demonstrate clinical or mucosal improvement after two cycles, they underwent autologous hematopoietic stem cell transplantation [24]. Both cladribine monotherapy and step-up therapy resulted in improved survival and less progression to EATL when mucosal healing was demonstrated [24].

IL-15 has become a potential treatment target in type II RCD as IL-15 appears to be involved in expansion of CD3+ IELs, which can develop an enhanced response to IL-15 and progress toward EATL [25, 26]. Early, randomized, placebo-controlled phase 2a study evaluating anti-IL-15 monoclonal antibody (AMG 714) demonstrated improvement in progression of aberrant IELs, villous atrophy, and symptoms, yet as

mentioned above published data showed no decrease in aberrant IELs compared to placebo [27, 34].Other therapies include Janus Kinase (JAK) 1 and 3 inhibitors (i.e., tofacitinib which is used in IBD) alone or in combination with budesonide [35].

Complication monitoring and management is pivotal in RCD. Complications include malnutrition, vitamin and mineral deficiencies, metabolic bone disease, opportunistic infections, ulcerative jejunoileitis, and malignancy [28–32]. These need to be monitored and aggressively managed, including the need for complete parenteral nutrition, vitamin and mineral supplementation, and utilizing bisphosphonates, often requiring a multidisciplinary team.

Survival differs dramatically between type I and type II RCD with 5-year survival reported at 80% for type I and 45% for type II [33]. In this single-center cohort, 67% progressed to EATL with a median time of progression of 18 months [33]. These results are prior to extensive enteric budesonide use [13]. More recently, a model was developed to predict survival in RCD (both subtypes combined), which includes weighted variables of age, sex, body mass index (BMI), hemoglobin, albumin, total villous atrophy, and aberrant IEL. Ultimately, a three-factor prediction tool was developed utilizing age at diagnosis of RCD, serum albumin, and immunophenotype of IELs. Quartiles were developed with points for older age, lower albumin, and abnormal IELs predicting poorer survival [28]. Five-year survival differed from 97.6% in the best quartile to 48.5% in the worst quartile [13, 28]. This shows that survival likely has improved with time, but is still high for those with type II RCD [13]. Leading causes of death in patients with RCD include EATL, sepsis, intestinal failure, and thrombosis [28].

Case Outcome

After initiation of open-capsule budesonide therapy, symptoms improved, and gradually over the following 2 years, he had normalization of villous architecture. Subsequent

TCR gene rearrangement studies remained positive for clonal T-cell population. Five years after initiation of budesonide and tapering to 3 mg every other day, he developed diarrhea. Repeat endoscopies revealed normal villous architecture with persistent T-cell clone, but colonoscopy with random biopsies showed lymphocytic colitis as the etiology of diarrhea. Identical T-cell aberrancies were seen in the colonic lymphocytes. This illustrates that the abnormal T-cells can involve other portions of the GI tract, including colon and stomach. The patient's diarrhea improved with an increased dose of open-capsule budesonide. Osteopenia was also diagnosed, treated, and monitored.

In patients with type II RCD, it is recommended to repeat endoscopy with a change in symptoms, concerning features of progression to lymphoma (weight loss, fever, night sweats), or every 1–2 years if stable. Assessment of treatment efficacy should include endoscopy with evaluation for improvement in villous architecture and stability or loss of the clonal T-cell population. Second-line therapies beyond budesonide should be entertained if there is primary non-response (clinically or histologically) or loss of response to budesonide. Second-line options will depend on patient characteristics and should include consideration of a clinical trial at a referral center with expertise in treating RCD.

Clinical Pearls/Pitfalls

1. In patients with NRCD, gluten ingestion and celiac mimics must be aggressively investigated and excluded. Given the variability in sensitivity of TCR rearrangement and clonal T-cell testing, this first step of excluding treatable mimics is critical.
2. Determining the presence of an aberrant T-cell population is important in differentiating type I from type II RCD, the latter considered pre-lymphoma.

3. Multiple therapies have been employed for the treatment of type II RCD, but enteric or systemic glucocorticoids have traditionally been first-line therapy.
4. Patients should be referred to tertiary celiac care centers and must be monitored for complications associated with type II RCD including EATL, malnutrition, vitamin and mineral deficiencies, osteoporosis, and opportunistic infections.

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Chapter 11
Enteropathy-Associated T-Cell Lymphoma

Karlton Wong and Monica Mead

Case Presentation

A 64-year-old Scandinavian woman presented to primary care for evaluation of a 2-month history of abdominal pain, nausea, and vomiting. She reported a chronic history of loose non-bloody stools, but had developed constipation more recently. Over-the-counter omeprazole did not provide symptom relief. One month later, she presented to the emergency department with severe abdominal pain and an unintentional weight loss of 6 kg. Physical exam was notable for a patient in moderate distress with tachycardia and moderate left lower quadrant abdominal tenderness. Laboratory work-up was significant for microcytic anemia (hemoglobin level of 9.2 g/dL, mean corpuscular volume of 66 fL), and a markedly elevated C-reactive protein (142 mg/L, normal<0.8 mg/dL). An upper endoscopy with cytological brushings disclosed esophageal candidiasis, with otherwise normal-appearing mucosa. No biopsy samples were obtained. A 2-week course of fluconazole did not alleviate her symptoms, and she re-presented to the emergency department with ongoing severe abdominal

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pain. Radiographic evaluation with CT scans of the chest and abdomen did not disclose intra-abdominal pathology. The patient then reported her previously mentioned history of chronic diarrhea and mild abdominal pain. As part of her diarrhea evaluation, celiac serology was sent and returned elevated. A repeat upper endoscopy with duodenal biopsies demonstrated subtotal villous atrophy with increased intraepithelial lymphocytes (IELs), compatible with Marsh 3b lesions. Shortly after endoscopy, she developed acute worsening of her abdominal pain. Repeat CT scan showed peritoneal free air, concerning for bowel perforation. She underwent urgent exploratory laparotomy that demonstrated two areas of perforation of the small intestine distal to recent duodenal biopsy sites, a 5-centimeter mesenteric mass, and thickening of the small intestinal wall. Pathologic evaluation of the mesenteric mass was consistent with EATL. A diffuse mucosal infiltration consisting of large, atypical lymphocytes was observed. Immunohistochemical analysis showed that the atypical lymphocytes were positive for CD45RO, CD3, and CD30 and were negative for CD20, CD56, and ALK. Flow cytometry and T-cell receptor (TCR) gene rearrangement studies were not available.

The patient was referred to hematology-oncology clinic for further management. Bone marrow aspirate and biopsy were negative for lymphomatous involvement. Postoperative CT scans demonstrated interval gastric wall thickening, concerning for rapid EATL progression. She was thin and hypoalbuminemic with an ECOG of 2. She was considered a reasonable candidate for combination chemotherapy, and if responsive disease was confirmed, proceeding with consolidative high-dose chemotherapy and autologous stem cell transplantation (SCT). She commenced treatment with biweekly CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for a total of six cycles. Treatment was complicated by infections successfully managed with intravenous antibiotics following cycles 1 and 3 and grade 3 peripheral sensory neuropathy necessitating omission of vincristine starting with cycle 5. Interim CT scans after the third cycle of

CHOP demonstrated a complete response (CR). Mobilized stem cells were successfully collected after the fourth cycle of CHOP, and she proceeded to a consolidative autologous SCT preceded by BEAM (BCNU, etoposide, cytarabine, and melphalan) conditioning.

Diagnosis

EATL is a rare T-cell lymphoma, comprising less than 1% of all non-Hodgkin's lymphomas [1]. EATL was previously categorized as type 1 and type 2 based on an association with CeD. Through improved understanding, these disease subtypes were amended in the 2016 revisions to the World Health Organization (WHO) classification as EATL (formerly type 1) and monomorphic epitheliotropic intestinal T-cell lymphoma (formerly type 2) [2]. EATL primarily occurs in older patients, with a median age at diagnosis of 60 years, and in geographic areas with a high incidence of CeD including Northern Europe, Ireland, Italy, and France, with a slight male predominance [3].

Clinical Presentation and Risk Factors

Clinical features of EATL include GI manifestations such as abdominal pain (30–50%) with or without bowel obstruction or perforation (20–55%), nausea, vomiting (30–40%), diarrhea (30–50%), and weight loss (30–80%) and systemic B symptoms (30–40%) including fever and night sweats. Less common features including infection, adenopathy, and hepatosplenomegaly are also observed [4]. Rarely, EATL can be associated with mesenteric lymph node cavitation, peripheral eosinophilia, and splenic atrophy [5–7], though the latter can be seen in CeD alone. Most patients present with advanced stage disease and are malnourished with compromised functional status at the time of diagnosis.

Patients with untreated CeD, those with nonadherence to a strict GFD, and those with RCD have an increased risk of developing EATL [8]. Characterization of IEL on biopsy specimens allows for categorization of RCD into type I and type II (see Chaps. 9 and 10). As previously mentioned, type I RCD lesions are characterized by IELs that lack atypia and have a normal immunophenotype and a polyclonal pattern on T-cell receptor (TCR) gene rearrangement studies [9], while type II RCD lesions demonstrate a clonal expansion of IELs with loss of surface TCR and a monoclonal TCR gene rearrangement [10]. EATL is preceded almost exclusively by type II RCD, with up to 50% of those patients developing EATL [11], suggesting a pre-lymphoma or low-grade lymphoma state. Some studies report an association of ulcerative jejunitis with RCD and EATL, suggesting this might represent an intermediate step during transformation to EATL [12, 13].

Pathologic Features

Histologic hallmarks of EATL include a transmural infiltration of inflammatory cells comprised of medium-to-large pleomorphic lymphocytes, eosinophils, and histiocytes, extensive necrosis, and a high mitotic rate (Fig. 11.1). The surrounding mucosa is characterized by villous atrophy and cryptic hyperplasia [14]. The presence of Epstein-Barr virus (EBV) is uncommon [15]. The immunophenotype is characterized by expression of CD3 and CD7 and absence of expression of CD4, CD5, and CD56 [14, 15]. There is variable expression of CD8 (43%) and TCRβ (19%) [16]. Cytotoxic T-cell proteins including T-cell-restricted intracellular antigen (TIA-1), granzyme, and perforin are expressed in many cases [14, 15]. The intraepithelial homing integrin CD103 is positive in a subset of EATL, while the large cell component commonly expresses CD30 [14, 15, 17].

Genetic alterations of EATL result from a variety of mechanisms including clonally rearranged TCR beta and

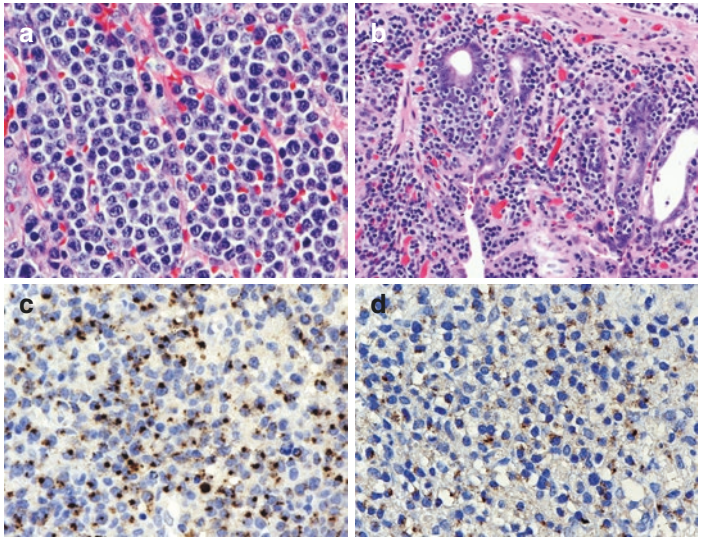

Figure 11.1 Histologic features of EATL. A transmural infiltration of inflammatory cells comprised of medium-to-large pleomorphic lymphocytes, eosinophils, and histiocytes is evident in the small bowel. (**a**: H&E stain, original magnification ×40). Features of active CeD, including crypt hyperplasia, villous atrophy, and increased IEL, can be seen in surrounding mucosa (**b**: H&E stain, original magnification ×20). The lesion is characterized by granzyme (**c**: granzyme immunostain, original magnification ×40) and TIA-1 expression (**d**: TIA-1 immunostain, original magnification ×40). (Reproduced with permission by Dr. Jonathan Said)

gamma genes, the presence of characteristic HLA haplotypes, gene amplifications, recurrent chromosomal gains, and gene mutations involved in oncogenic signaling pathways (Fig. 11.2). Many patients have a DQA1*0501 or DQB1*0201 HLA haplotype, which is also observed in association with CeD [18]. An analysis of 38 EATL cases employing comparative genomic hybridization demonstrated chromosomal gains in 9q (58%), 7q (24%), 5q (18%), and 1q (16%) and deletions in 8p (24%), 13q (24%), and 9p (18%) [19]. Of these genetic changes, complex segmental amplification of 9q represents

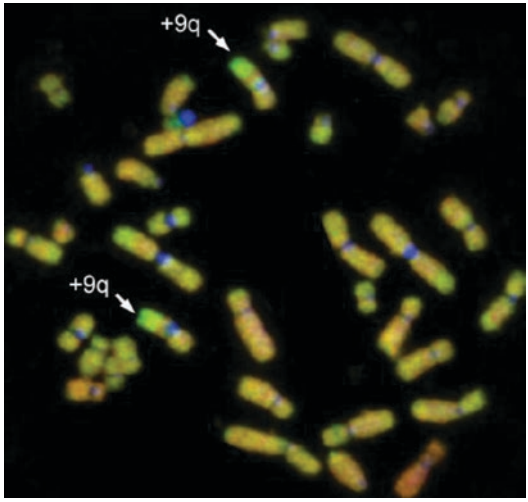

FIGURE 11.2 Photomicrographs of FISH patterns obtained in paraffin-embedded tissue sections with a single locus probe for the detection of amplifications of 9q. Arrows demonstrate cells showing gains of 9q. (Reproduced with permission by Dr. Jonathan Said)

the most frequent aberration in EATL with additional studies reporting a prevalence of 70–80% in patients with EATL [19–21]. Alterations of 9q34 involve gene loci for ABL-1, Notch-1, and CDK2a/b [20, 22, 23]. These genes are involved in normal T-cell proliferation and survival. Mutations in these critical pathways lead to the stepwise progression of T-cell transformation to a malignant phenotype [24]. Notably, 9q alterations are uncommon in other peripheral T-cell lymphoma (PTCL) subtypes [19–21]. Whole-exome DNA sequencing of 69 EATL tumors identified SETD2, a gene encoding a histone methyltransferase involved in epigenetic regulation, as the most frequently mutated gene, occurring in approximately one third of cases [25]. Mutations in genes involved in pro-growth JAK/STAT signaling were observed, including STAT5B, JAK1, JAK3, STAT3, and SOCS1 [25]. Less commonly, mutations in KRAS, TP53, and TERT were described [25].

Staging

Evaluation of suspected EATL includes laboratories, imaging, endoscopic evaluation, and careful pathologic analysis of tissue specimens. Laboratories include a complete blood count (CBC) with differential, complete metabolic panel (CMP), lactate dehydrogenase (LDH), CRP, uric acid, and phosphorus. If not previously diagnosed, evaluation for CeD with EMA and tTG with total IgA levels is indicated. CT scans, MRE, or PET can be used to assess extent of disease [26]. Though there is controversy regarding the most effective imaging modality, a 2006 study demonstrated PET-CT compared to CT scans had improved sensitivity (100% vs. 87%) and specificity (90% vs. 53%) in detecting EATL in patients with RCD [27]. PET-CT scans may also allow for early detection of EATL in patients with long-standing CeD [28].

The majority of EATL involves the jejunum, limiting the usefulness of upper endoscopy and colonoscopy for diagnostic purposes [4, 29]. Wireless capsule endoscopy (WCE) is often utilized as a minimally invasive way to inspect the small bowel [30]. Ulcerations and intestinal wall induration may be observed [31], and approximately 25% of patients present with multifocal lesions [29] (see Chap. 13). When suspicious-appearing lesions are identified, advanced endoscopic techniques, such as double-balloon enteroscopy, may be used to obtain biopsies [32]. Approximately one third of patients present with bowel perforation, and tissue is obtained at the time of exploratory laparotomy [4].

Lymphomatous involvement of the bone marrow with EATL is uncommon (<10%) [4]. Thus, a bone marrow biopsy and aspirate are not routinely indicated but can be considered in the presence of hematologic abnormalities or an abnormal marrow signal observed on staging PET-CT [4].

Prognostic indices more commonly used for B-cell lymphoma, such as the International Prognostic Index (IPI) alone, do not accurately risk stratify EATL patients. The Prognostic Index for T-cell lymphoma (PIT), utilizing the patient's age, performance status, serum LDH, and presence

of bone marrow involvement, was reported to be more predictive for overall survival in patients with EATL [3, 33], but could not be validated in a subsequent study [34]. A retrospective study that included 62 patients with EATL demonstrated statistically improved prognostic ability of the PIT compared to the IPI with respect to overall survival [3]. Further, the study demonstrated that LDH, CRP, a tumor greater than 5 cm at diagnosis, and non-ambulatory performance status were associated with worse survival and failure-free survival (FFS) [3].

Management

Randomized clinical trials to guide management of EATL patients are lacking. Treatment of EATL is extrapolated from that employed for other histologic subtypes of PTCL and includes systemic anthracycline-based chemotherapy followed by consideration of an autologous SCT in first remission. Surgery plays a limited role in EATL and is typically utilized in evaluation and management of an initial presentation of intestinal perforation, hemorrhage, or high-grade bowel obstruction [31]. The benefits of surgical debulking and bowel resection are limited and not validated [31, 35] but do not seem to convey a poorer prognosis [34]. Additionally, the time needed for postoperative recovery can result in delayed initiation of chemotherapy [31].

Combination chemotherapy with CHOP is the most common frontline regimen used to treat EATL patients [31]. Other regimens that have been utilized include BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone), ProMACE-MOPP (prednisone, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, and procarbazine), VAMP (vincristine, doxorubicin, high-dose methotrexate, and prednisolone), PEACE-BOM (prednisolone, etoposide, doxorubicin, cyclophosphamide-bleomycin, vincristine, and methotrexate), and CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide,

prednisone) [31]. Expected outcomes with this approach are derived from single [35] and multicenter [36] retrospective series and a multi-institutional prospective series [37]. These regimens result in an overall response rate (ORR) of 40–60%, a CR rate of 30–50%, and a median overall survival of less than 1 year. The median duration of response is approximately 6 months, with the majority of patients suffering relapsed disease [31]. A subset of EATL patients (17–38%) is refractory to initial chemotherapy [3, 4, 31].

Given the limited duration of CR following combination chemotherapy in EATL patients, consolidative strategies with high-dose chemotherapy followed by autologous SCT have been evaluated in patients with chemo-sensitive disease. Randomized studies are lacking, and support for this approach is based on single-arm prospective and retrospective studies.

A single-arm prospective study conducted by the Scotland and Newcastle Lymphoma Group evaluated a single course of CHOP followed by 6 cycles of alternating IVE (ifosfamide, epirubicin, and etoposide) and methotrexate in 26 EATL patients. Those achieving a response proceeded to autologous SCT. Fourteen patients (58%) successfully completed front-line chemotherapy and underwent autologous SCT, resulting in a 5-year PFS and OS of 52% and 60%, respectively [38]. In a large prospective phase II trial, the Nordic Lymphoma Group evaluated six cycles of bi-weekly CHOEP followed by autologous SCT in responding patients. A total of 160 patients with PTCL were included, 21 of which had EATL, resulting in a 5-year PFS and OS of 38% and 48%, respectively [39].

In 2013, the European Society of Blood and Marrow Transplantation performed a retrospective study utilizing the EBMT database to evaluate outcomes of EATL patients who underwent an autologous SCT as a consolidation or salvage strategy. Of the 44 patients with EATL, outcomes included a 4-year PFS of 54% and 4-year and OS of 59% [40]. With a median follow-up of 46 months, only one relapse occurred beyond 18 months, suggesting the possibility for durable responses in a subset of EATL patients [40].

A 2014 retrospective study using clinical data from the Swedish Lymphoma Registry compared outcomes of 252 PTCL patients (34 EATL) who underwent frontline combination chemotherapy with or without autologous SCT. The group that proceeded to autologous SCT had improved PFS and OS compared to the group that received chemotherapy alone [41].

The poor outcomes in EATL are partially due to the malnourished state and poor functional status of patients at the time of presentation, rendering them poor candidates for multi-agent chemotherapy or autologous SCT. Adequate nutrition, strict adherence to a GFD, and treatment of infection when present are an essential component to the treatment plan of EATL patients [42].

Published data on outcomes in patients with relapsed EATL are limited, and participation in a clinical trial is encouraged. The therapeutic armamentarium for EATL is expanding. Novel targeted therapies have been implemented in case reports with some success, including alemtuzumab, an anti-CD52 monoclonal antibody, and brentuximab vedotin (BV), a CD30-directed antibody-drug conjugate. Gallamini et al. evaluated alemtuzumab combined with CHOP in different histologic subtypes of PTCL. A CR was observed in the only EATL patient, although long-term outcome was not reported [43]. A case report described successful treatment of a frail elderly patient with alemtuzumab combined with gemcitabine at initial presentation and at the time of relapsed 1 year later [44]. Interestingly, a single case report demonstrated efficacy of alemtuzumab to prevent the development of EATL in a patient with steroid-refractory RCD. After a 12-week course of alemtuzumab, a pathologic CR was observed and the patient was able to discontinue prednisone [45]. Treatment with BV resulted in a CR after eight cycles of treatment in a patient with CD30+ EATL refractory to five prior lines of therapy [46].

Ongoing clinical trials are evaluating novel approaches to EATL treatment in the frontline and relapsed/refractory (R/R) setting. Ongoing frontline trials include evaluation of BV combined with cyclophosphamide, doxorubicin, and

prednisone followed by ASCT (NCT03217643) [47] and CHOEP combined with lenalidomide (NCT02561273) [48]. Ongoing investigative options in the R/R EATL population include immunotherapy-based treatments such as CD30-directed chimeric antigen receptor T-cells (CAR-T) (NCT03049449) [49] and PD-1 inhibition with nivolumab (NCT03075553) [50] and epigenetic modification utilizing romidepsin combined with combination chemotherapy (NCT01590732) [51] and panobinostat combined with a proteasome inhibitor (NCT00901147) [52].

Case Outcome

Despite adhering to a strict GFD, the patient developed recurrent diarrhea, abdominal pain, and a 4 kg unintentional weight loss 1 year post-SCT. Her celiac serology has normalized, but an upper endoscopy with biopsies showed persistent enteropathy, and in the absence of aberrant T-cells, diagnosed with type I RCD. Over the next year, she was repeatedly counseled on the importance of strict gluten avoidance. Two years post-SCT, surveillance endoscopy revealed a clonal expansion of aberrant CD8-negative IEL. Immunosuppression was initiated with corticosteroids, which the patient was unable to tolerate. She was transitioned to infliximab that provided a transient reduction in clinical symptoms, but she ultimately developed antibodies to infliximab (ATI). A trial of adalimumab was successful, and on last follow-up, the patient had no evidence of lymphoma relapse.

Clinical Pearls/Pitfalls

1. EATL presents with symptoms similar to RCD. Clinicians must maintain a low threshold for endoscopic evaluation in these patients to avoid delayed diagnosis.

2. A significant subset of newly diagnosed EATL patients are malnourished with poor functional status, making them poor candidates for aggressive frontline treatment. Aggressive nutritional supplementation and strict avoidance of gluten, ideally under the direction of a specialized dietitian, are a critical component of management of all EATL patients.
3. The addition of a consolidative autologous SCT in responding EATL patients may improve outcomes. Early referral to a center experienced in hematopoietic SCT should be offered to these patients.
4. Outcomes in EATL patients with conventional therapies are suboptimal. Enrollment onto a clinical trial should be considered when available.

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Chapter 12
Celiac Crisis

Jonas Zeitz and Peter H. R. Green

Case Presentation

A 65-year-old male was admitted to the hospital with severe watery diarrhea and dehydration. His past medical history included bilateral hip replacement and hypertension. He had profound weight loss of 10 kg. The patient was hyponatremic and hypokalemic; sodium, 129 mmol/l (normal range 131–146 mmol/l); and potassium, 3.2 mmol/l (normal range 3.5–5.0 mmol/l). His further laboratory tests revealed renal impairment with creatinine 2.2 g/dL, normocytic anemia, ESR 58 mm/hr., gastrin 125 pg/ml (normal range 0–180 pg/ml), vasoactive intestinal peptide (VIP) normal, tTG IgA 125 U (normal<20 U), and normal total IgA; colonoscopy was normal. Endoscopy revealed scalloping of duodenal mucosal folds, and the biopsy revealed total villous atrophy

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with intraepithelial lymphocytosis, compatible with Marsh 3c lesions. HLA DQ2 was present.

Diagnosis and Management

Celiac crisis is a rare presentation in CeD. It is defined by acute worsening and rapid progression of chronic diarrhea and vomiting followed by severe dehydration, multiple metabolic derangements, and a marked decrease of body weight [1]. See Fig. 12.1 for definition.

Patients can present with hemodynamic instability, electrolyte imbalance, hypoalbuminemia, and acidosis. Various triggers of a celiac crisis have been described in the past. These include infections with cytomegalovirus (CMV) and salmonella, major surgeries, and pancreatitis. The cause is likely a combination of severe mucosal inflammation, immune activation, and disruption of normal patterns of motility resulting in rapid decompensation in someone with preexisting but usually undiagnosed CeD [1].

Most cases of celiac crisis were reported in children (Table 12.1). It was first described in 1953 by Andersen and Di

Acute onset or rapid progression of gastrointestinal symptoms attributable to celiac disease requiring hospitalization and/or parenteral nutrition along with at least 2 of the following [1]:

- Signs of severe dehydration including: hemodynamic instability and/or orthostatic changes
- Neurologic dysfunction
- Renal dysfunction: creatinine >2.0 g/dL
- Metabolic acidosis: pH <7.35
- Hypoproteinemia (Albumin < 3.0 g/dL)
- Abnormal electrolytes (including: hyper/hyponatremia, hypocalcemia, hypokalemia or hypomagnesemia)
- Weight loss > 10 lbs

Figure 12.1 Definition of Celiac Crisis. (Adapted from Jamma et al. [1])

Table 12.1 Reported Celiac Crisis cases

Author	Country	Cohort	Symptoms	Precipitating conditions
Andersen and Di Sant'Agnese (1953) [2]	USA	35 infants, age 4–48 months of age	Vomiting, persistent, or recurrent diarrhea. Steatorrhea, abdominal enlargement, weight was two standard deviations or more below the normal mean for the age	
Wolf I et al. (2000) [3]	Israel	36-year-old woman	Acute diarrhea leading rapidly to dehydration, severe acidosis, and hypokalemia	
Özaslan E et al. (2004) [7]	Turkey	75-year-old man and 55-year-old woman	– Severe diarrhea, fatigue, weight loss, cramping, and paresthesias in the hands and legs – Fatigue, weakness of the lower extremities, and diarrhea	
Kelly et al. (2006) [10]	Ireland	23-year-old woman	Nausea, vomiting, and loose stools	Cytomegalovirus (CMV) infection
Gupta et al. (2006) [11]	India	30-year-old woman	Acute quadriparesis due to refractory hypokalemia	

(continued)

Table 12.1 (continued)

Author	Country	Cohort	Symptoms	Precipitating conditions
Al Shammeri et al. (2008) [16]	Canada	50-year-old woman	Diarrhea, severe dehydration, hypokalemia, and metabolic acidosis	Immunosuppressive therapy for autoimmune hepatitis. Comorbid microscopic colitis
Jamma et al. (2010) [1]	USA	12 cases (8 women and 4 men)	Severe dehydration, renal dysfunction, and electrolyte disturbances	5 after a major medical event (pregnancy, GI surgery, and gallstone pancreatitis)
Mrad et al. (2015) [8]	Lebanon	64-year-old woman	Profuse diarrhea, weight loss, hemodynamic instability, hypokalemia, hypoproteinemia, acidosis, and vitamin and iron deficiency	
Yilmaz et al. (2015) [15]	Turkey	82-year-old woman and 75-year-old man	Severe diarrhea, abdominal cramping, fatigue, cachexia, and dehydration	
Kumar and Badhan (2015) [12]	India	3-year-old boy	Watery diarrhea and vomiting with dehydration, hypokalemic paraparesis	

Sbai et al. (2016) [13]	France	A 43-year-old male patient	Severe nonfebrile profuse watery diarrhea, hypovolemic shock with severe dehydration, metabolic acidosis, and mild hypokalemia	Multi-trauma patient after car accident
Radlovic et al. (2016) [6]	Serbia	6 of 367 children	Acute worsening and rapid progression of chronic diarrhea followed by severe dehydration, metabolic acidosis, hypotension, renal dysfunction, abdominal distension, hypoproteinemic edema, and a marked decrease of body weight	3 rotavirus, 1 salmonella enteritidis infection
Chen et al. (2016) [9]	USA	24-year-old woman	Profuse watery diarrhea, mild cramping abdominal pain, nausea, vomiting, heartburn symptoms, odynophagia, fatigue, and weight loss	HSV esophagitis

Sant'Agnese, at Babies Hospital, Columbia University [2].Celiac crisis is considered to have become less common due to earlier diagnosis and effective therapy of CeD though there is little evidence to support this [3], and possibly underdiagnosed.

Treatment of celiac crisis includes nutritional support with a GFD, correction of abnormal electrolyte levels and metabolic changes, and fluid resuscitation. Furthermore, reports in the literature have shown that patients may respond rapidly to high-dose corticosteroids [4, 5].

Review of the Literature

In 1953 an acute phase of idiopathic CeD was studied in 58 pediatric patients, 35 of these children presented with celiac crisis [2]. A retrospective study of 367 Serbian children with CeD demonstrated celiac crisis in 6 children (1.63%), 5 in the first, and 1 in the second year of life. In three of these patients, celiac crisis was precipitated by rotavirus and in one by *salmonella enteritidis* infection. In the remaining two patients, except for a long-standing disease and severe malnutrition, no additional causes of celiac crisis were found [6]. In this study children exclusively below the second year of life presented with celiac crisis.

Adult reports about celiac crisis are rarer. In 2004, two adult Turkish patients, a 75-year-old man and a 55-year-old woman, with celiac crisis were reported [7]. In 2015, a published case described a 64-year-old woman who presented with celiac crisis with profuse diarrhea, weight loss, hemodynamic instability, hypokalemia, hypoproteinemia, acidosis, and vitamin and iron deficiency [8]. In 2016, celiac crisis was shown to be associated with herpes simplex virus (HSV) esophagitis in a 24-year-old woman, suggesting that nutritional deficiencies seen in CeD can result in a relative immunodeficiency [9]. Also, celiac crisis was precipitated by CMV hepatitis in a 23-year-old female [10]. Another case from Israel described an adult without a previous celiac diagnosis who presented with acute diarrhea leading rapidly to dehydration, severe acidosis, and hypokalemia [3].

Abnormal electrolyte levels are a key feature of celiac crisis. Hypokalemia can lead to muscle weakness, in severe cases even to paralysis. In India a 30-year-old woman presented with celiac crisis including hypokalemic paralysis [11]. Another case from India reported a 3-year-old thriving boy, who suffered of watery diarrhea and vomiting with dehydration. Due to severe hypokalemia, he developed paraparesis. Serology and histology from the duodenum confirmed the diagnosis of CeD. Following a therapy with corticosteroids (unreported route) and a GFD, he showed significant improvement [12]. In France a 43-year-old multi-trauma adult patient after a car accident developed severe nonfebrile profuse watery diarrhea shortly after introduction of antibiotic treatment with amoxicillin and rifampicin for osteoarticular infection. In the further course, he developed hypovolemic shock with severe dehydration metabolic acidosis and mild hypokalemia. Serology, histology, and HLA genotyping confirmed CeD, and the patient showed complete resolution of diarrhea in 5 days, and significant improvement of the metabolic disturbances after a GFD was introduced [13].

CeD is also more frequently being reported in the elderly, also with an atypical presentation like celiac crisis [14]. For example, in Turkey two elderly patients with a first presentation of CeD by celiac crisis were reported. An 82-year-old woman presented with severe diarrhea with more than ten bowel movements daily with abdominal cramping and fatigue and a 75-year-old man presented with diarrhea, cachexia, and dehydration. In both patients CeD was confirmed, and both rapidly improved on a GFD [15].

Twelve cases of celiac crisis were reported in 2010 from two referral centers in the USA [1]. These cases were identified over an 8-year period indicating the patients presenting in a celiac crisis is not that uncommon. Of the 12 cases, 8 were women and 4 were men. Patients were older with a mean age of 58.9 years. The majority, 11 of 12 patients, presented with CeD in the form of crisis, while 1 had known of the disease but was not adherent to a GFD. Five presented after a major medical event (pregnancy, GI surgery, and gallstone pancreatitis). Six patients received corticosteroids.

A unique case was reported in Canada of a 50-year-old woman who developed celiac crisis while receiving corticosteroids and azathioprine for autoimmune hepatitis at the time of her presentation. Furthermore, she also had histological signs of microscopic colitis during this presentation. This case demonstrates that modest immunosuppression does not prevent a celiac crisis, although reports in the literature have shown that patients may respond rapidly to high-dose corticosteroids [16].

While a GFD is the mainstay of therapy for CeD, the use of corticosteroids has been advocated for the treatment of severely affected patients with CeD and those with RCD [17]. Currently, corticosteroids are used for patients severely ill, as in a celiac crisis, as well as those with RCD, both types I and II [18]. With the availability of locally acting, potent corticosteroids with limited systemic manifestations, such as budesonide, these drugs have become more widely used in patients with CeD [19]. In a recent series of patients with celiac crisis, budesonide was used in combination with parenteral and oral corticosteroids [1]. Budesonide, as available in the US, is formulated for release in the distal small intestine and right colon. Greater efficacy of this drug for those with CeD, a proximal small intestinal disorder, could possibly be obtained by administering some (or all) of the dosage of the medication after opening the capsule [20] (see Chap. 10 for open-capsule budesonide protocol).

Several additional adult and pediatric cases with celiac crisis from the literature not discussed in detail in this article [21–40].

Case Outcome

The patient met the criteria for celiac crisis. He was treated with intravenous fluid resuscitation and was started on a GFD. The patient did not require corticosteroid therapy and improved with normalization of renal function and electrolytes and was discharged from the hospital after 7 days. He has adhered to the GFD, a follow-up serology showed a normalized tTG IgA (1 U), and a follow-up endoscopy is planned 2 years after diagnosis.

Clinical Pearls/Pitfalls

1. Celiac crisis occurs when patients (both children and adults) present with a severe, life-threatening, diarrhea-predominant form of CeD.
2. The syndrome may not be as rare as previously considered.
3. Hospitalization is necessary as is correction of the metabolic disarray that frequently a component of the syndrome.
4. Corticosteroids are frequently necessary.

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Chapter 13
The Role of Capsule Endoscopy in Celiac Disease

Neil Marya and Stephen Kim

Introduction

Endoscopic evaluation for CeD is recommended in adult patients following a positive serologic testing and in patients with a high suspicion of CeD despite negative serology (seronegative CeD). While an upper endoscopy with duodenal biopsies [1] is still the gold standard for the diagnosis of CeD in North America, it is not without notable limitations. First, upper endoscopy is an invasive test that typically requires sedation and, therefore, may have limited utility in patients with significant medical comorbidities. Second, the extent of the small bowel involved, rather than the severity, may be a better correlate for clinical status of CeD. Hence, panendoscopic evaluation of the small intestine could provide better

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insight in select CeD patients with distal involvement of their disease [2]. Finally, patients with CeD often have patchy involvement of the small intestine, and biopsies may sample uninvolved areas resulting in false negative results [3]. Given these limitations, there is a role for a tool that provides non-invasive, panendoscopic evaluation of the small intestine.

Since 2001, wireless capsule endoscopy (WCE) has become a vital tool for the evaluation of small bowel diseases, including suspected small bowel bleeding and small bowel Crohn's disease (CD). The role of small bowel WCE in the diagnostic algorithm for patients with CeD has been considered since its introduction almost two decades ago. WCE provides a non-invasive, magnified view of the mucosa during transit from the esophagus to the colon. Contraindications to WCE include dysphagia, GI surgery, abdominal radiation, or presence of an implanted cardiac device. Overall, it is a very well-tolerated procedure associated with a minimal risk of complications compared to upper endoscopy. This chapter explores the role of WCE in the evaluation of patients with suspected or known CeD and refractory celiac disease (RCD).

Capsule Endoscopy in Patients with Suspected Celiac Disease

The diagnosis of CeD is typically determined using serologic testing along with confirmatory histology from duodenal biopsies obtained during upper endoscopy. Mirroring the histologic changes of CeD that are described in the Marsh criteria, the endoscopic changes of CeD also occur along a spectrum. CeD patients with findings of Marsh 1 or Marsh 2 have small bowel mucosa with atrophic foci and subtle mosaic patterns. Those with Marsh 3 lesions have more significant changes in villous architecture including reduction of the duodenal circular folds (plicae circulares or valves of Kerckring), scalloped mucosa, and nodularity. The same mucosal changes seen on endoscopy can be appreciated on WCE (Fig. 13.1) [4]. Studies have demonstrated that WCE can only reliably detect mucosal abnormalities in CeD with Marsh 3 lesions [5–7].

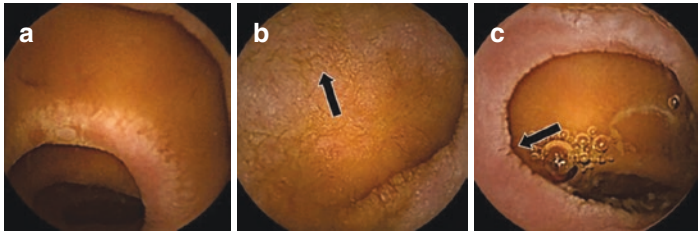

Figure 13.1 Examples of characteristic changes of celiac disease on wireless capsule endoscopy. (**a**) Reduction of Kerckring folds suggestive of loss of typical duodenal architecture. (**b**) Black arrow indicates mosaicism. (**c**) Black arrow indicates mucosal scalloping

Studies regarding upper endoscopy show that without biopsy, visual interpretation of mucosal changes carries low sensitivity (47%) for the identification of CeD [8]. As such, guidelines do not recommend endoscopic visualization of the mucosa as sufficient to rule out the presence of CeD. A major pitfall of the endoscopic evaluation of CeD is that clinicians evaluating patients for iron deficiency anemia (IDA) or chronic diarrhea will often avoid performing biopsies of the duodenum if they do not detect mucosal abnormalities. Alternatively, identification of classic mucosal findings on endoscopy is useful in the diagnostic evaluation of CeD as these are highly specific [9]. To improve endoscopic visualization of CeD, studies have investigated the role of chromoendoscopy, water immersion, and magnification to highlight the subtle endoscopic changes in CeD patients. When these additional techniques are used, studies demonstrate that sensitivity and specificity for the endoscopic detection of CeD improves [10]. This emphasizes the perceived benefits of WCE in the evaluation of patients with CeD.

With the eightfold magnification of the capsule lens, subtle mucosal changes can be appreciated. In one small study of 20 patients with newly diagnosed CeD, WCE was able to identify corresponding mucosal abnormalities in 85% of cases compared to 80% on upper endoscopy [6]. These findings have been confirmed by other studies which demonstrate that WCE has improved sensitivity for the evaluation of CeD compared to upper endoscopy [5, 7].

One of the initial studies to demonstrate the value of WCE in suspected CeD was performed by Rondonotti and colleagues [7]. In their multicenter study, the authors evaluated 43 patients with suspected CeD and compared the accuracy of a WCE to the gold standard of upper endoscopy with small bowel biopsies. They demonstrated that WCE is 87.5% sensitive and 90.9% specific for the diagnosis of CeD with a positive predictive value of 96.5% and a negative predictive value of 71.4%. The identification of fissures, mosaic patterns, and scalloping is highly predictive of the diagnosis of CeD; however, a negative WCE study does not necessarily rule out the presence of underlying CeD. Therefore, if there is strong clinical suspicion for CeD despite a negative WCE, an upper endoscopy with duodenal biopsies along with the serologic work-up to evaluate for CeD are still warranted.

Researchers have also investigated the role of WCE in patients with suspected CeD who have a discordant serologic and endoscopic findings. Sixty-two patients with an "equivocal" diagnosis of CeD (defined as seronegative with villous atrophy or seropositive with Marsh 1 or Marsh 2 lesions) underwent a WCE to further investigate the possibility of CeD. Among this cohort of equivocal CeD patients, 14.5% of patients were found to have significant findings on WCE including evidence of small bowel Crohn's disease (CD) and confirmation of CeD [11]. The majority of the significant findings on WCE were identified in equivocal cases of seronegative enteropathy.

Summarizing the findings described above, see the proposed algorithm for the use of WCE in patients with suspected CeD (Fig. 13.2).

Capsule Endoscopy in Patients with Non-Responsive Celiac Disease

Non-Responsive CeD (NRCD) is relatively common, occurring in up to third of CeD (see Chap. 8), mostly associated with unknown dietary gluten contamination, but other pos-

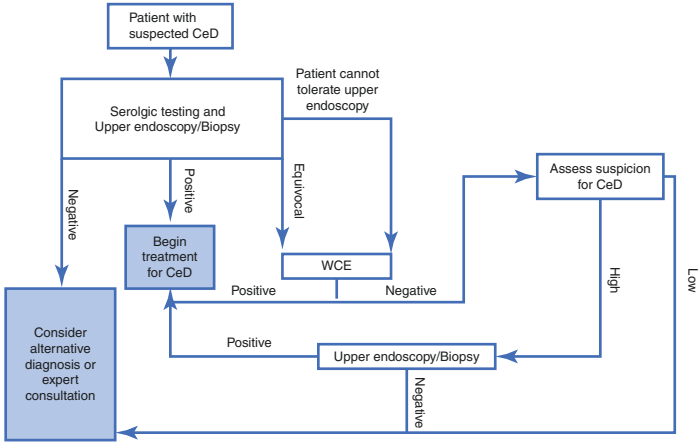

FIGURE 13.2 Proposed algorithm for the role of capsule endoscopy in the diagnosis of suspected celiac disease

sibilities include small intestinal bacterial overgrowth (SIBO), microscopic colitis, pancreatic insufficiency, and refractory celiac disease (RCD).

As discussed in Chaps. 9 and 10, RCD is comprised of two subtypes based on the phenotypic variations of duodenal intraepithelial lymphocyte (IEL) population [12]. Compared to type I RCD, type II RCD is associated with a higher mortality rate due to progression to enteropathy-associated T-cell lymphoma (EATL). The two subtypes of RCD also differ from one another in terms of management. Thus, the identification of RCD and the distinction of the two subtypes are clinically important when managing patients presenting with NRCD. Given that the complications and manifestations of RCD often occur distally to the duodenum, WCE carries a diagnostic significance.

Researchers compared the value of WCE among three cohorts of patients – NRCD, uncomplicated CeD who responded to a GFD, and a group of age-/sex-matched patients without CeD. The study demonstrated that the incidence of erosions and ulcerations were not significantly dif-

ferent among these three groups, and macroscopic atrophy did not differ between patients with NRCD and those with uncomplicated CD [13]. Alternatively, another study of patients with NRCD demonstrated that WCE predicts the presence of underlying type II RCD. In this study, identification of extensive enteropathy, described as mucosal changes extending beyond the duodenum and into the jejunum and ileum, had a significantly greater association with type II RCD compared to patients found to have type I RCD [14]. Importantly, in both of these studies, WCE also identified several cases of severe complications of CeD, including ulcerative jejunitis (Fig. 13.3) and EATL.

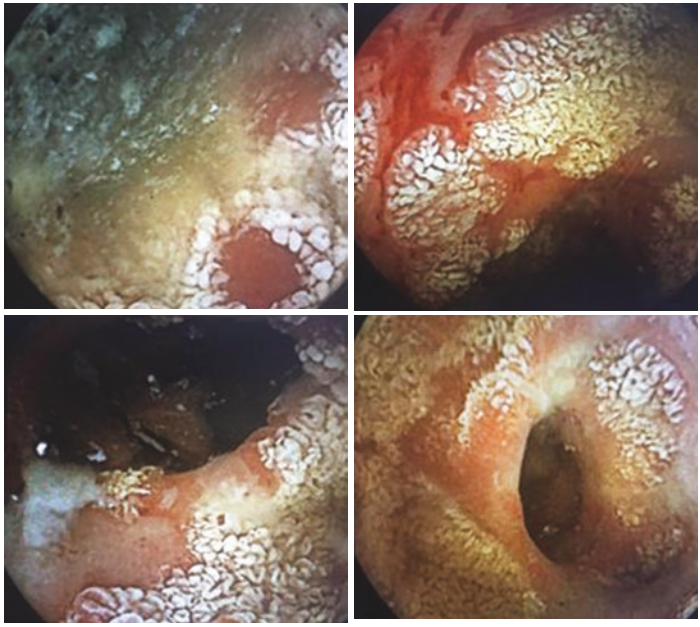

Figure 13.3 Example of ulcerative jejunitis as seen on capsule endoscopy. These capsule images demonstrate changes consistent with ulcerative jejunitis such as villous dropout, villous edema, ulcerations, and strictures

These studies show that WCE in NRCD is capable of identifying features suggestive of significant complications such as type II RCD, ulcerative jejunitis, (which is currently considered type II RCD-defining entity), small bowel adenocarcinoma, and EATL. Mucosal evaluation via WCE alone is not sufficient to distinguish ulcerative jejunitis from EATL. Case reports suggest that in both ulcerative jejunitis and EATL, the capsule will detect diffuse small bowel mucosal changes characterized by ulcerations, villous denudation, and bleeding [15, 16]. If a WCE were to detect such abnormalities in a patient with CeD, then single- or double-balloon enteroscopy with biopsies is required for a definitive tissue diagnosis.

Despite the aforementioned benefits, there is no clear algorithm for the use of WCE in NRCD patients. Given the low incidence of such complications of CeD, it is difficult to identify which patients would truly benefit from WCE. Further study investigating the pretest likelihood of identifying such complications on WCE is necessary before recommendations can be made regarding the routine use of WCE in NRCD. Expert opinion suggests proceeding with WCE in patients with persistent enteropathy (Marsh 3 lesions), especially those with aberrant IELs compatible with type II RCD.

Future Directions

Advanced imaging techniques are currently being studied to improve WCE detection of mucosal changes in the small intestine. Virtual chromoendoscopy such as flexible spectral imaging color enhancement (FICE) alters white light endoscopic images using a proprietary, mathematical algorithm to highlight particular wavelength ranges. The goal of FICE and other forms of virtual chromoendoscopy is to enhance mucosal visualization. Examples of FICE imaging in CeD patients are demonstrated in Fig. 13.4. A study by Cotter and colleagues suggests that FICE imaging may be helpful in delineating mucosal changes such as villous atrophy and, therefore,

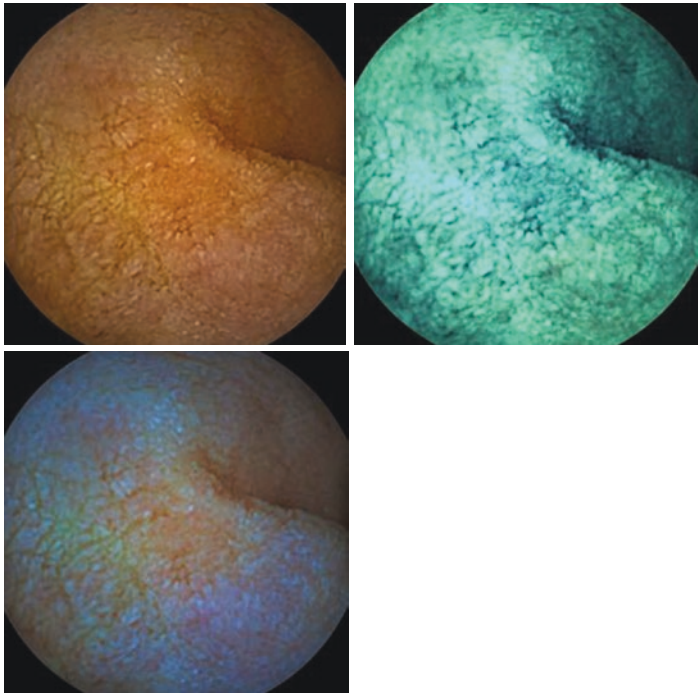

FIGURE 13.4 Example of using FICE overlays to highlight mosaicism in a patient with celiac disease

may be useful in highlighting subtle changes in CeD patients [17], but further studies are needed.

Another recent technological advancement focuses on the interpretation of acquired images on WCE. Accurate reading of capsule recordings is highly variable among physicians, and, therefore, subtle findings like those found in CeD can be missed by inexperienced readers. In an effort to improve detection of abnormalities, researchers have studied the efficacy of computer-aided diagnosis (CAD), which utilizes artificial intelligence (AI) to process images and detect pathology [18]. The role of WCE in CeD would

expand significantly if future studies successfully demonstrate that CAD can be used to detect subtle mucosal variations that are associated with CeD with high sensitivity and specificity.

Finally, ongoing advancements in WCE design and optics will continue to improve the noninvasive visualization of the small bowel. Improved resolution, higher frame rates, and wider fields of view will likely lead to increased detection of small bowel pathology. The ability to remotely control WCE during its transit through the GI tract would allow physicians to re-evaluate and focus attention on problem areas. While current WCE can only obtain and transmit images, future WCE may be equipped with forceps or additional tools that may be capable of targeted tissue sampling of the small bowel and thus avoiding the need for subsequent upper endoscopy and balloon enteroscopy.

Conclusion

1. Wireless capsule endoscopy (WCE) is a noninvasive device for the evaluation of small bowel diseases, including patients with suspected celiac disease (CeD) who either cannot tolerate upper endoscopy or may have an indeterminate diagnosis after conflicting serologic testing and duodenal biopsies.
2. WCE is less sensitive for Marsh 1 and 2 lesions.
3. It is also used in patients with nonresposive celiac disease (NRCD) with signs and symptoms concerning for possible complications such as ulcerative jejunitis, refractory celiac disease, enteropathy-associated T-cell lymphoma, or small bowel adenocarcinoma.
4. It is important not to misdiagnose ulcerative jejunitis as Crohn's disease.
5. Further advancements to WCE including optical enhancements and artificial intelligence for recognition of small bowel pathology will lead to an increasing role for WCE in celiac disease.

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Chapter 14
Between Functional Gastrointestinal Disorders and Celiac Disease

Adrienne Lenhart and Lin Chang

Case Presentation

A 30-year-old female presented to a gastroenterology clinic with a several year history of intermittent abdominal pain and diarrhea that had worsened over the past 8 months. She reported 3–4 daily non-bloody bowel movements, at least 50% of them being loose to occasionally watery. She had sporadic urgency without nocturnal bowel movements, unintentional weight loss, or fecal incontinence. Her abdominal pain was described as mild to moderate in severity, crampy in nature, located mostly in her bilateral lower quadrants, and partially relieved with defecation. Additionally, she reported associated symptoms of fatigue, nausea, bloating, and excessive flatulence. For years, she had associated periods of increased stress with flares in her gastrointestinal (GI) symptoms, but more recently

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she believed that certain foods, including bread, pasta, and cereals also exacerbated her symptoms. She frequently avoided these foods but denied strictly adhering to any restrictive diet, including a gluten free diet (GFD).

Her past medical history was significant for anxiety, occasional migraine headaches relieved with sumatriptan, and gastroesophageal reflux disease (GERD), for which she was prescribed a daily proton pump inhibitor. She had also filed for divorce from her husband 6 months prior after experiencing marital discord for a couple of years. She denied any previous abdominal surgeries or any family history of inflammatory bowel disease (IBD), celiac disease (CeD), or GI malignancy. However, she recalled that her mother had chronic GI issues but did not seek health care for her symptoms. Physical examination, including body mass index and abdominal and rectal exams, was unremarkable.

Diagnosis

The main differential diagnoses for patients presenting with chronic diarrhea, abdominal pain, and bloating include irritable bowel syndrome (IBS), microscopic colitis, CeD, nonceliac gluten sensitivity (NCGS), small intestinal bacterial overgrowth (SIBO), and IBD. The first step in evaluating recurrent abdominal pain associated with altered bowel habits is to obtain a pertinent and detailed clinical history. The patient does not report alarm features such as GI bleeding, significant weight loss, nocturnal stools, or a positive family history of IBD, CeD, or colorectal cancer. A physical examination including a rectal examination should also be performed to exclude organic pathology.

Based on the patient's medical history, lack of alarm signs, and normal physical exam, she most likely has IBS. Her symptoms meet the Rome IV criteria for IBS [1], which requires the presence of abdominal pain associated with defecation or a change in stool form or frequency (Table 14.1). The prevalence of IBS is estimated to be 5.5–11% depending

Table 14.1 Rome IV criteria for Irritable Bowel Syndrome [1]

Recurrent abdominal pain (≥1 day per week, on average, in the previous 3 months), with symptom onset at least 6 months prior to diagnosis
Abdominal pain is associated with at least two of the following:
Pain related to defecation
Change in frequency of stool
Change in form (appearance) of stool
IBS subtype
IBS-D: >25% of bowel movements with Bristol stool scale types 6–7 and <25% with types 1–2
IBS-C: >25% of bowel movements with Bristol stool scale types 1–2 and <25% with types 6–7
IBS-M: >25% of bowel movements with Bristol stool scale types 1–2 and >25% with types 6–7
IBS-U: Patients meet diagnostic criteria for IBS, but bowel habits are not accurately characterized by above subtypes

on the criteria used [2, 3]. IBS is a stress-sensitive disorder in which chronic stress can increase the onset and symptom exacerbations [4]. Functional GI disorders such as IBS have been reclassified as disorders of brain-gut interactions [5], which are secondary to combinations of abnormalities in intestinal motility, visceral hypersensitivity, intestinal permeability, immune activation, neuroendocrine function, alterations in the microbiome, and changes in central nervous system processing [5].

Once the diagnosis of IBS is established, patients should further be classified into specific bowel habit subtypes based on their predominant stool form: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), or IBS unclassified (IBS-U) (Table 14.1). The Bristol Stool Form Scale is a useful tool to help in the evaluation of bowel hab-

its. Given that this patient describes her stool form as predominantly loose to watery, her symptoms would be classified as IBS-D.

Previous studies and position statements have emphasized that the diagnosis of IBS should be made with limited, but not extensive testing [1, 4, 6]. Diagnostic colonoscopies are not recommended in cases similar to this patient, given her young age and lack of alarm features. However, a complete blood count (CBC) should be obtained to evaluate for iron deficiency anemia, and a C-reactive protein (CRP) or a fecal calprotectin can help to rule out systemic inflammation and IBD in patients with non-constipated IBS. The presence of a normal CRP or fecal calprotectin is associated with a <1% chance of having IBD [7]. Both a CBC and a CRP level were obtained in our patient and were unremarkable. In addition to the above workup, current guidelines and the American College of Gastroenterology (ACG) IBS Task Force also recommend serologic screening for CeD in patients with symptoms of IBS-D or IBS-M (Grade 1B recommendation) [6, 8, 9].

CeD can lead to abdominal pain, bloating, and chronic diarrhea [8], symptoms that overlap considerably with those of IBS, which can sometimes lead to a delay in the diagnosis of CeD [10–12]. However, it is essential to distinguish between these two conditions, as their treatments are different and untreated CeD may result in sequelae including osteoporosis, IDA, and malignancy [13]. Several studies have also suggested that screening for CeD in patients with IBS-type symptoms is likely to be cost-effective when the prevalence of CeD is greater than 1% [14, 15].

Studies show that the prevalence of CeD is higher among patients with IBS compared to healthy controls. A recent meta-analysis examining 36 studies of over 15,000 individuals found that the pooled prevalence of a positive serological test for CeD in patients with IBS is between 2.6–5.7%, with a pooled odds ratio (OR) for a positive tTGIgA or EMA of 2.75 (95% CI 1.35–5.61) among those with IBS. The pooled prevalence of biopsy-proven CeD was 3.3% in patients with IBS-type symptoms compared to healthy controls, with an

OR of 4.49 (95% CI 1.33–15.1) and 4.46 (1.88–10.6) in population based and secondary/tertiary care centers, respectively [16]. However, when only studies conducted in North America or in the general population were included, the odds of having a positive serologic test or a biopsy-proven diagnosis of CeD were no longer significantly different between patients who met criteria for IBS and those who did not [17]. For instance, one prospective, multicenter US study found that the prevalence of CeD in patients with non-constipated IBS-type symptoms was similar to that in controls [17]. This supports screening for CeD in IBS patients presenting to secondary or tertiary care centers, but the value of screening individuals for CeD at the population level or within North America is less clear [16].

The highest probability of having positive celiac serologies was among patients with IBS-D; however, the odds of biopsy-proven CeD were significantly higher for all IBS subtypes compared to controls [16]. Overall, data from this meta-analysis supports continued screening for CeD in patients with symptoms compatible with IBS, with around 30 patients needing to undergo testing in order to diagnose one new case of biopsy-proven CeD [16].

Similar to the increased prevalence of CeD among patients with IBS, patients with CeD also commonly report symptoms compatible with IBS. One meta-analysis found that the pooled prevalence of IBS-type symptoms in biopsy-confirmed CeD patients was 38.0%, and the pooled OR for IBS symptoms was significantly higher in patients with CeD compared to controls (OR 5.60; 95% CI 3.23–9.70) [18]. The pooled prevalence of IBS-type symptoms among CeD patients who were strictly adherent to a GFD was 29%, and CeD patients were more likely to report IBS-type symptoms than controls, despite adherence to a GFD (OR 4.28; 95% CI 1.56–11.75) [18]. As discussed in Chap. 8, overlap IBS may be a cause of non-responsive CeD (NRCD). Given our patient's symptoms of abdominal pain, bloating, and chronic diarrhea, she underwent serologic testing for CeD while on a gluten containing diet. Her tTG titers were normal, and total IgA levels did not indicate IgA deficiency, nearly excluding the diagnosis CeD.

Management

Our patient's diagnosis of IBS-D was confirmed with negative CeD serologic testing (see Chap. 7). Her clinical history suggested that not only did stress precipitate abdominal pain, but she also avoided consuming foods such as bread, pasta, and cereals, which she believed exacerbated her symptoms. While true food allergies are uncommon in IBS, several studies have indicated that symptoms worsen after meals in the majority of IBS patients [19]. This has led to an increased interest in the role that diet plays in the treatment of IBS, with particular attention paid to the efficacy of GFD, lactose-reduced diet, and diets low in short-chain, poorly absorbed carbohydrates known as fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). FODMAPs, which are found in foods such as wheat, garlic, onions, artificial sweeteners, and some fruits and vegetables, are thought to promote intestinal discomfort through osmotic effects and increased gas production after rapid fermentation by colonic bacteria. These physiologic mechanisms have been confirmed through functional magnetic resonance imaging (fMRI) [20]. See also Chaps. 16, 17, and 18.

Observational and randomized controlled trials have also demonstrated that a low FODMAP diet reduces the frequency and severity of GI symptoms in IBS patients [21–23]. A randomized controlled trial conducted in Australia showed that IBS patients on a low FODMAP diet had significantly lower overall symptom scores compared to a traditional Australian diet containing FODMAPs, with improved abdominal pain, bloating, and gas [22]. Given that our patient associated certain foods with her mild to moderate abdominal pain and bloating, she was referred to a GI dietitian experienced in the low FODMAP diet (see Chap. 17).

It is also important to acknowledge that the low FODMAP diet is not a strict lifetime elimination diet, and it usually extends across three distinct stages: restriction, reintroduction, and maintenance [24]. When our patient initially met with the dietitian, she underwent a comprehensive dietary

evaluation and symptom assessment, received education on the role of FODMAPs in IBS symptom generation, and was counseled regarding FODMAP restriction. Randomized controlled trials have studied dietary FODMAP elimination for a duration of up to 6 weeks, but in clinical practice, 4 weeks of FODMAP restriction is usually recommended to avoid potential nutritional deficiencies or deleterious effects on the microbiome [24].

After 4 weeks of eliminating all FODMAPs from her diet, our patient was reassessed by our dietitian and reported a substantial reduction in abdominal cramping and bloating, and her bowel movements improved to around two semi-formed stools per day. Reintroduction of certain FODMAPs was discussed with the patient. The goal of FODMAP reintroduction is for patients to be able to identify which particular FODMAPs may trigger their IBS symptoms and which FODMAPs they can tolerate. Our patient was able to tolerate the reintroduction of milk (lactose) and sourdough bread (which contains gluten but is low in fructans), but experienced recurrent symptoms with the reintroduction of several other fructan-containing foods, including wheat bread, pasta, onions, and asparagus. This is of interest, because despite a recently increased prescription of GFD in non-CeD patients, there is minimal evidence to suggest that gluten is actually a trigger. The few existing randomized controlled trials evaluating dietary gluten in IBS found that patients experienced increased overall IBS symptoms, abdominal pain, bloating, fatigue, bowel movement frequency, and intestinal permeability while on a gluten containing diet [25, 26]. These effects were particularly pronounced in HLA-DQ2/DQ 8 positive patients, although further studies are needed to confirm the findings [26]. However, subsequent studies have shown no effect of gluten reintroduction when non-CeD IBS patients had already been on a low FODMAP diet, and it may actually be the fructan component of gluten containing foods that induces GI symptoms in non-CeD IBS patients with reported gluten sensitivity [27, 28] (see Chap. 18). For those IBS patients whose symptoms improve on a GFD, this may be due

to restriction of poorly absorbed carbohydrates such as fructans, or proteins such as gluten and amylase trypsin inhibitors, or the nocebo effect. In our patient, it may have been the fructan component of wheat bread, pasta, and cereals, rather than the gluten component, that was inducing her IBS symptoms.

In addition to dietary modifications, IBS can also be treated using pharmacologic agents, which are primarily prescribed based on patients' most predominant symptoms. Pharmacologic management of IBS-C can include the use of osmotic laxatives such as polyethylene glycol, the secretogues that enhance electrolyte and fluid into the lumen, lubiprostone (a chloride channel activator), and linaclotide and plecanatide (both are guanylate cyclase C agonists), and the newly FDA approved sodium hydrogen exchanger (NHE3) inhibitor, tenapanor. Chronic idiopathic constipation (CIC) can also be managed with prokinetic agents like prucalopride. Patients with IBS-D can be managed with antidiarrheal agents such as loperamide, eluxadoline (a peripherally acting mixed μ- and κ-opioid receptor agonist and -δ-opioid receptor antagonist), bile acid sequestrants, rifaximin (antibiotic), and alosetron ($5HT_3$ antagonist) in females. Antispasmodics such as dicyclomine or hyoscyamine can be used on an as-needed basis to help alleviate symptoms of abdominal pain. Given our evolving understanding of brain-gut interactions in IBS patients, neuromodulators including low-dose tricyclic antidepressants (i.e., desipramine, amitriptyline), selective serotonin reuptake inhibitors (i.e., fluoxetine), and selective norepinephrine reuptake inhibitors (i.e., duloxetine) have also been used to relieve abdominal pain (Table 14.2).

Case Outcome

Following the reintroduction phase of the low FODMAP diet, our patient was able to personalize a long-term dietary plan that continued to restrict the FODMAP foods that induced her GI symptoms (predominantly fructans), but included those FODMAP foods that did not produce symp-

Table 14.2 Examples of commonly used pharmacologic agents for the treatment of IBS

Category	Pharmacologic agent	IBS-subtype	Comment
Sodium hydrogen exchanger (NHE3)	Tenapanor	IBS-C	Improves abdominal and bowel symptoms in IBS-C
Osmotic laxative	Polyethylene glycol	IBS-C	Relieves constipation symptoms but not abdominal pain
Selective ClC2 chloride channel activator	Lubiprostone	IBS-C	Improves abdominal and bowel symptoms in IBS-C
Guanylate cyclase agonists	Linaclotide, plecanatide	IBS-C	Improves abdominal and bowel symptoms in IBS-C
Antidiarrheal	Loperamide	IBS-D	Relieves diarrhea but not abdominal pain
Bile acid sequestrants	Cholestyramine, colestipol, colesevelam	IBS-D	Can reduce IBS-D type symptoms in patients with bile acid diarrhea
Mixed μ-opioid receptor agonist, −δ-opioid receptor antagonist, and κ-opioid receptor agonist	Eluxadoline	IBS-D	Improves abdominal and bowel symptoms in IBS-D

(continued)

Table 14.2 (continued)

Category	Pharmacologic agent	IBS-subtype	Comment
Antibiotic	Rifaximin	IBS-D	Administered as 2-week course of treatment
Antispasmodics	Dicyclomine, hyoscyamine, peppermint oil	All IBS subtypes	Reduces postprandial abdominal symptoms
Tricyclic antidepressants (TCAs)	Desipramine, amitriptyline, doxepin, imipramine	All IBS subtypes	May be more preferable in IBS-D because of constipation side effect due to anticholinergic properties
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine, citalopram, paroxetine	All IBS subtypes	Improves overall well-being with less proven efficacy in abdominal symptoms
Selective norepinephrine reuptake inhibitors (SNRIs)	Duloxetine	All IBS subtypes	Limited data in IBS but proven efficacy in chronic pain disorders

toms. At her 6-month follow-up, she continued to report significant improvement in her bloating and diarrhea, but still described intermittent postprandial abdominal pain. She was therefore started on dicyclomine as needed with good control of her symptoms. This therapy was chosen as anticholinergics have shown particular benefit when taken before meals, via suppression of the postprandial gastrocolic response [29, 30].

Clinical Pearls/Pitfalls

1. There is considerable clinical overlap in the symptoms of CeD and IBS, sometimes leading to a delay in the diagnosis of the former. It is important to distinguish between these two conditions, as their treatments differ and untreated CeD can be associated with morbidity and mortality.
2. Guidelines recommend screening patients with symptoms of IBS-D or IBS-M for CeD via serologic testing.
3. In light of CeD-associated constipation, patients with symptoms of IBS-C can be also considered for celiac screening.
4. A low FODMAP diet may help alleviate IBS symptoms, possibly due to reduction in fructan-induced GI symptoms in non-celiac IBS patients with reported gluten sensitivity.

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Chapter 15
The Dietitian Role in Celiac Disease

Janelle Smith

Case Presentation

A 38-year-old male was referred by his gastroenterologist to the dietitian in a specialized digestive diseases clinic with a diagnosis of NRCD after a year on a GFD. His symptoms at the time of diagnosis were daily bloating and abdominal pain, hard bowel movements that were difficult to pass (Bristol stool scale 1–2 approximately every other day), and fatigue. His celiac serology was elevated with tTG 226 U/ml (normal <20 U/ml) and positive EMA titer of 1:100 (negative <1:10). Endoscopy with duodenal biopsies showed Marsh 3b-c lesions, confirming the diagnosis of CeD. On initiation of a GFD, he experienced significant symptom improvement for the first 1–2 months. After that point he began to have recurrence of bloating, abdominal pain and fatigue, along with daily alternating bowel movements (Bristol stool scale 2–5). He reported following a strict GFD: he only chose foods that were labeled gluten-free, he took measures to separate food preparation at home, and he requested gluten-free dishes at

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restaurants when dining out. The patient lived with his wife and 3-year-old daughter, who remained on gluten-containing foods at home. He dined out approximately 4 days per week and used a portable gadget to test for gluten content in prepared food about 2–3 times per restaurant. He avoided dishes that received "low gluten" or "gluten found" readings and continued to eat dishes with "smiley face" readings. Serologies improved 6 months after initial diagnosis with tTG 158 U/ml and EMA titer 1:40. At the time of the consultation with the dietitian, 1 year after diagnosis, the patient's tTG was 199 U/ml with a negative EMA.

Diagnosis and Management

A food diary was collected at the first visit:

- *Breakfast*: oat cereal (labeled gluten-free), lactose-free milk, blueberries, coffee with lactose-free milk
- *AM snack*: string cheese
- *Lunch*: gluten-free dish at restaurants near work. E.g., chicken rice bowl with beans, salsa and avocado or chicken pad Thai
- *PM beverage*: coffee with lactose-free milk
- *Dinner*: home-prepared meal, e.g., gluten-free rice pasta with marinara sauce and ground beef, steamed broccoli
- *Water*: 4–8 cups per day

The patient had no intentional gluten ingestion and greatly reduced his dietary intake of gluten, consistent with normalized EMA. Patient had risk factors for continued unintentional gluten intake including high frequency of dining out, home cookspace shared with gluten, inadequate label-reading practices. tTG initially declined after initiating the GFD (though slightly less than expected for 6-month time period), then increased, suggesting continued gluten exposure. He was likely to have continued unintentional gluten ingestion and was in need of thorough dietary evaluation and education.

Nutrition-Related Diagnosis

Excessive dietary gluten intake related to cross-contamination in food as evidenced by elevated tTG, continued symptoms of bloating, abdominal pain and fatigue, and patient reports of not asking questions when dining out or taking adequate measures at home to prevent cross-contact with gluten.

Dietitians who specialize in CeD care often find that patients report following a strict GFD but are not fully educated on the details of a strict GFD. A thorough dietary evaluation frequently reveals unknown sources of gluten ingestion. For all patients with CeD, there is significant risk of exposure to gluten via dining out at restaurants depending on the knowledge and precautionary measures taken by that establishment, and many patients are reticent to ask adequate questions to evaluate that risk. The dietitian starts with investigating the patient's current diet and lifestyle for sources of gluten ingestion.

Medications and Supplements

Reviewing all ingested medications and supplements is crucial. Regarding medications, the current limited research suggests that very few prescription and over-the-counter medications contain significant amounts of gluten to be harmful to those with CeD, even if taken on a consistent basis [1]. Drug manufacturers are not required by the US Food and Drug Administration (FDA) to declare allergens in ingredients [1]. Most will disclose inactive ingredients by patient request (i.e., phone or email) and some disclose inactive ingredients in product insert; however, some inaccurately state that their products contain gluten due to ingredients that are considered safe by FDA according to the Gluten-Free Labeling Guidelines [2]. Examples of gluten-free ingredients that are frequently mistaken as unsafe in medications include sugars and sugar alcohols possibly derived from wheat, such as maltodextrin, maltose, and maltitol. Dietary supplements are

required to disclose allergens according to Food Allergen Labeling Consumer Protection Act of 2004, so patients may identify gluten-containing ingredients by reading the packaging. A 2015 study analyzing content of probiotics, however, called into question the safety of some dietary supplements labeled gluten-free [3]. This patient was consuming a probiotic daily, and he was advised to discontinue the product.

Nonconsumable Sources of Gluten

Patients frequently ask providers if they need to avoid gluten exposure from nonfood sources such as lipstick, shampoo, and hand soap. There is very little scientific data on the risks of nonconsumed gluten to the health of individuals with CeD. Thompson and colleagues (2012) found no detectible gluten in six different cosmetic products in the USA, while Verma and colleagues (2018) found that 6% of oral hygiene and cosmetic products in Italy contained unsafe levels of gluten [4, 5]. They concluded, however, that the actual amount consumed of these products is negligible in regular use. Airborne gluten can be hazardous to health when inhaled in an occupational setting [6]; thus some theorize that this may also be a cause of NRCD [7]. Our patient was not instructed to take any precautions with nonconsumable sources of gluten.

Reading Food Labels

Next, dietitians need to evaluate patients' proficiency at reading food labels. This patient was unfamiliar with ingredients that contain gluten and instead relied on the presence of a gluten-free claim on the product. This practice was adequate for avoiding gluten but limited his options more than necessary. Research to date sampling products labeled gluten-free shows that 94.6–98.9% of foods labeled gluten-free are correctly labeled and test below 20 ppm of gluten [8, 9]. He was encouraged to read ingredient labels for all ingested products

to increase his food selection. He was not checking beverages such as tea and juice, or grains and cereals that he believed to be naturally gluten-free, such as rice, puffed rice cereal, and cornflakes. In this education part, it was revealed that the patient was in fact consuming foods not labeled gluten-free and likely was ingesting gluten given his low understanding of label reading. A 2010 study suggests that gluten-free grains and seeds are susceptible to cross-contact with gluten [10]. This has implications that patients may need to be even more selective when purchasing or consuming naturally gluten-free grains.

Cross-Contact at Home

If a patient with CeD lives with others who do not follow a GFD, it is very important to prevent cross-contact between gluten-free and gluten-containing foods in food preparation [11]. Likewise, it is important to eliminate traces of gluten from the kitchen when a patient is newly diagnosed with CeD [11]. Our patient reported purchasing a new toaster when he was diagnosed with CeD and continued to keep it separated from his family's gluten-containing products. He did not have precautions in place for baking with loose flour or for condiments that are shared among the family.

Unfortunately, there are only few peer-reviewed studies guiding the specific practices of preventing cross-contact at home for individuals with CeD. Studerus and colleagues (2018) found no gluten contamination in a series of experiments aimed at replicating cross-contact via kitchen utensils including a contaminated wooden spoon, unwashed colander, unwashed ladle, and unwashed knife [12]. Weisbrod and colleagues (2019) found few incidents of detectible gluten in gluten-free foods in their experiments replicating cross-contact in a home kitchen. Gluten was detected at levels >20 ppm in gluten-free pasta that was cooked in water shared with gluten-containing pasta, but it was found to be <20 ppm in samples using a shared toaster and a shared pot rinsed with

water [13]. Further studies are needed to illuminate which practices are safe and if current sampling methods are adequate for detecting significant gluten in cross-contact in domestic kitchens.

Dining Out

Dining outside of the home, where food is prepared by individuals with varying knowledge about cross-contact, poses a significant risk to patients with CeD. The FDA has stated that restaurants using gluten-free claims "should be consistent with FDA's definition" for packaged foods [14]. Local governments have jurisdiction over the enforcement of such claims in public and private dining; however, this varies widely based on the local government [15]. Our patient was utilizing an unvalidated self-monitoring gadget to test for gluten content of food he was eating outside the home. Such devices are discouraged by the Association of Official Analytical Chemists International due to several limitations, including false-negative and false-positive results, inadequate sampling and homogenization, and inability to detect fermented and hydrolyzed protein fragments [16]. Our patient was using the gadget instead of asking questions about gluten content of dishes. One of the places he was using this device was a Thai restaurant, where soy sauce could possibly be present but not detected.

Literature regarding gluten cross-contamination in food service indicates that loose wheat flour is especially likely to contaminate food preparation areas [6, 7]. Only one peer-reviewed study to date has examined the frequency of gluten contamination in restaurant-prepared gluten-free foods in the USA, though the method of gluten detection in this study remains unvalidated. The researchers reported gluten detection by portable gluten detection device (Nima) in 32% of gluten-free foods in restaurants across the USA, mainly in

association with gluten-free pizza and pasta, and more in the Northeast compared to West [17]. International studies have reported both safe food service produced gluten-free food and significant gluten contamination in gluten-free restaurant foods [18–21].Again, additional research is essential to providing evidence-based guidelines for patients with CeD who dine outside the home. Current recommendations for celiac patients when dining out are to ask questions about food preparation and sources of possible cross-contact similar to those precautions taken at home [11].

Oat Intake

Recommendations on oat intake vary among experts in the field of CeD. All agree that conventionally produced oats and oat products are contaminated with errant gluten-containing grains in significant amounts to be harmful to those with CeD [22, 23]. A 2017 meta-analysis showed no adverse effects of long-term consumption of "pure, uncontaminated oats" [24]. There are currently two types of gluten-free oats: conventionally grown oats that are mechanically and/or optically sorted to remove errant grain and "purity protocol oats," wherein growers take measures to prevent the presence of errant grain at every step of production during growing, harvesting, transporting, storage, and processing [25]. Purity protocol oats were endorsed by the Canadian Celiac Association in 2007 [26]. The technology of sorted oats is relatively new, occurring after the 2007 position statement. Current literature about this technology shows several challenges to ensuring that the final product is safe for individuals with CeD [27, 28]. The latest published recommendations by both the Academy of Nutrition and Dietetics and Health Canada advise that gluten-free oats be introduced after at least 6 months on the GFD and/or after symptoms have resolved, and that patients be monitored by their physician for tolerability [11, 23].

Screening for Micronutrient Deficiencies

The dietitian coordinated with the gastroenterologist to order serum labs checking micronutrient status of the patient. This screening is recommended at the time of diagnosis and had not yet been completed. Given that the patient continued to have gluten intake and elevated serology, it is logical to expect continued malabsorption. Labs ordered were based on the most prevalent nutrient deficiencies in patients with CeD: CBC along with iron studies (including ferritin), vitamin D, RBC folate, vitamin B12, and zinc [29]. Additional tests including vitamin A/carotene, vitamin E, vitamin K, vitamin B6, selenium, carnitine, and copper are ordered based on specific patient symptoms. In addition, current guidelines suggest testing transaminases and thyroid function. The patient's labs were notable for low ferritin, vitamin D, and folic acid.

Recommendations Based on Dietary Assessment

The patient was recommended to correct nutrient deficiencies with oral supplements of folic acid, iron, and vitamin D. Lab values were repeated following 3 months, with the patient withholding all supplements for 3 days prior to the lab draw in order to prevent skewed results. All values were within normal limits, and the patient were told to discontinue the oral supplements but continue a multivitamin.

For a patient such as this, who continued to exhibit symptoms and elevated autoantibodies while on a GFD, improving label-reading skills and behaviors to prevent cross-contact at home is key. The next step is eliminating high-risk sources of cross-contact with gluten in the food supply, namely, dining out and oats. In collaboration with the primary gastroenterologist, we monitor tTG in 3–6 months for >50% decline based on the half-life of the autoantibody [30]. Furthermore, an early repeat endoscopy per NRCD management is advised (see Chap. 8) rather than the customary endoscopy within 2 years of diagnosis to confirm histological remission.

If these interventions do not result in improvement of symptoms, a decline in tTG IgA titer, and an improved Marsh score on duodenal biopsy in the 12-18 months after diagnosis, we would proceed to recommend a gluten contamination elimination diet. This diet is proposed to differentiate between individuals with true RCD and those with NRCD [31]. Small studies have demonstrated improvement in clinical symptoms, serology, and histology but without full normalization (to Marsh 0) after 3 months of the gluten contamination elimination diet [32].

After patients show a positive response to a GFD, they are educated about ways to lower the risk of cross-contact in order to improve quality of life and nutritional quality of diet [33]. For dining out we begin with reintegrating dedicated gluten-free establishments, then restaurants with low risk of cross-contact, and practice asking adequate, question of restaurant staff. We would reintegrate oats and continue to monitor symptoms, serology, and later histology after this liberalization.

Case Outcome

The patient's extensive education with the specialized dietitian led to behavioral changes to eliminate hidden sources of gluten intake, including naturally gluten-free grain products that were not labeled gluten-free, potential risks for cross-contact in food preparation at home and when dining out, and high intake of oats. After 3 months of intervention, the patient's serologies improved by more than 50% with tTG 83 U/ml (normal <20 U/ml) and EMA negative. The patient maintained their symptom improvement. Negative gluten immunopeptide (GIP) in multiple stool samples confirmed that gluten was not ingested during this time period. At that point the patient was instructed to integrate gluten-free oats in the amount of ¼ cup per day and take additional precautions when dining out at restaurants. A gluten contamination elimination diet was not necessary.

Clinical Pearls/Pitfalls

1. Celiac serology does not normalize immediately following a GFD, nor is it an absolute indicator of dietary adherence or histological remission.
2. Overrestricting the diet is often unnecessary as it impairs patients' quality of life, increases anxiety and fear, and may lead to disordered eating.
3. Referral to specialized dietitians to assess for continued gluten ingestion is crucial in order to avoid misdiagnosis of overlap functional GI disorders or RCD.
4. Patients should be discouraged from relying on unvalidated methods for monitoring gluten content of food.
5. Urinary and stool gluten immunopeptide detection may have a future role in assessing gluten exposure and adherence.

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Chapter 16
Non-Celiac Gluten Sensitivity

Giulia N. Catassi, Loris Naspi, and Carlo Catassi

Case Presentation

A 45-year-old woman presented to the GAD clinic with a history of chronic intestinal (excessive gas, abdominal pain, and recurrent diarrhea) and extraintestinal (chronic fatigue and headache) complaints. Since symptoms were exacerbated following ingestion of gluten-containing food, the patient self-initiated GFD 3 months prior to her clinic visit, with a clear-cut amelioration of symptoms, associated with some weight loss. After 2 weeks of GFD, her primary care physician checked her serum tTG IgA which yielded a normal result. Her doctor suggested resuming a normal diet and performing a duodenal biopsy because of suspected celiac disease (CeD), but the patient was scared by the possibility of symptom recurrence and presented for a second-opinion consultation.

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Diagnosis

NCGS is a poorly defined syndrome characterized by a wide range of intestinal and extraintestinal symptoms, typically occurring soon after ingestion of gluten-containing foods and disappearing quickly upon their withdrawal, occurring in individuals in whom both CeD and wheat allergy have been excluded [1]. Although cases of NCGS were already reported in 1978 [2], this disorder has been characterized only in 2010 [3], and this is the reason why several aspects remain unclear (e.g., lack of biomarker, natural history, level of gluten restriction), and many providers still regard the diagnosis as controversial. In Western countries the prevalence of NCGS is estimated to be around 2–3%, higher than CeD. The disorder is more common in females aged 25–50 years. Evidence is accumulating that NCGS is caused by an inappropriate innate immune response to gluten and/or other wheat protein components, e.g., amylase/trypsin inhibitors [4]. Due to the possibility that non-gluten wheat proteins might trigger this disorder, at least in some cases, the broader term "non-celiac gluten/wheat sensitivity" has been recently coined, but for our purposes, the abbreviation "NCGS" is used [5].

Patients with NCGS do not show a significant increased prevalence of CeD-predisposing genes, i.e., HLA-DQ2 and HLA-DQ8, compared to the general population. Despite a tendency to run in families, no NCGS-predisposing gene has been detected so far.

Although the DBPC gluten challenge is still considered the gold standard for diagnosis of NCGS, recent studies highlight the limitations of this procedure, which is complex, difficult to manage in clinical practice, and, above all, negatively affected by a strong nocebo effect [6, 7] (see Chap. 6). Further studies are currently under way to detect a biomarker, or a set of biomarkers, that could help to confirm the diagnosis of NCGS.

NCGS is a clinical diagnosis. Table 16.1 shows the most common manifestations of NCGS; however many other presenting symptoms have been described, e.g., arthralgia, cysti-

Table 16.1 Common manifestations of non-celiac gluten sensitivity

Intestinal	Extraintestinal
Bloating	Foggy mind
Abdominal pain	Headache
Diarrhea	Chronic fatigue
Constipation	Weight change
Epigastric pain/heartburn	Anemia
Stomatitis	Pruritic dermatitis

tis, and hallucinations. IBS-type symptoms are usually part of the presenting picture, and it is estimated that NCGS is responsible for one third of cases of IBS in adults [8] (see also Chap. 14).

In patients with IBS, it may be difficult to differentiate NCGS from FODMAPs intolerance. There is an overlap between NCGS-IBS and FODMAPs-induced IBS, since wheat is a major source of both gluten and fructan, one of the major FODMAP component (see also Chap. 18). Likewise, there is an overlap between a GFD and a low-FODMAP diet. Patients on a long-term low-FODMAP diet appear to view the reduced intake of wheat as essential to their maintained symptomatic response. Thus, a GFD, rather than a low-FODMAP diet, may be a more practical option for IBS patients with subsequent improved quality of life [9].

Pruritic dermatitis is sometimes seen in patients with NCGS. This should be differentiated from dermatitis herpetiformis (DH), the dermatological manifestation of CeD (see Chap. 2). In NCGS, the lesions are polymorphic, initially erythematous, and papulovesicular-like eczema and DH, and then later, due to constant scratching, they appear psoriatic-like. Similar to DH, the lesions are more frequently localized on the extensor surfaces of the limbs, in particular on the elbows, followed by the knees. Time of disappearance of the skin lesions after starting the GFD is much shorter than in DH. In contrast to DH, no specific histological dermal pattern has been associated with NCGS [10].

Autism spectrum disorders (ASDs) are chronic behavioral conditions, with onset before 3 years of age. ASDs are one of the fastest growing developmental disabilities in the United States. One of the most popular interventions for ASD is the gluten-free casein-free diet (GFCFD). The possible effect of the GFCFD in children with autism is not due to underlying CeD, but rather it has been hypothesized that symptoms may be caused by interaction between brain opioid receptors and peptides derived from gluten and casein absorbed due to increased intestinal permeability. Removing gluten from the diet may positively affect the clinical outcome in some children diagnosed with ASD, indicating that autism may be part of the spectrum of NCGS, at least in some cases [4], but this is still controversial.

In contrast to CeD, the latency between the ingestion of gluten-containing food and the appearance of symptoms is typically short, within hours or few days, and this is an important diagnostic feature of NCGS. Many affected individuals, as with our patient, recognize the cause-effect relationship and tend to exclude gluten-containing food from their diet. Amelioration of symptoms with a strict GFD adds weight to the suspected NCGS diagnosis.

There are no biomarkers of NCGS; however the finding of anti-native gliadin antibodies (AGAb), particularly of IgG class, is a frequent finding, while specific CeD autoantibodies, such as tTG-IgA and EMA, are negative by definition [11]. CeD-associated antibodies, as well as wheat-specific IgE in cases of suspected wheat allergy, should be sought when the patient is still on a normal diet to exclude CeD. Given the high negative predictive value of tTG and EMA testing, a small intestinal biopsy is usually not necessary to exclude seronegative CeD. Duodenal biopsies, if performed in NCGS patients, usually show normal mucosal architecture or isolated increase of intraepithelial lymphocytes (IEL), compatible with Marsh 1 lesion [3].

According to the recent Salerno Experts' Criteria for NCGS, the DBPC gluten challenge with crossover, performed after at least 4 weeks of GFD, is the gold standard for

diagnosing NCGS. The gluten challenge includes a 1-week challenge with 8 g of daily gluten (or placebo), followed by a 1-week washout of strict GFD and by the crossover to the second 1-week challenge. During the challenge, patients will identify and report one to three main symptoms. A variation of at least 30% between the gluten and the placebo challenge should be detected to discriminate a positive from a negative result [12]. (Please see Chap. 6.)

Management

Currently an individualized GFD remains the proper available treatment for NCGS. Strict gluten avoidance is usually suggested in cases of NCGS, but the real toxicity of rye and barley and/or gluten traces in these patients is still doubtful. Given the wide interpatient variability in the degree of gluten sensitivity, a flexible approach to the diet may be indicated, i.e., recommending attention to minimal amounts of contaminating gluten only in those reporting clinical symptoms after ingestion of gluten traces. Patients diagnosed with NCGS should be monitored by a gastroenterologist and an experienced dietitian to counsel them and their families in navigating the GFD [13] (see Chap. 17).

Since NCGS may be a transient condition, GFD should be followed for a specific period of time, e.g., 12 to 24 months, before testing gluten tolerance again. Based on the severity of symptoms, some gluten-sensitive patients may choose to follow a GFD indefinitely.

Case Outcome

The suspicion for NCGS was appropriate due to the consistent clinical picture and the cause-effect relationship between gluten ingestion and appearance of symptoms. Although CeD serology was incorrectly tested after starting a GFD, 2 weeks of gluten restriction are not enough to invalidate the normal

result; therefore CeD was reasonably excluded on the basis of the normal tTG-IgA level. Along with the dramatic response to the GFD, there was no need for an immediate diagnosis confirmation by the DBPC gluten challenge, a procedure that could be performed later to verify persistence of gluten sensitivity. After 12 months of treatment, the patient was doing well on the GFD, under the supervision of a specialized dietitian. A DBPC gluten challenge is scheduled after 24 months of dietary treatment, to check persistence of NCGS.

Clinical Pearls/Pitfalls

1. NCGS is a poorly defined syndrome characterized by a wide range of intestinal and extraintestinal symptoms, typically occurring soon after ingestion of gluten-containing foods and disappearing quickly upon their withdrawal, occurring in individuals in whom both CeD and wheat allergy have been excluded.
2. NCGS is a clinical diagnosis. IBS-type symptoms are usually part of the presenting picture, and it is estimated that NCGS is responsible for one third of cases of IBS in adults.
3. Individualized GFD is the current available treatment for NCGS.
4. Since NCGS may be a transient condition, GFD should be followed for a specific period of time, e.g., 12–24 months, before testing gluten tolerance again.

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Chapter 17
The Dietitian Role in Non-Celiac Gluten Sensitivity

Nancee Jaffe

Case Presentation

A 32 year-old female presented to the dietitian in a specialized digestive diseases clinic with a longstanding history of abdominal pain, bloating, diarrhea, and fatigue that worsened during her first year of law school. She was aware that stress played a big role in the development of her symptoms but stated that she may have symptoms even when not feeling anxious or stressed. The patient has a first cousin and a niece with celiac disease (CeD) and thought she might have it as well. She underwent extensive workup with her gastroenterologist, including stool studies for infectious etiology. She underwent an unremarkable colonoscopy with random biopsies without evidence of microscopic colitis and an unremarkable upper endoscopy with duodenal biopsies without enteropathy. The patient was also seen by an allergy-immunology expert who found no clinical or ancillary finding to support wheat allergy. The doctor deferred wheat-specific IgE radioallergosorbent test (RAST) and skin prick test,

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since she thought these were unnecessary in this clinical scenario in light of high rates of false-positive results.

The patient had previously met with a naturopathic practitioner who told her that she had gluten sensitivity and lactose intolerance. She was encouraged to follow an elimination diet for 3–6 months that restricted all dairy, gluten, soy, citrus fruit, beans, corn, peanuts, sugar, alcohol, and caffeine. The patient stated that she felt 50% reduction in symptoms within 4 weeks of starting the diet but found the diet too difficult to follow. Instead, she switched to a less restricted gluten- and dairy-free diet. She noted a 30% reduction of original symptoms with the removal of these two food categories. The patient was wondering what she should try next, as she feels modestly better but continues to have chronic symptoms.

Diagnosis and Management

The patient noted a 50% reduction in abdominal pain, bloating, diarrhea, and fatigue when dairy, gluten, soy, citrus fruit, beans, corn, peanuts, sugar, alcohol, and caffeine were removed from her diet. By removing dairy, gluten, soy, beans, and certain processed sugars, the patient had inadvertently been placed on a modified low-FODMAP diet.

The low-FODMAP diet is a three part dietary intervention that removes fibers and specific sugars (**f**ermentable **o**ligosaccharides, **d**isaccharides, **m**onosaccharides, **a**nd **p**olyols) that have been demonstrated over the past decade of research to aid with reduction of abdominal pain and bloating for irritable bowel syndrome (IBS) patients [1, 2] (see also Chap. 14). The high-FODMAP carbohydrates (fructans, galacto-oligosaccharides (GOS), polyols, lactose, and excess fructose) as listed in Table 17.1 are easily fermented and poorly absorbed, pulling water into the intestines, resulting in many of the characteristic symptoms associated with IBS and NCGS [3]. Since the patient's symptoms increased when she switched the strict elimination diet to a modified one which

Table 17.1 Examples of high-FODMAP foods

Lactose	Excess fructose	Fructans/GOS	Polyols
Yogurt, milk (cow, goat, sheep), ricotta cheese, cottage cheese, ice cream, custard	Asparagus, sugar snap peas, apple, pear, mango, cherries, honey, high-fructose corn syrup, rum	Wheat/ barley/rye, onions, garlic, artichokes, chickpeas, pistachios, cashews, watermelon, nectarines	Peaches, nectarines, plum, mushrooms, cauliflower, snow peas, xylitol, sorbitol, mannitol

only removed dairy and gluten, it would make sense that other high-FODMAP foods besides lactose and wheat fructans were playing a role in her symptom production. Fructan intolerance is further discussed in Chap. 18.

A food diary was collected at the first visit:

- *Breakfast*: 2 eggs with gluten-free toast and 1 banana (ripe)
- *Lunch*: tostada salad with lettuce, tomato, guacamole, salsa, corn chips, black beans, and cashew creme
- *Dinner*: grilled salmon in gluten-free teriyaki marinade, steamed broccoli (2 cups), and brown rice
- *Snacks/desserts*: vegan tofu pudding with mixed berries; gluten-free pretzels; trail mix
- *Beverages*: unsweetened iced tea; coffee with coconut creamer; chamomile tea before bed

The patient was found to be eating a wide variety of high-FODMAP foods, especially rich in fructans and GOS:

- *Breakfast*: 2 eggs with gluten-free toast (agave, fructose; chicory root, fructan; pear juice, fructan/polyol) and 1 banana (ripe, fructan)
- *Lunch*: vegan tostada salad with lettuce, tomato, guacamole (avocado, polyol; onion, fructan), salsa (onion and garlic, fructans), corn chips, black beans (GOS), and cashew creme (fructan)

- *Dinner*: grilled salmon in gluten-free teriyaki marinade (honey and garlic, fructans), steamed asparagus (fructose), and brown rice
- *Snacks/desserts*: vegan tofu (carob, fructan; silken tofu, GOS) pudding with mixed berries (blackberries, polyol); gluten-free pretzels; trail mix (cashews, fructan)
- *Beverages*: unsweetened iced tea; coffee with coconut creamer (inulin, fructan); chamomile tea before bed (fructan)

Since the patient has been ruled out for other gluten-associated disorders (GADs), including wheat allergy and CeD, it was clinically appropriate to trial the patient on a strict low-FODMAP elimination diet to see if further symptom reduction could be achieved.

Therefore, she was placed on low-FODMAP elimination diet. She was counseled by an expert dietitian on the low-FODMAP diet and given recipes, meal planning guides, grocery lists, and tips/tricks to help ensure success with the diet. The patient was scared to try low-FODMAP wheat and dairy products such as slow fermentation sourdough bread and aged cheeses; thus it was determined that tolerance testing for these foods would wait until the reintroduction phase. She was educated on the three phases of the low-FODMAP diet and encouraged to follow the initial elimination phase for 2–6 weeks [4]. The patient experienced a 70% improvement of overall symptoms on the low-FODMAP diet elimination phase after 4 weeks.

The patient was educated at her first follow-up session about the reintroduction phase, which includes staying on the low-FODMAP diet and strategically and specifically reintroducing one carbohydrate category at a time in varying doses over several days to test tolerance. This data would then be used for phase 3, or maintenance/personalization/liberation, when the diet is individualized to the patient's tolerance levels [2, 4].

The patient was instructed to trial slow fermentation sourdough bread for fructan (wheat) tolerance. This low-FODMAP form of sourdough bread can be used to assess

for gluten versus fructan intolerance. Sourdough culture used to make sourdough bread contains wild yeasts and lactobacillus bacteria strains. Microbes during the leavening process consume sugar (specifically the fructans in the wheat flour) and create gas as a by-product, thus reducing the amount of fructans left in the end product [5]. The patient was instructed to choose a sourdough bread made with no other high-FODMAP ingredients such as honey or high-fructose corn syrup, made with no added sugar or yeast and that was allowed a 1–2 day natural leavening period. Sourdough breads such as these are found at local farmers markets and health food stores.

Her reintroduction phase results were as follows:

- Excess fructose (honey) - no symptoms.
- Sorbitol (1/4 avocado) - symptoms on day 1 (diarrhea, bloating).
- Mannitol (mushrooms) - no symptoms.
- Fructan onions - no symptoms.
- Fructan garlic (1 clove) - symptoms on day 1 (bloating, distention).
- Fructan wheat (sourdough bread 1 slice) - symptoms on day 2 (diarrhea, bloating, fatigue); patient decided to retest this amount two more times with the same results.
- GOS (lentils 2 tbsp.) - symptoms on day 2 (bloating, distention).
- Lactose (Parmesan cheese - low FODMAP) - no symptoms.
- Lactose (cow's milk ½ glass) - symptoms on day 2 (7 grams).

Given that the patient's low-FODMAP reintroduction phase results showed no symptoms with excess fructose, mannitol, fructans (onion), and low lactose dairy, these categories were liberated, and the patient was encouraged to slowly bring foods from these categories back into the diet.

The patient symptomatically responded to sorbitol, fructans (garlic), GOS (beans), and lactose. The patient was encouraged to avoid sorbitol-rich foods including stone fruits

and sugar-free products containing sorbitol; use garlic-infused oils, chives and green portions of scallions instead of garlic when cooking and ask for no garlic when eating out at restaurants; use 300 units of alpha-galactosidase enzymes when consuming beans, soy, and legumes; and read labels for plain dairy products to check for lactose content and opt for products with less than 7 grams lactose as well as distribute the quantity throughout the day to not overwhelm the digestive tract. The patient was also encouraged to consider reintroducing these foods again in 3–6 months to see if tolerance levels have changed.

Case Outcome

When the patient tested sourdough bread that was low in FODMAP (low fructan), she had symptoms. The patient was previously ruled out for CeD and wheat allergy and had remission of symptoms when gluten was removed and return of symptoms when gluten was reintroduced to the diet. With this knowledge as well as her family history of CeD, it is reasonable to clinically diagnose her with NCGS, even given the possible nocebo effect [6].

The differences between CeD and NCGS were discussed at length with the patient (see Chaps. 1 and 16), highlighting that NCGS does not result in intestinal damage when gluten is consumed, only troublesome symptoms, which are important to minimize for improved quality of life [3, 6]. Thresholds for gluten consumption based on patient's reintroduction charts were noted, encouraging the patient to not worry about small amounts of cross-contamination or contact, and allow for small amounts of gluten-containing foods to enter the diet without concerns.

The patient continued to have 20% of her original symptoms, mainly abdominal pain and diarrhea, which she noted to be associated with big cases at work or speaking in front of a jury. She was aware that her fears regarding having symptoms made them worse and she felt incapable of "stopping the vicious cycle" of this anticipatory anxiety.

The final plan for the patient was as follows:

- Modified GFD with small amounts allowed without contributing to symptoms.
- Modified lactose-free diet with use of lactase enzymes 9000 ALU when consuming lactose-rich food products [7, 8].
- Digestive enzyme with 300+ units of alpha-galactosidase for use with consumption of GOS-rich foods [9].
- Liberation of fructose, mannitol, and onion as well as low-lactose dairy foods.
- The brain-gut axis was discussed, and stress management skills were encouraged; gut-directed cognitive behavioral therapy or hypnosis to work with anxiety and symptoms was suggested [10] (see Chap. 14).

Clinical Pearls/Pitfalls

1. Gluten-free and low-FODMAP are not synonymous.
2. A specialized dietitian can assist in differentiating between fructan intolerance, IBS, FODMAP intolerance, and NCGS.
3. A FODMAP-friendly sourdough bread trial can help differentiate whether gluten or fructan is the culprit for a patient's symptoms.
4. Low-FODMAP diet is not an elimination only diet; reintroduction and maintenance phases are crucial.

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Chapter 18
Fructan Intolerance

Elizabeth B. Hastie and Sheila E. Crowe

Case Presentation

A 63-year-old woman presented to a gastroenterology clinic with a 7-year history of chronic constipation and abdominal pain, bloating, and vomiting after eating certain foods. She had unremarkable average-risk screening colonoscopies at ages 50 and 60 years old. She denied any association between symptoms and defecation or any changes in her frequency of stool when these symptoms began. Celiac serology and endoscopic evaluation showed no evidence of celiac disease (CeD). After hearing about non-celiac gluten sensitivity (NCGS), she adopted a gluten-free and lactose-free menu. Without complete resolutions of her symptoms, she continued omitting foods. She found that onions, peppers, scallions, and cilantro triggered her symptoms, and she was concerned about an allergy to these foods.

Her presentation strongly suggested the presence of an intolerance to indigestible carbohydrates or fermentable oligosaccharide, disaccharide, monosaccharide, and polyols (FODMAP) (see Chaps. 16 and 17). She has self-reported

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NCGS, suggesting that gluten, or more accurately, gluten-containing foods, trigger her symptoms. However, she did not achieve complete resolution of her symptoms with a strict GFD, suggesting that the gluten component of these foods may not be the culprit. Imperative to her diagnosis is the fact that she has self-limited foods with particularly high amounts of indigestible carbohydrates and specifically fructan.

Diagnosis

Fructans are indigestible carbohydrates. These oligo- and polysaccharides are made up of short chains of fructose units with a single glucose unit at one end. The human small intestinal epithelium, however, lacks the hydrolase enzyme necessary to break these chains into their absorbable components or monosaccharides [1, 2]. As a result, undigested carbohydrates reach the colon, where their presence alone is believed to cause GI symptoms in patients with fructan intolerance (FI).

With about 15% of the population having irritable bowel syndrome (IBS) and with diet often thought to trigger IBS symptoms, the majority of research on fructan and FODMAP intolerance has been focused on patients with IBS [3] (see Chap. 14). It has been applied to patients like ours, because not only is there a significant overlap in their clinical symptoms but the pathophysiology is believed to be the same [4]. When intact fructans make their way into the large intestines, two pathophysiological processes occur that lead to luminal distension: water is osmotically drawn into the colonic lumen, and gases, including carbon dioxide, methane, and hydrogen, are produced by bacterial hydrolase enzymes [1, 2, 5]. This rapid colonic distension is translated as pain and discomfort in patients with hypersensitive, visceral, stretch receptors believed to be commonly found in patients with IBS and FI (Fig. 18.1).

Unlike CeD, no standardized test has been developed to accurately diagnose FI, and there are no identifiable changes in serum or stool biomarkers when these patients are exposed

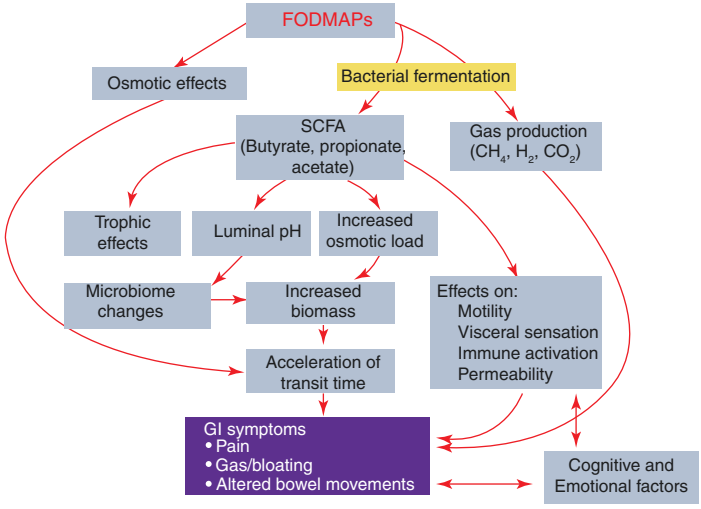

FIGURE 18.1 Components of FODMAP digestion with resulting symptoms. (From Food: The Main Course to Wellness and Illness in Patients with Irritable Bowel Syndrome. American Journal of Gastroenterology, 2016)

to dietary changes [2, 6]. The gold standard for determining food intolerance in research is the double-blind placebo-controlled (DBPC) crossover trial. This type of study has been translated into a clinically practical tool for diagnosing non-celiac gluten sensitivity (NCGS). The recommended parameters for such a trial include a 6-week gluten-free period followed by a 1-week challenge with gluten [4] (see Chaps. 6 and 16). Similar recommendations have been applied to fructan and FODMAP intolerance in general [1]. Research on low-FODMAP diet has shown that symptoms progressively improve over the first 6 months of the diet [2]. To confirm our suspicion of FI in this patient, it would therefore be recommended that she adheres to a strict, low-FODMAP diet for 6–8 weeks to assess whether her symptoms improve.

Research studies have also utilized hydrogen and methane breath tests to evaluate for carbohydrate fermentation by bacteria in the colon. The utility of a breath test in this clinical

setting has not yet been determined, and aside for the specialized dietitian's assessment, there is currently no standardized method for diagnosing fructan intolerance outside of research [3, 7] (see Chap. 17).

Management

Fructans are ubiquitous components of the Western diet, making management of FI challenging. Fructan's most common structural form, inulin, is particularly common with an estimated 1–4 grams of inulin consumed daily in the USA [2, 8]. Fructan is found in tens of thousands of plants as storage carbohydrates [8]. Vegetables, including onions, garlic, and artichokes, and grains, including wheat, barley, and rye, have particularly large amounts of fructans [5, 9]. Wheat has been estimated to contribute over 75% of daily inulin intake in the North American population, providing a potential explanation for why this patient had some relief from her symptoms when adopting a GFD [9].

The presence of such high amounts of fructans in wheat may also explain why research has shown that more than 80% of patients with self-reported NCGS do not meet significant diagnostic criteria for gluten sensitivity in DBPC crossover trials [6, 10]. Furthermore, a study that specifically compared gluten to fructan found that fructan induced more symptoms than gluten in patients with self-reported gluten sensitivity. These findings have led to the theory that NCGS may be a misnomer [4]. This is supported by the fact that early research into the cause of symptoms in patients with NCGS did not consider the other components of wheat [6] (see Chap. 16).

Fructans are also commercially synthesized or extracted from chicory root and used in many processed foods. With about 30–50% of the sweetness of table sugar and fewer calories, fructans can be found in many low-calorie foods. They are also utilized by food manufacturers to increase fiber content without affecting flavor, mouth-feel, or stability [8]. In

addition to its ubiquity, fructans are difficult to accurately measure in foods, and the absolute amount of fructans in foods cannot be found in nutritional tables [5, 9].

For these reasons, having the close assistance of a dietitian is essential to the successful treatment of patients like ours in this case [2]. Studies have also shown that patients benefit from a basic explanation of the pathophysiology of the low-FODMAP diet, which a dietitian could also assist with [1]. In general, research has focused on the low-FODMAP diet and not specifically a low-fructan diet, as the pathophysiology behind the indigestible FODMAPs and fructans is believed to be the same, but the low-FODMAP diet actually stemmed from research initially focused on just fructose and fructan. Limiting these indigestible carbohydrates alone resulted in improvement in more than three-fourths of patients with IBS [11]. Patients with IBS develop improvement in their GI symptoms within 2–8 weeks of starting a low-FODMAP diet, so it is reasonable to ensure monthly follow-ups to monitor for adherence and to assess for clinical improvement [12]. The low-FODMAP diet has also been shown to reduce heartburn and lethargy and to increase vitality [3, 4, 13].

It is important to educate patients that the long-term side effects of maintaining a low-FODMAP diet are unknown and limiting fructan consumption is controversial [14]. Research conducted in the 1990s to early 2000s was actually more focused on the health benefits of fructans instead of their potential to trigger GI symptoms. Animal studies revealed a variety of mechanisms by which fructans enhance intestinal health through nurturing healthy flora growth, warding off pathogens, and stimulating the immune system [15]. Bacteria capable of fermenting fructans have been identified to consist of *Bifidobacterium*, which is considered to be a healthy bacterium like *Lactobacillus*, and the consumption of higher amounts of fructans has been shown to increase *Bifidobacterium* levels while reducing the levels of other, potentially harmful bacteria [16]. A recent randomized control study showed that patients on a low-FODMAP diet had an increase in *Bifidobacterium* after a probiotic was added to

their diet [17]. Therefore, it is reasonable to discuss adjunct probiotics as a low-risk means to offset one of the known side effects of the diet.

Case Outcome

This patient met with a registered dietitian four times over the next year and adopted a low-FODMAP diet. Her symptoms of constipation, bloating, and vomiting resolved. On reintroduction phase only FI was noted, and her diet was therefore liberalized. One year later she still maintained a low-fructan diet with daily probiotics. Her resolute and persistent adherence to the diet reinforced her diagnosis with adherence to the diet having been shown to be a strong predictor of improvement in symptoms in research [1]. In addition, she lost 12lbs and reported near-normalization of her bowel habits. She is planned for fructan rechallenge to assess for ongoing intolerance.

Clinical Pearls/Pitfalls

1. Fructans and other indigestible carbohydrates cause rapid colonic distension via two mechanisms: they increase osmotic load, drawing fluid into the colon, and they are fermented by bacteria, leading to the production and buildup of gas.
2. Foods rich in fructan, aside from wheat, include garlic, onions, shallots, leeks, and artichokes.
3. The low-FODMAP diet is key to the diagnosis and management of fructan intolerance, but the diet is complex, making a referral to a skilled dietitian essential.
4. The long-term effects of maintaining a low-fructan diet are unknown. It is important to encourage liberalization of patients' diets when possible, and it may be reasonable to add a probiotic.

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