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Case Report

Strict Serological and Clinical Follow-up in Celiac Disease Can Unmask Underlying Threats: A Case of Concomitant Pancreatic Cancer

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Abstract

Monitoring adherence to a gluten-free diet (GFD) in patients with celiac disease (CD) remains a significant clinical challenge. Accurate assessment of dietary compliance is crucial not only for controlling symptoms but also for preventing long-term complications associated with persistent intestinal inflammation. Current guidelines generally recommend follow-up serological testing at 6 and 12 months after diagnosis, followed by annual assessments. However, these intervals may not be sufficient in all cases, particularly for patients presenting with atypical symptoms, overlapping gastrointestinal complaints, or comorbid conditions that can obscure the true disease activity. We report the case of a 46-year-old male patient diagnosed with CD who was subsequently found to have pancreatic cancer. This case highlights the potential limitations of standard follow-up intervals and underscores the importance of shortened and more frequent serological monitoring immediately after diagnosis. Early testing can facilitate timely detection of complications or comorbidities and enable prompt differential diagnosis, ultimately improving patient outcomes. Adult CD patients may present with subtle or overlapping clinical features, making early and proactive surveillance especially critical. This experience emphasizes the need to individualize follow-up strategies, taking into account patient age, clinical presentation, and risk factors for additional gastrointestinal or systemic diseases. Optimizing the timing and frequency of serological assays may enhance clinical decision-making, allow earlier detection of comorbidities, and support more effective management of CD in everyday practice. Furthermore, these observations could encourage exploration of more flexible and risk-adapted monitoring schedules in future evidence-based guidelines, particularly for adult patients potentially at higher risk of serious complications, including malignancies.

Keywords

Celiac disease, Serology, Follow-up, Gluten-free diet, Differential diagnosis, Pancreatic cancer

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1. Introduction

Celiac disease (CD) is an autoimmune disorder triggered by gluten ingestion and has an estimated prevalence of 1%. Gluten is a protein complex found in wheat, barley and rye. Gluten-derived peptides–particularly gliadin–are able to stimulate innate and adaptive immune responses in susceptible individuals, leading to intestinal and systemic inflammation [1].

CD develops in genetically predisposed individuals who express HLA-DQ2 and/or HLA-DQ8 haplotypes; however, these genetic markers are present in approximately 30%-40% of the general population without developing CD [2].

CD diagnosis is made on the basis of histological evidence of villous atrophy in duodenal biopsies performed during esophagogastroduodenoscopy while on a gluten-containing diet. In most of cases, CD diagnosis is supported by the positivity of sensitive and specific serum antibodies, such as immunoglobulin A (IgA) and/or G (IgG) anti-tissue transglutaminase (anti-tTG), anti-endomysial antibodies (EMA), and anti-deamidated gliadin peptide (DGP) antibodies [3]. The biopsy-sparing approach proposed by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) allows diagnosis without duodenal biopsy in paediatric patients with anti-tTG levels ≥ 10 times the upper limit of normal and positive EMA [4].

An exception is seen in seronegative CD, which accounts for approximately 2%-5% of cases (up to 10% in some series). These cases are generally associated with IgA deficiency, advanced CD with severe villous atrophy, reduced gluten intake prior to testing, older age, or conditions associated with autoimmune enteropathy or immunodeficiency [5,6].

CD can manifest with both intestinal and extraintestinal symptoms. Classic symptoms include chronic diarrhea or constipation, abdominal bloating and pain, nausea or vomiting, weight loss, or failure to thrive. Refractory anemia is one of the most common atypical intestinal symptoms. In adults, extraintestinal symptoms may predominate over intestinal ones as a systemic/multiorgan manifestation of the disease and may include: asthenia, osteopenia or osteoporosis, dermatitis herpetiformis, neuropathies, headache, ataxia, infertility, amenorrhea, increased transaminases, stomatitis, joint pain. [7]. Approximately one third of adult patients diagnosed with CD present with at least one organ-specific autoantibody at the time of diagnosis, including those associated with type 1 diabetes, thyroid disease, atrophic gastritis, and Addison's disease. Approximately 20%-30% of patients may exhibit a silent or paucisymptomatic form with mild intestinal disturbances [8].

Psychological and neuropsychiatric manifestations may also occur and negatively affect quality of life. Depression, anxiety, altered eating behavior, and cognitive symptoms have been reported both before and after diagnosis and may persist despite adherence to a gluten-free diet (GFD). Children and adolescents appear particularly vulnerable. Patients with delayed diagnosis, severe disease, or poor adherence to the GFD may experience greater psychological burden, highlighting the potential role of multidisciplinary management including psychological support [9].

Currently, the only effective treatment for CD is a strict lifelong GFD. Several alternative therapeutic approaches are under investigation, including strategies aimed at reducing gluten immunogenicity, sequestering gluten peptides in the intestinal lumen, modulating intestinal permeability, inhibiting tissue transglutaminase activity, and inducing immune tolerance. Although some agents have reached phase II/III clinical trials, these strategies are still considered potential adjuncts rather than substitutes for the GFD [10].

Monitoring adherence to the GFD in patients with CD remains a significant clinical challenge. Currently, several methods have been proposed to evaluate compliance, including dietary and symptom-based questionnaires, serological markers of CD and the detection of gluten immunogenic peptides in stool or urine samples. Dietary assessment tools and structured questionnaires are commonly used in clinical practice to estimate adherence and identify possible sources of inadvertent gluten exposure. However, these methods rely heavily on patient self-reporting and may therefore be subject to recall bias or underestimation of gluten intake. Serological testing, particularly the measurement of antibodies such as anti-tTG and EMA, represents another widely used approach. Although normalization of antibody levels generally reflects improved adherence to the GFD, serology may lack sensitivity in detecting occasional or low-level gluten exposure, especially in patients who have been on a long-term GFD. More recently, detection of gluten immunogenic peptides in stool or urine has emerged as a promising direct biomarker of gluten ingestion. These peptides resist gastrointestinal digestion and can provide objective evidence of recent gluten exposure. However, routine use remains limited by cost, availability, and variability in detection windows.

Therefore, although a gold standard for monitoring adherence to the GFD has not yet been established, a combined approach integrating clinical evaluation, follow-up serology–typically performed 6 and 12 months after diagnosis and annually thereafter–and emerging biomarkers is currently considered the most effective strategy for assessing compliance in patients with CD [11-13].

In addition to its gastrointestinal manifestations, CD has been associated with an increased risk of malignancies, particularly involving the gastrointestinal tract. The strongest association concerns enteropathy-associated T-cell lymphoma (EATL) and small bowel adenocarcinoma. This risk appears higher in patients with delayed diagnosis or

poor adherence to a strict GFD, suggesting that prolonged gluten-induced inflammation and chronic immune activation may contribute to carcinogenesis.

Persistent mucosal damage, villous atrophy, and chronic inflammatory signaling may create a pro-oncogenic microenvironment. Recent studies have also explored possible associations with other gastrointestinal cancers, including colorectal, esophageal, gastric, and pancreatic malignancies, although the magnitude of risk remains uncertain. Potential mechanisms include chronic inflammation, impaired immune surveillance, alterations of the gut microbiota, and micronutrient deficiencies affecting mucosal integrity and DNA repair. These observations underscore the importance of early diagnosis, strict GFD adherence, and adequate long-term follow-up in patients with CD [14].

More specifically, pancreatic cancer remains a rare occurrence in patients with CD, yet epidemiological evidence suggests a moderately increased risk compared with the general population (approximately 1.3-1.5). Although the absolute incidence is very low, this elevated risk appears to persist beyond the first year after diagnosis, suggesting a potential role of chronic inflammation and immune dysregulation. Nevertheless, available evidence is limited and heterogeneous, and further studies are required to clarify the magnitude and mechanisms of this association [15,16].

2. Case Presentation

We report the case of a 46-year-old Caucasian male who was diagnosed with CD approximately four months after the onset of gastrointestinal and systemic symptoms. The patient initially presented with unintentional weight loss, recurrent abdominal pain, intermittent episodes of vomiting, and frequent loose stools. Specifically, the patient experienced a weight loss of approximately 5 kg over four months, reaching 55 kg at a height of 172 cm (BMI 18.6 kg/m²). These symptoms had gradually worsened over the preceding months, prompting further clinical evaluation.

Serological screening for CD demonstrated clearly positive IgA EMA and markedly elevated anti-tTG 1126 U/mL (reference range: < 10 U/Ml). In order to confirm CD diagnosis, an upper gastrointestinal endoscopy with duodenal biopsies was performed. Histopathological examination of the biopsy specimens revealed lesions classified as type 3B according to the Marsh–Oberhuber classification [17], characterized by subtotal villous atrophy associated with crypt hyperplasia and increased intraepithelial lymphocytosis, thus confirming the diagnosis of active CD.

As part of the diagnostic workup, additional investigations were conducted to exclude other gastrointestinal diseases and possible complications. Abdominal ultrasonography did not reveal any structural abnormalities of the abdominal organs, and colonoscopy showed no evidence of colonic pathology. Routine laboratory testing was largely unremarkable, with the exception of hemoglobin level 13.5 g/dL, corresponding to the lower limit of the normal reference range for adult males (13.5-17.5 g/dL), and hypocholesterolemia (total cholesterol 120 mg/dL). These findings were considered consistent with the malabsorptive state typically associated with untreated CD.

Following a comprehensive gastroenterological and nutritional assessment, the patient was advised to initiate a strict GFD. In addition to dietary intervention, psychological support was recommended due to the presence of a depressive state, which was considered potentially related to the chronicity of symptoms and their impact on the patient's quality of life. Close serological monitoring of CD-specific antibodies was recommended in order to detect possible poor adherence to the GFD and to ensure an appropriate immunological response to dietary treatment.

Remarkably, after only two months of adherence to the GFD, follow-up serological testing revealed a rapid and significant decrease in antibody levels. EMA became negative, while anti-tTG levels decreased to borderline values (12 U/mL with reference range < 10 U/mL). Despite this apparently favorable serological response, the patient reported only minimal improvement in clinical symptoms. In particular, weight loss persisted and gastrointestinal complaints showed only limited attenuation. Specifically, at the follow-up visit two months after initiating the GFD, the patient had lost an additional 3 kg, reaching a weight of 52 kg and a BMI of 17.6 kg/m².

The discrepancy between the rapid serological normalization and the persistence of clinically relevant symptoms raised concerns regarding the possibility of additional underlying pathological processes. Consequently, further diagnostic investigations were undertaken in order to exclude potential complications of CD as well as the presence of neoplastic disease.

Magnetic resonance imaging (MRI) of the abdomen, including MR enterography, was therefore performed to allow a comprehensive evaluation of both the small bowel and adjacent abdominal structures (Figure 1a) [14]. Unexpectedly, imaging revealed the presence of a pancreatic lesion with radiological features suggestive of pancreatic adenocarcinoma (Figures 1b-c). These findings prompted additional confirmatory investigations. A contrast-enhanced computed tomography (CT) scan was subsequently performed and corroborated the MRI findings. A mixed solid–cystic pancreatic lesion measuring approximately 5 × 6 cm was identified at the level of the pancreatic body and isthmus. The mass appeared inseparable from surrounding soft tissue encasing the celiac trunk, suggestive of nodal involvement. Additionally, imaging findings were consistent with diffuse peritoneal carcinomatosis. Overall, the disease was consistent with stage IV pancreatic cancer.

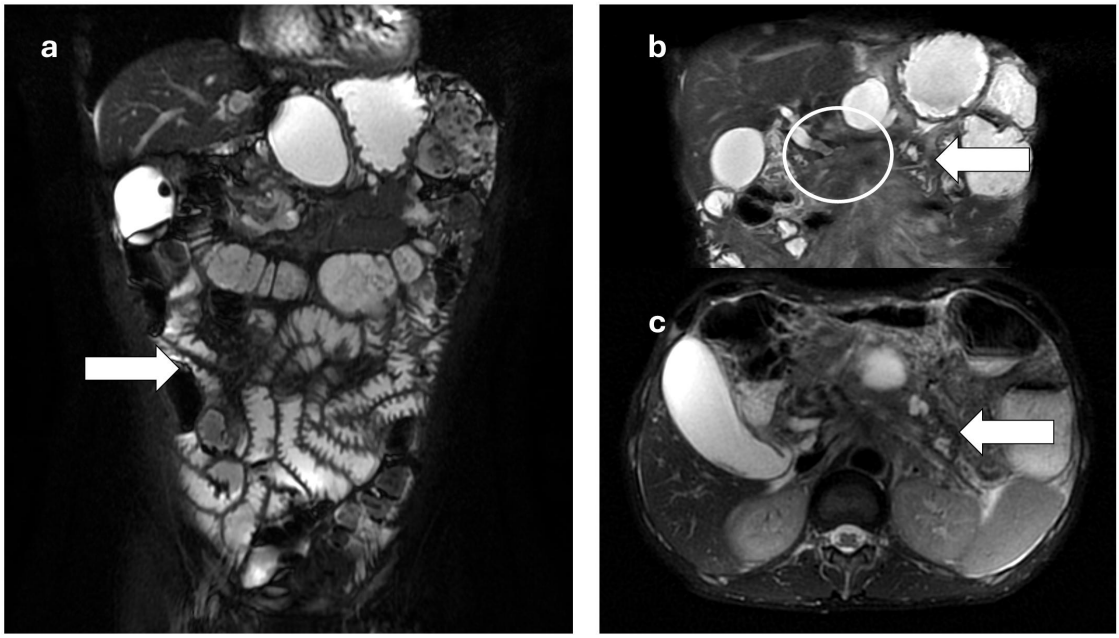

Figure 1. Magnetic resonance images showing signs of CD and concomitant pancreatic cancer. (a) Coronal T2 scans showing increased ileal folds (ileal "jejunalization", arrow), as expected in CD. (b-c) Coronal and axial T2 scans showing pancreatic pathological tissue, pancreatic tail atrophy with pancreatic duct dilatation (arrow in both), stenosis of common bile duct (circle in both), portal thrombosis and cavernomatosis (circle in b).

Laboratory testing showed normal liver function tests (AST, ALT, ALP, GGT, bilirubin) and normal pancreatic enzymes (amylase, lipase). The diagnosis was ultimately confirmed through endoscopic ultrasound-guided biopsy. The patient subsequently started first-line chemotherapy with the FOLFIRINOX regimen, which was administered for three months. The treatment was discontinued after this period due to clinical disease progression and deterioration of the patient's general condition, ultimately leading to death approximately one month later.

The timeline of clinical events is reported in Table 1. Summary of the patient's clinical course from CD diagnosis to pancreatic cancer treatment and outcome.

Table 1. Timeline of clinical events.

Time Point	Key Events
Month -4	Onset of gastrointestinal symptoms and weight loss
Month 0	Diagnosis of celiac disease (EMA positive; anti-TG 1126 U/mL, reference <10 U/mL; Marsh 3B) and start of GFD
Month +2	EMA negative; anti-TG decreased to 12 U/mL (reference <10 U/mL), but persistent symptoms and further weight loss
Month +3 to +4	MRI and CT identify pancreatic mass; findings consistent with stage IV pancreatic cancer (peritoneal carcinomatosis); normal liver and pancreatic enzymes; diagnosis confirmed by EUS-guided biopsy
Month +5	Initiation of first-line chemotherapy (FOLFIRINOX)
Month +8	Chemotherapy discontinued due to disease progression and clinical deterioration
Month +9	Death

Note: EMA: anti-endomysial antibodies; anti-tTG: anti-tissue transglutaminase antibodies; MRI: magnetic resonance imaging; CT: computed tomography; EUS: endoscopic ultrasound.

3. Discussion

The clinical course observed in this case highlights the importance of maintaining a high level of diagnostic vigilance in patients with CD who fail to show parallel clinical improvement despite rapid serological normalization after the initiation of a GFD. In routine clinical practice, serological markers are widely used to monitor disease activity and assess adherence to dietary therapy, and their normalization is often considered an indicator of adequate disease control. However, this case illustrates that serological improvement does not necessarily reflect the overall clinical condition of the patient, particularly when other pathological processes coexist. For this reason, clinicians should interpret serological responses in the broader clinical context and carefully evaluate persistent or unexplained symptoms.

In the present case, careful clinical evaluation combined with close monitoring of serological antibodies allowed the early exclusion of poor adherence to the GFD. Notably, antibody levels were reassessed earlier than generally

recommended in standard follow-up protocols–approximately two to three months after diagnosis rather than the usual six to twelve months. This earlier testing, together with clear dietary counseling provided by clinicians and the patient's correct adherence to the GFD, made it possible to confidently rule out ongoing gluten exposure as the cause of persistent symptoms. As a result, alternative diagnostic hypotheses could be explored without delay, including non-responsive or refractory CD, malignancies, or other conditions that may mimic or overlap with CD-related manifestations.

From an epidemiological perspective, the relationship between CD and malignancy has been widely investigated. CD is known to be associated with an increased risk of certain gastrointestinal cancers, particularly EATL and small bowel adenocarcinoma. However, its potential association with pancreatic cancer remains less clearly defined. Some observational studies have suggested a modestly increased risk, whereas others have not demonstrated a significant correlation. A recent systematic review and meta-analysis including nearly 48,000 patients indicated that CD patients with other malignancies had a pooled odds ratio (OR) of 1.46 (95% CI 1.26-1.70) for pancreatic cancer, although this finding was affected by significant heterogeneity and does not establish causality [15]. Some population-based cohort data also suggest persistence of pancreatic cancer risk along with other solid tumors in CD, but evidence is inconsistent and absolute risk remains low [18]. Thus, current literature indicates that the link remains uncertain, and any potential association may be influenced by confounding factors. Thus, the coexistence observed in this case may reflect a coincidental association, although a contributory link cannot be entirely excluded. The biological mechanisms that could link chronic immune-mediated intestinal inflammation with pancreatic carcinogenesis remain also poorly understood.

Several hypotheses have been proposed to explain a possible connection between CD and pancreatic malignancy. These include chronic systemic inflammation, immune dysregulation, alterations in intestinal permeability, and shared genetic or environmental factors. In addition, emerging evidence suggests that alterations in the gut microbiota associated with CD may influence systemic immune responses and metabolic pathways that could potentially contribute to carcinogenic processes beyond the intestine. Although these mechanisms remain speculative, they represent important areas for future investigation [15].

Further research is therefore needed to clarify the molecular and immunological pathways that may connect CD with pancreatic cancer and to determine whether specific subgroups of CD patients may be at higher oncological risk. Identifying such subgroups could help guide targeted surveillance strategies and improve early detection of malignancies in selected patients.

In conclusion, this case highlights the importance of careful evaluation of persistent or unexplained symptoms in patients with CD, emphasizing the value of serological reassessment and the need to consider alternative or coexisting diagnoses when the clinical course is atypical. Furthermore, these observations highlight the possibility that future evidence-based guidelines might consider more flexible, risk-adapted monitoring schedules, especially for adult patients who may be more susceptible to serious complications, including malignancies.

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Patient Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Data Availability Statements

The data underlying this article are available in the article. Further data underlying this article will be shared on reasonable request to the corresponding author.

Author Contributions

Borghini R. contributed in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. Spagnuolo A., Iannitti M. and Trecca A. contributed in data collection, interpretation of data and critical review. All authors approved the version to be submitted.

Conflict of Interest

No conflicts of interest to declare for all authors.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

References

[1] Picarelli A, Borghini R, Isonne C, Di Tola M. Reactivity to dietary gluten: New insights into differential diagnosis among gluten-related gastrointestinal disorders. Polish Archives of Internal Medicine, 2013, 123(12), 708-712. DOI: 10.20452/pamw.2019

[2] Sollid LM, Jabri B. Triggers and drivers of autoimmunity: Lessons from coeliac disease. Ature Reviews Immunology, 2013, 13(4), 294-302. DOI: 10.1038/nri3407

[3] Sheppard AL, Elwenspoek MMC, Scott LJ, Corfield V, Everitt H, Gillett PM, et al. Systematic review with meta-analysis: The accuracy of serological tests to support the diagnosis of coeliac disease. Alimentary Pharmacology & Therapeutics, 2022, 55(5), 514-527. DOI: 10.1111/apt.16729

[4] Sunkoj Y, Talathi S. Utility of the ESPGHAN biopsy-sparing guidelines for celiac disease in children. The American Journal of Gastroenterology, 2025, 120(9), 2190-2193. DOI: 10.14309/ajg.0000000000003402

[5] Rahmanipour E, Ghorbani M, Ganji A, Mirzaei Z, Ghavami V, Shahbazkhani B, et al. Clinical profile of patients with seronegative celiac disease. Gastroenterology and Hepatology from Bed to Bench, 2023, 16(2), 203-209. DOI: 10.22037/ghfbb.v16i2.2756

[6] Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. Diagnosis and management of adult coeliac disease: Guidelines from the British Society of Gastroenterology. Gut, 2014, 63(8), 1210-1228. DOI: 10.1136/gutjnl-2013-306578

[7] Tiberti C, Panimolle F, Borghini R, Montuori M, Trovato CM, Filardi T, et al. Type 1 diabetes, thyroid, gastric and adrenal humoral autoantibodies are present altogether in almost one third of adult celiac patients at diagnosis, with a higher frequency than children and adolescent celiac patients. Scandinavian Journal of Gastroenterology, 2020, 55(5), 549-554. DOI: 10.1080/00365521.2020.1754898

[8] Santonicola A, Wieser H, Gizzi C, Soldaini C, Ciacci C. Associations between celiac disease, extra-gastrointestinal manifestations, and gluten-free diet: A narrative overview. Nutrients, 2024, 16(12), 1814. DOI: 10.3390/nu16121814

[9] Zingone F, Secchettin E, Marsilio I, Valiante F, Zorzetto V, Cataudella G, et al. Clinical features and psychological impact of celiac disease at diagnosis. Digestive and Liver Disease, 2021, 53(12), 1565-1570. DOI: 10.1016/j.dld.2021.05.016

[10] Yoosuf S, Makharia GK. Evolving therapy for celiac disease. Frontiers in Pediatrics, 2019, 7, 193. DOI: 10.3389/fped.2019.00193

[11] Wieser H, Ruiz-Carnicer Á, Segura V, Comino I, Sousa C. Challenges of monitoring the gluten-free diet adherence in the management and follow-up of patients with celiac disease. Nutrients, 2021, 13(7), 2274. DOI: 10.3390/nu13072274

[12] Paolini A, Sarshar M, Felli C, Bruno SP, Rostami-Nejad M, Ferretti F, et al. Biomarkers to monitor adherence to gluten-free diet by celiac disease patients: Gluten immunogenic peptides and urinary miRNAs. Foods, 2022, 11(10), 1380. DOI: 10.3390/foods11101380

[13] Husby S, Murray JA, Katzka DA. AGA clinical practice update on diagnosis and monitoring of celiac disease-changing utility of serology and histologic measures: Expert review. Gastroenterology, 2019, 156(4), 885-889. DOI: 10.1053/j.gastro.2018.12.010

[14] Wang M, Yu M, Kong WJ, Cui M, Gao F. Association between intestinal neoplasms and celiac disease: A review. World Journal of Gastrointestinal Oncology, 2021, 13(9), 1017-1028. DOI: 10.4251/wjgo.v13.i9.1017

[15] Gromny I, Neubauer K. Pancreatic cancer in celiac disease patients-a systematic review and meta-analysis. International Journal of Environmental Research and Public Health, 2023, 20(2), 1565. DOI: 10.3390/ijerph20021565

[16] Krishnan A, Hadi YB, Shabih S, Mukherjee D, Patel RA, Patel R, et al. Risk of pancreatic cancer in individuals with celiac disease in the United States: A population-based matched cohort study. World Journal of Gastrointestinal Oncology, 2023, 15(3), 523-532. DOI: 10.4251/wjgo.v15.i3.523

[17] Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterology Journal, 2019, 7(5), 583-613. DOI: 10.1177/2050640619844125

[18] Lebwohl B, Green PHR, Emilsson L, Mårild K, Söderling J, Roelstraete B, et al. Cancer risk in 47,241 individuals with celiac disease: A nationwide cohort study. Clinical Gastroenterology and Hepatology, 2022, 20(2), e111-e131. DOI: 10.1016/j.cgh.2021.05.034