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The Role of Endoscopy in Assessing Small Intestine Mucosal Recovery in Patient with Celiac Disease

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Aim: to present a clinical case of celiac disease with intestinal and extraintestinal manifestations, as well as demonstrate the possibilities of endoscopic diagnosis in assessing the mucosal recovery of the small intestine on a gluten-free diet.
Key points. Celiac disease is a genetically determined disease of the small intestine with a wide range of intestinal and extraintestinal clinical manifestations associated with gluten intake. The main treatment strategy for this disease is strict adherence to a gluten-free diet. The therapeutic goal of a gluten-free diet is to achieve healing of the small intestinal mucosa, which occurs slowly and, according to research, is recorded in only a third of patients. Celiac disease was revealed during esophagogastroduodenoscopy in 30-year-old female patient with symptoms of dyspepsia, anemia and suspected localized scleroderma, morphologically confirmed total atrophy of Marsh 3C villi, and received serological verification of the diagnosis. Two and a half years later complete mucosal recovery was detected on strict gluten-free diet.
Conclusions. Achieving and controlling remission of celiac disease has important role in the treatment strategy of patients. The gluten-free diet has demonstrated successful results within the expected timeframe. Today, modern endoscopic technologies and use of prognostic classifications of the severity of atrophy have great diagnostic value in assessing the mucosal recovery of small intestine.
Keywords: celiac disease, gluten-free diet, mucosal recovery
Conflict of interest: the authors declare no conflict of interest.

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Возможности эндоскопического исследования для оценки динамики восстановления слизистой оболочки тонкой кишки у пациентки с целиакией

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Цель: представить клиническое наблюдение пациента с кишечными и внекишечными проявлениями целиакии, а также проиллюстрировать возможности эндоскопической диагностики в оценке степени восстановления слизистой оболочки тонкой кишки на фоне безглютеновой диеты.
Основные положения. Терапевтическая цель применения безглютеновой диеты при целиакии заключается в достижении восстановления слизистой оболочки тонкой кишки. Этот процесс происходит медленно и регистрируется лишь у трети пациентов. У пациентки 30 лет с симптомами диспепсии, анемией и подозрением на локализованную склеродермию при эзофагогастродуоденоскопии выявлены эндоскопические признаки энтеропатии, характерной для целиакии: отсутствие кишечных ворсинок, сглаженность складок, мозаичность слизистой оболочки; морфологически подтверждена тотальная атрофия ворсин Marsh 3C, получена серологическая верификация диагноза. Спустя 2,5 года на фоне приверженности строгой безглютеновой диете обнаружено полное восстановление слизистой оболочки — появление складок, наличие ворсинок на всем протяжении, отсутствие мозаичного рельефа.
Заключение. Достижение и контроль ремиссии целиакии играют важную роль в стратегии лечения пациентов. Диета с полной элиминацией глютена продемонстрировала получение успешного результата в ожидаемые сроки. На сегодняшний день эндоскопические технологии, включая улучшенное изображение, увели-

чение, узкий спектр, и использование прогностических классификаций тяжести атрофии обладают большой диагностической ценностью в оценке восстановления слизистой оболочки тонкой кишки.
Ключевые слова: целиакия, безглютеновая диета, восстановление слизистой оболочки
Конфликт интересов: авторы заявляют об отсутствии конфликтов интересов.

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Introduction

Celiac disease is a genetically determined disorder of the small intestine associated with the presence of HLA-DQ2 and/or HLA-DQ8 haplotypes, dietary gluten intake, and the development of immune-mediated inflammation of the small intestinal mucosa. It is characterized by a wide spectrum of intestinal and extra-intestinal clinical manifestations [1, 2]. The global prevalence of celiac disease varies depending on the method of verification, ranging from 0.7 % based on histological findings to 1.4 % according to serological diagnosis [3].

Currently, the primary treatment for this disease is strict gluten-free diet adherence [4, 5]. According to the American College of Gastroenterology guidelines on the diagnosis and management of celiac disease, the main goal of therapy for gluten enteropathy is the recovery of the small intestinal mucosa [5]. However, achieving histological remission on a gluten-free diet depends on the patient's age and often does not correlate with clinical and serological responses. For instance, according to P. Wahab et al., mucosal healing in the small intestine was observed in 95 % of children within two years of starting a gluten-free diet [6]. In adults, histological remission is recorded in only 34 % of patients after two years and in 66 % after five years of diet therapy [7, 8].

The aim of this clinical case report is to describe the manifestation of celiac disease with gastrointestinal and atypical cutaneous symptoms, and to illustrate the successful recovery of the small intestinal mucosa in an adult patient following a gluten-free diet.

Clinical case

In June 2021, a 30-year-old female patient first noticed the onset of nausea, epigastric pain that worsened after eating, dizziness without loss of consciousness, and weight loss from 52 to 49 kg. She did not seek medical attention at that time. During this time dense lesions appeared on the skin of her anterior shins, with occasional local erythema.

In November 2021, the patient again began to suffer from nausea, occasional vomiting, and further weight loss down to 43 kg. She consulted a local therapist with these complaints. Her condition was diagnosed as "unspecified dyspepsia, localized scleroderma". To rule out systemic connective tissue diseases and paraneoplastic syndrome, the patient was examined by a rheumatologist at the Chelyabinsk Regional Clinical Hospital in January 2022.

The patient had an asthenic build and was underweight (the body mass index 17 kg/m^2). Dense erythematous-squamous plaques with a yellowish tint, measuring up to 5 cm was noted on the anterior surface of the shins (Fig. 1).

Laboratory tests revealed mild iron-deficiency anemia (hemoglobin — 113 g/L, ferritin —

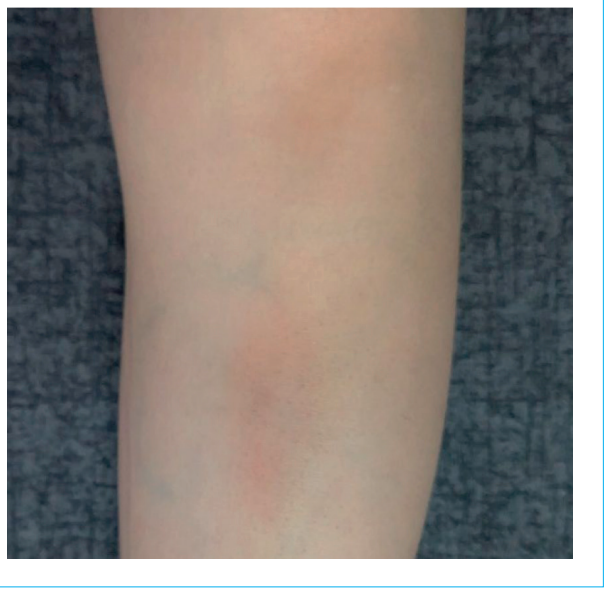

Figure 1. Dense erythematous-squamous lesions with yellow color on the skin of anterior surface of shins up to 5 cm in size

4.4 μg/L, serum iron — 5.8 μmol/L, folic acid and vitamin B_{12} — within reference ranges). Levels of immunoglobulins A, M, G, antibodies to double-stranded DNA, and circulating immune complexes were within normal limits, and the ANA profile was negative.

The patient underwent an esophagogastroduodenoscopy (EGD) using an Olympus HQ 190 endoscope and EVIS EXERA III video system. No pathology of the esophageal mucosa was observed. Examination of the gastric body revealed smooth, pale-pink mucosa with a regular distribution of collecting venules and focal areas of atrophy in the gastric antrum. The duodenal bulb and postbulbar duodenal mucosa was pale pink with mosaic pattern and visible mucosal grooves (Fig. 2).

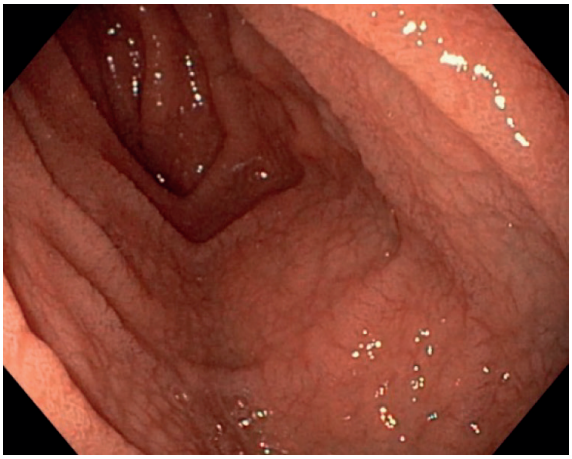

Figure 2. Mosaic duodenal mucosa with smoothed folds

The folds were effaced and scalloped due to the grooves and areas of atrophy (Fig. 3). Duodenal villi were absent. Type III mucosal architecture according to the Bonatto classification and total villous atrophy corresponding to 2 points on the Gulati scale was observed with image enhanced endoscopy (narrow-band imaging NBI mode with Dual focus (Fig. 4) [7, 8].

Signs of gastritis with focal foveolar hyperplasia and enteropathy characteristic of celiac disease were identified on the EGD. Biopsies were taken from the stomach, duodenal bulb and descending duodenum.

The histological examination revealed chronic moderate inactive atrophic antral gastritis with focal complete intestinal metaplasia; chronic mild inactive superficial gastritis of the gastric body and chronic severe low-activity atrophic duodenitis Marsh type 3C, Grade B2 / type 3 (Fig. 5).

The patient was consulted by a gastroenterologist, and serological testing for celiac disease was recommended. The results observed anti-tissue transglutaminase IgA antibodies at > 200 U/mL (normal < 10 U/mL) and anti-endomysial IgA antibodies at 1:640 (normal < 1:5). Based on these findings, a diagnosis of adult celiac disease was established. Necrobiosis lipoidica was diagnosed by dermatologist due to clinical presentation. Given the known association of this dermatosis with carbohydrate metabolism disorders and autoimmune thyroid pathology, additional laboratory tests were performed. Levels of blood glucose, glycated hemoglobin, thyroid-stimulating hormone, free thyroxine, and anti-thyroid peroxidase antibodies were all within reference ranges. The

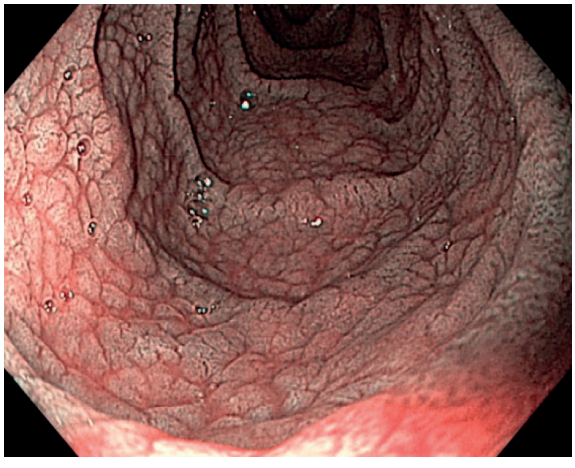

Figure 3. Mosaic duodenal mucosa with serrated folds (NBI image)

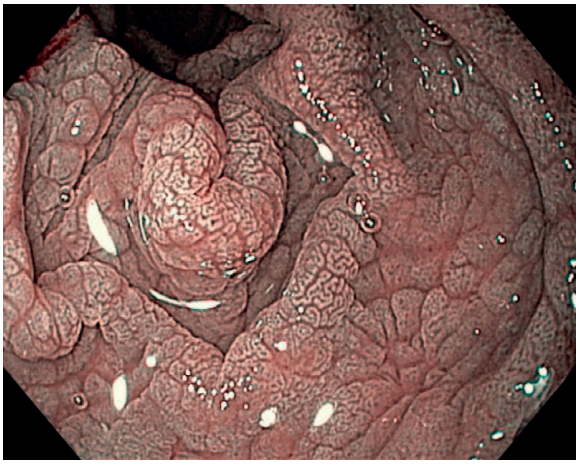

Figure 4. Mosaic duodenal mucosa and absence of the intestinal villi — type III according to Bonatto classification (NBI image)

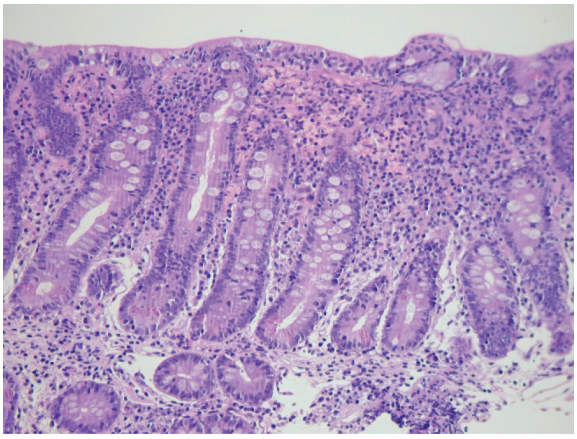

Figure 5. Microscopic image of the duodenal mucosa before starting gluten-free diet. Total villous atrophy, hyperplasia and elongation of crypts, pronounced intraepithelial lymphocytes (×100, hematoxylin and eosin staining)

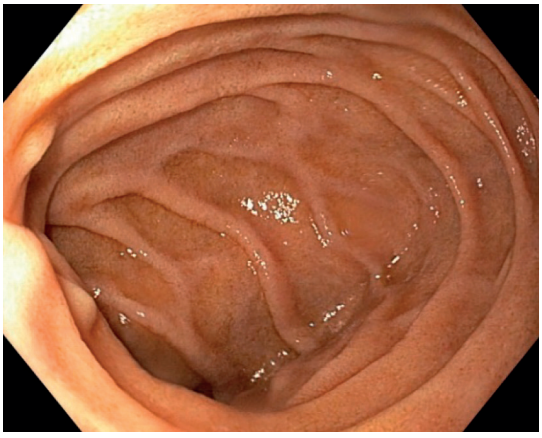

Figure 6. Recovery of the duodenal mucosa on gluten-free diet

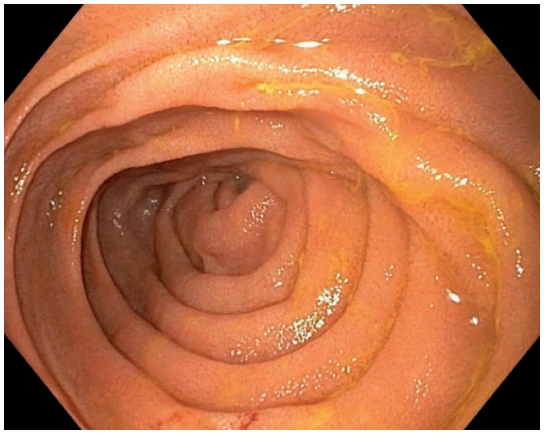

Figure 7. The appearance of duodenal folds and intestinal villi

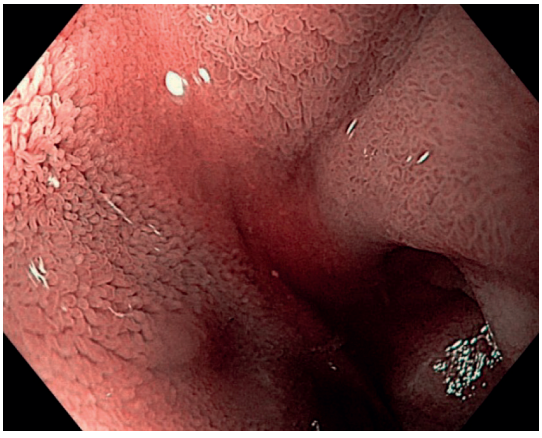

Figure 8. The appearance of duodenal bulb villi on gluten-free diet (NBI image)

patient declined histopathological confirmation of the skin diagnosis.

The patient was educated about the gluten-free diet and advised to adhere strictly to it.

One year later, treatment adherence was assessed using the Celiac Disease Adherence Test (CDAT) and the Biagi scale. The CDAT is a standardized questionnaire for quantitative assessing dietary adherence, developed by Leffler et al. It includes seven questions about dietary habits, symptoms, self-efficacy, and psychosocial aspects related to living with the diet, where a total score greater than 13 indicates poor adherence [9]. The Biagi scale is a very brief screening tool for quickly checking dietary adherence, consisting of four questions about the patient's awareness of gluten content in foods and their eating habits, where a score of 3–4 indicates strict dietary adherence [9]. The patient scored 11 on the CDAT questionnaire and 3 on the Biagi scale, indicating high compliance with the dietary recommendations. Following complete gluten exclusion, the patient reported positive clinical dynamics: absence of dyspeptic symptoms, infrequent abdominal pain, a weight gain of 5 kg, and a decrease in the induration and erythema of the skin lesions on her shins. In April 2022, level of anti-tissue transglutaminase IgA antibody normalized to 3.25 U/mL (normal < 10 U/mL).

After 2.5 years, a follow-up EGD was performed. It revealed no additional changes in the esophagus and stomach compared to the previous

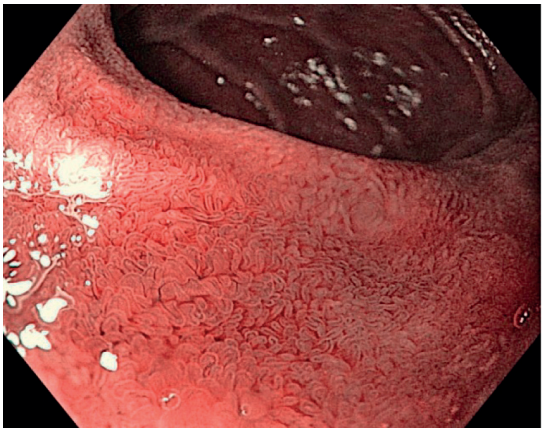

Figure 9. Normal height and shape of villi in the descending duodenum (NBI image with Dual Focus)

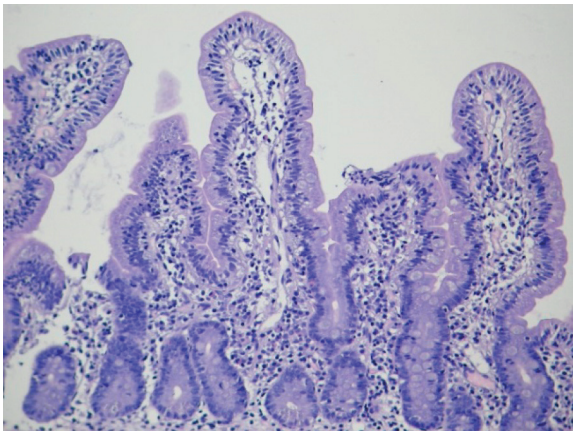

Figure 10. Microscopic image of the duodenal mucosa on gluten-free diet. Appearance of villi, shortening of crypts, single intraepithelial lymphocytes (×100, hematoxylin and eosin staining)

examination. Examination showed the notable appearance of duodenal folds, the presence of intestinal villi throughout and the absence of a mosaic pattern and grooves indicating normal architecture (type 0) according to the Bonatto classification and normal findings (0 points) on the Gulati scale (Fig. 6–9). The gluten-free diet adherence assessed using the CDAT and Biagi questionnaires continued to demonstrate good results.

Histological examination verified chronic mild diffuse low-activity duodenitis (Fig. 10).

Discussion

The presented clinical case demonstrates the manifestation of celiac disease in adulthood with multiple features, both common such as weight loss and iron deficiency anemia, and uncommon, including skin lesions. Although necrobiosis lipoidica (NL) is classically associated with diabetes mellitus (DM) (preceding DM in 14 % of cases, occurring synchronously in 24 %, and manifesting in the context of an established DM diagnosis in 62 % of cases), the presence of this dermatosis requires exclusion of other conditions: thyroid dysfunction, inflammatory bowel disease, sarcoidosis, and rheumatic diseases. According to the literature, in patients with NL presenting with gastrointestinal symptoms, serological screening for celiac disease is warranted [10]. According to guidelines, NL is often diagnosed clinically; however, to rule out similar conditions (granuloma annulare, necrobiotic xanthogranuloma), biopsy is preferable. In our case, a skin biopsy was not performed due to the patient's reluctance to undergo an invasive procedure; therefore, the diagnosis was established based on the characteristic clinical presentation. Given the absence of carbohydrate metabolism disorders, thyroid dysfunction, or rheumatic diseases in our patient, and the presence of verified celiac disease, it seems reasonable to consider the identified skin lesion as a possible extra-intestinal manifestation of gluten enteropathy [10, 11].

It should be noted that in 60–70 % of cases, gluten enteropathy is diagnosed in females [12].

Although the cornerstone of celiac disease treatment is strict gluten-free diet adherence, issues of compliance and monitoring the effectiveness of gluten exclusion often pose challenges in the management of these patients [13]. The therapeutic goal of a gluten-free diet is to achieve normalization of the small intestinal mucosal architecture (Marsh 0), the frequency of which in celiac disease averages about 36 % in the general patient population, with significant differences observed between children and adults, as well as depending on the strictness of dietary adherence [14, 15]. It is known that mucosal recovery of the small intestine on a gluten-free diet occurs slowly; moreover, histological manifestations of gluten enteropathy may persist in some adults during follow-up over 5 years [1]. Incomplete mucosal recovery in celiac disease is primarily associated with persistent inadvertent gluten consumption despite a strict gluten-free diet. Currently, a "safe" level of gluten in food is considered to be no more than 20 parts per million [16]. However, the problem of food products cross-contamination with gluten is widespread. Studies report the frequency of cross-contamination gluten exposure ranging from 25 to 89 % [17]. This is related to dining

in public places where gluten-containing and gluten-free foods are handled in the same environment with standard cleaning methods, as well as insufficient control over the production of gluten-free products [13]. Another reason for the lack of mucosal recovery may be related to the prolonged maintenance of immune system activation independent of gluten presence [1]. R. Nemteanu et al. reported that patient age under 35 years (OR = 2.05; 95% CI: 1.059–4.393; p = 0.034) and total villous atrophy of the small intestinal mucosa (OR = 8.503; 95% CI: 1.590–45.478; p = 0.007) were independent risk factors for failure to achieve small intestinal mucosal recovery after 12 months of a gluten-free diet [14]. However, the presented clinical case demonstrates restoration of the duodenal mucosal structure, which we attribute to the patient's high adherence to the gluten-free diet.

In this regard, we consider the assessment of gluten-free diet adherence to be particularly significant in the management of these patients. A standardized dietary assessment, conducted by a registered dietitian and including a detailed analysis of consumed foods, is important and should be applied in patients during the initial stages of therapy [18]. The CDAT questionnaire, which considers five important aspects of dietary adherence (symptom occurrence, patient awareness of the disease, confidence in treatment efficacy, motivating factors for dietary adherence, and self-reported adherence) is accepted as a screening tool. The CDAT does not demonstrate a correlation with histological and serological markers [18]. According to a systematic review, the Biagi test was recognized as the preferred tool for assessing gluten-free diet adherence compared to the CDAT [9]. The total questionnaire scores in our patient, who was motivated to achieve good treatment outcomes, showed excellent adherence to a strict gluten-free diet. However, many authors report that currently, a significant proportion of adult celiac disease patients (up to 50 %) do not fully adhere to the diet, and patient knowledge regarding gluten content in foods is generally poor [18].

Along with clinical improvement, normalization of anti-tissue transglutaminase IgA antibody levels was achieved. As is known, seroconversion increases the likelihood of small intestinal mucosal healing but does not reflect adequate dietary adherence and does not always correlate with histological remission [19, 20].

Currently, biopsy is considered the gold standard for assessing mucosal healing and is recommended no earlier than two years after starting a gluten-free diet [21]. The optimal biopsy strategy should include at least four biopsies (two — from the duodenal bulb and two — from the descending duodenum), as villous atrophy may have a patchy distribution or be confined exclusively to the duodenal bulb, known as ultra-short celiac disease [4].

Advances in endoscopic examination techniques undoubtedly improve the diagnosis of celiac disease from 78 % with standard white-light endoscopy to 91 % with water-immersion visualization of the intestinal villi, and up to 99 % with vital chromoendoscopy or magnifying narrow-band imaging endoscopy [22]. M. Scheppach et al. developed an artificial intelligence algorithm for detecting villous atrophy that significantly outperformed experts in diagnosing celiac disease during EGD [23].

The use of endoscopic Bonatto and Gulati classifications, based on chromoscopy and magnifying endoscopy which correlate with histopathological changes enables optical biopsy and targeted sampling from altered areas, allows staging of the severity of small intestinal mucosal atrophy and facilitates monitoring of disease dynamics. Normal villous morphology can be confidently diagnosed due to the high negative predictive value (97.71 %) of the Gulati scale, it potentially avoiding the current strategy of multiple biopsies [8]. In our clinical observation, type III architecture according to the Bonatto classification and 2 points on the Gulati scale corresponded to histologically verified severe villous atrophy (Marsh 3C), just as dynamically, type 0 confirmed normal villi.

Most authors emphasize that monitoring the small intestinal mucosal changes is extremely important. Numerous studies have confirmed that mucosal healing reduces the long-term risk of other complications, such as malignant lymphoproliferative neoplasms, liver diseases, osteoporosis, microcytic anemia, psychiatric disorders, reproductive dysfunction, and other autoimmune diseases [24]. Verification of small intestinal villous recovery in our patient acquires particular relevance in the context of preconception preparation. It is reported that the risk of adverse pregnancy outcomes is significantly reduced upon achieving celiac disease remission [25].

Currently, the main goal in the management of our patient is maintaining remission which directly depends on to the gluten-free diet adherence.

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