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DIAGNOSTIC APPROACH AND MANAGEMENT IN CELIAC DISEASE

DOCTORAL THESIS ABSTRACT

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Content

I. General Part

Introduction

Celiac disease is an autoimmune enteropathy triggered by the ingestion of gluten in genetically predisposed individuals. It manifests with a broad spectrum of clinical symptoms, ranging from chronic diarrhea and malabsorption to silent or atypical forms, including anemia, osteoporosis, or infertility. In recent decades, the incidence of the disease has increased significantly (1), emphasizing the need for a comprehensive understanding of its pathophysiological mechanisms, diagnostic criteria, and effective monitoring strategies.

Pathophysiology and Immunological Mechanisms

The pathogenesis of celiac disease involves activation of the immune system upon gluten exposure in individuals carrying the HLA-DQ2 or HLA-DQ8 haplotypes (2–4). The main autoantigen is tissue transglutaminase, against which specific autoantibodies are produced (5). Chronic inflammation leads to intestinal mucosal damage, characterized by an increased number of intraepithelial lymphocytes (IELs) and the development of villous atrophy. These immune-mediated changes result in malabsorption and may also contribute to various systemic symptoms.

Clinical Manifestations

The clinical presentation is heterogeneous. Classical forms are more commonly observed in children and include chronic diarrhea, abdominal distension, and failure to thrive. In adults, extraintestinal manifestations predominate, such as fatigue, anemia, osteopenia, depression, or hepatic dysfunction. The disease may also be diagnosed incidentally through routine laboratory testing or in the context of associated autoimmune disorders.

Diagnosis

Diagnosis relies on the integration of clinical, serological, and histological findings (6). The primary serological markers include anti-tissue transglutaminase (anti-tTG) and anti-endomysial antibodies (EMA). In both adults and pediatric patients, upper gastrointestinal endoscopy with duodenal biopsies typically reveals villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytosis. The Marsh-Oberhuber and Corazza-Villanacci classifications are commonly used to grade histological severity (7,8).

ESPGHAN Criteria and Challenges

The guidelines of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) allow for a non-biopsy diagnosis of celiac disease in selected pediatric cases, where anti-tTG antibody levels exceed 10 times the upper limit of normal (ULN) and EMA is positive in a second, independently collected blood sample (9). While this approach reduces procedural invasiveness, it raises concerns regarding long-term dietary adherence and appears to introduce differences in monitoring and follow-up practices for these patients.

Treatment and Monitoring

The cornerstone of treatment for celiac disease is strict adherence to a lifelong gluten-free diet (GFD) (10). Monitoring involves regular clinical evaluations, serological testing, and, in selected cases, repeat endoscopic assessment. Patient adherence varies depending on the availability of medical and nutritional support, education, and individual motivation. Complications range from severe nutritional deficiencies (e.g., anemia, hypoalbuminemia, vitamin deficiencies), osteoporosis, reproductive and neurological impairment, to oncologic complications—particularly enteropathy-associated T-cell lymphoma (EATL), which carries an increased risk in patients with delayed diagnosis or severe malabsorptive presentations (11).

Scope and Objectives of the Thesis

This doctoral thesis aims to investigate the multifaceted nature of celiac disease, with emphasis on its clinical implications and therapeutic management strategies. A multidisciplinary approach—encompassing perspectives from gastroenterology, endoscopy, nutrition, and pathology—will contribute to a more comprehensive understanding of the disease and support the improvement of current diagnostic and therapeutic practices. The global relevance of the topic is underscored by the growing body of dedicated research and the pressing need for coordinated international strategies in awareness and effective management of celiac disease.

The research further explores the histopathological characteristics and clinical implications of immune-mediated enteropathies, with a particular focus on celiac disease and its differentiation from non-celiac enteropathies. It is hypothesized that enhanced histopathological evaluation, in conjunction with refined diagnostic algorithms, will increase diagnostic accuracy, facilitate early therapeutic intervention, and improve patient outcomes. Moreover, the study assesses whether the non-invasive serological diagnostic criteria proposed

by ESPGHAN have a long-term impact on disease management and patient adherence to the gluten-free diet.

Scientific Objectives

The primary scientific objectives of this study include:

1. Analysis of histopathological variations in immune-mediated enteropathies and their role in differential diagnosis.
2. Evaluation of the clinical impact of adopting serology-based diagnostic criteria for celiac disease (CD) in the pediatric population, and their influence on treatment adherence and long-term outcomes.
3. Comparison of outcomes between patients diagnosed with CD based on serology and those with biopsy-confirmed diagnoses, focusing on dietary adherence, nutritional status, and serological response.
4. Investigation of the prevalence and clinical significance of upper gastrointestinal lesions in patients diagnosed with CD and their implications for disease management.

This study employs retrospective analyses to assess diagnostic and management strategies in celiac disease. The histopathological component includes the evaluation of duodenal biopsies using the standardized Marsh-Oberhuber classification. The clinical component analyzes serological markers, adherence to the gluten-free diet (GFD), and nutritional outcomes. Statistical comparisons between biopsy-based and serology-based diagnostic strategies provide a critical appraisal of the ESPGHAN criteria. Furthermore, a cohort analysis of upper GI lesions in adult patients with CD offers broader clinical context to the diagnostic process.

Key Findings

1. Histopathological assessment confirmed that non-celiac immune-mediated enteropathies exhibit overlapping features with CD, complicating differential diagnosis. However, careful interpretation of biopsy specimens, use of immunohistochemical techniques, and clinical context significantly improve diagnostic accuracy.
2. The shift toward biopsy-free diagnosis in pediatric CD cases introduced new challenges, particularly regarding patient adherence, with higher rates of dietary

transgressions and slower serological normalization compared to biopsy-confirmed cases.

3. Long-term follow-up data indicate that children with biopsy-confirmed diagnoses demonstrate better adherence to the GFD, improved nutritional recovery, and greater compliance with ongoing monitoring, compared to those diagnosed solely through serological testing. These findings suggest that, while serology-based diagnosis is valuable, its application should be carefully considered in the context of long-term disease management.
4. In adult patients with CD, endoscopic findings reveal a high prevalence of concomitant upper gastrointestinal lesions, highlighting the continued relevance of endoscopic evaluation, even as non-biopsy diagnostic approaches gain popularity in pediatrics.

Study Limitations

The main limitations of this study include its retrospective design, which may introduce selection bias and limit the ability to establish causal relationships. Additionally, the relatively small sample size, lack of detailed dietary adherence monitoring (despite assessment of adherence to the GFD, systematic dietary evaluations, regular consultations with a specialized dietitian, and biochemical markers of gluten exposure were not consistently applied), and limited long-term follow-up are noteworthy constraints. Although follow-up data were available, further longitudinal studies are necessary to fully assess the impact of diagnostic strategies on disease progression and complications.

Conclusion

This study underscores the complexity of diagnosing and managing celiac disease in both adult and pediatric populations. It emphasizes the importance of integrating clinical, serological, and histopathological data to optimize patient management and improve long-term outcomes.

II. Personal contribution

10. Diagnostic Challenges in Enteropathies: A Histopathological Review (12)

10.1 Abstract

Immune-mediated enteropathies (IMEs) are conditions characterized by an abnormal immune response of the small intestinal mucosa to non-pathogenic antigens, frequently leading to malabsorption syndrome. Typical clinical symptoms include weight loss, chronic diarrhea, and nutritional deficiencies. Although celiac disease (CD) is the most common immune-mediated enteropathy in adults, several other disorders with overlapping histopathological features have been increasingly recognized in recent years, including autoimmune enteropathy (AIE), common variable immunodeficiency (CVID), olmesartan-induced enteropathy, tropical sprue, and small intestinal bacterial overgrowth (SIBO). These conditions share clinical, serological, and histological features, making their differentiation from CD challenging.

Accurate diagnosis is essential to ensure timely initiation of appropriate therapy, thereby preventing disease progression and severe complications such as profound malabsorption or enteropathy-associated T-cell lymphoma (EATL).

The small intestine plays a dual role in both nutrient absorption and immune regulation. This dual functionality renders it susceptible to immune dysregulation, which may disrupt mucosal integrity. In IMEs, immune system hyperactivity leads to mucosal injury and impaired nutrient absorption.

While celiac disease remains the classical model of immune-mediated enteropathy, the increasing recognition of non-celiac enteropathies highlights the need for meticulous interpretation of intestinal biopsies. Histopathological evaluation must account for disease-specific features to avoid diagnostic errors and ensure appropriate clinical management.

10.2 Working Hypothesis and Objectives

The small intestine fulfills two principal functions: nutrient absorption and immune system regulation. It provides the largest surface area for efficient absorption of nutrients from ingested food and also constitutes the most extensive component of the human immune system. This dual role is critical, given the constant exposure of the intestinal mucosa to a wide range of environmental antigens. The intestinal immune system must accurately distinguish between

harmless substances and harmful antigens, responding either by initiating an immune reaction or by developing tolerance, depending on the nature of the encountered antigens (12).

Enteropathies disrupt both the absorptive and immunological functions of the intestine. Exaggerated immune responses to non-pathogenic molecules can trigger immune-mediated enteropathies (IMEs), leading to mucosal damage and subsequent malabsorption syndromes. A detailed understanding of the complex relationship between the small intestine and the immune system is essential for the accurate diagnosis and management of various gastrointestinal disorders. IMEs frequently share overlapping clinical, serological, and histological features, which complicates their differential diagnosis.

Early recognition of IMEs is crucial for the prompt initiation of effective treatment, which can prevent disease progression and the development of severe complications, particularly profound malabsorption. Malabsorption may result in significant nutritional deficiencies and systemic health issues. One particularly concerning complication is the increased risk of enteropathy-associated T-cell lymphoma (EATL). Patients diagnosed with celiac disease (CD), refractory celiac disease (RCD), or autoimmune enteropathy (AIE) are at higher risk of developing this aggressive malignancy (13).

Celiac disease remains the most common immune-mediated enteropathy in adults (14). However, over time, the spectrum of IMEs has expanded to include conditions such as autoimmune enteropathy, common variable immunodeficiency (CVID), olmesartan-induced enteropathy, tropical sprue, and small intestinal bacterial overgrowth (SIBO).

This analysis aims to highlight the clinical and histopathological characteristics of the most frequently encountered IMEs, with a particular focus on non-celiac conditions that may mimic CD. Improved understanding of these entities can enhance diagnostic precision, allowing for timely initiation of appropriate therapies and reducing the risk of complications associated with delayed or incorrect diagnosis.

A multidisciplinary approach—incorporating the expertise of gastroenterologists and pathologists—is essential for optimizing the care of patients with immune-mediated enteropathies.

10. 3 Research Methodology

To conduct this analysis, a comprehensive literature review was performed focusing on immune-mediated enteropathies. The search was carried out in March 2024 using the PubMed (MEDLINE) database. The following search terms were used: “immune-mediated enteropathy histopathology,” “autoimmune enteropathy histopathology,” “olmesartan-induced enteropathy histopathology,” “non-celiac villous atrophy histopathology,” “celiac-like enteropathy histopathology,” “protein-losing enteropathy histopathology,” “HIV-associated enteropathy histopathology,” and “common variable immunodeficiency enteropathy histopathology.”

The search was restricted to full-text articles published in English over the past ten years (2014–2024), focusing exclusively on adult patients. Case reports, editorials, and studies involving animals or pediatric populations were excluded. Titles and abstracts were screened for relevance to the subject of interest.

The analysis included the following immune-mediated enteropathies: celiac disease, autoimmune enteropathy, drug-induced enteropathies, infectious enteropathies (e.g., tropical sprue), enteropathy associated with common variable immunodeficiency (CVID), and small intestinal bacterial overgrowth (SIBO). From a total of 863 articles initially identified, 50 were selected for in-depth analysis. In addition, older studies published prior to 2014 were included when frequently cited in recent literature, particularly those offering foundational classifications or essential histopathological descriptions.

10.5 Celiac Disease – Histopathological Examination

Histologically, celiac disease primarily affects the small intestine, with intraepithelial lymphocytic (IEL) infiltration exceeding 25 lymphocytes per 100 enterocytes, predominantly concentrated at the villous tips (6). Other notable changes include enterocyte alterations such as reduced mucin layer and cytoplasmic vacuolization, as well as lamina propria inflammation due to immune cell proliferation. Crypt apoptosis, although subtle, holds diagnostic relevance. The presence of neutrophils or subepithelial collagen may suggest alternative pathological processes.

The histological classification systems commonly used for assessment include the Marsh-Oberhuber and Corazza-Villanacci systems (7,8), which quantify lesion severity from

isolated IEL elevation to complete villous atrophy. Accurate diagnosis requires multiple biopsies, ideally from both the duodenal bulb and distal duodenum, with careful analysis of well-oriented sections to assess villous architecture (6).

Mucosal healing following the initiation of a gluten-free diet (GFD) is a key therapeutic goal but may take longer than one year, and often up to three years in adults (15). The need for repeat biopsy is a subject of debate; current guidelines generally recommend it only in selected cases, such as persistent symptoms, suspected dietary non-compliance, or risk of complications (6,16–18). A significant proportion of patients—up to 30%—develop non-responsive celiac disease (NRCD), which may be attributed to various causes, including poor dietary adherence, delayed healing, refractory forms of the disease, or misdiagnosis.

10.6 Refractory Celiac Disease (RCD)

Refractory celiac disease (RCD) is a rare and severe form of celiac disease, diagnosed when clinical symptoms and histological lesions persist despite strict adherence to a gluten-free diet (GFD) for at least 12 months, in the context of negative serology and confirmed absence of gluten exposure (19,20). Histologically, villous atrophy and intraepithelial lymphocytosis persist, and additional features such as basal plasmacytosis or thickening of the subepithelial collagen band may be present, suggesting a possible overlap with collagenous sprue. RCD is classified into two subtypes: **type I RCD** is characterized by intraepithelial lymphocytes (IELs) with a normal immunophenotype (CD3+, CD8+) and is associated with a more favorable prognosis; **type II RCD** involves aberrant IELs, with cytoplasmic expression of CD3ε and clonal T-cell receptor gamma (TCRγ) gene rearrangement, it carries a high risk of progression to enteropathy-associated T-cell lymphoma (EATL), with an estimated incidence of approximately 50% within five years (21–27).

RCD is almost always symptomatic. Type II is associated with severe ulcerative jejunitis, malnutrition, and protein-losing enteropathy, often manifesting as severe diarrhea and hypoalbuminemia. Accurate distinction between the two subtypes is crucial, as treatment approaches and prognosis differ significantly.

10.7 Enteropathy-Associated T-Cell Lymphoma (EATL)

EATL is a rare but severe complication of celiac disease and can occasionally occur in the context of autoimmune enteropathy.

Histologically, EATL is characterized by severe mucosal damage, including marked villous atrophy, crypt hyperplasia, and a polymorphic inflammatory infiltrate in the lamina propria, frequently including plasma cells—features less commonly observed in uncomplicated CD. The neoplastic process often infiltrates the glandular epithelium and invades the deeper layers of the intestinal wall.

The 2008 WHO classification distinguishes two major subtypes: **EATL Type I**, typically found in Europe, presents with a heterogeneous lymphoid infiltrate (monomorphic or anaplastic, with variable cellular polymorphism) and is associated with a relatively better prognosis; **EATL Type II**, more commonly reported in Asia, consists of monomorphic small- to medium-sized lymphocytes with hyperchromatic nuclei and granular cytoplasm, and is associated with a more aggressive clinical course and poor treatment response. The distinction between subtypes has major prognostic and therapeutic implications, influencing management strategies and survival expectations. Accurate diagnosis requires comprehensive histological and immunophenotypic evaluation (28–32).

10.8 Collagenous Sprue (CS)

Collagenous sprue is a rare small intestinal disorder, considered either a complication of celiac disease or a distinct pathological entity.

Histologically, CS presents with features similar to those of CD, such as severe villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. The hallmark of the condition is a markedly thickened, irregularly distributed subepithelial collagen band (>10 μm). The IEL count is variable, and a chronic inflammatory infiltrate is usually present in the lamina propria (21,33).

10.9 Tropical Sprue (TS)

Tropical sprue is an incompletely understood infectious cause of malabsorption syndrome, predominantly found in tropical regions such as South Asia and Central America.

Clinically, it may present in acute or chronic forms. Unlike celiac disease, TS does not respond to a gluten-free diet but rather to antibiotic therapy.

Histological findings are less severe and more variable than in CD. Features include Marsh 3a-type villous atrophy, increased IELs, prominent eosinophilic infiltrates, and megaloblastic changes in enterocytes in cases of severe vitamin B12 deficiency. The condition often involves widespread small bowel involvement, including the terminal ileum (34).

10.10 Common Variable Immunodeficiency (CVID)

CVID is the most common primary immunodeficiency, characterized by defective B-cell maturation and impaired immunoglobulin production. The dominant gastrointestinal symptom is chronic diarrhea, often caused by recurrent infections—particularly *Giardia lamblia*, which can induce villous atrophy (VA) and malabsorption. Other infections, such as Norovirus, have also been associated with VA in these patients, with some cases showing reversibility after resolution of the infection.

Histologically, CVID-related changes include: increased intraepithelial lymphocytes (IELs), a marked reduction in plasma cells in the lamina propria, lymphoid hyperplasia, pronounced crypt apoptosis, intraepithelial neutrophils, and occasional small mucosal granulomas. VA is rare but possible and does not always correlate with active infections. In CVID, disease-specific antibodies for celiac disease are not produced, limiting the utility of serological testing. Furthermore, immunoglobulin replacement therapy may lead to false-positive results for anti-transglutaminase (tTG) or anti-endomysial (EMA) antibodies (35–37).

10.11 Autoimmune Enteropathy (AIE)

Autoimmune enteropathy is a rare condition that occurs predominantly in pediatric patients but can also present in adults, often in association with other autoimmune diseases (e.g., type 1 diabetes mellitus, autoimmune thyroiditis, autoimmune hepatitis, CVID). AIE may present in hereditary forms, such as: **IPEX syndrome** (immune dysregulation, polyendocrinopathy, enteropathy, X-linked), associated with anti-75 kDa enterocyte autoantibodies; **APECED syndrome** (autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy), associated with anti-tryptophan hydroxylase autoantibodies.

Isolated forms of AIE are diagnosed through the detection of circulating anti-enterocyte and anti-goblet cell antibodies; however, these are non-specific and may also be detected in other conditions, including celiac disease, HIV, and inflammatory bowel disease (IBD).

Histologically, AIE is characterized by: consistent villous atrophy, epithelial apoptosis, crypt infiltration with neutrophils, relative absence of marked IELs (in contrast to celiac disease), and absence of goblet and Paneth cells in some cases. Features of collagenous colitis or enteritis may also be present (38–41).

10.12 Drug-Induced Enteropathies

Non-steroidal anti-inflammatory drugs (NSAIDs) are a common cause of duodenitis, with possible extension to the distal ileum and colon. Although the clinical manifestations of NSAID-induced duodenitis are generally not suggestive of celiac disease (CD), histological changes can mimic this condition. Duodenal lesions associated with NSAID use include intraepithelial lymphocytic infiltration and nonspecific lamina propria inflammation characterized by the presence of neutrophils and plasma cells. Villous atrophy is typically absent. Other mucosal morphological changes such as erosions, ulcerations, and foveolar metaplasia may further contribute to the histological appearance observed in NSAID use (42).

Olmesartan, an angiotensin II receptor blocker, has been associated with severe enteropathy, initially described in 2012 and later confirmed through epidemiological studies. It predominantly affects elderly patients treated for hypertension. Histologically, olmesartan-induced enteropathy may mimic CD through the presence of villous atrophy, although intraepithelial lymphocyte (IEL) density is variable. In some cases, the pattern resembles autoimmune enteropathy (AIE), with loss of Paneth and goblet cells and crypt apoptosis. Distinctive features include a mixed inflammatory infiltrate in the lamina propria and thickening of the subepithelial collagen band. Clinical and histological remission following drug withdrawal supports the diagnosis (43,44).

Mycophenolate mofetil (MMF), an immunosuppressant used to prevent post-transplant rejection, can induce MMF-related enteropathy (MMF-E) with histologic features similar to graft-versus-host disease. MMF-enteropathy is characterized by villous flattening without a significant increase in IELs. A key diagnostic feature is the presence of eosinophilic infiltrates (>15 eosinophils/10 high-power fields). Other findings include crypt architectural disarray,

chronic lamina propria inflammation, crypt apoptosis, and cystic dilatation of duodenal crypts. Clinically, it manifests as reversible diarrhea upon discontinuation of the drug (45,46).

Ipilimumab, a monoclonal antibody against CTLA-4 and a member of the immune checkpoint inhibitor (ICI) class, is used in the treatment of various metastatic cancers. By enhancing immune responses, it can trigger autoimmune adverse events, including immune-mediated enteropathy. Histologically, this manifests as villous atrophy, increased IELs, crypt apoptosis, and mixed lamina propria inflammation—features that may mimic CD, AIE, or graft-versus-host disease.

While ICI-induced diarrhea most commonly reflects colonic involvement, the small intestine may also be affected. Colonic changes include cryptitis, crypt abscesses, and ulcerations, with some cases mimicking ulcerative or microscopic colitis. Ileal involvement has been reported in up to 20% of cases. Diagnosis of ICI-induced enteropathy is based on the correlation between histologic changes, immunotherapy history, and symptom location (47–49).

10.13 Small Intestinal Bacterial Overgrowth (SIBO)

SIBO is defined by excessive bacterial growth and/or altered microbial composition in the upper gastrointestinal tract. Definitive diagnosis requires the isolation of $\geq 10^5$ CFU/mL from jejunal aspirate, though hydrogen breath testing serves as a non-invasive alternative. SIBO often occurs secondary to motility disorders, post-surgical anatomical alterations, or chronic hepatic, renal, or pancreatic diseases.

Histologically, findings are nonspecific and range from normal mucosa to villous atrophy or increased IELs, which may resemble early celiac disease (Marsh 1). Differentiation requires clinical and serological correlation. SIBO generally responds well to antibiotic therapy, resulting in symptom relief and rebalancing of the intestinal microbiome (50).

10.14 Inflammatory Bowel Disease

Crohn’s disease is a chronic inflammatory bowel condition that can affect any segment of the gastrointestinal tract, most commonly the terminal ileum. Involvement of the proximal small intestine is rare (≈5%). The hallmark transmural inflammation may lead to complications such as ulcers, strictures, fistulas, and abscesses.

Histologically, Crohn's disease is characterized by cryptitis, crypt abscesses, architectural distortion, and a mixed inflammatory infiltrate. The presence of non-caseating granulomas, although relatively uncommon (15–36%), represents a useful diagnostic marker, particularly in the absence of infectious etiologies.

The differential diagnosis includes celiac disease, drug-induced lesions, peptic disease, and notably intestinal tuberculosis (ITB), which may closely mimic Crohn's disease. Caseating granulomas, the presence of acid-fast bacilli (AFB), positive PCR testing, and clinical response to anti-tuberculous therapy support the diagnosis of ITB. Clinical and histological correlation is essential, especially in endemic regions (51–53).

10.15 Idiopathic Eosinophilic Gastroenteritis (EGE)

Idiopathic eosinophilic gastroenteritis (EGE) is a rare, diagnosis-of-exclusion condition defined by eosinophilic infiltration of the gastrointestinal tract in the absence of secondary causes such as infections, inflammatory diseases, drugs, or malignancies. The infiltrate may affect the mucosa, submucosa, or serosa, resulting in variable clinical manifestations ranging from obstructive symptoms and malabsorption to ascites in cases with serosal involvement.

Histologically, EGE is characterized by crypt hyperplasia, villous shortening, increased intraepithelial lymphocytes (IELs), and a dense eosinophilic infiltrate, including degranulated eosinophils, intraepithelial eosinophils, and eosinophilic crypt abscesses. These features are critical for distinguishing EGE from other gastrointestinal disorders (54).

10.16 Graft-versus-Host Disease (GvHD)

Gastrointestinal GvHD is a well-recognized complication following bone marrow transplantation and, more rarely, solid organ transplantation or blood transfusion. It presents with a spectrum of symptoms ranging from nausea and diarrhea to severe hemorrhage and protein-losing enteropathy.

Histologically, GvHD progresses from isolated epithelial apoptosis to extensive crypt loss and mucosal denudation, typically in the presence of minimal inflammatory infiltrate. A hallmark feature is the selective depletion of Paneth cells, the degree of which correlates with disease severity (55).

10.17 Conclusions

The expanding spectrum of immune-mediated enteropathies has introduced significant diagnostic challenges, primarily due to overlapping clinical features. In this context, histological assessment becomes essential, as clinical signs are often non-specific, and pathognomonic histological markers for drug-induced etiologies are rare. Therefore, close interdisciplinary collaboration between gastroenterologists and pathologists is critical.

Duodenal mucosal examination contributes not only to establishing a definitive diagnosis but also to monitoring disease progression, therapeutic response, and potential complications. This study aims to highlight subtle histopathological differences among various immune-mediated enteropathies to enhance diagnostic precision and optimize clinical management.

11. Impact of ESPGHAN no-biopsy strategy on the outcome of celiac disease treatment in children (56)

11.2 Introduction

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) permits the diagnosis of celiac disease without biopsy under certain conditions. This study aimed to evaluate the impact of this diagnostic algorithm on the long-term outcomes of patients by comparing children diagnosed based on serology with those diagnosed through intestinal biopsy.

11.3 Methods

Medical records were retrospectively analyzed for children with anti-tissue transglutaminase IgA (tTG-IgA) titers greater than 10 times the upper limit of normal (ULN), who were consecutively diagnosed with celiac disease between 2010 and 2014. This period encompassed the 2012 revision of ESPGHAN criteria, which allowed for a biopsy-sparing diagnosis in selected cases. The following parameters were assessed in the non-biopsy group versus the biopsy group: clinical and laboratory data (serum biochemistry and autoantibodies), adherence to the gluten-free diet (GFD), and compliance with follow-up visits at 1, 2, and 8–10 years post-diagnosis.

11.4 Results

Clinical and laboratory parameters (including serum biochemistry and autoantibodies) indicated slower recovery in the 33 children diagnosed based on serology compared to the 30 children diagnosed via biopsy. Compliance with follow-up visits was higher in the biopsy-confirmed group.

Patient Characteristics at Diagnosis

A total of 63 out of 82 newly diagnosed children with celiac disease met the inclusion criteria. Among them, 63.5% were female, with no significant differences between the serology-based group (n = 33, median age 3.3 years, range 1.1–14.5 years) and the biopsy group (n = 30, median age 4.8 years, range 1.2–15.9 years).

All included patients had tTG-IgA titers >10× ULN, and endomysial antibody (EMA) tests were positive, with comparable titers across groups. In the biopsy group, 8 of 30 children (along with their parents) opted for biopsy despite meeting ESPGHAN criteria for a non-biopsy diagnosis. At diagnosis, 39.7% of patients were underweight, with no significant differences

in growth parameters, age, or sex distribution between the two groups. The biopsy group showed a tendency toward a higher prevalence of family history of celiac disease and associated autoimmune disorders.

Most children presented with one or more gastrointestinal symptoms, most frequently abdominal pain and diarrhea. Notably, all patients presenting with constipation were in the serology-based group. There were no significant differences in hemoglobin (Hb), mean corpuscular volume (MCV), or serum iron levels between groups. However, serum alkaline phosphatase levels were significantly lower in the serology group compared to the biopsy group.

Anemia was initially present at similar rates in both groups (27.3% in the serology group vs. 26.7% in the biopsy group). The median symptom duration before diagnosis was longer in the biopsy group (median 9 months, range 0–84 months) compared to the serology group (median 4 months, range 0–132 months), although the difference was not statistically significant ($p = 0.370$). This information was available in the medical records of 88% of patients.

The median interval between diagnosis and initiation of the gluten-free diet was slightly longer in the serology group (2.3 months) compared to the biopsy group (1.6 months), with no statistically significant difference ($p = 0.568$).

One-Year Follow-Up After Initiation of a Gluten-Free Diet (GFD)

Only 57.6% of children diagnosed based on serology attended the one-year follow-up visit after starting the GFD, compared to 73.3% of those diagnosed by intestinal biopsy. Most patients with consistent follow-up attendance were girls raised in urban environments. BMI Z-scores improved in both groups: from a median of -1.51 to -0.8 in the serology group ($p = 0.071$) and from -1.5 to -0.2 in the biopsy group ($p = 0.018$), the latter showing more favorable results.

During the first year after diagnosis, most patients in both groups reported improvement in gastrointestinal symptoms compared to baseline, although symptoms persisted in approximately one-third of cases. No child presented with overt malabsorption syndrome, and diarrhea was rare.

Anemia was evaluated in 16 of 19 children in the serology group and in 14 of 22 in the biopsy group. No significant improvement in hemoglobin levels was observed in the serology

group after one year of GFD (p = 0.661). In contrast, a trend toward improvement was noted in the biopsy group (p = 0.055). While there was no statistically significant difference in hemoglobin levels between groups, ferritin levels were significantly lower in the serology group. Alkaline phosphatase and ALT levels were more frequently within normal limits in the biopsy group after one year.

tTG-IgA titers decreased compared to baseline in both groups, with no significant intergroup differences. After one year of GFD, 73.7% of the serology group and 76.2% of the biopsy group remained tTG-IgA positive. EMA titers also declined, though 53.9% of the serology group and 40% of the biopsy group remained EMA-positive. Occasional dietary transgressions were reported in both groups—83% in the serology group versus 62% in the biopsy group.

Two-Year Follow-Up

At the two-year follow-up, 12 children (36.3%) in the serology group and 19 (63.3%) in the biopsy group returned for evaluation. Similar to the one-year visit, most children attending the follow-up were girls living in urban areas. The BMI Z-score worsened in the serology group (median -1.35), compared to the improvement seen at one year (-0.8). In contrast, the biopsy group showed a median BMI Z-score of -0.2 (p = 0.023), with only 5.3% still underweight (BMI <5th percentile), compared to 27.3% in the serology group.

Gastrointestinal symptoms were more frequently reported in the serology group (58.3%) than in the biopsy group (26.7%), including general complaints, vomiting, and flatulence. However, no child presented with malabsorption syndrome or diarrhea at this stage.

Anemia was assessed in all 12 children from the serology group and in 12 of 19 in the biopsy group. In both groups, 16.6% continued to exhibit anemia after two years on a GFD. Hemoglobin levels did not significantly improve in the serology group (p = 0.791), whereas the biopsy group showed a significant increase (p = 0.025). Ferritin levels and liver enzymes were within normal limits in both groups.

tTG-IgA and EMA titers declined over the course of the GFD, with no significant intergroup differences. However, at two years, tTG-IgA remained positive in 58.3% of the serology group and 50% of the biopsy group. EMA remained positive in 50% of the serology

group and 28.6% of the biopsy group. Occasional dietary infractions were again reported but were less frequent than at the previous visit (37% vs. 18% in the serology and biopsy groups, respectively).

Final Follow-Up Visit

A total of 24 children (72.7%) in the serology group and 21 (70%) in the biopsy group attended the final follow-up, at a median of 8.7 and 10 years after diagnosis, respectively. Various symptoms continued to be reported in both groups. Notably, no diarrhea was reported in the biopsy group at the two-year follow-up, but two patients experienced recurrence over the long term.

No children in either group had anemia at the final evaluation. Long-term laboratory parameters showed no significant differences between groups. While tTG-IgA and EMA titers significantly declined, 4 children in the serology group and 8 in the biopsy group (27% overall) remained positive for tTG-IgA.

Children in the biopsy-confirmed group demonstrated significantly better long-term follow-up adherence. Of these, 15 out of 30 (50%) attended all scheduled annual evaluations up to age 17, after which transition to adult care typically occurs. The remaining 6 children attended follow-up visits intermittently. The mean age at last evaluation in the biopsy group was 15.4 years. In the serology group, 10 out of 33 children (30%) attended all annual follow-ups, while the rest had irregular evaluations. The median age at final follow-up for the entire cohort was 12.8 years.

11.5 Conclusion

This study evaluates the impact of the modified diagnostic strategy for pediatric celiac disease (CD) following the 2012 ESPGHAN guidelines, which allow for a serology-based diagnosis without biopsy under specific conditions. The results demonstrate that children diagnosed via biopsy exhibited better adherence to the gluten-free diet (GFD), higher compliance with follow-up visits, and more favorable clinical and nutritional outcomes compared to those diagnosed based solely on serology. Children in the serology-based group more frequently presented with persistent symptoms, poorer nutritional status, and continued seropositivity two years after initiating the GFD, suggesting incomplete mucosal healing.

Persistent positive serology (51.6% for tTG-IgA and 37% for EMA) after two years of treatment, combined with self-reported dietary adherence, underscores the need for specialized and objective dietary assessments—including the measurement of gluten immunogenic peptides (GIP).

Study limitations include its retrospective design, low follow-up attendance rates, and the absence of repeat histological assessment. These findings highlight the necessity for enhanced monitoring strategies in children diagnosed without biopsy and the potential benefit of adjunctive therapies to GFD.

The study supports the importance of a personalized approach to long-term management of pediatric CD, emphasizing patient education, nutritional support, and the incorporation of objective tools for assessing adherence. Further research is needed to optimize the care of these patients and to evaluate the role of emerging therapeutic options.

12. Upper Gastrointestinal Tract Associated Lesions in Patients with Newly Diagnosed Celiac Disease (57)

12.2 Introduction

Current clinical guidelines require upper gastrointestinal (GI) endoscopy with duodenal biopsies for the diagnosis of celiac disease (CD) in adults. Drawing on pediatric experience, there has been growing interest in the feasibility of diagnosing adult CD based solely on serologic findings. The aim of this study was to assess concurrent upper GI lesions in newly diagnosed adult CD patients, to determine whether significant pathologies are identified during initial endoscopy that could influence patient management independently of CD.

12.3 Methods

We conducted a retrospective analysis of adult patients newly diagnosed with CD over a 7-year period (2014–2020). Demographic, clinical, laboratory, endoscopic, and histopathological data were extracted from patient records. Diagnosis was established according to the 2013 ACG guidelines.

12.4 Results

A total of 79 patients were included in the study, 75.9% of whom were female, with a median age of 39 ± 11 years (range: 19–83 years). Typical clinical presentation was observed in 57% of patients, atypical forms in 19%, and 13.9% were diagnosed through screening.

Anemia was present in 31.6% of newly diagnosed patients. Autoimmune comorbidities were identified in 16.5%, including type 1 diabetes (3.8%), autoimmune thyroid disease (8.9%), and Sjögren's syndrome (3.8%). Dermatitis herpetiformis was found in 5.1% of cases.

All patients tested positive for CD-specific serology, with 96.2% positive for tTG-IgA and 3.8% IgA-deficient patients positive for tTG-IgG. High tTG titers (>10x upper limit of normal) were observed in 29 patients. Histological examination of duodenal biopsies revealed Marsh 3 mucosal atrophy in all cases.

In addition to villous atrophy, 42 patients (53.16%) presented with associated endoscopic findings:

- Esophageal (e.g., reflux esophagitis, esophageal candidiasis, gastric heterotopia, short-segment Barrett's esophagus): 10 cases
- Gastric (e.g., hiatal hernia, chronic gastritis, gastric ulcer, subepithelial lesion): 36 cases
- Duodenal (e.g., small sessile polyp): 1 case
- Five patients had multiple concurrent lesions.

Most gastric lesions were minor, but significant findings included 2 cases of peptic ulcer, 1 of metaplastic gastritis, 6 of atrophic gastritis, and 1 subepithelial lesion. Only one patient had a non-CD-related duodenal lesion (inflammatory polyp). No malignancies were identified.

Importantly, in 28 out of 79 patients (35.44%), the synchronous findings observed during endoscopy led to clinical management changes (e.g., additional prescriptions, investigations, or monitoring plans), even if the indication for duodenal biopsies had not existed.

12.6 Conclusions

In contrast to pediatric protocols that permit a biopsy-free diagnosis under specific serologic criteria, adult CD diagnosis continues to rely on a triad of clinical, serological, and histological evidence. Although temporary pandemic-era guidelines (e.g., BSG 2020) introduced biopsy-free pathways for adults, their broader applicability remains limited and still under evaluation.

Our findings suggest that while a substantial proportion of adult CD cases may be diagnosed based on serology alone, omitting histologic confirmation may reduce disease perception, dietary adherence, and diagnostic accuracy—particularly in low-titer, seronegative, or mild enteropathy cases. Additionally, upper GI endoscopy facilitates the detection of clinically significant coexistent pathologies (e.g., infections, atrophic changes, premalignant lesions) that can meaningfully alter patient management.

Conversely, duodenal biopsy adds cost, requires protocol adherence (including sampling from multiple sites), and is subject to inter-observer variability and specimen quality limitations. As such, interest in biopsy-sparing strategies is growing but should be applied cautiously, with attention to individual clinical context, risk of underdiagnosis, and need for personalized assessment.

While biopsy-free diagnosis in adult CD shows promise—particularly in patients with high serologic titers and no comorbidities—endoscopy with histological assessment remains a valuable diagnostic and management tool for many patients. It is critical for differential diagnosis, complication screening, and long-term monitoring guidance.

General conclusions and personal contributions

Summary

This doctoral thesis aimed to investigate the histopathological features of celiac disease, with a focus on the differential diagnosis of immune-mediated enteropathies and the impact of diagnostic strategies on patient follow-up. The studies integrated retrospective data from both adult and pediatric patients with celiac disease, evaluating clinical, biological, and histological parameters to identify the most effective methods for diagnosis and long-term monitoring.

1. The analysis of histopathological descriptions in immune-mediated enteropathies revealed overlapping features between celiac disease and other immune-related conditions, such as autoimmune enteropathy and drug-induced enteropathies. These morphological similarities underscore the need for accurate differential diagnosis, integrating histological assessment with clinical and serological data.
2. The evaluation of the clinical impact of adopting serology-based diagnostic criteria for pediatric celiac disease demonstrated that patients diagnosed without biopsy exhibited a higher rate of gluten-free diet (GFD) non-adherence, potentially negatively affecting long-term prognosis. This approach also raised concerns regarding compliance and the reliability of serological monitoring, especially in the absence of a histological baseline.
3. A comparative analysis of serological versus histopathological diagnostic strategies identified significant differences between patient groups. Those with biopsy-confirmed diagnosis showed more rapid nutritional recovery and better adherence to the GFD, suggesting that eliminating biopsy from the diagnostic process in adults may be premature without additional selection criteria for eligible patients.
4. The investigation of gastrointestinal lesions associated with celiac disease highlighted the diagnostic value of endoscopy in adults. Over half of newly diagnosed adult patients exhibited endoscopic abnormalities, and in 35.4% of cases, these findings influenced clinical management. Thus, the role of upper endoscopy remains critical, even amid international trends toward serology-based diagnosis.

Original Contributions

1. Detailed histopathological examination of duodenal biopsies enabled clear differentiation between celiac disease and other immune-mediated enteropathies, providing practical guidance for differential diagnosis.
2. Assessment of the non-biopsy diagnostic strategy in children revealed its limitations and contributed to refining recommendations for its appropriate use.
3. The correlation between serology-based diagnosis and clinical outcomes showed that non-biopsy-diagnosed patients are more likely to struggle with strict adherence to the GFD, thereby delaying nutritional recovery.
4. Endoscopic evaluation of adult patients with celiac disease confirmed a high prevalence of concurrent gastrointestinal lesions at diagnosis, reinforcing the importance of maintaining endoscopy in the diagnostic pathway.
5. The study identified future research directions in the field of celiac disease, including the development of more specific biomarkers to detect dietary transgressions or to monitor mucosal healing, and the exploration of the intestinal microbiome as a potential factor in disease progression.

Final Remarks

The findings of this thesis contribute to a deeper understanding of celiac disease and underscore the continuing relevance of biopsy as the diagnostic gold standard in adults, despite recent interest in serology-only approaches. Furthermore, the study emphasizes the importance of multidisciplinary monitoring, involving specialists in nutrition, psychology, and close collaboration between clinicians and pathologists to ensure optimal patient care.

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