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Diagnostic difficulties in inflammatory bowel disease unclassified (IBD-U) - a narrative review

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ABSTRACT

BACKGROUND

Inflammatory bowel disease unclassified (IBD-U) is a diagnostic category used in patients with overlapping symptoms of Crohn's disease and ulcerative colitis in whom a definitive diagnosis cannot be made despite comprehensive clinical, laboratory, imaging, endoscopic, and histopathological evaluation. Although medical advances have improved diagnostic yield, IBD-U remains a significant clinical challenge due to its heterogeneous clinical presentation and the potential for subsequent diagnostic reclassification.

AIM OF THE STUDY

The aim of this review is to analyze and present the latest research on the problem of unclassified inflammatory bowel diseases, compare IBD-U with Crohn's disease and ulcerative colitis, and present the role of available diagnostic methods.

MATERIALS AND METHODS

A narrative review of the PubMed database was conducted. Original articles, systematic reviews, meta-analyses, and international guidelines published between 2011 and 2026 were analyzed. Studies addressing the epidemiology, clinical presentation, diagnostic methods, reclassification, and pediatric aspects of IBD were included.

DISCUSSION

The available evidence indicates that IBD-U is primarily a diagnosis of exclusion requiring comprehensive evaluation and long-term follow-up. Although ileocolonoscopy remains the cornerstone of diagnosis, magnetic resonance enterography, capsule endoscopy, and selected serological markers improve diagnostic accuracy in uncertain cases. Disease reclassification is common, particularly in pediatric patients, reflecting the dynamic nature of IBD-U.

CONCLUSION

Accurate diagnosis of IBD-U requires repeated multidisciplinary assessment rather than reliance on a single diagnostic test. Earlier identification of reliable biomarkers and refinement of diagnostic algorithms may improve disease classification and support more individualized patient management.

KEY WORDS: *IBD; inflammatory bowel disease; IBD-U; inflammatory bowel disease unclassified; Crohn’s disease; ulcerative colitis; ileocolonoscopy;*

1. INTRODUCTION

Inflammatory bowel disease (IBD) is a group of gastrointestinal diseases, primarily Crohn's disease and ulcerative colitis. The etiology of both conditions is not fully understood and involves genetic, immunological, and environmental factors [1]. They share some common features, but also differentiating factors. The main differences include the varying extent of disease in the gastrointestinal tract. In Crohn's disease, inflammatory lesions can involve the entire gastrointestinal tract, from the mouth to the anus. Ulcerative colitis, as the name suggests, is located in the large intestine. The second most important differentiating feature is the depth of the lesions. In Crohn's disease, all layers of the gastrointestinal tract can be affected, whereas in ulcerative colitis, only the mucosa is affected [2,3]. The incidence of IBD is steadily increasing, with the majority of cases diagnosed in Europe and North America [4]. In Europe, incidence rates range from 10.5 to 46.14 per 100,000 inhabitants, and in North America, from 7.3 to 30.2 per 100,000 inhabitants [5]. Both diseases can also present with a variety of extraintestinal manifestations. Ulcerative colitis most often predisposes to arthritis and primary sclerosing cholangitis, whereas Crohn's disease often presents with skin lesions (such as erythema nodosum), aphthous stomatitis, arthritis, and uveitis [2]. There is no single test that can distinguish Crohn's disease from ulcerative colitis. The diagnosis of IBD includes history, physical examination, clinical findings, as well as laboratory, imaging, and endoscopic tests, including histopathology [1]. Despite the increasing availability of tests and investigations, in up to 10% of patients it is impossible to differentiate IBD and make a specific diagnosis. In 1970, the term "indeterminate colitis" was first used by Kent et al. to refer to colectomies in which a definitive diagnosis was impossible. In 2005, the World Congress of Gastroenterology introduced the term "inflammatory bowel disease unclassified" (IBD-U) for patients with overlapping features of both diseases [6]. Some experts consider IBD-U a transient condition requiring observation and further diagnosis. Others suggest that IBD-U may be a distinct disease entity. The lack of a definitive diagnosis can have numerous consequences for patients, including available treatments, treatment outcomes, and prognosis [7].

2. AIM OF THE STUDY

The aim of this narrative review was to summarize the current evidence regarding unclassified inflammatory bowel disease (IBD-U), with a particular focus on the diagnostic challenges associated with this condition. The review aims to compare the clinical, endoscopic, histopathological, radiological, and serological characteristics of IBD-U with Crohn's disease and ulcerative colitis, assess the role and limitations of currently available diagnostic methods,

and discuss the frequency and clinical significance of disease reclassification during follow-up. Furthermore, the review highlights specific diagnostic considerations in pediatric patients, in whom IBD-U is more common and often presents with atypical symptoms.

3. MATERIAL AND METHODS

A narrative literature review was conducted using the PubMed database. The literature search included the following keywords and combinations: "inflammatory bowel disease (IBD-U)," "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "diagnosis," "endoscopy," "magnetic resonance enterography," "capsule endoscopy," "serology," "ASCA," and "pANCA." Original scientific articles, systematic reviews, meta-analyses, and international clinical guidelines published between 2011 and 2026 were eligible for analysis. Studies addressing the epidemiology, diagnostic criteria, clinical presentation, diagnostic methods, disease reclassification, and pediatric aspects of IBD-U were included.

4. STATE OF KNOWLEDGE

4.1. IBD

4.1.1. Epidemiology and etiology

The incidence of Crohn's disease is estimated at 30–50 cases per 100,000 people in developed countries [8]. The peak incidence is between 16 and 30 years of age, with comparable diagnosis rates in both sexes [9]. The peak incidence of ulcerative colitis is diagnosed between the second and third decades of life [10], with a subsequent peak occurring between the ages of 50 and 70. Some studies indicate a predominance of the disease in men [4]. The incidence of ulcerative colitis is estimated at 187 per 100,000 people in the European population [11], making it more common than Crohn's disease [4]. The main cause of the development of Crohn's disease is considered to be a disturbance of the intestinal microbiota, but risk factors also include gastrointestinal infections, overuse of antibiotics or nonsteroidal anti-inflammatory drugs, stress, smoking, and in women, oral hormonal contraception and hormone replacement therapy. [12,13] Genetic factors undoubtedly influence the risk of developing IBD [10,12,13]. The etiology of ulcerative colitis also shares similar risk factors as Crohn's disease. The main differentiating factor is smoking. Interestingly, ulcerative colitis is less common in current or recent smokers, and the course of the disease is also milder in them [4,10].

4.1.2. Course of the disease and symptoms

In both diseases, their natural course is usually periods of disease exacerbation followed by periods of remission [12,14].

Inflammation in Crohn's disease can involve the entire length of the gastrointestinal tract, and histopathologically, it can involve all layers of the gastrointestinal tract, from the mucosa to the serosa. The main clinical symptoms include abdominal pain, sometimes severe, often located in the right lower quadrant of the abdomen [8]. Abdominal pain may resemble acute appendicitis, and the location of the pain is due to the frequent location of inflammation in the area of the ileocecal valve [15]. The ileum and colon are the site of disease in half of patients. Additionally, 25% of patients present with perianal lesions (fissures, fistulas, abscesses). As many as 30% of patients have only the small intestine involved, and in 20% only the colon [12]. In Crohn's disease, a characteristic feature is the absence of inflammatory changes in the rectum [2]. In addition to abdominal pain, patients often report diarrhea and unintentional weight loss. Patients also often report unexplained fever or fatigue [12,15]. In the case of involvement of the upper gastrointestinal tract (13% of patients), epigastric pain, nausea or vomiting may occur [9,15]. Extraintestinal symptoms occur in up to 20-30% of patients in Crohn's disease and may precede the development of extraintestinal symptoms. The most common are axial and/or peripheral arthritis [12]. The rest include skin lesions such as erythema nodosum or pyoderma gangrenosum, arthritis or osteoporosis, uveitis, and oral aphthous ulcers [2,9]. In addition, due to absorption disorders, pancreatic, liver and biliary tract diseases, as well as kidney diseases such as kidney stones, may occur [2]. Inflammatory changes located in the small intestine lead to malnutrition, weight loss, and in children also to growth retardation [8,9]. Depending on the disease phenotype, complications may include intestinal obstruction or abscesses and fistulas [12]. The overall risk of death in patients with Crohn's disease is higher than in the general population [8].

Ulcerative colitis is characterized by inflammation exclusively in the large intestine, involving only the mucosa and developing proximally in a continuous manner. Studies indicate that isolated rectal involvement occurs in 30-60% of patients, left-sided involvement in 16% to 45%, and pancolitis in 14% to 35% [4]. In ulcerative colitis, rectal involvement is not detected at the time of diagnosis in only 5% of cases [14]. The most frequently reported symptoms include diarrhea with fresh blood [10]. Other common symptoms include abdominal pain and/or tenesmus [10,11]. The location of abdominal pain depends on the location of inflammation in

the large intestine [11], while left-sided pain is much more common than in Crohn's disease [8]. In advanced cases, weight loss and fever may occur. When the disease affects only the rectum, constipation may be an uncommon symptom [11]. In ulcerative colitis, extraintestinal symptoms are generally less common than in Crohn's disease, but they can also be the first manifestation of the disease. Arthritis is also the most common extraintestinal symptom, but occurs less frequently than in Crohn's disease, especially when Crohn's disease affects the entire colon. Primary sclerosing cholangitis and autoimmune hepatitis may occur more frequently than in Crohn's disease. PSC, in particular, is significantly associated with ulcerative colitis (up to 75% of patients diagnosed with PSC have concomitant UC). Pyoderma gangrenosum is more common, and erythema nodosum is less common compared to Crohn's disease. Ocular symptoms occur with similar frequency in both IBDs, whereas uveitis is more common in Crohn's disease [16,17]. In many studies, the risk of death in patients with ulcerative colitis is no higher or only slightly higher than in the general population [8,14].

4.1.3. Laboratory diagnostic

In both IBDs disease laboratory abnormalities most commonly include elevated inflammatory parameters (such as C-reactive protein and erythrocyte sedimentation rate), however, these tests are highly nonspecific. [14,15]. Iron deficiency anemia, vitamin B12 deficiency, thrombocytosis, or hypoalbuminemia may also be observed. In stool examination, especially in patients with colon disease, elevated fecal calprotectin levels are an indicator of the risk of Crohn's disease and a marker of disease progression [9]. Calprotectin may be a valuable marker for differentiating between IBD and irritable bowel syndrome [14]. Calprotectin levels accurately reflect IBD activity in the large intestine [9,11]. Serological markers are only supportive and not conclusive. ASCA (Anti-Saccharomyces cerevisiae antibodies) occur in 60% (50-70%) of patients with Crohn's disease and only 10-15% of those with ulcerative colitis, while pANCA (perinuclear anti-neutrophil cytoplasmic antibodies) occur in up to 70% of patients with ulcerative colitis and only 20-25% of those with Crohn's disease [9,11,14,18].

4.1.4. Endoscopic and imaging diagnostic

In both IBDs, endoscopic examinations are crucial for diagnosis, treatment, and prognosis. The key endoscopic examination for any suspected IBD is ileocolonoscopy [19]. In Crohn’s disease endoscopy reveals characteristic changes - alternating inflammatory and uninfected segments. Gastrointestinal stenosis and, less frequently, fistulas may also be observed [12]. Linear ulcerations or perianal lesions also support the endoscopic appearance of Crohn's disease [8,12].

Histopathological examinations typically reveal noncaseating granulomas, but they occur in no more than a quarter of patients [12]. Additionally, transmural inflammatory infiltrates, submucosal fibrosis, and irregular crypt arrangement are also observed [18]. Gastroscopy is necessary in every patient with suspected Crohn's disease, in which lesions in the upper gastrointestinal tract may occur in up to 13% of patients [9]. In the diagnosis of ulcerative colitis, the most important procedure also is ileocolonoscopy, which involves collecting histopathological samples from each part of the large intestine. In patients with severe disease, rectosigmoidoscopy is preferred, as it is an examination that does not require preparation of the large intestine with laxatives, which could exacerbate the patient's clinical condition. In the endoscopic image of ulcerative colitis, a characteristic feature is a clear boundary between the healthy and the diseased intestinal wall [11], while in Crohn's disease, cobblestone-like appearance resulting from the presence of longitudinal, deep ulcerations among the swollen mucosa can often be observed [2]. Endoscopically in colitis ulcerosa, the ileocecal valve is usually intact. The mucosa is friable, and erosions and, in severe inflammation, ulcerations and spontaneous bleeding may occur [14]. Histopathologically, the primary characteristic is involvement of the mucosa alone, with distorted crypts with abscesses, infiltration, and inflammation, ulceration and goblet cell loss [16]. Capsule endoscopy can be useful in diagnosing Crohn's disease to assess the small intestine, which cannot be visualized during gastroscopy or colonoscopy. However, prior MRI enterography is necessary, as intestinal strictures can cause capsule impaction. Among imaging tests, MRI enterography is the most useful, especially in diagnostically questionable cases [12]. Imaging does not play a significant role in the diagnosis of ulcerative colitis, especially in adults [14].

4.2. IBD-U

4.2.1. Definition

A diagnosis of inflammatory bowel disease unclassified occurs when a patient presents with symptoms characteristic of IBD, but despite a medical history and physical examination, laboratory, imaging, endoscopic, and pathological diagnostics, the patient cannot be confidently classified as having Crohn's disease or ulcerative colitis [6,20]. Situations in which making a specific diagnosis is particularly problematic include: severe clinical condition, absence of inflammation in the rectum, uneven distribution of disease in the large intestine, inconclusive or limited histopathological samples, and variability in clinical condition after initiation of treatment [6]. IBD-U is a particularly pronounced diagnostic challenge in the pediatric

population [20]. Another term, "indeterminate colitis", is used in the context of patients undergoing colectomy, in whom a specific diagnosis cannot be obtained with certainty [1].

4.2.2. Epidemiology and reclassification

Epidemiological data in the available literature are variable. They range from 5% to 15%, or 10-15% of cases generally diagnosed as IBD [6,7]. In a 2009 meta-analysis by Prenzel et al., the prevalence of IBD-U was estimated at 12.7% [20]. IBD-U is significantly more common in the pediatric population, particularly in young children. According to available analyses, up to 80% of young patients are later diagnosed with Crohn's disease or ulcerative colitis [21], while others indicate that IBD-U diagnosis is more often due to incomplete or incorrect diagnostics. In the EUROKIDS registry, after completing diagnostics and a median follow-up of 5.7 years, the prevalence of IBD-U was estimated at 5.6%. Furthermore, only 54% of these children underwent a complete endoscopic re-diagnosis, and 38% underwent radiological re-diagnosis, which could have been even lower if a complete diagnostic test had been performed in all children. After further diagnostic evaluation and a median follow-up of 5.7 years, 12% were diagnosed with Crohn's disease (CD), and 20% were diagnosed with ulcerative colitis (UC) [22]. In the analysis by Rinawi et al., of 53 pediatric patients, 45% were reclassified as CD, with a median reclassification time of 9.4 years [23]. A large meta-analysis, including 5,580 pediatric patients (also taking into account the aforementioned studies) and data through July 2021, included 397 patients initially diagnosed with IBD-U. After from 1 to 6.8 years of follow-up, 50% of IBD-U patients were reclassified into one of the two IBD types. Among this group, 17% received a diagnosis of Crohn's disease and 32,7% of ulcerative colitis. The results of this meta-analysis revealed a prevalence of IBD-U in children of 7.1%. Authors suggest that the assumption of a higher prevalence of IBD-U diagnosis in children is incorrect and may be due to incorrect or incomplete diagnostics [20].

Among adult patients, an analysis published in 2026, after 7 years of follow-up of 153 patients initially diagnosed with IBD-U, 12 were diagnosed with ulcerative colitis and 6 with Crohn's disease. The overall IBD-U reclassification rate was 11.8%. In most of these cases, the change of diagnosis occurred during the first years of follow-up, after repeated diagnosis, while late reclassifications usually resulted from the discovery of features typical of CD or CU. [3]. In an analysis by Everhov et al., which included 44,302 patients with IBD, 18% of patients changed their diagnosis during a median follow-up of 3.8 years. Children were more likely to change their diagnosis than adults (29% vs. 17%). Diagnoses of Crohn's disease and ulcerative colitis were highly stable (97%), while IBD-U was only stable in 67%. Among patients whose

diagnosis changed, 47% changed their diagnosis once and 31% changed it twice. Ultimately, it was concluded that a change in diagnosis occurred in 18% of cases. [24].

4.2.3. Diagnostic possibilities

Endoscopy

Endoscopic examinations are the most important foundation for the diagnosis of inflammatory bowel disease, of which ileocolonoscopy is crucial. A properly performed examination allows for a correct diagnosis in as many as 89% of cases [19]. Complete imaging of the large intestine, including assessment of the ileocecal valve and the terminal ileum, is essential [14]. A study by Per et al., analyzing 606 colonoscopies, demonstrated an accuracy of 89%, with 7% of these being IBD-U and 4% being errors. The highest number of errors was noted in patients with high inflammatory disease activity. It should also be noted that endoscopic examinations are a fundamental tool for monitoring the course of an already diagnosed disease [19]. Regular, repeat endoscopic examinations, along with histopathological examinations, also provide the basis for potential reclassification of patients with IBD [3]. The most distinguishing changes for Crohn's disease were perianal lesions, mucosal cobblestones, and discontinuous disease, while for ulcerative colitis, mucosal erosion and granulation were the most distinguishing features for ulcerative colitis [19]. Endoscopic findings in patients diagnosed with IBD-U most often showed extensive and severe colonic involvement, sparing of the rectum, segmental changes, and uneven distribution of colitis. The time of diagnosis was most common in patients with fulminant disease, acute onset, or early stage disease [6,7]. In the IBD-U group, progression of inflammation to complete colonic involvement was also most common, but a slow and chronic course was demonstrated. Patients with IBD-U had ileal inflammation less frequently than those with Crohn's disease, but more frequently than those with ulcerative colitis. Studies also demonstrated a tendency for spontaneous bleeding to be the most common in this group [7]. In addition to the macroscopic appearance, microscopic evaluation is necessary, but this image is often not very diagnostic and helpful in differentiating [6], especially in the early stages of the disease [25]. Histopathological findings are estimated to be conclusive in only 30% of cases [9]. The presence of noncaseating granulomas in histopathological specimens suggests Crohn's disease, but the key to diagnosis is their location away from the crypts [18] and their non-rupture [3]. Mucosal granulomas may also occur in ulcerative colitis and IBD-U, especially near ruptured crypts, so their presence in biopsy alone does not necessarily indicate Crohn's disease [7]. However, the transmural inflammation typical of Crohn's disease in patients diagnosed with IBD-U was not characterized by the presence of

lymphoid aggregates or ruptured ulcers. However, it has been shown that the presence of crypt abscesses is a common microscopic finding in IBD-U [7]. It should be noted that the endoscopic and histopathological appearance changes with time and treatment [25].

Ultrasound of intestinal

Another diagnostic method is ultrasound imaging. Its major advantages include its wide availability and non-invasive nature. A disadvantage is that accurate imaging requires extensive knowledge and experience of the physician performing the examination. Ultrasound can visualize intestinal wall thickness, changes in vascularity, and lesions occurring outside the intestinal wall. Sensitivity for detecting lesions has been estimated at 54-93%, and specificity at 97-100% [1].

Enterography MRI/CT

Enterography should be performed when the patient presents with abdominal symptoms that are inconsistent with the endoscopic findings, when a full colonoscopy is contraindicated, or when symptoms more typical of Crohn's disease are present [14]. In all patients whose endoscopy and pathological examinations yield negative results for pathological changes in the ileocecal valve region and the terminal segment of the small intestine, MRI enterography, or CT enterography, is recommended. MRI or CT enterography allows for precise imaging of the small intestine in areas inaccessible to traditional endoscopic methods. MRI is preferred due to the patient's exposure to significant amounts of ionizing radiation associated with CT [1,9], and some reports indicate a diagnostic advantage for MRI [9]. While the examination allows for the visualization of active lesions in the intestinal wall, it does not allow for the visualization of mild inflammation or lesions occurring solely in the mucosa. It may also yield negative results in early lesions associated with Crohn's disease [1]. An additional advantage of enterography is the diagnosis of possible intestinal and extraintestinal complications, such as strictures = which is particularly important when we plan to perform small bowel capsule endoscopy or abscesses or fistulas [1,9].

Small bowel capsule endoscopy

Small bowel capsule endoscopy is a diagnostic method used when lesions in the small intestine are suspected and not visualized on previous examinations. Imaging the entire mucosa of the small intestine is a significant advantage [1,9]. A study published in 2023 demonstrated the diagnostic effectiveness of small bowel capsule endoscopy in 28 patients with IBD-U. All

patients underwent small bowel enterography (MRI or CT), which did not alter the diagnosis. In nine patients, the results of capsule endoscopy led to a diagnosis of Crohn's disease (in six of whom the inflammation was assessed as mild, and in three as moderate to severe). Of the remaining 19, nine were reclassified as having ulcerative colitis during a follow-up period ranging from 12 to 60 months (with a median of 32.5 months), one was diagnosed with ulcerative colitis after colectomy, and the remaining nine remained with the diagnosis of IBD-U. Capsule endoscopy was found to be more effective, especially for the assessment of lesions in the initial section of the small intestine [1,9]. The risk of complications such as capsule impaction is estimated at 3% in patients with suspected Crohn's disease (and 8% in patients with diagnosed Crohn's disease) [1].

Serology tests

The appropriate antibody configurations described in the previous sections may be helpful in the differential diagnosis of IBD. ASCA+/ANCA- may suggest Crohn's disease, while ASCA-/ANCA+ may correspond to ulcerative colitis. A retrospective study was conducted on 406 children, 36% of whom were patients with IBD-U. These children were followed for a median follow-up of 2.8 years. In 41% of the children with IBD-U, both antibody classes were negative. The ASCA+/ANCA- profile was shown to have a high positive predictive value (96% for IBD-U, 90% for ulcerative colitis) and high specificity (83% for IBD-U and 97% for ulcerative colitis) for the diagnosis of Crohn's disease, while the negative predictive value was only 40% for ulcerative colitis and 13% for IBD-U. The ASCA-/ANCA+ profile was not effective or useful in differentiating the disease. The diagnostic value of antibody titers was also assessed. ASCA IgG >32.7 U/ml and ASCA IgA >11.9 U/ml allowed for the differentiation of Crohn's disease with a sensitivity of 50.0% and 42.6%, respectively, and a specificity of 80.0% for both ASCA antibody classes. [26]. The usefulness of ASCA, pANCA, PR3-ANCA, and MPO-ANCA antibodies in differentiating subtypes of inflammatory bowel disease in children was also examined in a more recent study (Kip et al.). ASCA IgG and IgA antibodies were found more frequently in patients with Crohn's disease (CD) - IgG in 75.4% and IgA in 23.8% of CD patients, respectively - than in patients with ulcerative colitis (UC) (17.5%, 2.5%) and IBD-U (60.0%, 20.0%). pANCA antibodies were positive in 33.6% of patients with IBD-U, 28.0% with UC, and 1.4% with CD, and PR3-ANCA was found in 24.0% of patients with UC, 17.6% with IBD-U, and 0% with CD. MPO-ANCA were negative in all patients [23]. In Crohn's disease involving only the large intestine, ASCA may be negative; serological tests are not diagnostic in such patients. [18]

4.2.4. Unclassified inflammatory bowel disease in children

The course of inflammatory bowel disease in children differs from that described in adults, making diagnosis more difficult, and making a diagnosis of IBD-U is more common (up to 13% in children, 6% in adults; in large cohorts in adults, from 1 to 20%, and in children, from 4 to 22%) [21,24]. Ulcerative colitis in children often involves the entire length of the colon and rarely affects only the rectum [21]. In adults, the absence of rectal involvement occurs in less than 5% of patients, while in children, it affects as many as one-third of patients [14]. Histopathological differences in children also occur (including normal crypt structure), and in a fulminant course with very severe inflammation, it may be transmural. In young children, chronicity in biopsy specimens may also be absent [18]. In children, histopathological specimens should also always be collected from the rectum, even if macroscopically normal [14]. Crohn's disease in children often affects the stomach or duodenum. Symptoms of IBD-U in children more often resemble those typical of ulcerative colitis, and the most common symptom of pediatric IBD-U is diarrhea with blood [21]. In the pediatric population, with mild IBD, normal results of albumin, hemoglobin, and inflammatory parameters occur in 21% of patients with Crohn's disease and 54% of patients with ulcerative colitis [18]. The revised Porto criteria published in 2014 facilitated the diagnosis of children and adolescents with suspected IBD. They emphasized the importance of extending the diagnostic process with additional tests, as many features of IBD types overlap, and the diagnosis of IBD-U remains a diagnosis of exclusion. All children with suspected IBD should undergo gastroscopy, ileocolonoscopy, and imaging of the small intestine with MRI enterography or capsule endoscopy [18,21]. Gastroscopy is necessary in children - as many as 8% of the pediatric population receive a change in diagnosis towards Crohn's disease after gastroscopy [14]. Detailed examination of the small intestine can be postponed only if a macroscopic and microscopic diagnosis of ulcerative colitis is confirmed. Up to 35% of children in the 1811 group with IBD had lesions in the upper gastrointestinal tract, 24% of which were characteristic of Crohn's disease. In children, infectious gastrointestinal infections, common in this age group, as well as conditions such as celiac disease and allergies, should also be excluded before initiating invasive diagnostics [18]. In children, growth retardation may be the only symptom of IBD [2].

5. DISCUSSION

Unclassified inflammatory bowel disease (IBD-U) remains one of the most challenging entities within the IBD group. Despite ongoing advances in diagnostic techniques, differentiating IBD-

U from Crohn's disease and ulcerative colitis is often impossible at the time of diagnosis because many patients present with overlapping clinical, endoscopic, and histopathological features. The reviewed literature indicates that no single diagnostic method is sufficient to establish the diagnosis. Ileocolonoscopy with multiple biopsies remains the cornerstone of diagnosis; however, histopathological findings alone are often equivocal, particularly in the early stages of the disease or after initiation of treatment. Radiological imaging methods, particularly magnetic resonance enterography and small bowel capsule endoscopy, provide valuable information in patients with suspected small bowel disease and can contribute to diagnostic reclassification. Similarly, serological markers such as ASCA and pANCA can aid in differential diagnosis but should not be used as standalone diagnostic tools due to their limited sensitivity. A significant observation from available studies is the dynamic nature of IBD-U. A significant proportion of patients are ultimately reclassified as having Crohn's disease or ulcerative colitis during long-term follow-up, most often after repeated endoscopic evaluations or the appearance of symptoms characteristic of the disease. These findings suggest that IBD-U often represents an intermediate diagnostic step rather than a permanent disease entity. However, a subset of patients persist with the diagnosis of IBD-U even after long-term follow-up, still not meeting clear criteria for a specific diagnosis, suggesting that IBD-U may represent a distinct clinical phenotype in at least some individuals. Diagnostic uncertainty is particularly pronounced in the pediatric population. Children are more likely than adults to have an atypical disease course, sparing of the rectum, upper gastrointestinal involvement, and less characteristic histopathological findings. Therefore, current pediatric guidelines recommend a more thorough initial diagnostic workup, including upper gastrointestinal endoscopy and small bowel imaging, to reduce the risk of misclassification. Although recent studies have advanced our understanding of IBD-U, significant limitations remain. Most available evidence comes from retrospective cohort studies or observational analyses with heterogeneous diagnostic criteria and variable follow-up periods. Standardization of diagnostic algorithms, along with the identification of new molecular, genetic, and serological biomarkers, may improve diagnostic accuracy in the future and reduce the proportion of patients remaining unclassified.

6. CONCLUSION

Unclassified inflammatory bowel disease (IBD) remains a diagnosis of exclusion and continues to pose a significant diagnostic challenge in clinical gastroenterology. Accurate diagnosis requires combining clinical findings with endoscopic, histopathological, radiological, and laboratory findings, as no single test provides sufficient diagnostic certainty. Endoscopy with

histopathological assessment remains the cornerstone of diagnosis, while magnetic resonance enterography, capsule endoscopy, and selected serological markers provide valuable complementary information in diagnostically uncertain cases. The diagnosis of IBD is dynamic, and during long-term follow-up, many patients are reclassified as Crohn's disease or ulcerative colitis, emphasizing the importance of repeated clinical and endoscopic reassessment. Diagnostic challenges are particularly acute in children due to the higher incidence of atypical symptoms. Early disease classification and the optimization of individualized treatment strategies are essential, and further research is needed to identify reliable biomarkers and refine diagnostic algorithms. Furthermore, to ensure patients receive appropriate care and the most effective treatment, even those diagnosed with Crohn's disease or ulcerative colitis should be monitored for disease activity, as subsequent tests often result in a change in diagnosis.

Disclosure

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