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UPPER GASTROINTESTINAL MORPHOLOGICAL CHANGES IN CROHN'S DISEASE (LITERATURE REVIEW)

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Abstract. In 1932, Burrill Bernard Kron, Leon Ginsberg and Gordon Oppenheimer published an article entitled "Regional Ileitis:Pathological and Clinical Essence", in which they first described terminal ileitis, later named B. Kron. Crohn's disease (CD) is a recurrent systemic inflammatory disease affecting the gastrointestinal tract with extraintestinal manifestations and systemic immunological disorders. It can be localized in all parts of the gastrointestinal tract and is characterized by a variety of intestinal and extraintestinal manifestations, which depend on the depth, length of the affected organ and the characteristics of immune (systemic) complications. Upper gastrointestinal tract lesions in this disease are an understudied area. Routine screening showed a higher prevalence of the described pathology among children compared to adults. Upper gastrointestinal involvement in Crohn's disease is an understudied area. Routine screening showed a higher prevalence of this pathology among children compared to adults. In most patients, damage to the upper gastrointestinal tract remains asymptomatic, but pathological changes in the mucous membrane, diagnosed by morphological examination, are possible. In routine practice, endoscopic examination is recommended for patients with pre-existing lesion symptoms. This literature review considers morphological changes in the upper gastrointestinal tract in Crohn's disease, which are a consequence of both the underlying disease and the side effects of drugs used in the treatment of this pathology.

Keywords: *inflammation, morphology, Crohn's disease*

МОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В ВЕРХНИХ ОТДЕЛАХ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА ПРИ БОЛЕЗНИ КРОНА (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. В 1932 г. Беррилл Бернард Крон, Леон Гинзберг и Гордон Оппенгеймер опубликовали статью «Региональный илеит: патологическая и клиническая сущность», в которой впервые описали терминальный илеит, получивший в дальнейшем имя Б. Крона. Болезнь Крона (БК) — рецидивирующая системная воспалительная болезнь, поражающая желудочно-кишечный тракт (ЖКТ) с внекишечными проявлениями и системными иммунологическими нарушениями. Может локализоваться во всех отделах желудочно-кишечного тракта и характеризуется разнообразными кишечными и внекишечными проявлениями,

которые зависят от глубины, протяженности пораженного органа и особенностей иммунных (системных) осложнений. Поражение верхних отделов ЖКТ при данном заболевании представляет собой недостаточно изученную область. Рутинный скрининг показал более высокую распространенность описываемой патологии среди детей по сравнению с взрослыми. У большинства пациентов поражение верхних отделов ЖКТ остается бессимптомным, однако возможны патологические изменения слизистой оболочки, диагностируемые при морфологическом исследовании. В рутинной практике эндоскопическое исследование рекомендуется пациентам с уже имеющимися симптомами поражения. В данном литературном обзоре рассмотрены морфологические изменения в верхних отделах ЖКТ при болезни Крона, являющиеся следствием как основного заболевания, так и побочного действия лекарственных препаратов, используемых при лечении данной патологии.

Ключевые слова: *воспаление, морфология, болезнь Крона*

INTRODUCTION

Crohn's disease (CD) along with ulcerative colitis is one of the predominant clinical entities in the structure of inflammatory bowel disease. At present, CD continues to be considered a chronic disease resulting from a complex interplay of environmental, microbial and genetic factors, despite ongoing research on the etiology and pathogenesis of CD and the progress made in understanding the mechanisms of disease development. Any part of the gastrointestinal (GI) tract can be affected in CD, but the process is usually associated with involvement of the terminal ileum or colon. Cases of CD with isolated or combined involvement of the upper GI tract (esophagus, stomach, and duodenum) are rare and the least studied variants of the disease. This literature review considers upper GI lesions in this pathology.

MORPHOLOGIC CHANGES IN THE ORAL MUCOSA

Oral manifestations of Crohn's disease are both a consequence of primary exposure to the disease, a symptom of a disease of another etiology, or a secondary reaction to drug treatment. The appearance of morphologic changes may also be associated with a secondary manifestation of the intestinal form of Crohn's disease. The results of the study of clinical and morphological features of CD accompanied by oral lesions showed that 33 (38.4%) patients had oral cavity changes, in particular chronic recurrent aphthous stomatitis in 9 (10.46%) patients. In 19 (22.1%) patients, oral symptoms appeared earlier than intestinal manifestations, which is confirmed by the results of histologic examination of the oral mucosa, namely the presence of granulomatous inflammation [1].

Specific mucosal lesions include granulomatous changes that have been noted on histopathologic examination. Although less common than nonspecific lesions, they may occur simultaneously with or even before intestinal symptoms. The oral mucosa is hyperplastic, resembling cobblestone, on which nodular granulomatous swelling is noted. Compacted polyposis fringed lesions of the vestibule and retromolar region are typical. On the mucous membrane of the lips and cheeks, as well as in the retromolar areas are most often found plaques and deep ulcerations of the mucosa with hyperplastic edges, flabby or dense on palpation. The gingiva and alveolar mucosa are swollen, and become granular and hyperplastic with or without ulceration [2]. Swelling of the face, one or both lips and cheek mucosa may also be noted. This condition is unpleasant for patients because it can lead to facial deformity [1]. Granulomatous inflammation can be identified histologically in such lesions. The lips are most commonly affected and are usually painless and solid on palpation. Many patients with swollen lips also have painful vertical fissures in which many microorganisms may be isolated [3].

Non-specific oral lesions in CD include aphthous ulcers, orofacial symptoms predominantly characteristic of young patients, granulomatous cheilitis, and vegetative pyostomatitis [4]. Aphthous ulcers are the most common type of oral lesions, occurring in 20–30% of adult CD patients [2]. The characteristic site of oral lesions is the lips, followed by the mucosa of the cheeks, gums, vestibular and retromolar regions [5]. This phenomenon is a focal inflammation of the oral mucosa in which round ulcers (aphthae or erosions) form. Aphthae are covered with gray or yellowish plaque and cause pain and discomfort. Aphthae with an atypical course are almost indistinguishable from normal aphthae before biopsy. Biopsy material is taken from the upper GI tract

in the presence of clinical signs of the disease, but repeated biopsies in this area are not taken in the absence of clinical and macroscopic manifestations of the pathologic process [6]. It is worth noting that the frequency of aphthous ulcers in inflammatory bowel disease (IBD) is the same as in any other pathology in which they may occur. However, aphthous ulcers occurring in IBD are characterized by a persistent recurrent course [7]. Clinically, the ulcers are small, painful, but benign with a limited erythematous aureola. They may also be part of recurrent aphthous stomatitis or they may be isolated masses [8].

In addition to morphologic changes in the oral cavity, the immunologic profile of cells also changes. According to the results of the study by G.M. Damen et al. the oral cavity cells of CD patients were more immunologically active. Thus, buccal epithelial cells showed increased production of CXCL-8, CXCL-9 and CXCL-10. Lipopolysaccharide-stimulated dendritic cells originating from monocytes produced CXCL-8 [9, 10].

ESOPHAGEAL MORPHOLOGICAL CHANGES

Currently, the likelihood of esophageal involvement in Crohn's disease is considered unlikely. The prevalence of esophageal CD in adults, according to different data, varies from 1.2 to 1.8% and from 3.3 to 6.8%. In children the incidence ranges from 25.8 to 41.5% and from 7.6 to 17.6% [11]. However, histologic evidence of esophageal involvement was found in 54% of pediatric patients with CD: 11% were in association with esophagitis, 33% were in association with chronic inflammation, and 4% were in association with reflux esophagitis, according to S.P. Castellaneta et al. [12].

The diagnosis of the Crohn's disease of the esophagus is difficult to make, as the histologic features of this disease are usually nonspecific and it may present as erosive-ulcerative esophagitis, esophageal stricture or esophageal fistula, which occur in a number of other pathologies. According to K.M. De Felice et al. the most common sites of esophageal involvement were mid (29%), distal (29%), diffuse esophagitis also occurred in 21% of cases. At the time of endoscopic examination, superficial ulceration (58%), erythema and/or erosions (50%), deep ulceration (13%) and pseudopolyps (4%) were the most common findings on the background of hyperemia of the esophageal mucosa. According to De Felice et al. study, the most common localizations of esophageal lesions are middle and distal esophageal lesions — 29%, mid-distal lesions — 17%, diffuse lesions — 21%, proximal lesions — 4% [11].

The most common esophageal lesion in Crohn's disease is lymphocytic esophagitis. Lymphocytic esophagitis (LE) is histologically characterized by marked esophageal lymphocytosis with the absence or presence of only rare intraepithelial granulocytes. At the initial stage of the disease, macrophage and lymphoid infiltration is found only in the submucosal layer, then the pathologic process covers all layers of the digestive tube, incomplete or sarcoid-like granulomas may be found. At the next stage, ulcers occur, extending deep into the serosa until the formation of fistulas. According to a study by Don R. Ebach, the histologic diagnosis of LE is associated with pediatric CD and was found in 28% of CD patients. Esophagitis with granulomas was observed in 10% of CD patients studied [13]. Upon histologic examination, "wavy cells," which are dense intraepithelial lymphocytes, nonspecific for CD, characteristic of both celiac disease and reflux esophagitis, may also be found. The development of eosinophilic esophagitis is possible. It can be distinguished from esophagitis associated with Crohn's disease only by the pathologic Th1-type reaction typical of CD, in contrast to the Th2-type reaction in eosinophilic esophagitis [14].

MORPHOLOGIC CHANGES IN THE MUCOSA OF THE STOMACH AND THE DUODENUM

Gastric and duodenal involvement in CD is rarely clinically evident, but endoscopic examination of the upper GI tract is useful in the presence of distal involvement. Gastroduodenal lesions may present symptoms that imitate peptic ulcer disease, such as pain in the epigastric region, nausea/vomiting and abdominal bloating, and subfebrile body temperature. In pediatric practice, gastritis or duodenitis in CD is often asymptomatic and is usually diagnosed during routine endoscopy. It may manifest as mucosal hyperemia (erythematous gastroduodenitis), erosions or ulcers, fistula formation, stricture, or a combination of these.

The most common clinical picture is permanent involvement of the antral, gatekeeper and

proximal duodenum, affecting up to 60% of patients with duodenal CD [15]. Men and women are equally affected, with a ratio of 1.2:1. Granulomas are found both in abnormal macroscopic structure of the gastric and duodenal mucosa and in its normal structure. Focal acute (neutrophilic) and chronic (lymphocytic) inflammation is often observed [16]. The gastroduodenal mucosa often has focal subepithelial infiltration of macrophages throughout the intrinsic lamina of the mucosa. K. Yao et al. found that in duodenum and stomach, the incidence of macrophage aggregates throughout the intrinsic mucosal lamina was higher than in granulomatous lesions. No macrophage aggregates or granulomas were found in patients with ulcerative colitis. Macrophage infiltration of the intrinsic lamina of the gastroduodenal mucosa was observed in patients with diagnosed Crohn's disease. Researchers suggest that subepithelial accumulations of *lamina propria* macrophages in the absence of signs of inflammation may be one of the minute histologic changes leading to mucosal damage characteristic of CD [17]. The presence of granulomas, superficial intraepithelial accumulations of neutrophils, and infiltration of the intrinsic lamina propria by neutrophilic granulocytes were more frequently observed in *H. pylori* negative patients [18].

CONCLUSION

An increase in the number of people suffering from inflammatory bowel diseases is registered worldwide according to epidemiologic studies. In recent years, there are more and more publications concerning the state of the upper GI tract in these diseases. Unfortunately, the symptomatology at the initial stages of pathology is currently insufficiently studied. There are no views on the evaluation of the place of the lesion in the general picture of the disease, as well as whether it is a complication or refers to the individual course of the disease and does not affect the severity. Further study of this problem will make it possible to diagnose the lesion at early stages, which will significantly improve the prognosis in therapy.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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