DOI: 10.20514/2226-6704-2023-13-2-155-160
УДК 616.34-002.191-079.4-085
EDN: WZYSCA

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МИКРОСКОПИЧЕСКИЙ КОЛИТ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Microscopic Colitis: A Clinical Case

Резюме

Микроскопический колит — это воспалительное заболевание кишечника неизвестной этиологии, проявляющееся в виде хронической диареи водянистого характера, с отсутствием эндоскопических признаков поражения кишечника, но наличием микроскопических изменений. Диагностика микроскопического колита основывается на гистологическом исследовании биоптата кишечника и требует высокой квалификации гастроэнтеролога, эндоскописта и гистолога. В статье представлен клинический случай микроскопического колита у пациентки 42 лет, обсуждаются основные этапы дифференциальной диагностики и лечения.

Ключевые слова: *микроскопический колит, будесонид, коллагенозный колит*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 06.06.2022 г.
Принята к публикации 16.02.2023 г.

Для цитирования: Резник Е.В., Смирнова А.С., Гудилова Ю.Ю. и др. МИКРОСКОПИЧЕСКИЙ КОЛИТ: КЛИНИЧЕСКИЙ СЛУЧАЙ. Архивъ внутренней медицины. 2023; 13(2): 155-160. DOI: 10.20514/2226-6704-2023-13-2-155-160. EDN: WZYSCA

Abstract

Microscopic colitis is an inflammatory bowel disease of unknown etiology that presents as chronic watery diarrhea with no endoscopic evidence of the bowel involvement but with the microscopic changes. Diagnosis of microscopic colitis is based on the histological examination of the intestinal biopsy and requires a highly qualified gastroenterologist, endoscopist and histologist. The article presents a clinical case of microscopic colitis in a 42-year-old patient, reflects the main stages of diagnosis and treatment of the patient.

Key words: *microscopic colitis, budesonide, collagenous colitis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 06.06.2022
Accepted for publication on 16.02.2023

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For citation: Reznik E.V., Smirnova A.S., Gudilova Y.Y. et al. Microscopic Colitis: A Clinical Case. The Russian Archives of Internal Medicine. 2023; 13(2): 155-160. DOI: 10.20514/2226-6704-2023-13-2-155-160. EDN: WZYSCA

MC — microscopic colitis, CC — collagenous colitis, LC — lymphocytic colitis, IRS — irritable bowel syndrome, GCS — glucocorticosteroids, PPI — proton pump inhibitors

Microscopic colitis (MC) is an inflammatory bowel disease of unknown etiology, manifested as chronic watery diarrhea with no endoscopic signs of bowel involvement but with microscopic changes [1]. MC is classified into two types: collagenous colitis (CC) and lymphocytic colitis (LC). The prevalence of MC is 103.0 per 100,000 population: 39.3 per 100,000 population for CC and 66.7 per 100,000 population for LC. According to the Guidelines of the United European Gastroenterology (UEG) and European Microscopic Colitis Group (EMCG), 2021, sometimes a third type of MC (incomplete MC) is used. Diagnosis of MC is based on the histology of the bowel biopsy specimen and requires participation of a qualified gastroenterologist, endoscopy specialist and histologist. MC type is determined based on the morphological data. Different types have similar clinical presentation [2].

The prevalence of MC is higher in the elderly, median patient age in CC and LC is 64.9 and 62.2 years, respectively. Although recent studies have showed that up to 25 % of patients diagnosed with CC were younger than 45 years. Also, there were cases of CC in children and adolescents [3].

Etiology and pathogenesis of the MC are not fully studied. The literature discusses various mechanisms and risk factors potentially associated with MC, including genetic predisposition, impaired epithelial permeability, infectious and immunologic factors, impaired collagen metabolism (for CK), malabsorption of bile acids [2].

Most authors stand for the immune-mediated nature of MC, with a significant contribution of both the immune system and cytotoxic reactions. The inflammatory cascade is most likely to trigger exposure to certain intraluminal bacterial antigens that enter the lamina propria of the intestinal mucosa, as well as drug products that increase mucosal permeability. Genetic factors affect the processes of antigen presentation by immunocompetent cells in the intestinal mucosa, which leads to hyperactivation of the Th1- and Th17-type immune response and to the development of cytotoxic effects with subsequent injury to the epithelium. Elevated mucosal concentrations of profibrogenic cytokines such as transforming growth factor β, interleukins 6 and 22 appear to be highly associated with CC rather than with other forms of MC and are likely to mediate subepithelial collagen deposition, which is a distinctive histologic sign of CC [2, 4].

Below is a clinical case demonstrating the challenges of diagnosis in a patient with MC.

In January, 2021 a 42-year-old female patient visited a gastroenterologist at the ON CLINIC International Medical Center with complaints of loose, watery stool (type 6 according to the Bristol Stool Chart) up to 6 times a day, sudden uncontrollable urge to defecate, bloating accompanied by moderate pain. Historical data suggest that these signs have persisted for 4 years. The patient has no previously diagnosed chronic diseases. Over this period, repeated examinations were carried out, including abdominal ultrasound, clinical and biochemical blood tests, coprological examination, stool tests for microbiocenosis, for protozoa and helminth eggs. Test results were normal. Thyroid panel (thyroid stimulating hormone, triiodothyronine and thyroxine) is within normal range. One year before admission, a fiberoptic colonoscopy was carried out, which did not reveal any abnormalities in the large bowel. Celiac disease, lactase insufficiency, chronic pancreatitis and bacterial overgrowth syndrome have been ruled out. The patient underwent a number of cycles of therapy with various spasmolytics, enzyme products, prebiotics, probiotics, antidiarrheic products with no effect. The patient had to take loperamide chronically and use diapers.

The patient has no allergies or bad habits. Her father was diagnosed with the rectal cancer at the age of 70 years. From the mother's side family history is not burdened.

Physical examination: skin and visible mucous membranes were of normal color. Height: 177 cm, bodyweight 58 kg (body mass index 18.5 kg/m^2). The tongue was moist, covered with white fur. The abdomen was of regular shape, soft, moderately bloated, tender on superficial palpation in the epigastric area. Deep sliding palpation according to Obrazcov — Strazhesko showed no abnormalities.

According to the above data, the patient was diagnosed with the irritable bowel syndrome (IBS). Recommendations: fractional meals 5–6 times a day, excluding fatty, fried, spicy, smoked, pickled food and alcohol; a 10-day course of medical therapy: alverine + simethicone 1 capsule TID, smectite dioctaedric 1 sachet TID,

pancreatin in minimicrospheres 10,000 units 1 capsule TID, natural lyophilized homogenized avian gastric mucosa 300 mg TID (it has a cholinolytic, adsorbing and coating effect), as well as the biologically active compound calcium butyrate + inulin 1.36 g, 2–3 times a day for up to 3 months.

Laboratory tests: hematology showed an increase in ESR to 29 mm/h (hereinafter, normal range is indicated in parentheses: 1–20 mm/h), hemoglobin 120 g/l (120–140 g/L), white blood cells 5.15×10^9/L ($4.0–9.0\times10^9$/L). Stool is liquid, unformed, with single WBCs per HPF, and total lack of neutral fat and fatty acids. Slight reduction in typical Escherichia coli titer to 10^5 CFU/g (ref. range: $10^7–10^8$ CFU/g); Fecal calprotectin 2.8 mg/kg (0–50 mg/kg). To rule out intestinal infections, passive hemagglutination test to salmonella, shigella, yersinia was carried out with a negative result. To rule out parasitic invasions, tests for antibodies to ascaris, opisthorchis, *Entamoeba histolytica*, lamblia, toxocara, Fasciola hepatica were carried out. Anti-ascaris antibodies were identified: IgG 1.69 U (0–1.1 U). According to the abdominal ultrasound, gallbladder deformity was observed.

The patient was consulted by a mental health specialist. Psychoneurological state is normal.

After a repeated consultation of gastroenterologist after one month of treatment, the patient was followed up for IBS and diarrhea. It was recommended that the current chronic therapy should be supplemented with products containing Bifidobacterium adsorbed on activated carbon, 2 capsules once daily and Hylak forte 40–60 drops TID. Due to the increased titer of anti-Ascaris antibodies, it was decided to conduct antiparasitic therapy with mebendazole 100 mg BID for 3 days. At the repeated test after 6 weeks, anti-Ascaris antibodies were not detected. Diarrhea persisted.

At the repeated visit after 1 month there were no signs of clinical improvement. Due to the lack of therapeutic effect, colonoscopy with gradual biopsy was recommended for diagnostic purpose. According to fibrocolonoscopic data, the lumen of the cecum, ascending, transverse, descending and sigmoid colons was dilated by 2/3 of diameter. Intestinal mucosa was smooth, shiny, significantly thinned. The vascular patten was increased, not deformed. The sigmoid colon had an additional loop, significantly motile. Histology of the material sampled from four segments of the large bowel (ascending, transverse, descending colon and sigmoid) showed chronic erosive colitis with significant hyperplasia of the lymphoid follicles. Taking into account the clinical presentation that was not typical of erosive colitis, a decision was made to repeat histologic examination to rule out microscopic colitis. Medical therapy was started: 5-aminosalycilic acid (granulated, Mesalazine), 2000 mg/day.

Repeated histology of the endoscopy specimen showed the following: the colon mucosa showed changes of similar pattern (Figure 1): dystrophy, necrobiosis and large areas of desquamation of the superficial epithelial cells. A number of lymphocytes was noted between the epithelial cells (up to 20–25 per 100 epithelial cells), as well as single eosinophils. The subepithelial collagen layer thickness was increased, up to 20–30 μm in some areas (more in distal segments of the colon). The intestinal glands were shallow, with normal structure. The epithelial layer of the glands contained a large amount of goblet cells. The lamina propria was diffusely infiltrated with lymphocytes and plasmocytes with a significant admixture of eosinophils. Follicle-like aggregations of lymphocytes. Inflammatory infiltrative cells did not spread to the submucosa. According to the histologic data, MC in the form of CC was verified.

Therefore, taking into account the clinical signs, chronic watery diarrhea, moderate abdominal pain, lack of effect of enzyme preparations, probiotics and prebiotics, lack of significant abnormalities according to the instrumental data, as well as histological examination (increase in the thickness of the subepithelial collagen layer in separate areas up to 20–30 μm), collagenous MC

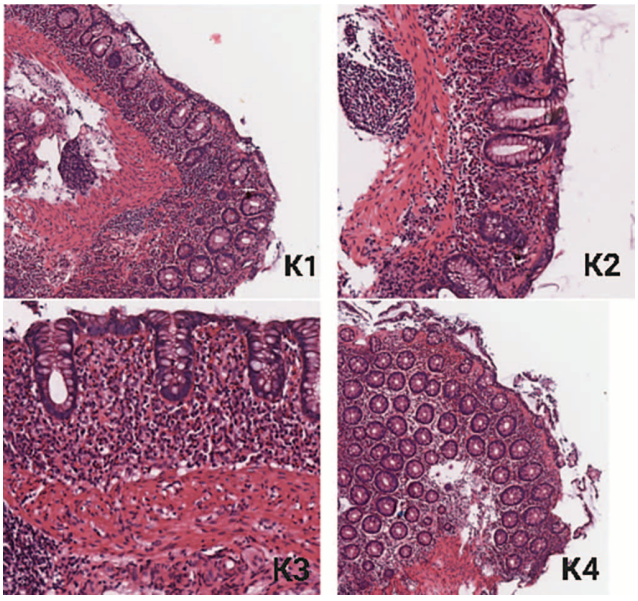

Figure 1. *Histological examination of endoscopic material from the ladder biopsy of the intestine (description in the text)*

Note: In the micropreparations shows fragments of the ascending (K1), transverse colon (K2), descending (K3) and sigmoid colon (K4). There is dystrophy, necrobiosis and extensive areas of desquamation of cells of the surface epithelium. The thickness of the layer of subepithelial collagen is increased, in some areas up to 20-30 microns

was diagnosed, continuously recurrent form, of moderate severity, which required prescription of a topical glucocorticosteroid (GCS) budesonide 9 mg per day.

Within two months after loading dose of GCS the patient noted normalization of stool, improvement of the general well-being, and stabilization of the emotional state. At the second visit after 6 months of treatment with GCS, there were no clinical signs of disease; the patient stopped using diapers. A decision was made to reduce a dose of budesonide to 6 mg/day with tapering of GCS. Currently the patient does not use GCS. After discontinuation, there were no signs of recurrence.

Discussion

In most cases MC is not life-threatening, but it affects quality of life. Therefore, timely diagnosis of the condition is an urgent problem [5].

MC has no specific syndromes or signs. MC can be suspected in the presence of the following conditions: watery diarrhea more than 3 times a day over a long time without blood admixture, infection and inflammation, complaints of fecal incontinence, patient's age >50 years, concomitant autoimmune diseases (e.g., Raynaud, Sjögren, rheumatoid arthritis, etc.), long-term use of cytostatics or monoclonal antibodies. The only method of diagnosis confirmation is fiberoptic colonoscopy with targeted biopsy and histologic examination. It is mandatory to perform sampling from all segments of the large bowel [2, 3].

MC treatment is aimed at reducing inflammation and diarrhea intensity. Treatment should be based on the use of GCSs: in the majority of cases, topical GCS (budesonide 9 mg/day) is recommended for three months. Due to the high frequency of relapses a number of experts consider it reasonable to continue budesonide at a dose of 6 mg/day up to 3 months followed by its use at a dose of 3 mg/day up to 6 months [3, 5].

It should be noted that MC is a diagnosis of exclusion, which requires a highly thorough examination and histologic examination by an experienced morphologist. Unfortunately, if MC is not verified, therapy is inadequate. Most commonly IBS is masked by MC, which leads to a prolonged lack of the appropriate therapy. The main differences between MC and IBS are age (most often, young age in IBS and old age in MC) and the character of stool (2–4 times/day, not abundant, unformed in IBS, 4–5 times/day, abundant, loose in MC). Malabsorption and weight loss, as well as comorbid with autoimmune condition, are not uncommon (Table 1). Histologic examination of the intestinal mucosa is the gold standard in the diagnosis of MC [2, 3, 5].

Taking into account the above data, it is important to apply the algorithm of diagnosis and examination of such patients to identify such rare condition as MC. It is necessary to develop domestic algorithms for routing patients with CM like in other chronic diseases [6].

The biomedical research database Pubmed contains 78 publications on the query "microscopic colitis clinical case" over the past 5 years (135 cases over 10 years). Although it should be noted that only 27 articles specifically described microscopic colitis; in other publications this condition is discussed with regard to differential diagnosis. Russian Science Citation Index (RSCI) contains information on only two clinical cases: lymphocytic and incomplete variants of microscopic colitis in women over 50 years of age [7, 8].

When comparing the published data with the presented clinical observation, the relatively young age of the patient (42 years) is noteworthy, while most described cases of microscopic colitis occur in patients older than 50 years.

A rather large number of clinical situations is associated with the use of drug products. Therefore, Monjur Ahmed and Gloria Francis (2018) described a clinical case of pembrolizumab-induced microscopic colitis. A 54-year-old patient received pembrolizumab for squamous cell nasopharyngeal carcinoma. After a long-term treatment period, persistent diarrhea developed within 3 weeks. Instrumental and laboratory data did not show organic abnormalities. Therefore, a decision was made to conduct gradual biopsy of the large bowel. Based on the results, LC was diagnosed. Pembrolizumab is

Table 1. *Clinical differences between irritable bowel syndrome and microscopic colitis*

	Irritable bowel syndrome	Microscopic colitis
Patient's age	In most cases under 50 years of age	In most cases over 50 years of age
Character of stool	2-4 times a day sparse, unformed	4-5 times a day, plentiful, liquid
Fecal incontinence	Rarely	Often
Maladsorption syndrome and weight loss	Rarely	Often
Comorbidity with autoimmune diseases	Rarely	Often
Comorbidity with psychosomatic diseases, stress	Often	Rarely

a G4 humanized immunoglobulin, which, in turn, may trigger autoimmune reaction in the form of MC [9].

Early publications describe some clinical cases associated with the use of proton pump inhibitors (PPI). Gilbert M. et al. (2009) described 4 clinical cases of MC during treatment with PPI. Long-term therapy with PPI was prescribed to the patients with peptic ulcer or gastroesophageal reflux. After long-term treatment with these products, persistent diarrhea with an unknown cause developed in 4 patients. Only after biopsy MC was diagnosed, after which budesonide was prescribed, and diarrhea resolved [10].

In the majority of the analyzed cases patients had extensive comorbidities, including various autoimmune conditions.

In the described clinical case, the patient did not receive any drug products that may cause MC. The patient had no comorbidities either. Although clinical course of the MC in a patient was similar to that described in literature. The only specific syndrome typical of MC in this patient was persistent watery diarrhea resistant to the symptomatic therapy. This underlines the importance of the thorough history taking and appropriate assessment of the clinical signs within the patient-oriented approach.

According to the literature, the treatment is based on the use of topical GCS (budesonide), although in a large number of patients it did not lead to a strong remission [2]. In this case, a rapid favorable effect of treatment was noted followed by a strong remission.

Conclusion

Therefore, histologic pattern plays a major role in the diagnosis of MC. In cases of diarrhea of unclear etiology and lack of visible changes on colonoscopy, a gradual biopsy is necessary to verify diagnosis. After accurate diagnosis, treatment with GCS is indicated to reduce the severity of clinical signs of MC and improve prognosis.

Вклад авторов

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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