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The Result of Timely Therapy for Whipple's Disease: a Clinical Case

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Aim: to provide basic information on Whipple's disease necessary for timely diagnosis and treatment, using the example of clinical observation.
Key points. Whipple's disease is a rare systemic infectious disease that internists, gastroenterologists, rheumatologists, and other physicians may encounter. The incidence of Whipple's disease is extremely low and amounts to 1 case per 1,000,000–10,000,000 people. The low prevalence of pathology can lead to underdiagnosis in favour of more common diseases. This, in turn, may worsen the patient's prognosis, as it will delay the time for establishing the correct diagnosis and initiating the necessary therapy. A 50-year-old man complained of losing 10 kg of weight over 5 months, abdominal pain and bloating, pain in the joints of feet, and shoulders, accompanied by swelling and hyperemia. The disease began with articular syndrome followed by diarrhea and manifestations of malabsorption (iron deficiency anemia, hypoalbuminemia, hypercholesterolemia). The diagnosis was established on the basis of morphological changes in biopsy samples of the postbulbar part of the duodenum. The identified changes were represented by thickening of the villi and accumulations in the stroma of large macrophages ($CD68^+$) with wide light cytoplasm containing abundant accumulations of PAS-positive, negative when stained with carbol fuchsin according to Ziehl — Nielsen and auramine-rhodamine (under microscopy in luminescence mode) short rods, as well as numerous optically empty small and larger cavities. Treatment with intravenous injections of ceftriaxone 2 g per day for 14 days and trimethoprim/sulfamethoxazole 1920 mg per day for 8 months led to improved health, normalization of laboratory parameters, endoscopic and morphological findings. Treatment with trimethoprim/sulfamethoxazole is planned to be continued for up to 12 months or longer if necessary.
Conclusion. Timely diagnosis and initiation of antibiotic therapy will help to avoid late complications of the disease, including death.
Keywords: Whipple's disease, *Tropheryma whipplei*, malabsorption, trimethoprim/sulfamethoxazole
Conflict of interest: the authors declare no conflict of interest.

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Болезнь Уиппла: клинический случай и обзор литературы

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Цель: предоставить основную информацию по болезни Уиппла, необходимую для своевременной диагностики и лечения данного заболевания, на примере клинического наблюдения.
Основные положения. Болезнь Уиппла — редкое системное инфекционное заболевание, с которым могут столкнуться терапевты, гастроэнтерологи, ревматологи и врачи других специальностей. Заболеваемость крайне низка и составляет 1 случай на 1–10 млн человек. Редкость болезни Уиппла приводит к гиподиагностике в пользу более часто встречаемых заболеваний. Это, в свою очередь, может ухудшить прогноз пациента, поскольку отсрочит время установления правильного диагноза и начала необходимой терапии. Пациент 50 лет предъявлял жалобы на похудание на 10 кг за 5 месяцев, абдоминальную боль и вздутие живота, боли в суставах стоп и кистей, плечевых суставах, которые сопровождались припухлостью и гиперемией. Заболевание началось с суставного синдрома с присоединением диареи и проявлений мальабсорбции (железодефицитная анемия, гипоальбуминемия, гипохолестеринемия). Диагноз установлен на основании морфологических изменений в биоптатах постбульбарного отдела двенадцатиперстной кишки с утолщением ворсин и скоплениями в строме крупных макрофагов (CD68$^+$) с широкой светлой цитоплазмой, содержащих обильные скопления ШИК-позитивных, негативных при окрашивании карболовым фуксином по Цилю — Нильсену и аурамином-родамином (при микроскопии в режиме люминесценции) коротких палочек, а также за счет формирования многочисленных оптически пустых мелких и более крупных полостей. Лечение внутривенными инъекциями цефтриаксона 2 г в сутки в течение 14 дней и триметоприм/сульфаметоксазолом 1920 мг в течение 8 месяцев привело к улучшению самочувствия, нормализации лабораторных показателей, эндоскопической и морфологической картины. Лечение триметоприм/сульфаметоксазолом планируется продолжить до 12 месяцев или более при необходимости.
Заключение. Своевременные установление диагноза и начало антибактериальной терапии позволят избежать поздних осложнений заболевания, в том числе летального исхода.
Ключевые слова: болезнь Уиппла, *Tropheryma whipplei*, мальабсорбция, триметоприм/сульфаметоксазол
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Epidemiology of Whipple's disease

Whipple's disease (WD) is a systemic infectious disease caused by the bacterium *Tropheryma whipplei*, affecting the small intestine, mesenteric lymph nodes, and accompanied by extraintestinal manifestations. The pathology was first described by the American pathologist George Hoyt Whipple in 1907 as intestinal lipodystrophy [1], and by 2021 (114 years later) about 1200 cases have been described in the literature [2]. The annual incidence is extremely low and, according to various sources, ranges from 1–6 cases per 10 million [3] to 1–3 cases per 1 million people [4, 5]. WD is thought to be more common in Caucasian men over 40 years of age [6].

At the same time, according to the results of a US national study, which included almost 36 million medical cards for the period 2012–2017, the prevalence of WD is 9.8 cases per 1 million population, with the disease more often detected in Caucasians and people over 65 years. No differences in prevalence by sex were found in this population-based study [7].

Etiology and pathogenesis

The prevalence of WD among people in contact with land, animals and wastewater is typical. *Tropheryma whipplei*, which causes the disease, is a Gram-positive actinomycete. Once in the human small intestine, they are captured by macrophages of the mucosa, which then migrate to the submucosal layer. *T. whipplei* can suppress immunological response, as a result of which macrophages, despite the preserved function of phagocytosis, lose the ability to lyse the pathogen. Increasing infiltration of macrophages affected by *T. whipplei* leads to compression of the lymphatic vessels of the small intestinal villi, causing lymphostasis and malabsorption syndrome. Lipids are the first to suffer from malabsorption, gradually accumulating in the lamina propria of the intestinal mucosa (hence the name "lipodystrophy"). Later the absorption of other macro- and microelements is disrupted. Apoptosis of affected macrophages is accompanied by the release of the pathogen followed by dissemination through the lymphatic and blood vessels with systemic spread to the small intestine, brain, heart, lungs, kidneys, bone marrow, skin, and joints [3, 6, 8–11].

Clinical manifestations

Features of pathogenesis determine the polymorphism of clinical manifestations. In the classic version (about 80 % of cases) WD has a staged progression.

The early (latent, prodromal) phase is characterized by nonspecific symptoms and can last up to 6–8 years. Up to 90 % of patients in this phase have migratory polyarthritis of peripheral joints (ankle, knee, shoulder, wrist, hand) and axial spondyloarthritis. Contacting a rheumatologist at this stage can lead to a false diagnosis of seronegative poly- or oligoarthritis, and the prescription of immunosuppressive therapy worsens the clinical situation.

In 40–60 % of patients low-grade intermittent fever, lymphadenopathy, and hyperpigmentation of exposed skin develop. This is often mistakenly interpreted as Addison's disease.

The disease enters a progressive form (advanced phase) 6–8 years later, which is characterized by the appearance of gastrointestinal symptoms: diarrhea (70–85 %), abdominal pain (50–90 %) and weight loss (80–90 %). The stool is usually watery, occurs periodically, and is accompanied by colicky abdominal pain. Isolated steatorrhea is quite rare. Weight loss averages 11 kg (cases of weight loss ranging from 3 to 36 kg have been reported).

In late phase (occurs on average after 8 years), neurological symptoms may appear, the range of manifestations of which is very wide (from headaches and insomnia to cerebellar palsy, epilepsy, and oculomotor nerve palsy). It is worth noting that central nervous system (CNS) involvement occurs relatively infrequently, occurring in only 20–30 % of cases.

Also, in the late phase of the disease, damage to the lungs (prolonged cough, pain associated with pleurisy; from 35 to 65 %), heart (pathological noises, including pericardial friction noise, conduction disturbances according to ECG; from 35 to 60 %), eyes (vision loss, uveitis, and retinitis) and other organs (isolated cases) are described [4, 6, 12].

Diagnostics

Laboratory tests often show elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count, and platelet count. In addition, malabsorption syndrome is characterized by iron deficiency anemia, hypoproteinemia and hypoalbuminemia, hypocholesterolemia, deficiency of vitamins and microelements (iron, calcium and others) [3, 4].

If Wipple's disease is suspected based on the clinical picture and blood tests, it is necessary to confirm the presence of the pathogen *T. whipplei* using histological examination or polymerase chain reaction (PCR). Any tissue, the damage to which explains the existing symptoms, can be used as a material for morphological investigation, but the standard is the examination of the mucosa of the distal duodenum. Taking cerebrospinal fluid is necessary to exclude involvement of CNS in pathological processes. A variant of the algorithm for examining patients with suspected WD is presented in Figure 1 [4].

For decades, confirmation of the diagnosis was based on the identification of diastase-resistant, non-acid-fast, PAS-positive inclusions in macrophages found primarily in the lamina propria of the duodenal mucosa (PAS-positive macrophages). The sensitivity of PAS staining is 70–80 % for various forms of WD, but another pathogen, *Mycobacterium avium*, can also give a positive reaction. Ziehl — Neelsen staining, which detects acid-fast microorganisms, including mycobacteria, should be performed for differential diagnosis [4]. In addition, 9 % of patients with WD have granulomas, predominantly located in the lymph nodes and liver, less often in other affected tissues, which is often mistakenly considered a diagnosis of sarcoidosis (if PAS staining was not performed) [6]. The accuracy of histological examination can be increased by additional immunohistochemical staining with antibodies to *T. whipplei* [4].

PCR (especially real-time PCR) of biopsies or cerebrospinal fluid has greater sensitivity and specificity compared to PAS staining, but the method is not available everywhere. Serological diagnosis of WD is considered impractical, since antibodies to *T. whipplei* can be detected in healthy people and asymptomatic bacteria carriers, and at the same time completely absent in patients with the classic course of the disease [4].

To take biopsy samples of the mucosa of the duodenum, all patients with suspected WD undergo gastroscopy, during which characteristic changes can also be identified. Although the endoscopic findings are variable, typical changes in WD include hyperemia and swelling of the duodenal mucosa, an increase in its folds, small and large lymphangiectasias, enlarged villi and white-yellowish ring-shaped structures inside the villi [13].

Treatment

Treatment regimens vary from country to country, but each is based on the ability of the antibacterial agent to cross the blood-brain barrier. Thus, the drugs of choice include penicillin antibiotics, tetracyclines, trimethoprim/sulfamethoxazole. In the absence of a response to antibacterial therapy, the use of γ-interferon is promising [4, 14]. In Germany, standard treatment includes intravenous induction therapy with ceftriaxone or meropenem for 14 days followed by oral maintenance therapy with trimethoprim/sulfamethoxazole for 12 months [15]. In Russia, a similar regimen is also being considered: for induction therapy, ceftriaxone (2 g once daily intravenously) or meropenem (1 g 3 times daily intravenously) is prescribed for 14 days. If CNS is affected, the doses of drugs are doubled or procaine benzylpenicillin 1.2 million units/day intramuscularly (or potassium benzylpenicillin 1.2 million units/day every 4 hours intravenously) is used in combination with streptomycin 1 g intravenously once a day. Next, it is necessary to switch to maintenance therapy of 80 mg trimethoprim/400 mg sulfamethoxazole, 2 tablets 2 times a day orally for 12 months. An alternative if this combination is intolerant is doxycycline (100 mg twice daily orally) and hydroxychloroquine (200 mg three times daily orally) for one year [3]. There is an opinion that antibacterial therapy for WD should last at least two years [14]. Clinical improvement may be observed already in the first week of treatment, neurological

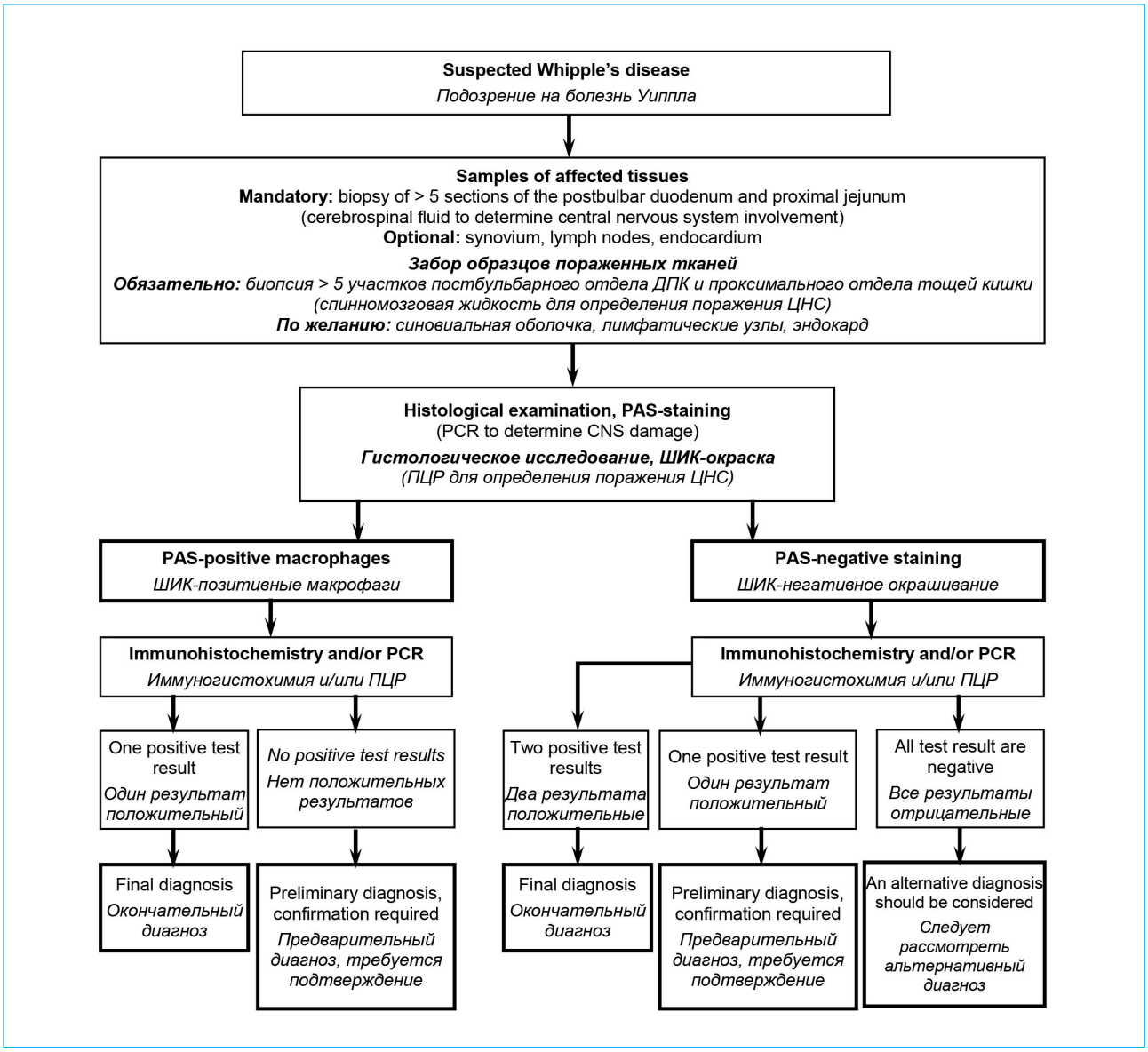

Figure 1. Algorithm for examining patients with suspected Whipple's disease

Рисунок 1. Алгоритм обследования пациентов с подозрением на болезнь Уиппла

symptoms persist longer, and regression of morphological changes is even slower and may be incomplete. The criterion for the effectiveness of therapy and the onset of remission is the disappearance of foamy macrophages in the histological material [3, 14].

Prognosis

With timely initiation of therapy, the prognosis for WD is generally favorable. However, in 8–35 % of cases, relapses of the disease are possible, which requires dynamic monitoring of patients with WD [9]. Without antibiotic therapy, WD can result in death, which usually occurs 1–2 years from the onset of intestinal symptoms [14].

Clinical case

Complaints

Patient K., 50-year-old male, applied to Gastroenterological Center "Expert" (St. Petersburg) at the beginning of November 2021. He complained about a pronounced decrease in body weight (lost 10 kg in 5 months), minor pain in the lower abdomen, not associated with food intake and stool, belching with air, bloating, flatulence, periodic pain in the first metatarsophalangeal joints, small joints of the hands, shoulder joints, which were accompanied by swelling and hyperemia, an increase in body temperature to subfebrile values.

Anamnesis morbi

The patient considered himself sick since 2016, when pain appeared in the small joints of the hands

and feet, accompanied by swelling, hyperemia and periodic low-grade fever. He took non-steroidal anti-inflammatory drugs on his own and did not consult a doctor. In May 2021, watery diarrhea occurred up to 5–6 times a day without pathological impurities, intense diffuse cramping pain in the abdomen. He independently took adsorbents, against the background of which a gradual improvement in well-being was observed over 2 weeks. The frequency of stools decreased to 1 time per day, but the mushy consistency remained. Muscle cramps in the upper and lower extremities began to bother the patient, with a positive effect from taking magnesium supplements, and he began to notice progressive weight loss on the background of a regular diet.

In June 2021, due to persistence of symptoms, the man consulted a gastroenterologist at his place of residence. In the biochemical blood test dated June 12, 2021, liver enzymes were within normal values (other indicators were not checked). Coprogram dated June 14, 2021: liquid consistency, a large amount of detritus, striated fibers and fatty acids – in small quantities, red blood cells, leukocytes, protozoa and helminth eggs – not found. Esophagogastroduodenoscopy (EGD) dated June 14, 2021, revealed cardia insufficiency, erosive reflux esophagitis of grade B according to the Los Angeles classification, superficial antral gastritis, duodenogastric bile reflux, and a positive express urease test. Eradication therapy was not carried out; an 8-week course of proton pump inhibitors, ursodeoxycholic acid, and probiotics were prescribed – without any significant effect.

Due to the continued weight loss and mushy stools, the patient independently resumed the examination in the autumn of 2021. In the laboratory tests (from October 18, 2021), there was a decrease in total cholesterol – to 2.59 mmol/L (norm – 3.9–6.5 mmol/L); hypochromic microcytic anemia: decrease in hemoglobin – to 107 g/L (norm – 128–172 g/L), MCH – to 24.4 pg (norm – 27.5–34 pg), MCV – up to 76.2 fl (norm – 79–94 fl); an increase in ESR – to 33 mm/h (norm – 2–15 mm/h).

Due to progressive weight loss and anemia, in November 2021, the man turned to a gastroenterologist at the Gastroenterological center "Expert". According to an objective examination, an asthenic physique was revealed, the body mass index was 22.1 kg/m^2, the skin was pale, dry, the tongue was coated with a white coating, the abdomen was sensitive in the lower parts, otherwise without features. Within the framework of differential diagnosis, the following are assumed: inflammatory bowel diseases, helminthic infestations, celiac disease, oncopathology.

The examination from December 5, 2021, revealed: hypoalbuminemia (albumin – 32.7 g/L; norm – from 40.2 g/L), a slight (< 2 relative to the norm) increase in α-1-globulins and γ-globulins, a decrease in serum iron (to 2.7 mmol/L; norm – 12.5–32.2 mmol/L), at normal ferritin levels (34.5 ug/L; norm – 20–250 μg/L) and the total iron binding capacity of serum (60.8 mmol/L; norm – 44.7–76.1 mmol/L), a decrease in vitamin B_{12} levels to 168 pg/mL (norm – 180–914 pg/mL), total cholesterol – to 2.6 mmol/L (norm – 4.1–7.2 mmol/L), a significant increase in CRP – to 30.18 mg/L (norm – 0.0–1.0 mg/L). In a clinical blood test, hypochromic microcytic anemia persisted (hemoglobin – 112 g/L), thrombocytosis (platelets – 407 × 10^9/L; norm – up to 308 × 10^9/L) with an increase in thrombocrit to 0.47 % (norm – up to 0.32 %), an increase in ESR to 66 mm/h (norm – 0–15 mm/h) were detected. Antibodies to helminths (echinococcus, opisthorchiasis, toxocara, trichinella) and giardia were negative. Immunological screening for celiac disease: antibodies to endomysium IgA, to tissue transglutaminase IgA, IgG, to deaminated peptides of gliadin IgA, IgG – negative, the total level of IgA was slightly increased – to 5.01 g/L (norm – 0.7–4.0 g/L). Genetic typing for HLA DQ2/DQ8 – the celiac disease haplotype has not been identified. Cancer markers (Ca 242, Ca 72-4, Ca 19-9, REA) were negative. An increase in calprotectin to 1300 μg/g was detected.

According to the results of intestinal ultrasound from December 12, 2021, diffuse changes in mesenteric fatty tissue by the type of inflammatory infiltration, moderate mesenteric lymphadenopathy were revealed. With EGD from December 12, 2021, in the postbulbar department, the mucosa is edematous, light gray in color, the height of the villi is sharply reduced, areas with reduced villi height alternate with lint-free zones, the preserved villi are heterogeneous, have different lengths and thicknesses, and pronounced lymphostasis is determined against this background. Conclusion: duodenopathy; it is necessary to exclude celiac disease, lymphoproliferative disease (Fig. 2).

During a video colonoscopy from December 12, 2021, in the ileum, the mucosa is light gray, edematous, with signs of lymphostasis, the villi are heterogeneous, have different heights and diameters. Conclusion: terminal ileitis with signs of lymphostasis; it is necessary to exclude lymphoproliferative disease.

Histological conclusion: biopsy from the duodenum – xanthoma of the duodenum mucosa (PAS-positive staining), to exclude signet-ring cell carcinoma, immunohistochemical examination of biopsy specimens in a specialized oncological institution is indicated; biopsy from the ileum – focal superficial inactive moderately pronounced enteritis (ileitis), without exacerbation of the process, with local hyperplasia of the lymphoid apparatus of the mucosa the small (ileum) intestine.

To exclude celiac disease, morphometry of biopsy specimens from the duodenum was performed

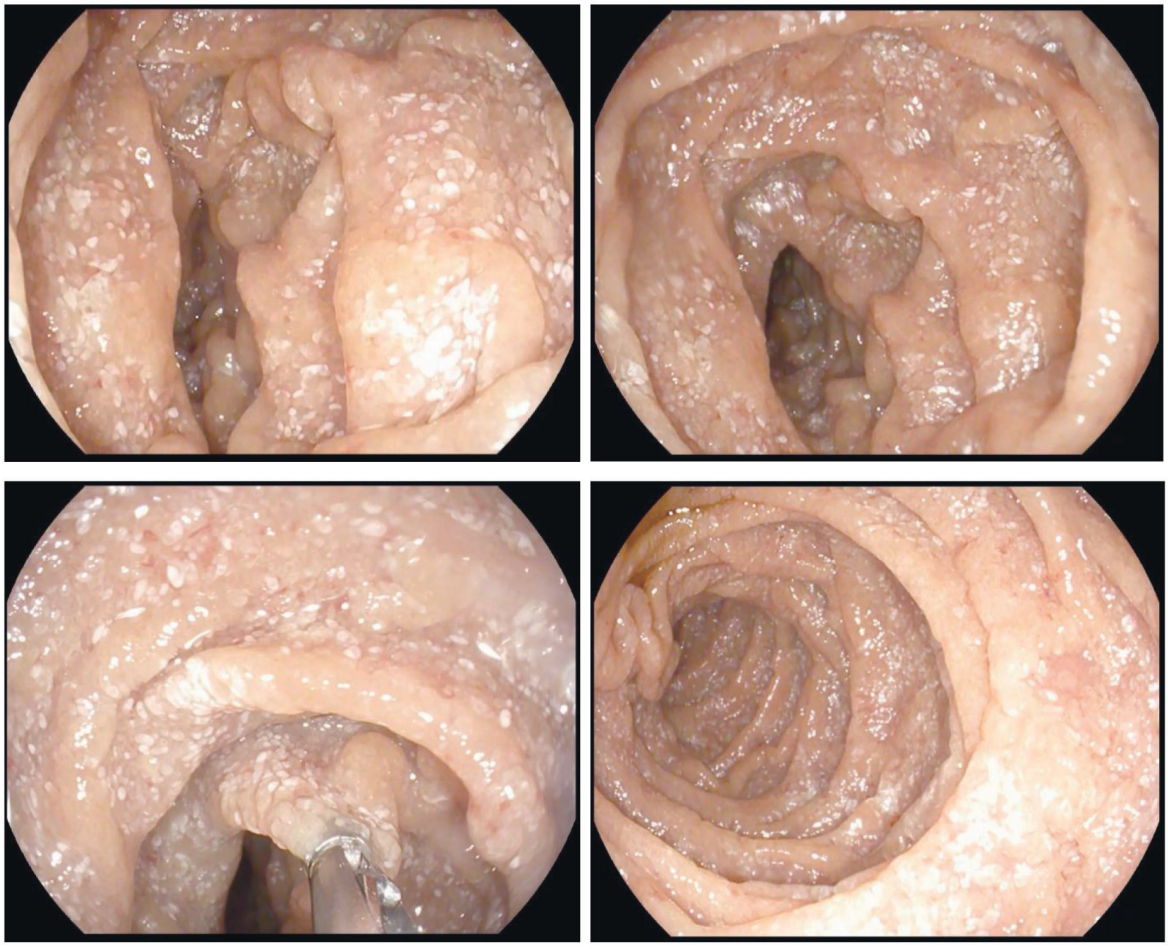

Figure 2. Duodenal mucosa of Patient K. on EGDS from December 12, 2021

Рисунок 2. Слизистая оболочка ДПК пациента К. на ЭГДС от 12.12.2021 г.

(Fig. 3), in which a pronounced focal multifocal violation of the architectonics of the mucous membrane was detected with thickening of the mucous membrane and deformation of the villi with the formation of large club-shaped structures, deepening of crypts. In its own plate of the mucosa, there is a pronounced expansion of lymphatic slits with the formation of cysts located close to each other, abundant dense macrophage infiltration with the presence of eosinophilic foamy masses in the cytoplasm of macrophages, a small number of neutrophil granulocytes, lymphocytes and plasmocytes diffusely located between macrophages. The number of goblet-shaped and Paneta cells is reduced, epithelial cells are flattened, and desquamated in places on the tops of the villi. The number of intraepithelial lymphocytes is not increased. Conclusion: chronic duodenitis of the third degree of severity, high degree of activity with the phenomena of lymphostasis and macrophage infiltration characteristic of Whipple's disease. There is no data for celiac disease. PCR is recommended for differential diagnosis with corynebacteriosis, sarcoidosis, histoplasmosis, mycosis, *Mycobacterium avium* infection.

During the examination, the patient received therapy with iron preparations, enzymes, antispasmodics, probiotics, prebiotics — without significant effect.

From May 9 to May 17, 2022, the patient was hospitalized in the Clinical Infectious Diseases Hospital named after. S.P. Botkin due to increasing weakness and dehydration against the background of ongoing diarrhea. During a hospital examination, according to computed tomography of the abdominal organs, single enlarged paraaortic lymph nodes, perilymphatic infiltration of the fiber of the abdominal cavity and retroperitoneal space were revealed. The clinical blood test showed a decrease in hemoglobin (to 74 g/L), an increase in platelets (to 595×10^9/L), leukocytes (to 9.64×10^9/L), ESR (to 89 mm/h). In the biochemical analysis of blood, an increase in the level of CRP (15.4 mg/L), a decrease in serum iron (7.39 mmol/L) were observed. Leukocytes were detected in the coprogram

(3–6 in the field of vision), helminth eggs were not detected. Fecal seeding into dysentery and typhoparathyphosis groups — without growth. The reaction of indirect hemagglutination with salmonella and dysentery antigens was negative. The condition was regarded as a lymphoproliferative disease complicated by iron deficiency anemia of moderate severity. Infusion, antibacterial (metronidazole), syndromic (sorbents, antispasmodics) and symptomatic therapy were performed. Upon discharging from the clinic, iron preparations, probiotics, and a hematologists consultation were recommended to resolve the issue of sternal puncture and routing to the oncological center.

By the time of discharge from the Clinical Infectious Diseases Hospital, the result of an additional histological examination of biopsy specimens of the duodenum (auramin-rhodamine staining, immunohistochemical study of CD68) was obtained: the structure of the mucous membrane of the duodenum was changed due to abundant accumulations in the stroma of large macrophages ($CD68^+$) with a wide light cytoplasm containing abundant accumulations of PAS-positive, negative when stained with carbol fuchsin according to Ziehl — Neelsen and auramine-rhodamine (under microscopy in luminescence mode) short rods, as well as due to the formation of numerous optically empty small and larger cavities. The villi are thickened, partially smoothed. The epithelial lining is preserved, mucus formation is uniform. Conclusion: the existing morphological changes are characteristic of Whipple's disease; the mycobacterial (tuberculosis, atypical mycobacteriosis) nature of the existing changes is excluded (Fig. 4).

After receiving the histology result on May 28, 2022, the patient appeared for a repeat appointment with the attending physician at the Gastroenterological center "Expert". After discharge

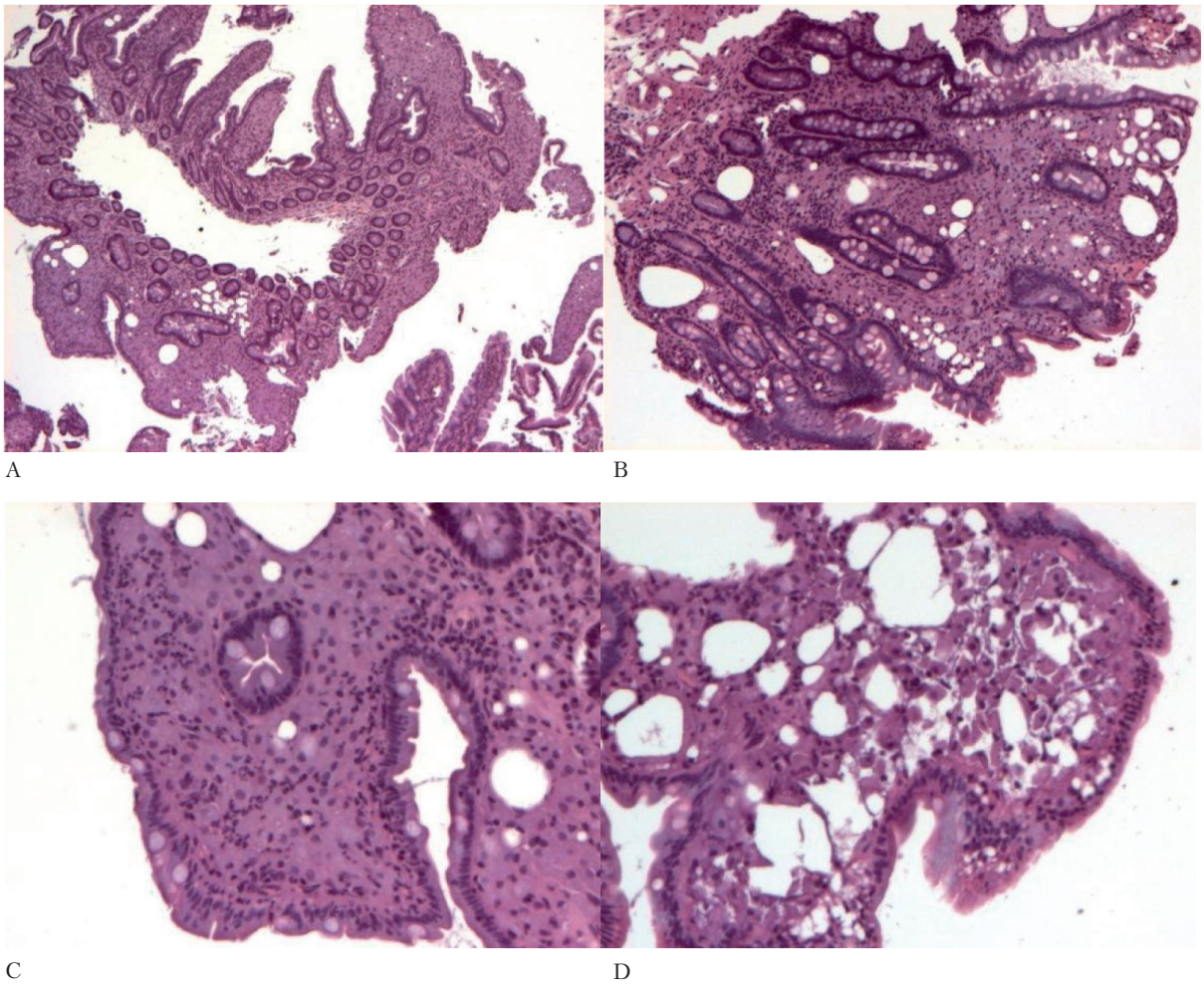

Figure 3. Histological examination of biopsy samples of the duodenal mucosa of Patient K. (hematoxylin and eosin staining; magnification: A — 40×, B — 100×, C, D — 400×)

Рисунок 3. Гистологическое исследование биоптатов слизистой оболочки ДПК пациента К. (окраска гематоксилином и эозином; увеличение: А — 40×, В — 100×, С, D — 400×)

from the hospital, the patient retained a mushy stool 2–3 times a day. Taking into account the confirmed diagnosis of "Whipple's disease", therapy was prescribed: ceftriaxone 2 g intravenously for 14 days; after it from June 13, 2022, trimethoprim/sulfamethoxazole 480 mg 2 tablets 2 times a day for 12 months; a course of iron supplementations (iron sulfate + ascorbic acid 100 mg + 60 mg, 1 tablet twice a day for 2 months), enzymes (pancreatin 25,000 units with each meal for 2 months), hepatoprotector (ademetionin 400 mg, 1 tablet twice a day for 2 months), probiotic (Saccharomyces boulardi 250 mg twice a day for 14 days).

Against the background of antibacterial therapy, the patient began to notice a significant improvement in well-being, complete normalization of stool, body weight gain (from 70 kg in autumn 2021 to 82 kg by January 2023). There was a positive dynamic of laboratory parameters (Table). During the control visits, iron therapy, enzyme replacement, antispasmodic, and hepatoprotective therapy were corrected.

The results of the control EGD on January 15, 2023: in the postbulbar department, the mucosa is edematous, the villi are smoothed, the height of the villi is reduced, against this background there

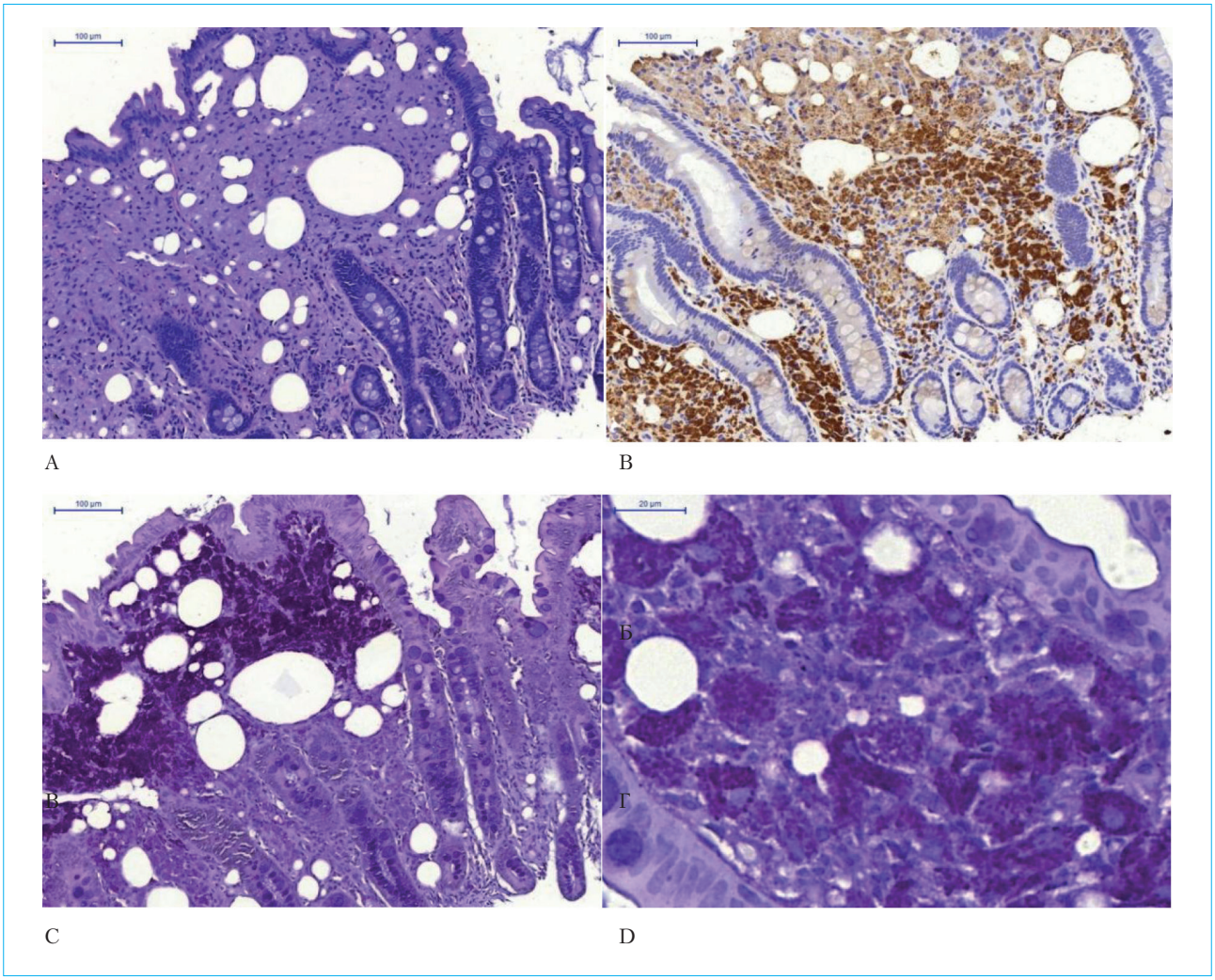

Figure 4. Additional histological examination of duodenal mucosa biopsy specimens of Patient K. Pathological changes in the duodenal mucosa: a significant expansion of the mucosal stroma (A) due to accumulations of numerous CD68^{+}-macrophages with a wide cytoplasm (B) containing numerous PAS-positive rods (C, D) (A — staining with hematoxylin and eosin; B — immunohistochemistry (CD68); C, D — PAS-reaction; scale bar length: A, B, C — 100 µm, D — 20 µm)

Рисунок 4. Дополнительное гистологическое исследование биоптатов слизистой оболочки ДПК пациента К. Патологические изменения слизистой оболочки ДПК: значительное расширение стромы слизистой оболочки (А) за счет скоплений многочисленных CD68^{+}-макрофагов с широкой цитоплазмой (В), содержащих многочисленные ШИК-позитивные палочки (С, D) (А — окраска гематоксилином и эозином; В — иммуногистохимический анализ (CD68); С, D — ШИК-реакция; длина масштабного отрезка: А, В, С — 100 мкм, D — 20 мкм)

is a whitish spot plaque. Conclusion: duodenopathy, positive dynamics in comparison with the study from December 2021 (as part of the endoscopic remission of Whipple's disease) (Fig. 5). A biopsy was performed. The conclusion of the histological examination: chronic duodenitis of the second degree of severity, moderate degree of activity with focal pronounced lymphangiectasia and macrophage infiltration persisting in part of the biopsies, characteristic of Whipple's disease (Fig. 6). According to colonoscopy, the mucous membrane of the ileum is pink, velvety, without defects.

Currently, the patient continues to receive antibacterial therapy with trimethoprim/sulfamethoxazole. The planned total duration of treatment is at least 12 months.

Discussion

This clinical case demonstrates the difficulty of establishing a diagnosis of Wipple's disease due to the non-specificity of the clinical manifestations, which necessitates differential diagnosis with rheumatological pathology (initial manifestations of the disease in the form of joint syndrome), a number of gastroenterological diseases (inflammatory bowel diseases, celiac disease, etc.), lymphoproliferative diseases and oncopathology. If Wipple's disease is suspected, in order to confirm the diagnosis, it is necessary to perform a complex of laboratory and instrumental studies that require certain technical equipment in the clinical diagnostic center and laboratory, and sufficient experience of specialists conducting these studies is required.

Table. Dynamics of laboratory parameters of the Patient K.
Таблица. Динамика лабораторных показателей пациента К.

Parameter *Показатель*	Date of the test / *Дата проведения анализа*					
	December, 2021 *декабрь 2021 г.*	May, 2022 *май 2022 г.*	Start of antibiotic therapy May 28, 2022 *Начало антибактериальной терапии 28.05.2022*	July, 2022 *июль 2022 г.*	October, 2022 *октябрь 2022 г.*	January, 2023 *январь 2023 г.*
Red blood cells, 10^{12}/L *Эритроциты, 10^{12}/л*	4.7	3.8		5.1	5.0	4.6
Hemoglobin, g/L *Гемоглобин, г/л*	112 ↓	73 ↓		138	149	148
Platelets, 10^9/L *Тромбоциты, 10^9/л*	407 ↑	540 ↑		299	249	274
White blood cells, 10^9/L *Лейкоциты, 10^9/л*	8.01	9.64 ↑		9.78 ↑	8.39	7.16
ESR, mm/h *СОЭ, мм/ч*	66 ↑	89 ↑		45 ↑	8	14
CRP, mg/L *СРБ, мг/л*	30.2 ↑	15.4 ↑		2.1 ↑	1.4 ↑	1.4 ↑
Total protein, g/L *Общий белок, г/л*	71.0	–		78.8	–	–
Albumin, g/L *Альбумин, г/л*	32.7 ↓	–		42.9	–	–
Total cholesterol, mmol/L *Холестерин общий, ммоль/л*	2.6 ↓	–		3.8 ↓	4.2	4.4
Triglycerides, mmol/L *Триглицериды, ммоль/л*	0.58	–		0.83	0.86	1.13
Iron, μmol/L *Железо, мкмоль/л*	2.7 ↓	7.4 ↓		25.1	23.2	18.1
Ferritin, μg/L *Ферритин, мкг/л*	34.5	16.0 ↓		85.4	129.2	138.0
Calprotectin, μg/g *Кальпротектин, мкг/г*	1300 ↑	–		74.6 ↑	28.5	–

Note: ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; ↑ – above normal values; ↓ – below normal values.
Примечание: СОЭ – скорость оседания эритроцитов; СРБ – С-реактивный белок; ↑ – выше нормальных показателей; ↓ – ниже нормальных показателей.

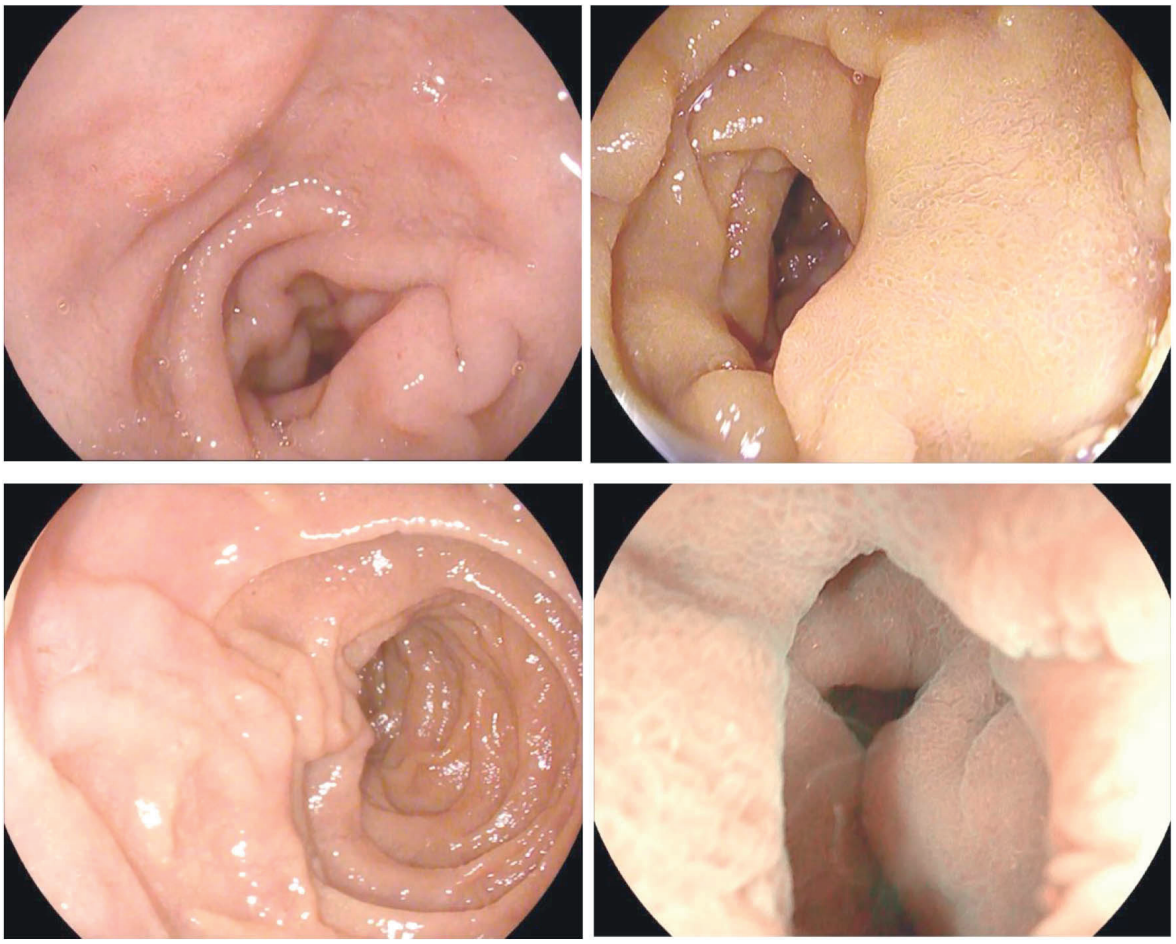

Figure 5. Duodenal mucosa of Patient K. on EGDS from January 15, 2023. Normal endoscopic appearance of the duodenum

Рисунок 5. Слизистая оболочка ДПК пациента К. на ЭГДС от 15.01.2023 г. Нормальная эндоскопическая картина ДПК

After the appearance of gastroenterological complaints in the form of diarrhea, severe weight loss and the development of malabsorption syndrome, 11 months later, as a result of patient K.'s visit to a specialized gastroenterological center, it was possible to diagnose this rare disease with the help of experienced clinicians, endoscopists and morphologists.

Conclusion

Thus, in a patient with the presence of articular syndrome, with the subsequent development of abdominal pain and diarrhea syndromes, with signs of systemic inflammation and with progressive malabsorption syndrome, it is possible to suspect Wipple's disease. Such a patient should be recommended to undergo an endoscopy with a biopsy from the subbulb sections of the duodenum and subsequent histological examination of the biopsy samples with the obligatory use of PAS staining and Ziehl — Neelsen staining. As an alternative, immunohistochemical examination of biopsies or PCR may be considered if these techniques are available.

Timely diagnosis and initiation of antibacterial therapy will avoid late complications of the disease, including death.

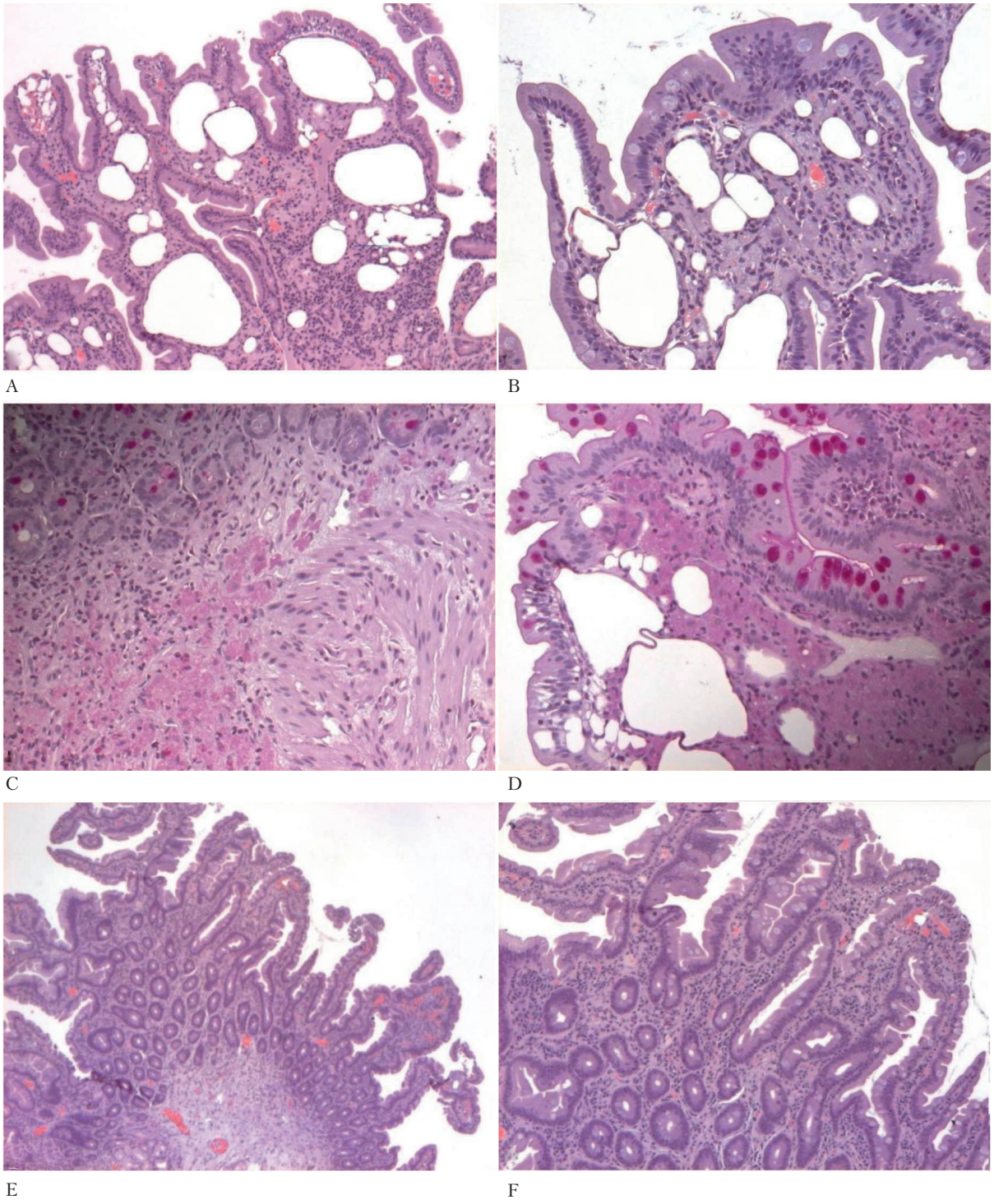

Figure 6. Histological examination of biopsies of the duodenal mucosa of Patient K. during therapy (A, B, C, D — stained with hematoxylin and eosin; E, F — PAS-reaction)

Рисунок 6. Гистологическое исследование биоптатов слизистой оболочки ДПК пациента К. на фоне терапии (A, B, C, D — окраска гематоксилином и эозином; E, F — ШИК-реакция)

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