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Granulomatous bowel disease: Crohn's disease and tuberculosis. Difficulties in differential diagnosis (case report and review)

Armen V. Vardanyan[1], Ekaterina S. Merkulova[1], Victoria A. Belinskaya[1], Ksenia S. Frolova[2], Olga A. Mainovskaya[1]

[1]Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya st., 2, Moscow, 123423, Russia)
[2]Moscow Scientific and Practical Center for Tuberculosis Control (Stromynka st., 10, Moscow, 107076, Russia)

ABSTRACT *Diagnosis of extrapulmonary forms of tuberculosis is still challenging. Abdominal tuberculosis has no pathognomonic signs, so most patients had various diagnoses. In this clinical case, the diagnostic difficulties are due to the absence of a history of tuberculosis and the manifestation of the isolated tuberculosis process in the intestine. This forced us for a wide differential diagnostic search to exclude inflammatory bowel diseases and neoplasms and required the multidisciplinary team. This approach, awareness and alertness of specialists regarding extrapulmonary forms of tuberculosis made it possible to achieve success in this patient.*

KEYWORDS: *abdominal tuberculosis, intestinal tuberculosis, Crohn's disease*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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ADDRESS FOR CORRESPONDENCE: *Armen V. Vardanyan, Ryzhikh National Medical Research Center of Coloproctology, Salyama Adilya st., 2, Moscow, 123423, Russia; e-mail: Vardanyan_avgnck.ru*

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INTRODUCTION

Recently, despite the positive trends in the epidemic situation with tuberculosis worldwide, the incidence of extrapulmonary tuberculosis (EPT) is unstable [1]. Diagnosis of extrapulmonary tuberculosis is difficult, the disease can occur covertly, under the "mask" of other pathological processes (infectious, gastroenterological, surgical, oncological) [2].

Abdominal tuberculosis is an infectious disease caused by mycobacterium tuberculosis, related to extrapulmonary forms of tuberculosis and characterized by the presence of a specific inflammatory process in the abdominal organs [3]. According to epidemiological data, of the extrapulmonary forms of tuberculosis, abdominal tuberculosis accounts for 4.4–8.3% to 17–21% of cases, which does not allow it to be considered a rare disease [4]. The official clinical classification of abdominal tuberculosis includes tuberculosis of the intestine, peritoneum, mesenteric lymph nodes and other forms [5]. The intestine is most often involved in the pathological process, namely the ileocecal zone (70–89.5% of cases), distal forms are rare [6]. It is known that there are no screening methods for the detection of abdominal tuberculosis [7], and all laboratory and instrumental examinations carried out do not always allow to verify the diagnosis.

Clinical Case

Female patient K., 89 years old, with complaints of periodic cramping pain in the lower abdomen, weight loss, an increase in body temperature in the evening to 37.3°C, vomiting once every three days, a half-formed stool 1–2 times per 24 hours without pathological mixtures.

It is known from the anamnesis that in the summer of 2021, against the background of complete

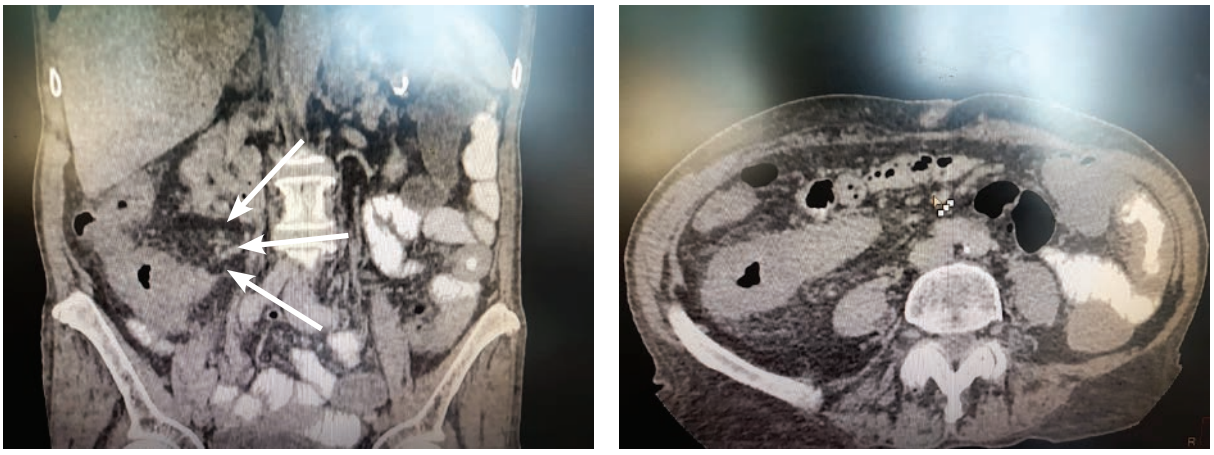

Figure 1. *CT scan. The arrows indicate the thickening of the wall of the ileum and ascending colon, inflammatory infiltrated tissue*

well-being, the patient began to notice episodes of fever up to 40°C. She turned to a therapist at her place of residence. An acute respiratory viral infection was suspected. The analysis for a new coronavirus viral infection was negative; systemic antibacterial therapy was prescribed (she could not specify the drugs) with a positive effect (no fever). Simultaneously she took probiotics.

In November 2021, abdominal pain without a definite site and episodes of unformed stool appeared. She applied to the outpatient clinic at her place of residence and was sent to one of the city hospitals for check-up. A colonoscopy performed in December 2021 revealed a circular narrowing of the lumen of the ascending colon — a tumor was suspected. Biopsies revealed no tumor.

She was sent to the RNMRC of Coloproctology of the Health Ministry of Russia for further examination and verification of the diagnosis.

The initial consultant was oncologist. Objectively: the general condition satisfactory, somewhat asthenized. Height of 158 cm, body weight of 50 kg (BMI = 20 kg/m^2). The skin colored pale, pasty of the lower limbs was noted. No hemodynamic disorders were detected. The tongue was moist, overlaid with a white coating at the root. There was a postoperative scar on the anterior abdominal wall after cholecystectomy without signs of inflammation. The abdomen was not swollen, soft on palpation, painless in all parts. Digital examination of the rectum and proctoscopy were without pathology. The lab tests dated January 17, 2022: total protein — 59.5 g/l, hemoglobin — 91 g/l, platelets — 454x10^9/l.

According to compute tomography (CT) dated January 21, 2022: pulmonary pattern with signs of focal pneumosclerosis, no obvious focal and infiltrative changes were found. The ascending intestine to the area of the hepatic flexure and the terminal part of the ileum were changed for 5 cm, the wall was thickened to 1.0–1.5 cm due to all layers. The surrounding tissues were strongly compacted. The infiltration extended to the peritoneum of the right lateral canal. Along the course of the mesentery vessels, the lymph nodes were up to 0.6 cm. (Fig. 1). Conclusion:

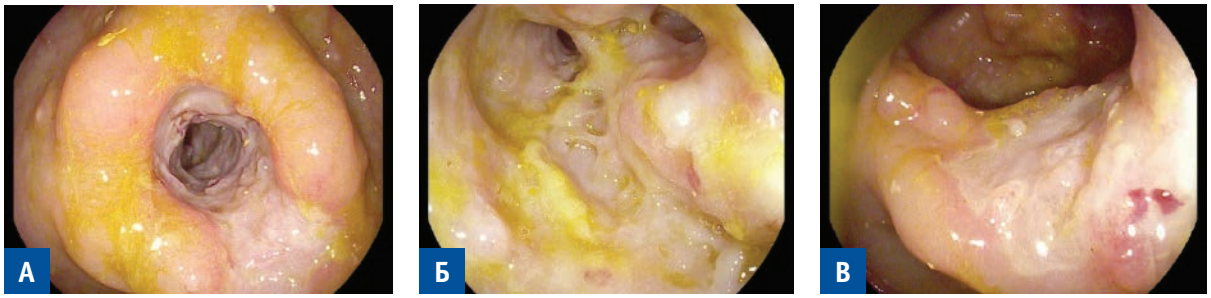

Figure 2 (а,б,в). *Endoscopic images of the ascending colon: а — distal edge of the circular ulcerative defect, б — fistulous openings of the ascending colon, в — ulcerative defect 1.0 cm in diameter.*

The CT picture of infiltrative changes in the ascending colon and ileum may correspond to the tumor process.

According to colonoscopy data dated February1, 2022: the device was carried out in the middle third of the ascending intestine, where the distal edge of the circular ulcerative lesion, elastic consistency is determined, the lumen is narrowed to 1.3 cm. The device was carried out proximally by 5–6 cm, the lumen narrowed to 0.6 cm and internal openings were visualized, which did not exclude the system of fistula tracks. The mucosa here was pale pink, represented by a circular ulcerative lesion, sometimes with a touch of fibrin, bleeding on contact. Distal to the haustra there is an ulcerative lesion occupying ½ of the circumference, bright red in color, with a touch of fibrin. In the hepatic flexure, there was an ulcer1.0 cm, bright red, with a touch of fibrin. In the distal third of the ascending colon — aphthae up to 0.2 cm in diameter with a corolla of hyperemia and a coating of fibrin, a biopsy was performed. The distal parts of the large intestine are not changed (Fig. 2).

Conclusion: the endoscopic picture is difficult to interpret, it is necessary to differentiate between the infiltrative tumor process, Crohn's disease in the stage of ulcers, lymphosarcoma and tuberculosis. The result of histological examination dated February 3, 2022: in the areas of the proper plate of the mucosal and submucosal layer, groups of histiocytic granulomas are determined, partially merging, with single giant multinucleated cells of the Pirogov-Langhans type (Fig. 3). Conclusion: signs of tumor growth (including lymphoproliferative processes) were not found, the morphological picture may correspond to Crohn's disease (differential diagnosis with tuberculosis).

The patient was consulted by a gastroenterologist. Taking into account the patient's age, anamnesis data, tests results, it was suggested that there was a high probability of the infectious nature of the disease. The diagnosis was established: Crohn's disease in the form of ileocolitis (?), intestinal tuberculosis (?). A phthisiologist's consultation was recommended, a study of the level of fecal calprotectin was prescribed, fecal analysis for toxins A and B *Clostridium difficile*, clinical infections. Prescribed treatment: mesalazine 3 grams per 24 hours, metronidazole 1 gram per 24 hours, ciprofloxacin 1 gram per 24 hours, antispasmodics for abdominal pain, a balanced mixture for enteral nutrition.

Against the background of the therapy, the condition remained stable, but the patient's initial complaints persisted. Tests for intestinal infections (yersiniosis, salmonellosis, shigellosis, giardiasis, amoebiasis) and toxins A and B of *Clostridium difficile* are negative. Fecal calprotectin dated February 25, 2022: 538 mcg/g (N = 0–150 mcg/g). At the place of residence, the patient was checked-up by a phthisiologist; the results of the chest CT dated January 21, 2022 were revised, a Mantoux test and sputum examination for the presence of acid-resistant mycobacteria (ARM) were performed, data for active tuberculosis were not received. Lab tests dated March 1, 2022: hemoglobin — 84 g/l, platelets — $574x10^9$/l, total protein — 62 g/l, albumin — 30 g/l.

Taking into account ineffective treatment, negative laboratory changes (progression of anemia, thrombocytosis, hypoalbuminemia), it is recommended to perform magnetic resonance imaging (MRI) of the intestine with contrast.

According to the MRI data dated March 24, 2022: in the terminal part of the ileum for 4.8 cm, in the cecum and ascending colon for 6.2 cm, there is a circular thickening of the wall to 1.0 cm, the lumen is circularly narrowed to 0.5 cm (Fig. 4). In the distal third of the ileum there was a section of circular thickening of the intestinal wall up to 0.9 cm for 4.9 cm, the lumen was narrowed to 0.3 cm. The ileum was proximal to the constriction throughout expanded to 4.5 cm. In the middle third of the ileum there was a section of circular thickening of the intestinal wall up to 0.9 cm for 2.5 cm, the lumen was narrowed to 0.3 cm. The changes accumulated contrast. Conclusion: MR image of segmental lesions of the ileum and ascending colon (it should be differentiated between inflammatory and neoplastic processes). Expansion of the small intestine lumen.

The patient was consulted by a coloproctologist: taking into account the anamnesis, the patient's age, the results of tests, negative

laboratory shifts (decrease in hemoglobin, albumin), ineffectiveness of conservative treatment, preservation of inflammatory narrowing of the small and large bowel, prestenotic dilation, indications for surgery were set. The patient's consent to the surgery was obtained. The patient was admitted with a diagnosis of Crohn's disease (?) in the form of ileocolitis, complicated by inflammatory strictures of the ileum and right colon, with signs of partial small bowel obstruction. Tumor (?) in the right colon; intestinal tuberculosis (?); chronic iron deficiency anemia of moderate severity.

On April 6, 2022, laparoscopic surgery was performed. Intraoperatively (Fig. 5), a deformed scar-altered ileocecal part of the intestine with severe inflammatory changes and a dense endophytic component was found. Seven inflammatory sites with narrowing of the lumen were identified in the ileum, while there was no inflammation in the mesentery of the intestine. After the 3rd narrowing site, there was a prestenotic expansion of the

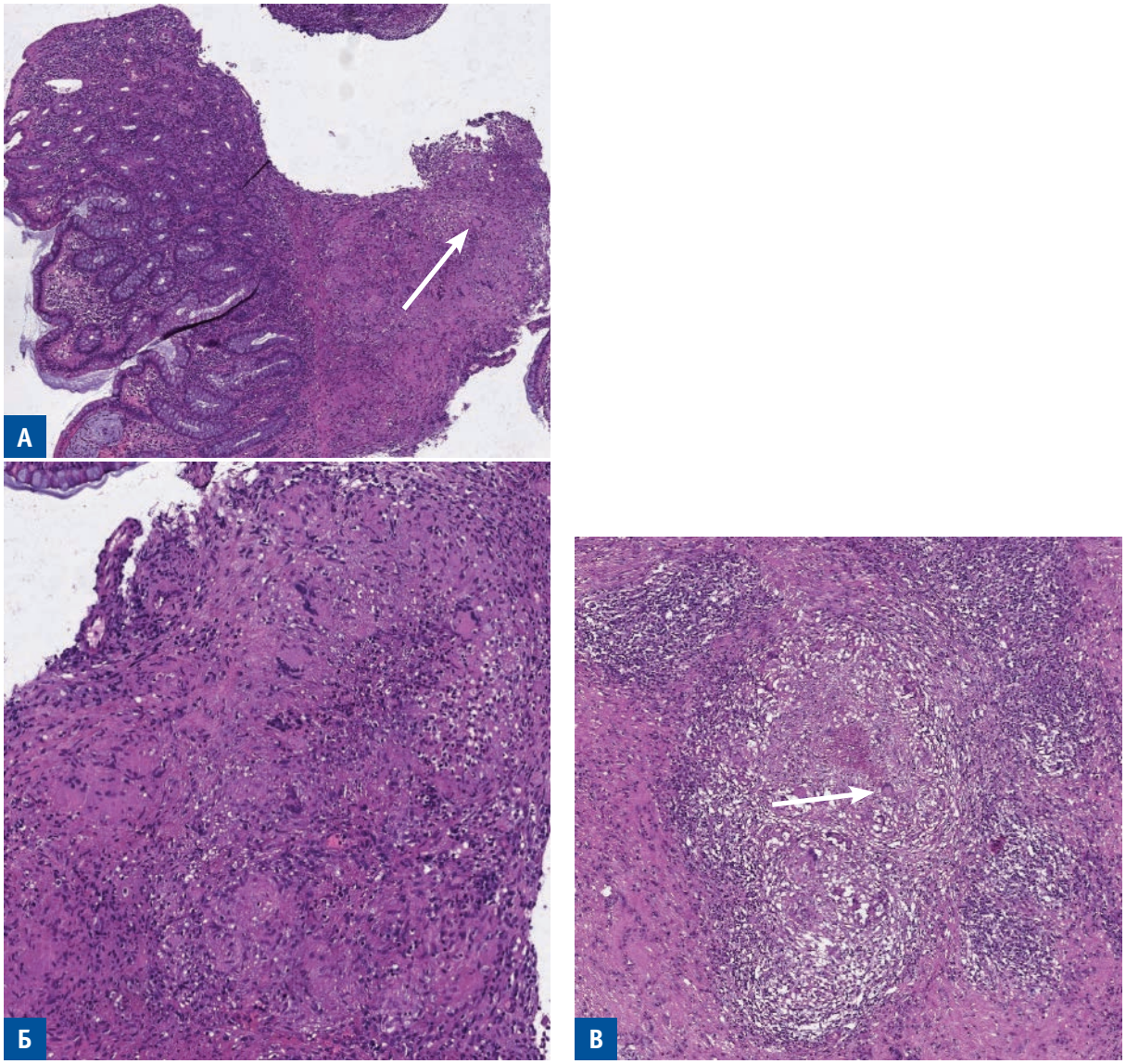

Figure 3. *A. The morphological picture in the biopsy from the edge of the ulcer: signs of chronic inflammation and granulation tissue with foci of necrosis, a large number of histiocytes that form granulomas with the presence of giant multinucleated cells of the Pirogov-Lankhgans type (magn. ×10). Б. Granulation tissue (detail, magn. ×100). B. Granuloma of epithelioid and lymphoid cells, Pirogov-Lankhgans cells and a necrosis focus in the center (detail, magn. ×100). Arrows indicate Pirogov-Langhans cells. А, Б, В — staining with hematoxylin and eosin.*

ileum. The picture was difficult to interpret. Visually, changes from the intestinal wall are not characteristic of Crohn's disease. Crohn's disease and tuberculosis should be placed in the differential series. Considering the lesion extent of the small intestine, taking into account the age of the patient, it was decided to refrain from extensive resection and stricturoplasty. A decision was made to resect the ileocecal part of the intestine (Fig. 6) with the ileo-ascendoanastomosis and bypass "side-to-side" ileo-ileoanastomosis between unchanged parts of the ileum of 40 cm from the proximal border of resection and the jejunum, thus "disabling" 3 areas of narrowing in the ileum with irreversible changes from the intestinal wall.

The result of a histology dated April 12, 2022: multiple merging histiocytic granulomas with a large number of giant multinucleated cells of the Pirogov-Langhans type are detected in all layers of the intestinal wall, in the adjacent fiber and lymph nodes. Part of granulomas was with fibrous changes in the center, isolated — with central small necrosis. Conclusion: the morphological picture highly likely corresponds to tuberculosis in the resected ileocecal part.

Thus, according to the results of histology of the removed specimen, the patient was verified with the final clinical diagnosis: Intestinal tuberculosis with lesions of the small and large bowel. Tuberculous mesadenitis.

The postoperative period was uneventful. The patient discharged with the supervision of a phthisiologist at the place of residence.

When trying to take combined anti-tuberculosis treatment, she noted the appearance of nausea, vomiting, diarrhea, and therefore the treatment stopped. Four months after surgery, the patient's condition was satisfactory, without complains, the phthisiologist continued follow-up.

DISCUSSION

Recently, despite various laboratory tests, the progress in endoscopic and radiation diagnostics, great difficulties arise in the differential diagnosis of two granulomatous intestinal diseases with different etiologies, but similar manifestations. These are intestinal tuberculosis and Crohn's disease, which is demonstrated by this clinical case.

Clinical signs of both diseases include abdominal pain, fever, weight loss, chronic diarrhea, hematocheesia, recurrent intestinal obstruction, extra-intestinal manifestations such as arthralgia, aphthous stomatitis, skin and eye lesions [8]. Due to its non-specificity, none of these signs alone or in combination, does not reliably suggest a particular disease.

Among the immunological tests for detecting a specific cellular immune response to mycobacterium antigens, the traditional Mantoux test with 2 TE PPD-L, a skin test with a recombinant tuberculosis allergen (DIASKINTEST®), as well as tests for the release of interferon-γ by T-lymphocytes (QuantiFERON® -TB Gold/ Gold Plus, T-SPOT®-TB). A positive result of the Mantoux test is registered in 50–100%

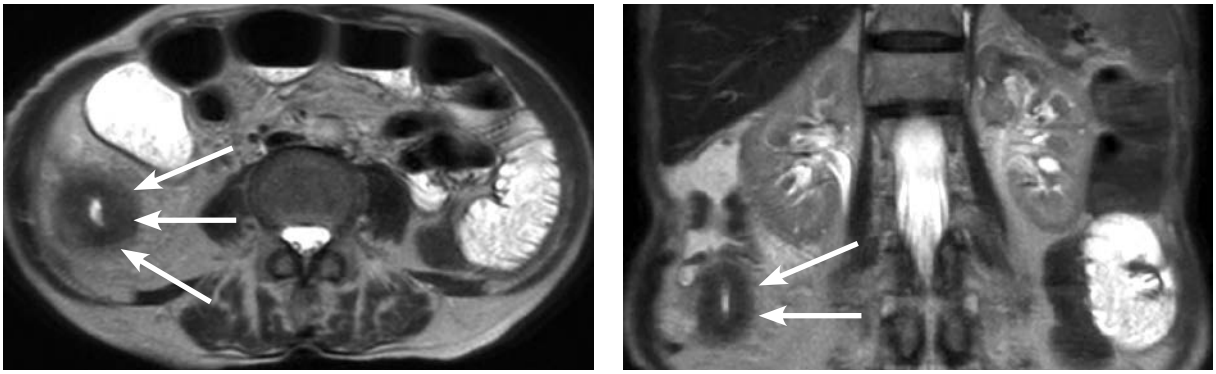

Figure 4. *MRI. The arrows indicate the circular narrowing of the ascending colon up to 5 mm, the circular thickening of the wall up to 10 mm, and the compaction of the surrounding tissue*

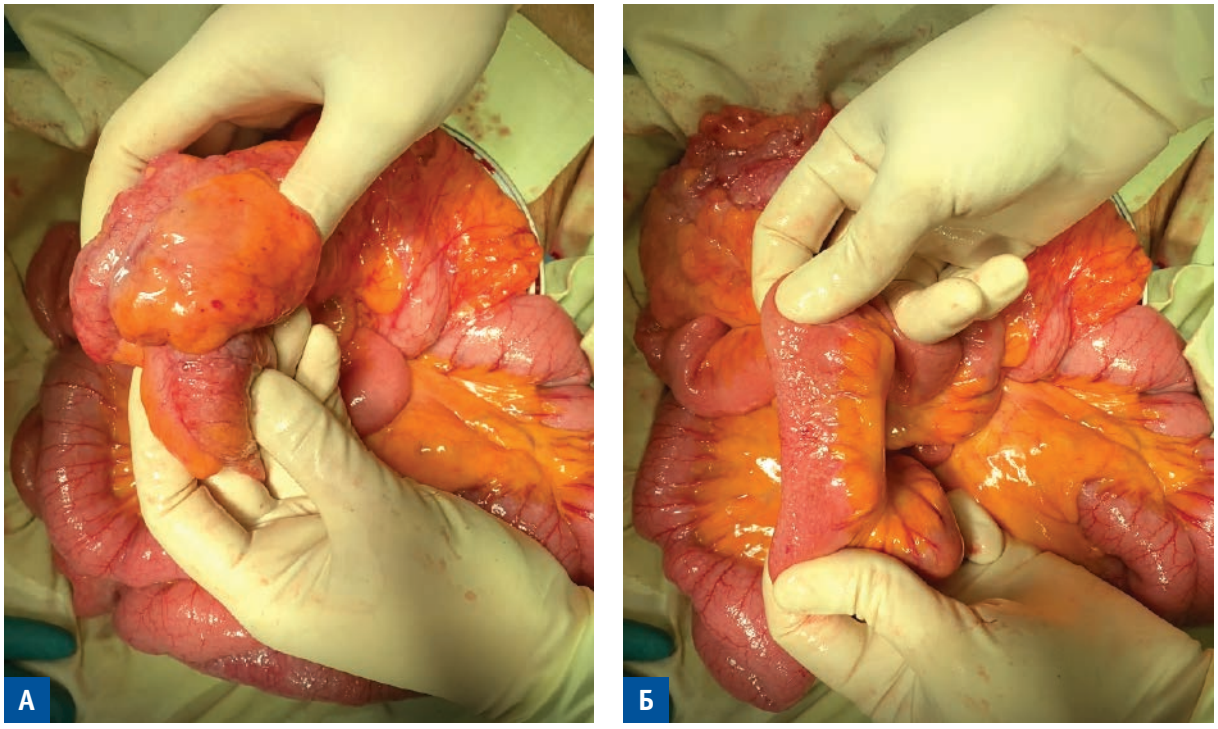

Figure 5(а,б). *Intraoperative photo: а — deformed ileocecal zone with inflammatory, б — one of the ileumstrictures.*

of patients with intestinal tuberculosis. However, according to the literature on the role of immunodiagnostics in the verification of pathology, several meta-analyses reported the sensitivity and specificity of about 80% of the Mantoux test [12]. This is due to the high percentage of false positive results of the Mantoux test in vaccinated and infected children [9–11], which makes this method ineffective for detecting tuberculosis infection.

Fecal mycobacteria test is not carried out due to the almost complete absence of positive results [5].

As with any other infectious disease, the detection of *M. tuberculosis* using microbiological methods in samples can be a diagnostic sign of tuberculosis, but since intestinal tuberculosis is

Figure 6. *Ileocecal region. Thickening of the intestinal wall and narrowing of the lumen at the ileocecal junction*

a low-bacillary (low concentration of mycobacteria) disease, their detection is difficult, which explains the low sensitivity of these tests [13]. In recent years, agar-based nutrient media with various growth additives and the use of a gas mixture have been proposed to accelerate the growth of mycobacteria. To obtain the growth of microorganisms on these media, an atmosphere with a high content of carbon dioxide (4%-7%) is created, special CO_2 incubators are used for this. Automated systems have received the greatest development: MGIT-BACTEC-960 and MB/Bact [5].

The sensitivity of this method varies from 19% to 70% [14].

The use of polymerase chain reaction (PCR) in the diagnosis of abdominal tuberculosis is associated with great difficulties. To perform PCR, deoxyribonucleic acid (DNA) molecules of the pathogen must be isolated from biopsies. For biopsy lysis, an enzyme (proteinase K) is used at a final concentration of 200–500 mg/l at a temperature of 56°C overnight. An excess of nonspecific DNA in PCR analysis often causes inhibition of the reaction, which requires repeated DNA extraction [5]. In a recent meta-analysis of nine studies, the combined sensitivity and specificity of PCR with the release of ARM was 44% and 95%, respectively [15].

Endoscopic diagnostics occupies one of the key places in the verification of diagnosis, but it is also quite complex and ambiguous. The criteria for the diagnosis of Crohn's disease during colonoscopy are regional (intermittent) mucosal lesion, a symptom of "cobblestone pavement" (a combination of deep longitudinally oriented ulcers and transversely directed ulcers with islands of edematous hyperemic mucosal layer), linear ulcers (ulcers-fissures), aphthae, and in some cases strictures and the mouth of fistulas [16]. Macroscopic manifestations of the large intestine tuberculosis are extremely diverse. Any part of the large intestine can be involved in the process, but changes are more often registered in the right sections with lesions of the ileocecal valve and ileum. As a rule, there is a loss of vascular pattern, straightening of mucosal folds, less often "millet-like" rashes on the intestinal mucosal layer are visualized. The characteristics of ulceration formed during the development of caseous necrosis in tuberculous granulomas, in most cases, depends on the timing of their occurrence. In the early stages of formation, single lesions, as a rule, are located against the background of a visually unchanged mucosal layer, have a rounded shape, smooth rounded edges, a smooth bottom covered with a coating of fibrin. The size of ulcers in most cases does not exceed 1 cm, their depth depends on the level of lesion to the intestinal wall (for the entire thickness of the mucosal layer or to the submucosal base). Due to reactive hyperplasia of lymphoid tissue in the area of ulcerative lesion formation, it always rises above the level of the surrounding mucosal layer. There is no contact bleeding. With the progression and chronization of the process, ulcers increase in size along the perimeter of the intestine, their bottom deepens (they often penetrate into the muscular layer of the intestinal wall), acquires a rough, fine-grained appearance, which is due to the formation of tuberculous granulomas. The development of granulation tissue at the edges of lesions gives them a bumpy appearance. The spread of ulcers is in the transverse direction. Large ulcers, as a rule, circularly cover the lumen of the intestine [17]. When the large intestine is affected, the inflammatory process can manifest itself by the development of strictures, hypertrophic lesions resembling polyps or tumors, segmental ulcers [18].

CT or MRI are the preferred methods of differential diagnosis of lesions of the small and large intestine [19]. In a meta-analysis by Kedia S., et al. a number of signs (crest symptom, lymph node lesion, asymmetric thickening of the intestinal wall, proliferation of adipose tissue, wall dissection, involvement of the ileocecal region) and their role in the verification of pathology were analyzed. The lymph node lesion had the highest accuracy (sensitivity — 23%; specificity — 100%) for the diagnosis of intestinal tuberculosis, and the crest sign (sensitivity — 82%, specificity — 81%) — for Crohn's disease. When analyzing the sensitivity of other signs, their diagnostic accuracy, with the exception of asymmetric thickening of the intestinal wall, remained the same [20].

A decisive role in the diagnosis of abdominal tuberculosis belongs to the detection of specific granulomas in the affected organs and tissues during histological examination, which in the classical version represent a site of cellular detritus — caseous necrosis surrounded by so-called epithelioid cells, giant Pirogov-Langhans cells and lymphocytes along the periphery [3]. Tuberculous granulomas are usually large, prone to fusion, dense, located in the submucosal layer and characterized by central caseosis, and granulomas in Crohn's disease are small (microgranulomas), discrete, rare and poorly defined, without areas of necrosis. The detection of ARM in biopsy samples with Cyll-Nielsen staining, although very specific, is infrequent [21].

If, after all, it is not possible to differentiate Crohn's disease and intestinal tuberculosis, and it is necessary to start treatment, then the use of glucocorticosteroids (GCS) in such a situation can contribute to the generalization of the tuberculosis process and be fatal. This problem can be circumvented with the help of empirical prescription of anti-tuberculosis therapy (ATT). The 2016 consensus of the Asia-Pacific Region on the management of patients with Crohn's disease mentions that in patients with the "IBD/abdominal tuberculosis" dilemma, the diagnosis of

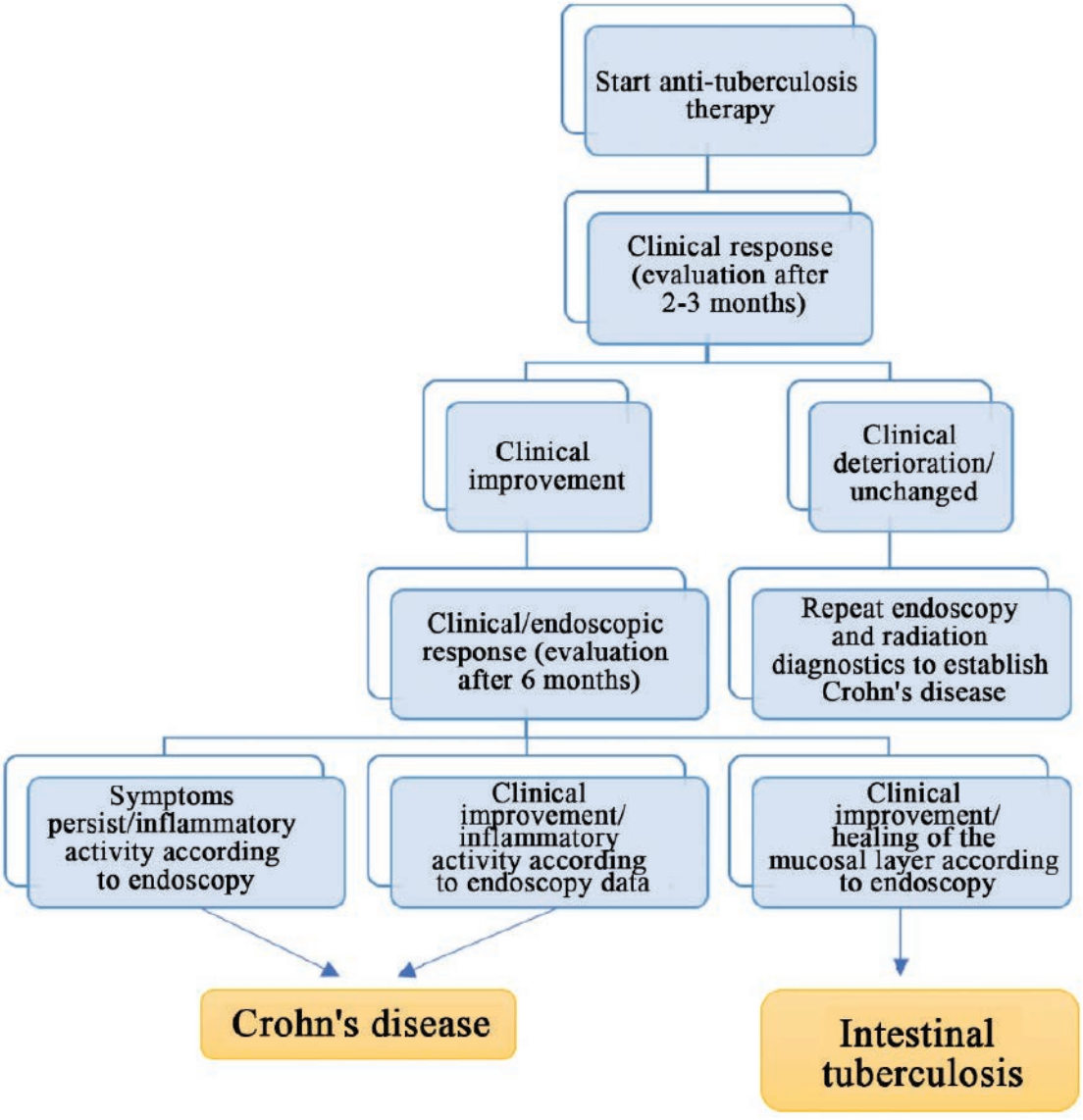

Figure 7. *Algorithm for the patients receiving empirical anti-tuberculosis therapy [13]*

Crohn's disease should be considered only if there is no response to ATT [22]. However, the time frame through which it is necessary to evaluate the effectiveness of therapy is still uncertain. In a study by Kedia, S., et al. out of 358 patients with Crohn's disease, 135 (38.0%) received ATT for at least 3 months before they were finally diagnosed with Crohn's disease. Their response to the therapy was compared with 157 patients with intestinal tuberculosis. After 3–6 months, more than 90% of patients with tuberculosis had a positive effect of treatment compared to 38% of patients with Crohn's disease. During the year, the response to the therapy was maintained with abdominal tuberculosis, and in 80% of cases, the condition of patients worsened with Crohn's disease. Moreover, repeated colonoscopy after 6 months of treatment showed mucosal layer healing in 100% of patients with intestinal tuberculosis, whereas an endoscopic response was observed in < 5% of patients with Crohn's disease. Therefore, based on these results, the authors proposed an algorithm for monitoring patients who underwent empirical ATT [12] (Fig. 7). Indications for surgical treatment of abdominal tuberculosis are defined as absolute: complications of tuberculosis of intra-abdominal lymph nodes and other abdominal organs (abscesses, peritonitis, intestinal fistulas, intestinal obstruction, perforation, bleeding), and individual: the question of surgery depends on the characteristics of clinical manifestations of the disease in a particular patient [5]. About 20–40% of patients with abdominal tuberculosis have a clinical picture of an "acute abdomen" and need surgical treatment [23]. In a prospective study by Barot M. et al., it was shown that the most common indication for surgical treatment was a lesion of the small intestine and ileocecal zone with the development of intestinal obstruction [24]. Surgeries performed for intestinal tuberculosis are mainly of three types [25]. The first type is surgeries that are performed to bypass the involved segments of the intestine, for example, enteroenterostomy or ileotransverzostomy. The second type is segmental resections, for example, limited ileocecal resection. At the same time, asthenization of patients and the prevalence of the lesion are often limiting factors. The third type is stricturoplasty. For cases with multiple strictures, it is suggested as a method that has advantages over multiple resections and enteroanastomoses, since it avoids the risk of short bowel syndrome or blind loops. Extended strictures with active inflammation or multiple strictures may require resection [26].

CONCLUSION

This clinical observation demonstrates the entire complex differential diagnostic path from the moment of the first symptoms to the verification of the diagnosis, which took the patient more than six months. The nonspecific nature of the symptoms forced the patient to consult a therapist, a general practitioner, a surgeon, an oncologist, a gastroenterologist, a phthisiologist. Various laboratory and instrumental examinations were performed. Radiation imaging methods described various pathological changes, but did not allow them to be identified by belonging to a certain nosological form. An endoscopic examination followed by a morphological description of the biopsy material provided significantly more information and helped clinicians to decide on a further search. But, as indicated in the literature, only a histological examination could finally confirm the diagnosis of intestinal tuberculosis. Thus, the awareness of specialists in relation to EPT, perseverance in the diagnostic search, the involvement of doctors of various specialties contributed to a favorable outcome.

AUTHORS CONTRIBUTION

Collection and processing of the material: *Ekaterina S. Merkulova, Victoria A. Belinskaya, Armen V. Vardanyan, Olga A. Mainovskaya*
Writing of the text: *Victoria A. Belinskaya, Ekaterina S. Merkulova*
Editing: *Armen V. Vardanyan, Ksenia S. Frolova*

INFORMATION ABOUT THE AUTHORS (ORCID)

Ekaterina S. Merkulova — 0000-0002-6983-9862
Victoria A. Belinskaya–0000-0001-5873-1074
Armen V. Vardanyan — 0000-0001-6781-2458
Ksenia S. Frolova — 0000-0002-7357-3550
Olga A. Mainovskaya — 0000-0001-8189-3071

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