

Management of wet ascitic type of peritoneal tuberculosis: single center experience

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Abstract. – OBJECTIVE: We aimed to present our experience with the management of 17 patients with ascites who underwent diagnostic laparoscopy or laparotomy, and histologic confirmation of wet ascitic type of peritoneal tuberculosis (TB).

PATIENTS AND METHODS: Between January 2008 and March 2019, 17 patients whose ascites were investigated by a gastroenterologist and who were thought to have non-cirrhotic ascites were referred to our Surgery clinic for peritoneal biopsy. The clinical, biochemical, radiological, microbiological, and histopathological data of the patients who underwent diagnostic laparoscopy or laparotomy were analyzed retrospectively. Histopathological examination of peritoneal tissue samples in hematoxylin-eosin-stained preparations revealed necrotizing granulomatous inflammation with caseous necrosis and Langhans type giant cells. Ehrlich-Ziehl-Neelsen (EZN) staining was studied with the suspicion of TB. Acid-fast bacilli (AFB) were detected in EZN stained slide. Histopathological findings were also considered.

RESULTS: Seventeen patients aged 18 to 64 years were included in this study. The most common symptoms were ascites and abdominal distention, weight loss, night sweats, fever and diarrhea. Radiological examination revealed peritoneal thickening, ascites, omental cacking, and diffuse lymphadenopathy. Histopathologically, necrotizing granulomatous peritonitis consistent with peritoneal TB were detected. While direct laparoscopy was preferred in sixteen patients, laparotomy was preferred in the remaining one due to previous surgical procedures. However, seven were converted to open laparotomy.

CONCLUSIONS: Diagnosis of abdominal TB requires high index of suspicion, and the treatment should be prompt to reduce the morbidity and mortality associated with delay in treatment.

Key Words:

Extrapulmonary tuberculosis, Peritoneal tuberculosis, Ascites, Real-time PCR, Quantiferon TB gold.

Introduction

Tuberculosis (TB) is a public health problem in many developing countries, and recently, its incidence has been increasing in many developed countries¹. TB is basically divided into two types: pulmonary and extrapulmonary TB. Extrapulmonary TB accounts for about 20 to 30% of all TB cases worldwide²⁻⁴. While the incidence of pulmonary TB is decreasing worldwide, the incidence of extrapulmonary TB, especially abdominal TB, is increasing. This increase is in parallel with the rise in diseases associated with immune system dysfunction^{5,6}. The spread of extrapulmonary TB occurs through the hematogenous spread, spread to adjacent organs, or by ingestion of infected sputum^{2,7}. The most common sites of extrapulmonary TB in the body are lymph nodes, bones, joints, pleura, spinal cord, brain, and abdominal cavity. Abdominal TB accounts for 1-12% of extrapulmonary TB and approximately 1-3% of all TB cases^{4,7}.

Abdominal TB is divided into the following: (i) ascitic type, which is characterized by the collection of fluid in the peritoneal cavity, (ii) obstructive type, which is characterized by adhesion and intestinal obstruction and (iii) glandular type, in which there is a lymphatic node enlargement and matted lymph node. Abdominal TB can also be classified into five sub-groups depending on the organs and tissues in which the TB bacillus is

located in the abdominal cavity: (i) luminal, (ii) peritoneal, (iii) nodal, (iv) visceral, and (v) mixed TB^{7,8}. Peritoneal type, which affects peritoneal leaflets, omentum, and mesentery, is the most common type of abdominal TB⁹. Considering the clinical signs and symptoms, peritoneal TB can be divided into three groups: (i) wet ascitic type, (ii) fixed fibrotic type, and (iii) dry plastic type.

The wet ascitic type is the most common and it is usually characterized by a significant amount of ascites in the peritoneal cavity. The most common symptoms of peritoneal TB are abdominal distention, fever, ascites, weight loss, diarrhea, and abdominal pain. These symptoms are not specific. That is why abdominal TB, which is characterized by ascites, should be considered a differential diagnosis of diseases that present with ascites, like cancer and chronic liver disease, especially in TB endemic areas. The need for a fast and correct diagnosis makes diagnostic laparoscopy the preferred approach¹⁰. It allows visual exploration of the abdominal cavity and also multiple biopsies can be taken from the suspicious lesions^{10,11}. In this study, we aimed to present our experience with 17 patients with ascites who underwent diagnostic laparoscopy or exploratory laparotomy, biopsy, and histologic confirmation of peritoneal TB.

Patients and Methods

Between January 2008 and March 2019, 17 patients whose ascites were investigated by the Department of Gastroenterology, Faculty of Medicine, Inonu University who were thought to have non-cirrhotic ascites were referred to the Department of Surgery for peritoneal biopsy. The clinical, biochemical, radiological, microbiological, and histopathological data of the patients who underwent diagnostic laparoscopy or laparotomy were analyzed retrospectively.

Study Protocol and Ethics Committee Approval

This descriptive and cross-sectional study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards. Ethical approval was obtained from the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval No.: 2019/401). STROBE (Strengthening the reporting of observational

studies in epidemiology) guideline was utilized to assess the likelihood of bias and overall quality for this study¹².

Real-Time Polymerase Chain Reaction (PCR) for Detection of Mycobacterium Tuberculosis

The DNA of *Mycobacterium tuberculosis* (MTB) complex in peritoneal biopsy specimens was investigated with FluoroType[®] MTB kits v. 1.0 (Hain Lifescience, Nehren, Baden-Wuerttemberg, Germany). This was a real-time PCR-based molecular diagnostic kit that was validated for the diagnosis of TB in extrapulmonary samples, which the amplification and detection run fully automated in a closed system. The analysis was carried out according to the manufacturer's instructions. The results were obtained as: no MTB complex DNA detected, or MTB complex DNA detected.

Interferon-Gamma Release Assays (IGRA) for Mycobacterium Tuberculosis

Latent or active TB was investigated with QuantiFERON[®]-TB Gold kits (Cellestis, Melbourne, Victoria, Australia). This was an FDA-approved and Centers for Disease Control and Prevention (CDC) -recommended ELISA-based IGRA. The assay was carried out in accordance with the manufacturer's instructions. In brief, a 3 mL whole blood sample was taken from each patient and divided into three test tubes, which were then incubated overnight at 36°C and analyzed in the DS2 ELISA device (Dynex Technologies, Chantilly, VA, USA). The test results were obtained as "positive", "negative", or "indeterminate".

Histopathological Evaluation of Peritoneal Specimens for Mycobacterium Tuberculosis

Histopathological examination of peritoneal tissue samples in hematoxylin-eosin-stained preparations revealed necrotizing granulomatous inflammation with caseous necrosis and Langhans type giant cells. Ehrlich-Ziehl-Neelsen (EZN) staining was studied with the suspicion of TB. Acid-fast bacilli (AFB) were detected in EZN stained slide (Figure 1). Histopathological findings were considered in favor of TB, and it was recommended to confirm the diagnosis with PCR.

Medical Approach to Histopathologically Proven Abdominal Tuberculosis

Antituberculous therapy for extrapulmonary TB, such as abdominal TB, is generally the same

as that for pulmonary TB. Antituberculous regimens consist of two phases: an intensive phase followed by a continuation phase. It is recommended that the intensive phase consists of four drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) administered for two months, these drugs are also named first-line agents. The continuation phase usually consists of two drugs (isoniazid and rifampin) administered for at least four months¹³. All patients should have individual case management with directly observed therapy to ensure adherence and prevent the emergence of drug resistance. Daily therapy is preferred over intermittent therapy to reduce the risk of relapse and drug resistance; this is particularly important during the intensive phase of treatment.

Statistical Analysis

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Qualitative variables were summarized as rate and percentages while quantitative variables were summarized with median, minimum-maximum, and interquartile range (IQR).

Results

A total of 17 patients aged between 18 and 64 years (median: 32; IQR: 29.5) were included in this study, of which 12 were female and 5 were male. The most common symptoms were significant ascites and abdominal distention (n=16; 94.1%), abdominal pain and weight loss (n=14; 82.4%), night sweats (n=7; 41.2%), persistent fever (n=4; 23.5%) and diarrhea (n=3; 17.6%). None of the patients had a history of pulmonary TB or active pulmonary TB. On the contrary, two of the patients had a family history of pulmonary TB. Cytology of the ascites fluid revealed benign findings in all patients. Peritoneal thickening, ascites, omental caking, and diffuse lymphadenopathy were seen during the radiological examination. However, these findings were not specific to peritoneal TB. All patients were negative for HIV, and none of them had a history of oncologic disease or use of immunosuppressive drugs. Only two patients had hepatitis B virus (HBV), hepatitis C virus (HCV) positive serology, and both had normal liver function tests. Sixteen patients

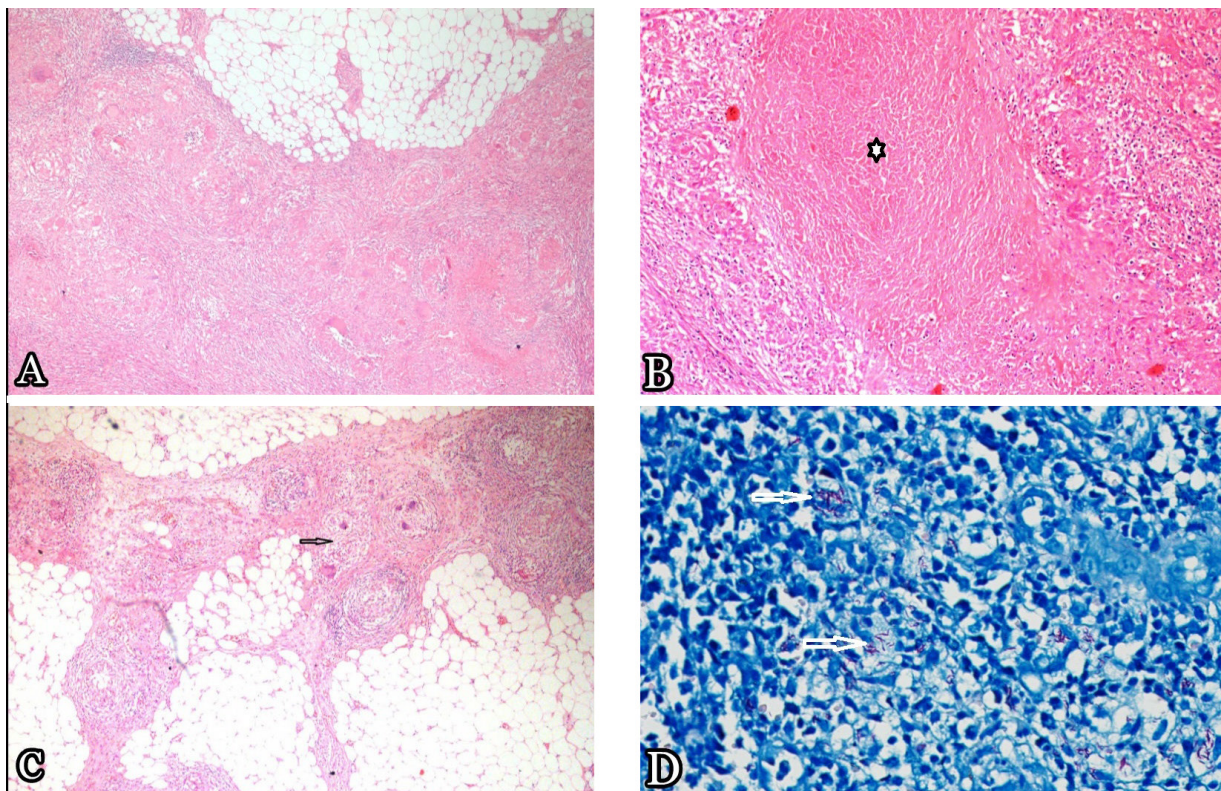


Figure 1. The pathological examination showing necrotizing granulomatous inflammation with caseous necrosis. **A**, Granulomatous inflammation with central caseous necrosis in the adipous tissue (HEX40); **B**, Acellular, eosinophilic area of caseous necrosis (star), surrounding epithelioid histiocytes (HEX100); **C**, Granuloma structures (black arrow) in the adipose tissue (HEX100); **D**, Acid-fast bacilli (AFB) in EZN stained slide (white arrows) (EZNx400).

Table I. Demographic, clinical and histopathological characteristics of 17 patients with peritoneal TB.

No.	Age	Sex	Residency	Liver Disease	Pulmonary TB	Familial TB	Ascitic fluid cytology	CRP	TB PCR	TB Culture	IGRA	SAAG ≤ 1.1	CA-125	PPD (mm)
1	35	M	Rural	No	No	No	Benign	NA	Neg.	Pos.	NA	No	28	NA
2	63	F	Rural	No	No	No	Benign	6.6	Neg.	Neg.	NA	Yes	255	NA
3	28	F	Urban	No	No	No	Benign	0.3	Neg.	Neg.	NA	NA	NA	NA
4	50	F	Urban	No	No	No	Benign	1.8	Neg.	Neg.	Pos.	NA	832	NA
5	22	F	Rural	HBV	No	No	Benign	9.4	Neg.	Neg.	NA	Yes	1,002	10
6	42	M	Urban	No	No	No	Benign	1.3	Pos.	Neg.	NA	NA	444	9
7	54	M	Urban	No	No	No	Benign	6.2	Neg.	Neg.	Pos.	NA	523	NA
8	21	M	Urban	No	No	No	Benign	2.7	Neg.	Neg.	Neg.	NA	742	NA
9	18	F	Urban	No	No	No	Benign	0.4	Neg.	Neg.	Pos.	NA	316	NA
10	39	M	Urban	No	No	No	Benign	5.7	NA	NA	NA	No	156	13
11	27	F	Urban	No	No	Yes	Benign	7.8	Neg.	Pos.	Pos.	NA	431	NA
12	32	F	Urban	No	No	Yes	Benign	9.6	Neg.	Pos.	NA	NA	1,103	NA
13	29	F	Urban	HCV	No	No	Benign	7.2	Neg.	Neg.	Neg.	NA	213	Normal
14	64	F	Rural	No	No	No	Benign	8.1	Neg.	Neg.	Neg.	Yes	195	NA
15	23	F	Urban	No	No	No	Benign	NA	Neg.	Pos.	NA	NA	NA	NA
16	18	F	Rural	No	No	No	Benign	19.9	Neg.	Neg.	NA	Yes	220	Anergy
17	63	F	Rural	No	No	No	Benign	2.3	Neg.	Neg.	Pos.	NA	355	NA

TB: Tuberculosis; CRP: C-reactive protein; PCR: Polymerase chain reaction; IGRA: Interferon-Gamma Release Assays; PPD: purified protein derivative skin test (Mantoux tuberculin skin test); HCV: Hepatitis C virus; HBV: Hepatitis B virus; NA: non-available; Neg: Negative; Pos: Positive; M: Male; F: Female; SAAG: Serum ascites albumin gradient.

Table II. Radiological, histopathological, intraoperative and postoperative characteristics of 17 patients with peritoneal TB.

Radiological Findings	Histopathological findings	First-line approach	Conversion to Laparotomy	Postoperative Complication	Anti-TB Treatment	Follow-up (days)	Outcome
Massive ascites	NGP	Laparoscopy	No	No	Yes	4,589	Alive
Massive ascites	NGP	Laparoscopy	No	No	Yes	3,402	Alive
Peritoneal thickening+Ascites+LAP	NGP	Laparoscopy	No	No	Yes	2,733	Alive
Peritoneal thickening+Ascites+LAP	NGP	Laparoscopy	Yes	No	Yes	1,927	Alive
Peritoneal thickening+Ascites	NGP (EZN: Positive)	Laparoscopy	No	No	Yes	1,227	Alive
Peritoneal thickening+Metastasis?	NGP	Laparoscopy	Yes	No	Yes	2,950	Alive
Peritoneal thickening+Ascites+LAP	NGP (EZN: Positive)	Laparoscopy	No	No	Yes	1,372	Alive
Peritoneal thickening+Ascites+LAP	NGP	Laparoscopy	Yes	No	Yes	3,328	Alive
Peritoneal thickening+Ascites+LAP	NGP	Laparoscopy	Yes	No	Yes	1,167	Alive
Massive ascites	NGP (EZN: Positive)	Laparoscopy	Yes	Yes?	Yes	3,771	Alive
Peritoneal thickening+Ascites+LAP	NGP (EZN: Positive)	Laparoscopy	No	No	Yes	1,567	Alive
Peritoneal thickening+Ascites	NGP (EZN: Positive)	Laparoscopy	No	No	Yes	2,708	Alive
Peritoneal thickening+Ascites+LAP	NGP	Laparoscopy	Yes	Abscess	Yes	2,825	Alive
Ascites+LAP	NGP	Laparoscopy	No	Yes?	Yes	3,149	Alive
Peritoneal thickening+Ascites	NGP	Laparotomy	Direct open surgery	Ileus	Yes	3,450	Alive
Peritoneal thickening+Ascites+LAP	NGP	Laparoscopy	Yes	Ileal perforation	Yes	1,439	Alive
Peritoneal thickening+Ascites+LAP	NGP (EZN: Positive)	Laparoscopy	No	No	Yes	767	Alive

LAP: Lymphadenopathy; NGP: Necrotising granulomatous peritonitis; EZN: Erlich Ziehl Neelson.

had a “tissue TB PCR” examination, and only one of them was positive. Sixteen patients had tissue culture examination, but only four (25%) of them yielded a growth. A total of eight patients underwent the IGRA test, and the test result was positive in five (62.5%) of them.

Histopathologically, findings of necrotizing granulomatous peritonitis consistent with peritoneal TB were detected in all patients, AFB were seen in EZN staining in the peritoneal tissue of only six (35.3%) patients. While direct laparoscopy was preferred in sixteen patients, laparotomy was preferred in the remaining ones due to previous surgical procedures. However, seven were converted to laparotomy, of which five were due to severe adhesion with an inability to explore the abdominal cavity by the laparoscope, one was due to technical reasons, and the remaining one was due to trocar injury to the small bowel. One of the patients converted to open developed enterocutaneous fistula for two months, which was treated medically. Complications developed in the early postoperative period in five patients (ileus=3, ileal perforation=1, abscess=1). While laparotomy was preferred in two of these complications, a conservative approach was adopted in the remaining three. No patient developed mortality during the median follow-up period of 2,733 days (IQR: 1,960; min-max: 767-4,589 days). Demographic, clinical, radiological, and histopathological characteristics of patients are summarized in Table I and Table II.

Discussion

It is estimated that more than 1.7 billion people worldwide are infected with TB bacillus, and 5-15% of these may become symptomatic TB at some point in their lives^{14,15}. TB is the ninth cause of death worldwide, and according to 2016 data^{14,15}, 10.4 million new TB cases were detected, while 1.3 million people died from TB in the same year. Although the incidence of TB disease worldwide is calculated as 140/100,000, this rate is below 24 in developed countries and over 300 in socioeconomically underdeveloped countries¹⁴. In Turkey, which is among the developing countries, the prevalence of TB was found to be 22/100,000 and its incidence was 18/100,000, according to 2014 data¹⁶. The main risk factors affecting the emergence of TB are poverty, large population, low education level, limited access to health institutions, diabetes, smoking, exces-

sive alcohol use, malnutrition, poor hygiene conditions, hemodialysis, HIV infection, an impaired immune system for any reason, immunosuppressive drug use, cancer, and chemotherapeutic drug use¹⁴. Extra risk factors of peritoneal TB include cirrhosis, chronic renal failure and chronic ambulatory peritoneal dialysis¹⁷.

Peritoneal TB is the most common form of abdominal TB. It classically involves peritoneal leaves, mesentery, and omentum⁷. Peritoneal TB accounts for 25-60% of all abdominal TB cases, and approximately 5% of pulmonary TB cases also have peritoneal involvement¹⁸. Peritoneal TB can be classified as wet ascitic, fixed fibrotic and dry plastic. Wet ascitic is considered the most common among the three¹⁹. The clinical manifestation of abdominal TB is nonspecific and high index of suspicion is required for the diagnosis especially in non-endemic areas. The findings in laboratory, radiology and endoscopy are not specific to the TB diseases. The most common clinical presentation is ascites in 59-93% of patients. Abdominal pain, fever and weight loss are seen in up to 76%, 53% and 53.2% of patients, respectively²⁰⁻²². In our study, the commonest symptom is abdominal distension followed by abdominal pain and weight loss. This is similar to most reported findings in literature.

Radiological evaluation (ultrasonography, computed tomography) of patients with suspected abdominal TB is an important step towards confirming diagnosis (peritoneal thickening, ascites, omental cake image, multiple lymphadenopathy). It is observed in some studies²³ that 15-25% of patients with abdominal TB have coexisting pulmonary TB, but in our study, none of our patients had coexisting pulmonary TB as the chest X-ray and chest computed tomography finding were negative in all. Two of the patients had family member who received treatment for pulmonary TB many years ago.

Crohn's disease should be considered as a differential diagnosis of abdominal TB especially the TB of the gastrointestinal tract. The two disease share similar clinical, radiological and endoscopic findings. One of the most important differentiating features between the two diseases is the finding of caseating, granulomatous necrosis on tissue examination. Crohn's disease also commonly presents with diarrhea, rectal bleeding, perianal fistulae and extra intestinal manifestations like reactive arthritis, erythema nodosum, uveitis etc. Other diseases that should be considered in the differential diagnosis of abdominal

TB include malignancies, lymphoma, *Yersinia* infections, bacterial peritonitis, heart failure and chronic liver diseases, and amoeboma^{13,20}.

The gold standard confirmatory test in abdominal TB is the histological examination of peritoneal tissues. Another option is DNA amplification using the PCR technology. There are various approaches to obtaining a peritoneal biopsy, each with a different yield. The most reliable method is the laparoscopic or open approach with a yield of 90.4%. Other approaches include percutaneous, endoscopic colonoscopy and paracentesis, each with a yield of 81.3%, 48.4% and 24.2%, respectively⁷. Detection of *Mycobacterium tuberculosis* can be achieved by microbiological staining, culturing the organism, and with a pathological evaluation of the specimen or PCR. The sensitivity and specificity of these methods of detection differ from one another. Tissue culture is associated with a specificity of 100% but the sensitivity is between 21-55%. It also takes about 3-8 weeks to culture the organism. The use of PCR is also associated with 100% specificity and a sensitivity of 30-80% while histopathological examination is associated with a sensitivity of 30-40%⁴.

An alternative to peritoneal biopsy is the EZN staining or culture of ascitic fluid. The yield is however lower than the evaluation of the peritoneal biopsy because the EZN stain detects AFB only in 3% while culture growth is only seen in 20% of patients²³. So negative evaluation does not exclude abdominal TB, but its positivity strongly confirms the diagnosis. Multiplex PCR has sensitivity and specificity of 90% and 100%, respectively, in confirmed (AFB/culture/histopathology) cases of gastrointestinal TB and positive results in 72.4% of the suspected gastrointestinal TB cases²⁴. In our study, TB PCR and tissue culture was done in 16 patients. Only one patient was positive for TB PCR while tissue culture yielded positive results in four patients. IGRA analysis was done on eight patients with five positive results.

Diagnostic laparoscopy is believed to be an early diagnosis tool in peritoneal TB because it helps in getting early diagnosis. Diagnostic laparoscopy has an accuracy of 72-95%²⁵. Over the past few decades, the role of laparoscopy in diagnosing abdominal TB has increased. Hyman et al²⁶ first described the use of laparoscopy for the diagnosis in 1962, and since then there was a hiatus in literature regarding its role until late '70s when Barry et al²⁷ and Wolfe et al²⁸ de-

scribed their experience and further highlighted the role of laparoscopy in the diagnosis of abdominal TB. In these studies^{27,28}, the morbidity associated with the use of laparoscopy was very low with Barry et al²⁷ reporting the incidence of 1.25%. The low incidence of complications and the improved skills in laparoscopy resulted in an increased use of laparoscopy for diagnosis. Diagnostic laparoscopy is believed to be an early diagnosis tool in peritoneal TB because it helps getting early diagnosis. Generally, the findings during diagnostic laparoscopy include avascular membranous adhesions, peritoneal inflammation, whitish or yellowish diffused tubercles on both visceral and parietal peritoneum and ascites. In 3-5% of peritoneal TB cases, diffused and fixed adhesion may be identified during radiological evaluation and this finding usually precludes laparoscopic approach. That is because there is an increased risk of bowel injury in this group of patients and there may be the need to convert to open surgery²⁸. Seven patients in our study had to be converted to laparotomy. The patient that had bowel injury developed enterocutaneous fistula which was managed non-operatively and it healed spontaneously after two months.

The primary treatment of uncomplicated abdominal TB is the use of anti-TB drugs²⁹. The role of the drugs is, however, limited in patients with acute surgical presentations like bowel obstruction or bowel perforation^{8,29}. In such patients, the acute surgical condition should be treated before the medical therapy is commenced. The standard treatment consists of 2 months of initial intensive therapy of 4 anti-TB drugs, namely, isoniazid, rifampicin, ethambutol and pyrazinamide followed by 4 to 6 months of treatment with only rifampicin and isoniazid³⁰. The duration of the therapy has been a subject of controversy, with some surgeons suggesting treatments of up to 12 months, but studies have shown that there is no significant difference between a treatment of 6 months and a treatment of a longer period³¹.

The mortality of TB is up to 47-49% if untreated, but with a treatment the mortality reported²⁹ is around 5%. This mortality increases to 12-15% if there is a delay in diagnosis and it may be up to 12-25% if the patients develop acute complications⁸. In our study, we recorded zero mortality. One of our patients had an acute complication in the form of bowel injury which was repaired. The same patient developed enterocutaneous fistula after surgery, but it healed spontaneously thanks to a non-operative treatment.

Conclusions

In patients with clinical and examination findings compatible with abdominal (peritoneal) TB, radiological, microbiological, and pathological evaluations should be evaluated together to support the diagnosis. Peritoneal and omental biopsy should be taken using diagnostic laparoscopy, as it allows rapid diagnosis. Considering the dense adhesions that may occur in the abdomen in patients with suspected abdominal TB, trocar entries should be made using the open-access technique, and conversion to laparotomy should not be delayed when necessary.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contributions

Gonultas F, Akbulut S, Sarici KB, Kilci B, Bilgic Y, Garzai IU, Kose A, Yakupogullari Y, and Yilmaz S contributed to the study's concept, design, data collection, data analysis, interpretation, and manuscript writing. Toprak S contributed to the histopathological examination. All authors have approved the manuscript's final version.

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Informed Consent

The informed consent requirement was waived due to this retrospective analysis.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study was approved by the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval No.: 2019/401).

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