

# A prospective evaluation of patients with tuberculosis peritonitis

Eşref Araç<sup>a,\*</sup>, Hakan Temiz<sup>b</sup>, Hakan Yıldız<sup>c</sup>, Idris Oruç<sup>a</sup>, Serdar Polat<sup>d</sup>

<sup>a</sup>Clinics of Internal Medicine, Diyarbakır Gazi Yaşargil Education and Research Hospital, Diyarbakır

<sup>b</sup>Laboratory of Microbiology, Diyarbakır Gazi Yaşargil Education and Research Hospital, Diyarbakır

<sup>c</sup>Clinics of Gastroenterology, Türkiye High Specialty Hospital, Ankara

<sup>d</sup>Clinics of Pulmoner Diseases, Diyarbakır Gazi Yaşargil Education and Research Hospital, Diyarbakır

**Abstract.** Peritoneal tuberculosis is one of the common form of abdominal tuberculosis and leading cause of ascites in developing countries. We aimed to evaluate the results of patients with tuberculous peritonitis in our clinic.

A total of 21 patients diagnosed with tuberculous peritonitis admitted to Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of Internal Medicine, Istanbul, Turkey, were prospectively included in the study. The distribution, demographic characteristics, physical examination findings, laboratory and imaging results of patient with tuberculous peritonitis were analysed.

Nineteen of the cases (81.5%) were female, mean age was 27.6 years (range 15-57). Two cases (9.4%) had underlying disease or facilitators. One of the cases (4.7%) had active pulmonary tuberculosis. Accompanying abnormal laboratory findings; increased erythrocyte sedimentation rate in all patients (%100), anemia, increased ascitic fluid adenosine deaminase levels and increased serum CA-125 levels. Chest radiograph were normal in 13 (62%) of the patients. *Mycobacterium tuberculosis* was not isolated from any of the samples taken for culture of 21 cases. During the period of hospitalization, mortality was found in one person.

Peritoneal tuberculosis is common in developing countries such as our country and should be considered in patient with fever, weight loss, abdominal pain, ascites in differential diagnosis. Early diagnosis and treatment will be able to prevent development of complications and mortality.

Key words: Tuberculosis, peritonitis, diagnosis

## 1. Introduction

Tuberculosis (TB) is an important and old infectious disease affecting people. According to The World Health Organization (WHO); 27.09 million new tuberculosis cases occur and 1.3 million people died due to tuberculosis per year, worldwide. In 2014, WHO was reported that TB incidence was 17.2 (per 100, 000 people), and extrapulmonary tuberculosis constituted approximately 35% of all tuberculosis cases in Turkey (1). Tuberculosis can involve all tissues and organs with a wide spectrum. Gastrointestinal tract tuberculosis and peritoneal tuberculosis are among the main involvements of extrapulmonary

tuberculosis. Peritoneal tuberculosis is one of the common form of abdominal tuberculosis and leading cause of ascites in developing countries. It may be associated with portal hypertension which is the most common cause of ascites. Tuberculous peritonitis may also appeared as a complication of peritoneal dialysis. Extrapulmonary tuberculosis should be considered in differential diagnosis of many infections in especially endemic countries for tuberculosis. In the United States (US) between the years of 1963 and 1986 pulmonary tuberculosis rate decreased; while extrapulmonary tuberculosis rate was 7.8 % in 1964, this rate rised to 17.5 % in 1986 (2-4). According to report by Ministry of Health of the Department of Tuberculosis Control, Turkey, there was 5936 extrapulmonary tuberculosis cases in 2012 and 330 of these cases were peritoneal tuberculosis (5). In recent years, due to increased number of patients with immune deficiency incidence of tuberculosis increased and emerging of multidrug-resistant mycobacterium strains led to the re-acceleration of tuberculosis studies (6).

\*Corresponding Author: Dr. Eşref Araç

Clinics of Internal Medicine, Diyarbakır Gazi Yaşargil Education and Research Hospital, Yenişehir, Diyarbakır

Phone: +90 412 2580060-2991

Fax: +90 412 2580047

E-mail: esrefarac@gmail.com

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In this study, we aimed to evaluate the distribution, demographic characteristics, physical examination findings, laboratory and imaging results of patient with tuberculous peritonitis in our clinic and to compare the obtained data of our country with the world.

## 2. Materials and methods

A total of 21 patients diagnosed with tuberculous peritonitis admitted to Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of Internal Medicine, were prospectively included in the study. All patients were hospitalized and diagnosed by a laparoscopic peritoneal biopsy and they were treated in our clinic. All pathology records, surgical notes, files of patients were archived to be used in the study.

The parameters were age, sex, TB history, family history, contact with TB patients, treatment history of TB, hospitalization due to TB, concomitant diseases, ultrasonography (USG) findings (abdominal ascites, organomegaly, peritoneal thickening, bowel edema, genital organ involvement), computed tomography (CT) findings (abdominal ascites, organomegaly, peritoneal thickening, genital organ involvement, lymphadenopathy), fever, abdominal pain, abdominal swelling, conventional radiography findings of lung during hospitalization, distribution of the patients according to age groups, leukocytosis, increased serum CA-125 levels, increased ascitic fluid adenosine deaminase (ADA) levels, anemia, increased erythrocyte sedimentation rate, elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase), The Mantoux tuberculin skin test (TST) results, weight loss, cough, nausea, vomiting, loss of appetite, night sweats, the occurrence of complications, mortality, involvement of organs other than peritoneum, respectively. Blood samples were taken from the antecubital vein of the forearm of the patients; complete blood count, prothrombin time and activated partial thromboplastin time were tested. Ascites and biochemical analyzes of patients without profound thrombocytopenia ( $<10000/\text{mm}^3$ ) and disseminated intravascular coagulopathy were also analysed. About to 50 ml ascitic fluid was collected from the abdominal left lower quadrant. Simultaneously, biochemical parameters, glucose, total protein, albumin, lactic dehydrogenase (LDH) were studied in ascitic fluids and as well as in serum. According to the serum-ascites albumin difference, feature of ascites (exudate or transudate) was detected. Also, a portion of ascites were sent to microbiology laboratory for the cell count,

tuberculosis culture, and searching acid fast bacilli with Ehrlich Ziehl-Neelsen (EZN) and Rhodamine-Auramine dying methods. In all cases, at different times, blood samples were taken and sedimentation rate, CA-125, thyroid function tests, serum ferritin, iron, total iron binding capacity were measured. All patients were monitorized by abdominal USG and abdominal CT. Upper limit of normal values were as follows;  $10,000 / \text{mm}^3$  for leukocyte count, 35 U / ml CA-125, 40 U / L for ADA, 20 mm (first hour) for erythrocyte sedimentation rate,  $400.000/\text{mm}^3$  for platelet value, 55 U / L for ALT and 34 U / L for AST. For mild anemia, the lower limit of hematocrit (Hct) was considered of 35%.

For treatment of patients, Isoniazid (INH) 300 mg / g, Rifampicin (RIF) 600 mg / day, Pyrazinamide (PZA) 15-30 mg / kg / day (or Morfozinamid 25-50 mg / kg) and EMB 15-25 mg / kg / day were given. Treatment was planned for 6 months. Treatment was continued until 9-12 months in some of the patients according to course of clinical follow-up. The first two months of treatment, four anti-tuberculosis treatment was given, then the INH + RIF combination therapy was continued. Data were evaluated by descriptive statistical methods (mean, standard deviation).

## 3. Results

A total of 21 patients diagnosed with tuberculous peritonitis hospitalized. Among the patients 9.5% (n=2) were male and 81.5% (n = 19) were female. The age of patients ranged from 15 to 57 (mean: 27.64 years). Highest number of cases were in age group of 15-20 (n = 10, 47.6%) years (Figure 1).

A total of 17 (80.9%) patients were living in Istanbul. Five of them (23.8 %) within one week after the initiation of symptoms, 14 (66.7 %) within one month, two (9.5 %) after a period of more than one month were admitted to our hospital. The number of patients with low socioeconomic level were 16 (76.1%). Previous pulmonary TB in our two cases, previous TB pericarditis in one patient, active pulmonary TB in one patient were determined and three patients had TB medical history of family or immediate vicinity. As facilitators, one case had diabetes mellitus Type 1 and chronic renal failure, one case had Type 2 diabetes mellitus. All of the patients had ascites and because of inadequate ascites, two patients were examined under ultrasound imaging. Acid-fast bacilli was not detected in any of fluids and samples and all of the samples were culture negative for *M.tuberculosis*. Periton fluids of two patients and abscess sample of one patient were Polimerase

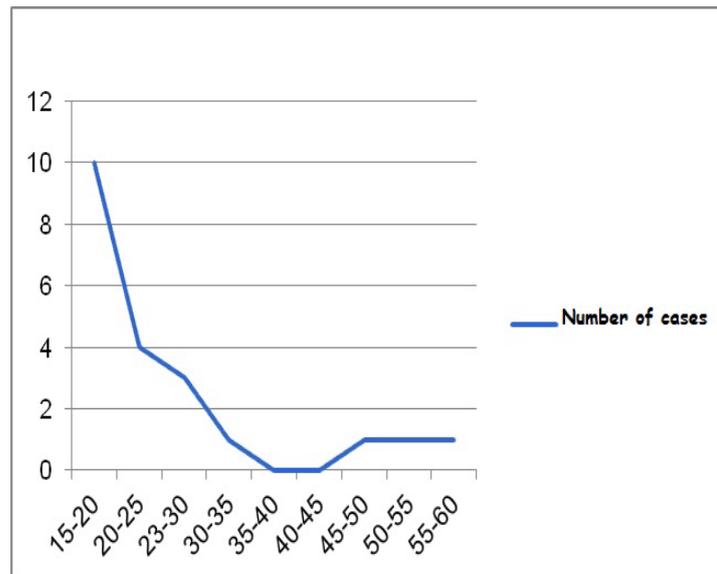


Fig. 1. The distribution of patients according to age group.

Table 1. Findings of CT and USG in patients

Findings (USG/CT)	n	%
Ascites (USG)	21	100%
Peritoneal thickening (USG)	0	0%
Omental edema (USG)	7	33,30%
Ascites (CT)	21	100%
Peritoneal thickening (CT)	11	51,70%
Lymphadenopathy (CT)	6	28,20%

Chain Reaction (PCR) positive for *M. tuberculosis*. Biochemical examination of peritoneal fluid was exudate in all patients except one patient. The most common symptoms were abdominal pain (n = 17, 80.9%), abdominal bloating (n = 19, 90.4%), fever (n= 5, 23.8%), nausea (n = 7, 33.3%), vomiting (n = 3, 14.2%), fatigue (n = 6, 28.4%), anorexia (n = 4, 19%), sweating (n = 2, 9%). All patients were imaged by abdominal USG and abdominal CT. The most common USG and CT findings and other findings are summarized in Table 1. Ascites and bloating were identified as the most common signs and symptoms, respectively (Table 1).

Anemia was present in all except one of our cases. Hematocrit values varied between 21 and 35. Two (9.5%) cases had leukocytosis ( $\geq 10.000/mm^3$ ), 5 (23.8%) leukopenia, 12 (57.1%), thrombocytosis and ESR was  $>20$  mm / h in all (100%) of the patients. Sedimentation values varies between 53 and 100. C-Reactive Protein (CRP) was found to be positive in all patients. ADA levels of ascitic fluid and serum CA 125 levels were detected significantly higher in all of the patients. TST positivity was 90.4 %. Eight

patients (38%) showed pathological lesion on chest radiography.

Four (19%) cases have pleural fluid, two (9.5%) consolidation, one (4.7%) nodular opacities, one (4.7%) pleural fluid and consolidation. Pleural fluid could be taken from only one patient and this was Acid-fast bacili and culture negative. Peritoneal biopsy was performed in all cases except one patient operated due to intra-abdominal abscesses; necrotic granulomatous peritonitis was observed in 18 patients, granulomatous peritonitis in 3 cases. Three cases have also retroperitoneal involvement (pulmonary involvement, splenic involvement and involvement of the genitourinary tract). Genitourinary tuberculosis was diagnosed based on pathology report (necrosis, granulomatous endometritis) of endometrial curettage material obtained by physician of gynecology. Spleen TB was diagnosed with PCR of patient's abscess. All of the patients were treated with combination therapy of isoniazid, rifampicin, pyrazinamide, ethambutol for 9 months. One patient with additional diseases (type 1 DM and end-stage renal failure) and retroperitoneal involvement died. Any severe side-effect to require discontinuation of treatment was not observed in our patients. Common side effects were nausea and vomiting (n = 6, 28.5%) and mild liver enzyme elevation (n = 5, 23.8%).

#### 4. Discussion

Lack of pathognomonic findings and specific symptoms lead to significant challenges on the diagnosis of periton tuberculosis (7). The general

belief is that only 20% of the patients have findings on Chest X-ray (8). Mihmanlı et al. (9) reported that 69 % of their cases with tuberculous peritonitis have lesions suggestive of tuberculosis on chest radiograph. The rate of 38% was within the boundaries of literature in our study. In a series of 90 patients abdominal tuberculosis, Palmer et al. (10) reported that mortality was seen in 5 patients. Due to 85 of their study patients were immigrants from Asia and Africa, they suggested that socio-economic status has played an important role for the course of this disease. Similarly, in our study 76% of patients were from the lower socioeconomic classes. In countries where tuberculosis is endemic, tuberculosis should be considered in differential diagnosis of the patients presenting with abdominal symptoms (10).

Tuberculous peritonitis takes place in the classroom of low albumin gradient in ascitic fluid classification (11). Shakil et al. (12) reported that  $>2.5$  g / dL total protein of ascites,  $<1.1$  percent of serum-ascites albumin gradient, and  $>90$  U / dL LDH values had quite high sensitivity for demonstrating of tuberculous peritonitis cases without the portal hypertension. The same study suggested that if tuberculous peritonitis accompanied by chronic liver disease, sensitivity of serum-ascites albumin gradient fell to 50%. In western countries like the US, half of the patients with tuberculous peritonitis were accompanied by cirrhosis (13, 14). In our series, we detected high serum-ascites albumin gradient in only one patient. In the literature, a similar phenomenon was observed in case of Gürbüz and colleagues (15). Surgery is recommended only in acute or subacute intestinal obstruction does not respond to conservative treatment (8). Wells et al. (16) could diagnose 17 patients with laparotomy and 2 patients with laparoscopic biopsy among 25 patients with suspected tuberculous peritonitis in a study of 30 cases. They detected mesenteric lymphadenitis in two of remaining cases without suspected tuberculous peritonitis. They performed laparotomy for one patient and laparoscopic biopsy for other patient with mesenteric lymphadenitis. We suggested that laparoscopic biopsy would be useful in diagnosis. In the series of Wells (16), the most frequent findings were fever, abdominal tenderness, and ascites. The most common hematologic abnormality was elevation of erythrocyte sedimentation rate, and half of patients had mild anemia. Only 3 patients had leukocytosis ( $>10.000/mm^3$ ). Our study data was consistent with these study (16). In addition in Wells' series, male / female ratio was 23/7. Immigration may be

reason of this rate. On the other hand, the higher rate of female patients in our study may be due to tuberculosis is an endemic disease in our country. The mean age of the patients in our series is consistent with literature (16).

Tuberculin skin test is more reliable in TB carriers than the hospitalized TB patients. Because of false-negative results in poor and hospitalized patients, it is recommended that TST should be used only for screening of TB. A big proportion (90.42%) of our patients were positive for TST. The most common complaints that lead patients to admitt to hospital were fever, abdominal pain, weight loss and fatigue (16). In our series, complaints were abdominal bloating, abdominal pain, loss of appetite, weight loss, nausea, vomiting, fever and sweating. In our case and literature data supported that the most common imaging findings were ascites, lymphadenopathy, and thickening of the peritoneum and mesentery (18-20). Our study and literature showed that culture was a low sensitive but laparoscopic biopsy and pathological examination of biopsy material were high sensitive methods for diagnosis (16). In addition, according to our study and the study of Findlay et al. (21), increased erythrocyte sedimentation rate and mild anemia were alarming laboratory findings.

Method of receiving biopsy material is controversial. Paracentesis is an easy method, but due to the height of false negative results it is an unreliable diagnostic method (16,21). Wells et al. (16) proposed laparotomy includes exploration of entire abdomen. The researcher could diagnosed all of the 16 patients which were performed laparotomy and received biopsy. Das et al. (22) suggested receiving of biopsy with mini-incision in the right lower quadrant under local anesthesia. Limitation of their methods was may be lack of lesion in the incision area of the peritoneum. Blindly peritoneal needle biopsy is applicable to patients with high amount of ascites but this method may lead to death, and also the success rate is generally low (16). Laparoscopic biopsy performed with detection of the target in experienced hands gives good results. On the diagnosis of tuberculous peritonitis, sensitivity of blindly peritoneal biopsy is 65-85%, sensitivity of laparoscopic biopsy rates up to 100% (23). Laparoscopy was also seen as a reliable method in our study.

A Pakistan study suggested that intestinal tuberculosis should be considered in an initial diagnosis of patient with bowel obstruction and fever, weight loss, night sweats and loss of appetite (24). Abdominal ascites were detected in

all of our patients. In our country, abdominal tuberculosis should be considered in patients with a similar clinical picture and the patients who have finding of ascites by USG. In a Turkey study, the most frequent symptom was reported as weight loss (25). In our series, the most common symptoms were abdominal bloating (90.4%) and abdominal pain (80.9%). Although presence of fever may be the most common finding (26), only five of our patients have fever. In a study from our country (25), ascites was found to be the most common finding. Similarly all of our patients had ascites. Due to serum CA-125 returns to normal after treatment in patients with peritonitis tuberculosis, this marker can be used in follow-up of this disease (7, 19, 27) and detecting of elevated CA-125 can recover patients from unnecessary laparotomy (9). Similarly, the levels of CA-125 was found to be higher than normal limits in all peritoneal tuberculosis patients. In addition the study of Fontan Bueso et al. (28) and our study revealed that testing of ADA level was a safety method for diagnosis.

The diagnosis of tuberculous peritonitis is usually done with peritoneal biopsy (28-30). Panoskaltis (27) suggested the laparotomy. In pulmonary tuberculosis prevalent societies with limited diagnostic opportunities (peritoneal biopsy, enema examination, colonoscopy etc.) peritoneal tuberculosis can be diagnosed with following of reponse to medical therapy in patients with fever, abdominal pain, weight loss and abdominal ascites (30,31). Requirement of surgery is a contradiction for abdominal tuberculosis. Because this infectious disease can be treated with medical therapy, succesfully. On the other hand, unable to start immediately effective treatment due to delayed diagnosis can cause mortality and morbidity. We suggested that surgical intervention should be avoided in the patients with low gradient ascites, elevated serum CA-125 levels, high ascitic fluid ADA levels and high erythrocyte sedimentation levels in tuberculosis endemic countries.

In conclusion, peritoneal tuberculosis is common in developing countries such as our country. The incidence is high in young female and the peak age range is 15-25 years. In our country in the presence of intestinal or abdominal pathology, tuberculosis should always be considered. Tuberculous peritonitis should be considered in differential diagnosis especially in patient with fever, weight loss, abdominal pain, ascites. Early diagnosis and treatment will be able to prevent the development of complications and mortality. For the diagnosis bacteriological and biochemical tests of peritoneal fluid should be

done but diagnosis should be supported by PCR based molecular diagnostic methods for *M.tuberculosis*. If ascitic fluid is exudate and PCR negative, primarily percutaneous peritoneal biopsy; if possible under USG; should be performed. If there is doubt in the diagnosis, invasive procedures such as laparoscopy, laparotomy should be made. Analysing of laboratory parameters such as increased erythrocyte sedimentation rate, increased ascites adenosine deaminase levels and serum CA-125 levels should not be ignored. In addition, tuberculous peritonitis should be investigated in patient with ascites, bloating and abdominal pain. We believed that the results obtained from our study will be the guiding for randomized prospective studies enrolled in numerous patients.

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