

EVALUATION OF TWENTY-SEVEN PATIENTS WITH TUBERCULOUS PERITONITIS

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ABSTRACT

Introduction: Tuberculosis (TB) remains a public health problem worldwide. Peritoneal tuberculosis or tuberculous peritonitis (TBP) is an uncommon form of extrapulmonary infection with a proportional increasing of its incidence. This disease is seen most commonly in young adults, and has a highly variable clinical symptomatology. Our aim is to highlight the nonspecific presentation and diagnostic difficulties of the TBP.

Materials and methods. We retrospectively reviewed 27 TBP cases diagnosed between 2003 and 2014. Clinical features, all diagnostic methods, and the outcomes of treatment were analyzed in view of literature.

Results: Abdominal distension and pain were the most frequent symptoms. A past history of pulmonary TB was obtained in 4 patients. Additionally, concomitant extraperitoneal TB was found in 15 cases. Ascites was the most sonographic finding. Acid-fast staining of ascitic fluid was positive in 1/19. Peritoneal biopsy via laparoscopy or laparotomy was positive for TBP in 13/14. Duration of symptoms prior to diagnosis was found to be associated with prolongation of the treatment ($p < 0.001$). In addition, pre-treatment c-reactive protein was found to be significantly different between the patients requiring a standard therapy of 9 months and the patients requiring additional therapy of 3 months ($p = 0.023$).

Conclusion: The diagnosis of TBP is often difficult due to diverse presentation. The patient's anamnesis and the presence of ascites are the most significant marks in diagnosis. Laparoscopy with peritoneal biopsy seems to be the gold standard diagnostic method.

Key words: Ascites, extrapulmonary tuberculosis, peritoneal tuberculosis, tuberculosis, tuberculous peritonitis.

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Introduction

Tuberculosis (TB) remains a public health problem as the second leading cause of infectious disease associated death worldwide⁽¹⁾. The lung is the primary site of TB, however extrapulmonary TB constitutes about 13%-20% of all cases of TB in immunocompetent patients. The incidence increases up to 50% in human immunodeficiency virus positive individuals^(2, 3). Peritoneal TB or tuberculous peritonitis (TBP) is an uncommon form of extrapul-

monary infection which constitutes about 5-13% of extrapulmonary TB cases with a proportional increasing of its incidence^(1, 4, 5). TBP may occur spontaneously in patients who are on ambulatory peritoneal dialysis. Infected lung, fallopian tubes and small intestines are the most reported sources of TBP⁽⁶⁾. This disease is seen most commonly in the 3rd and 4th decades of life, and the majority of patients with TBP present complaining abdominal pain and abdominal distension. However, TBP remains a diagnostic challenge for clinicians due to

its nonspecific signs and symptoms. Here, all clinical, diagnostic and therapeutic features of 27 patients with TBP were evaluated in view of literature.

Materials and methods

From January 2003 to December 2014, 27 TBP patients who were treated and followed up in a specialized clinical center on TB were evaluated retrospectively. Approval of the ethics committee was obtained from Ministry of Health. Informed consents of the patients were waived due to the retrospective nature of the study. Patients' demographic characteristics, past history of TB, coexisting medical problems, initial clinical symptoms and findings, duration of symptoms, purified protein derivative (PPD) skin test positivity (>12 mm induration), laboratory investigations including complete blood counts, routine biochemistry analysis, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), pretreatment and post-treatment serum CA-125, radiological findings such as chest radiography, abdominal ultrasonography (US), and abdominal computed tomography (CT), peritoneal fluid analysis including glucose, lactate dehydrogenase (LDH), ascites fast bacilli (AFB) smear, polymerase chain reaction (PCR), adenosine deaminase (ADA) and CA-125, histopathology and culture of peritoneum obtained by laparoscopy or laparotomy were recorded.

Diagnostic criteria of TBP

Diagnostic criteria of TBP were determined as follows: positive ascites fast stain from peritoneal fluid, elevated ADA levels in ascitic fluid (>35 U/l), positive paracentesis findings including <1.1 mg/dl serum ascites-albumin gradient (SAAG) and predominance of lymphocytes, positive mycobacterium tuberculosis by ascites PCR, determination of granuloma with or without caseification in the histopathological examination of peritoneal biopsy, positive culture results of ascitic fluid or peritoneal biopsy.

Anti-TB treatment

All patients were treated with isoniazid (15 mg/kg day, max. 300 mg/day) and rifampicin (15 mg/kg day, max. 600 mg/day) for 9 months. In the first 2-month period, pyrazinamide (30 mg/kg day, max. 2 g/day) and streptomycin (15 mg/kg day, max. 1 g/day) or ethambutol (20 mg/kg day, max.

1.5 g/day) were administered. All patients were evaluated at the end of the therapy, and if there was no resolution of symptoms and Mycobacterium tuberculosis was still present in any specimen, a treatment of 3 months was added. All complications during the follow up period were recorded. Patients were invited at regular intervals after the end of the treatment.

Statistical assessment

The Statistical package for social science (SPSS 21.0 IL-Chicago- USA) standard version was used for data analyses. Descriptive analysis was done for demographic, clinical and radiographic features. The results are presented as mean \pm SD/percentages for continuous variables and number/percentage for categorical variables. Chi-square (χ^2) test and Mann Whitney U test were used to test for the significance of association between the independent (predictor) and dependent (outcome) variables in the categorical variables. Significance level was accepted as $p < 0.05$. Study variable that was found to be statistically significant in univariate analysis were subjected to biserial correlation test. Biserial correlation analysis was used to determine predictor variables that predict the duration of treatment and complications.

Results

Among the 1531 TB patients, we found 33 (2.1%) TBP cases. 6 of these had irregular medical records, and therefore were excluded from the study. Demographic data and clinical features of the patients are presented in Table 1.

Patient characteristics	n
Age (mean, y*)	37.2 \pm 13.3 (18-69)
Gender	
Male	9 (33.3%)
Female	18 (66.7%)
Concomitant disease history	
Diabetes mellitus	1 (3.7%)
Chronic HCV carriers	1 (3.7%)
Chronic liver disease	1 (3.7%)
Chronic renal failure	1 (3.7%)
Amiloidosis	1 (3.7%)
Ovarian malignancy	1 (3.7%)
History of pulmonary TB	4 (14.8%)
Familial history of TB	9 (33.3%)
Contact history	8 (29.6%)
Extrapleural TB sites	
Pleural TB	9 (33.3%)
Genital TB	7 (25.9%)
Pulmonary TB	4 (14.8%)
Cervical lymph node TB	2 (7.4%)
Mean duration of symptoms (d*)	54.9 \pm 41.5 (5-155)

Table 1: Demographic data and baseline clinical characteristics of patients (n=27). y*: year, d*: day

Abdominal distension (55.6%), pain (44.4%), ascites (70.4%) and fever (29.6%) appeared to be the most frequent presenting symptoms and signs (Table 2). The majority of patients were admitted with chronic manifestations of peritoneal TB, however only two cases were presented with acute abdomen, and thus were operated on emergency.

Symptoms	n	%	Findings	n	%
Abdominal distension	15	55.6	Ascites	19	70.4
Abdominal pain	12	44.4	Fever	8	29.6
Nausea and vomiting	6	22.2	Genital discharge	2	7.4
Cough and sputum	5	18.5	Peritonitis	2	7.4
Night sweats	5	18.5	Diarrhea	1	3.7
Loss of appetite	5	18.5	Peripheric LAP*	1	3.7
Fatigue	4	14.8	Weight loss	1	3.7

Table 2: Presenting symptoms and findings (n=27).
LAP*: Lymphadenopathy

In diagnostic workup, each test was not applied to each patient unless it was necessary. On admission, ESR values of all cases were high. However, thrombocytosis ($>450.000/\text{mm}^3$) and leukocytosis ($>10.000/\text{mm}^3$) were obtained in 37.0% (n=10) and 29.6% (n=8) of patients, respectively. Decreased hemoglobin levels ($<10 \text{ g/dL}$) were found in 51.9% (n=14) of patients. Tuberculin skin test was positive in 7 of 9 patients (77.7%). However, of these 7 patients, 5 were vaccinated but none had prior history of TB. Radiological investigations including chest X-ray, abdominal US and CT were performed in all cases (Table 3).

Abdominal US	n/%	Abdominal CT	n/%
ascites	19/70.4%	ascites	20/74.0%
t.*peritoneum/mesentery/ omentum	7/25.9%	t.*peritoneum/mesentery/ omentum	14/51.8%
enlarged abdominal lymph nodes	3/11.1%	enlarged abdominal lymph nodes	7/25.9%
genital TB findings**	3/11.1%	genital TB findings**	5/18.5%
hepatosplenomegaly	2/7.4%	hepatosplenomegaly	8/29.6%
normal	2/7.4%	normal	1/3.7%

Table 3: The sonographic and tomographic findings of the patients with TBP (n=27).
t*: thickened, genital TB findings **: tubo-ovarian mass, irregular endometrial lining, and etc.

Up to half of the patients (n=11, 40.7%) had normal chest X-ray. The other findings on chest radiography were pleural effusion (n=9, 33.3%), sequel TB findings (n=5, 8.5%) and radiopacity/lesion (n=4, 4.8%).

Paracentesis was performed in 19 patients (70.4%), and low SAAG was seen in all cases.

However, lymphocytic predominance (n=15, 78.9%), decreased glucose levels and elevated LDH levels were obtained in 78.9% (n=15), 78.9% (n=15) and 63.2% (n=12) of patients, respectively. AFB staining of ascitic fluid was found to be positive only in one (5.2%). On the other hand, high ascitic ADA ($>35 \text{ U/L}$) and CA125 ($>35 \text{ U/ml}$) levels were detected in a ratio of 84.2% and 89.5% respectively. The measurement of serum CA125 was used only in six patients. Of these, five had increased values of serum CA125. After treatment, all high CA125 levels returned to normal limits. PCR analysis of ascites was performed for 8 patients, and 3 positive results were obtained (37.5%). Among PCR-positive patients, only one had positive AFB staining of ascites. Peritoneal biopsy via laparoscopy (n=12) or laparotomy (n=2, due to emergency condition) was performed in 14 patients. The histopathologic examination of peritoneal biopsy was positive for TB in 13 patients (92.8%). Of the biopsy specimens, 92.3% (n=12) revealed caseating granulomas, while 7.7% (n=1) was non-caseating. All tissue samples were also evaluated by Ziehl-Neelsen staining, and AFB positivity was seen in all. Cultures of ascites and peritoneal biopsy were examined in 19 and 14 patients, respectively. Diagnostic yield of all the investigations are presented in Table 4. Given the high prevalence of TB in our country, in one patient with strong clinical suspicion and negative diagnostic workup, response to anti-TB medication was the basis of diagnosis. He had no ascites and extraperitoneal TB. On CT, there were only multiple enlarged abdominal lymphadenopathies. He also refused peritoneal biopsy via laparotomy or laparoscopy.

Diagnostic method	n	Yield of diagnostic method
ADA in ascites (mean 144.4±79.3, range: 21-292)	19	16/84.2%
CA125 in ascites (mean 433.2±268.7, range 22-808)	19	17/89.5%
PCR analysis of ascites	8	3/37.5%
AFB stain positivity of ascites	19	1/ 5.2%
Histopathology of peritoneal biopsy	14	13/92.8%
Culture of peritoneum	14	11/78.5%
Culture of ascites	19	6/31.5%

Table 4: Diagnostic yield of the tests used in diagnosis.

Most of the patients (n=22, 81.5%) healed with a standard anti-TB therapy of 9 months. Additional treatment of 3 months was given to 5 (18.5%) patients at the end of 9 months. The duration of symptoms prior to diagnosis in patients who

received additional anti-TB treatment of 3 months (mean: 116 days, range: 100-155 days) was significantly higher than in those (mean: 41,09 days, range: 5-120 days) who were healed with standard treatment of 9 months ($p=0.001$). In biserial correlation test, a strong positive correlation (correlation coefficient= +0,77) was found between these two groups. In addition, pretreatment CRP was found to be significantly different between the patients with a standard therapy of 9 months (mean: 121.82 days, range: 4-288 days) and the patients required additional therapy of 3 months (mean: 44.2 days, range: 3-66 days) ($p=0.023$). On the other hand, no association was found statistically significant between these two group in terms of other continuous variables such as the presence of extraperitoneal TB ($p=0.413$), presence of concomitant chronic disease ($p=0.303$), hematological parameters including thrombocyte ($p=0.739$), leukocyte ($p=0.447$), hemoglobin levels ($p=0.485$), ascitic ADA ($p=0.736$) and CA 125 ($p=0.221$) levels.

Of 27 patients, 11 developed complications (6 had elevated liver function tests, 5 had nausea and vomiting). None of those were serious, and cessation of anti-TB drug for a short time was enough to improve these side effects. In addition, we found that no variables such as duration of symptoms before treatment ($p=0.645$), presence of concomitant chronic disease ($p=1.000$), presence of extraperitoneal TB ($p=0.391$), pretreatment CRP ($p=0.291$) and other hematologic parameters including thrombocyte ($p=0.368$), leukocyte ($p=0.481$), hemoglobin levels ($p=0.645$), ascitic ADA ($p=0.840$) and CA 125 ($p=0.270$) levels had statistically an effect on the development of complications. In our opinion, all complications were related to the anti-TB therapy. There was no mortality in our study population.

Discussion

The diagnosis of TBP is often difficult due to the variability of its clinical presentation, nonspecific radiological findings and insufficient microbiological tests⁽⁷⁾. It is usually an insidious disease with long-lasting symptoms and findings. Its insidious nature leads delay in diagnosis that is related to increased morbidity and mortality rates⁽⁸⁾. In our study, there was no mortality, but we found that the onset of symptoms prior to diagnosis was associated with the prolongation of treatment. Additionally, it was concluded that prolongation of diagnosis time led the treatment more difficult and longer, accord-

ing to the strong positive correlation in biserial correlation analysis. On the other hand, a small number of patients can be presented with acute abdomen findings, and underwent unnecessary operation. In our study, two patients were operated on emergency due to acute abdomen.

Abdominal pain and distension were the most common symptoms in our patients, similar to previous studies^(9,10). Most of patients with TBP suffer from ascites as a leading clinical finding^(8,11-13). In our study, more than half of patients with TBP were admitted with abdominal distension due to clinical ascites. However, almost all of the TBP patients had radiological-detected ascites. In fact, TBP constitutes only 1% of all causes of ascites⁽¹⁴⁾, and therefore a high index of suspicion is needed if the patient with ascites has lived in an endemic region. Although Turkey is a country with low prevalence on TB according to WHO data⁽¹⁵⁾, this disease remains still a public health problem in certain areas of the country. Patients with clinically suspicious of TBP should be questioned about their past history of TB. In the present study, four patients had a history of pulmonary TB. In addition, the presence of concomitant extraperitoneal TB should be investigated. Abdallah reported that up to half of patients with abdominal TB had extraabdominal involvement⁽¹⁶⁾. Similarly, Khan found radiological evidence of pulmonary TB in two thirds of patients with abdominal TB⁽¹⁷⁾. In our study, extraperitoneal TB was detected in 20 of 27 patients. However, the remaining seven patients had no concomitant extraperitoneal TB, and hence were considered as primer TBP.

Routine hematological parameters are nonspecific for TBP, and therefore have a little diagnostic yield^(8,9). In a study by Rai, low Hb and high CRP levels were found to be the most common laboratory findings⁽¹⁸⁾. We obtained similar results in our study. Additionally, we found that mean CRP level on admission was higher in patients who were given additional treatment of three months in comparison to patients who healed with standard therapy of nine months. Therefore, we suggest that CRP may be used as an indicator of the severity of disease. All patients in the present study had also high ESR values. ESR is almost always raised in patients with TBP, and can be used in determining the response to therapy. In our study, all ESR values returned to normal limits after treatment.

Ascitic fluid analysis is widely used in diagnosis of TBP. Typically, exudative fluid with decreased glucose level, elevated lymphocyte count, LDH and

total protein is seen in TBP. In our study, ascitic fluid had exudative features, and was mainly lymphocytic in character. In addition, low SAAG was detected in all patients consistent with previous studies^(12, 19).

The measurement of ADA activity in ascitic fluid is a helpful diagnostic tool with high sensitivity and specificity^(20, 21). However, Shen noted that this test is not a specific marker for TBP, and should be supported by clinical findings and microbiological tests⁽²²⁾. In addition, this test may show false-negative results especially in cirrhotic patients due to low-protein ascites. There was no cirrhotic patient in our study, and high ADA levels were detected in majority of the patients. In our opinion, ascitic ADA can be accepted as an effective diagnostic method due to its high positivity rate.

PCR is a rapid test to obtain a diagnosis, however high costs limit its use in general practice. Sensitivity of PCR is known to reach up to 95% in smear positive cases. However, test sensitivity decreases below 50% in smear-negative patients⁽²³⁾. In our study, PCR analysis of ascitic fluid was used in eight patients, and only three positive results were obtained. According to us, this was due to the large number of smear-negative patients.

Although CA125 is a well-known diagnostic marker in ovarian cancer, its diagnostic yield in TBP has been also documented in many studies^(9, 19, 24). Ascitic CA125 levels were found to be increased in 17 of 19 cases in our study; however, only one patient had an ovarian cancer. High ascites CA125 levels can be seen in other diseases with peritoneal involvement, and hence only indicate a suspicion index for TP⁽²⁵⁾. On the other hand, serum CA125 was reported as an indicator of anti-TB treatment success^(24, 25). Mas reported that high serum CA125 levels were as high as ovarian cancers associated with peritoneal involvement, and were returned to normal values after four months of treatment⁽²⁴⁾. In the present study, serum CA125 was not used as a routine test in diagnostic workup. However, in the lights of the results from previous studies, we suggest that serum CA125 can be used as a beneficial marker in both diagnosis and evaluation of therapy success.

Tuberculin skin test has only supportive value in the diagnosis of TBP because of its high false positivity rates in BCG-vaccinated people due to cross-reaction with bacillus Calmette-Guérin (BCG). In our study, this test was performed in nine patients, and positive results were obtained from

seven of those. However, five of those patients with positive skin test were vaccinated and had no prior history of TB.

Imaging methods such as US, barium X-Rays, and CT have a little diagnostic yield in TBP, and normal findings cannot rule out the diagnosis (26). In our study, chest radiography, US and CT were found to be normal in a portion of patients. The most common reported radiological findings are abdominal ascites, omental and peritoneal thickening, intraabdominal lymphadenopathy, and hepatomegaly^(9, 11). Similarly, ascites was the most frequent finding in both US and CT in our study.

As a result, diagnosis of TBP generally needs to be confirmed by the presence of positive AFB staining, positive culture or PCR analysis for *M. Tuberculosis*. AFB staining detects only a minority of cases⁽²⁶⁾. Similarly, positive AFB staining was observed in one of 19 patients who could performed paracentesis. Bacteriological confirmation can be performed using cultures for *Mycobacterium tuberculosis*, but at least one month is required for this procedure, and awaiting the results of culture means high mortality rate^(13, 26). Furthermore, failure to culture of *Mycobacterium tuberculosis* does not exclude the diagnosis. Currently, laparoscopy with peritoneal biopsy has become gold standard diagnostic method due to its fastness and effectiveness^(8, 18, 27, 28). Similarly, peritoneal biopsy was mainly obtained by laparoscopic approach in the present study. However, peritoneal biopsy obtained by mini laparotomy is also helpful in diagnosis of TBP when laparoscopy could not performed. In our study, laparotomy was performed for only two cases due to their emergency condition. In this study, among 14 patients who underwent laparoscopy or laparotomy, diagnosis was confirmed in 13 histopathologically.

At operation, multiple diffuse involvement of the peritoneum, white nodules or plaques, lymphadenomegaly, ascites, fibrinous strands, and omental thickening are the most common findings. Similarly, ascites, fibrinous strands, omental and peritoneal thickening were the most frequent operative findings in the present study.

In conclusion, no single test is sufficient in diagnosis of TBP, and a high index of suspicion should be required. The patient's anamnesis and the presence of ascites are the cornerstones in the diagnosis. Laparoscopy with peritoneal biopsy seems to be the gold standard diagnostic method, and also allows ruling out other intraabdominal pathologies.

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