



Analysis of cases with tuberculous peritonitis: A single-center experience

INFECTION

A. Cumhuri Dülger¹, Sevdegül Karadaş², Rafet Mete³, M. Kürşat Türkdogan⁴, Davut Demirkıran⁵, Bilge Gültepe⁶

¹Department of Gastroenterology, Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

²Department of Emergency Medicine, Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

³Department of Gastroenterology, Namık Kemal University Faculty of Medicine, Tekirdağ, Turkey

⁴Department of Gastroenterology, Bezmialem University Faculty of Medicine, İstanbul, Turkey

⁵Department of Internal Medicine, Van Education and Research Hospital, Van, Turkey

⁶Department of Medical Microbiology, Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

ABSTRACT

Background/Aims: Tuberculous peritonitis (TP) is a rare form of tuberculosis and is caused by peritoneal involvement with Mycobacterium tuberculosis. A distinctive correlation exists between socioeconomic state and disease prevalence. We aimed to evaluate the clinical, laboratory, and radiological findings of patients with TP.

Materials and Methods: We conducted a retrospective study in patients with peritoneal tuberculosis from January 2004 to October 2008 at Yuzuncu Yıl University Medical School Education and Research Hospital. During this time, the data of 21 patients (17 females) with TP were reviewed.

Results: Fever, abdominal pain, and anorexia were the most common symptoms. An analysis of ascites showed lymphocyte predominance and low albumin gradient in all patients. Patients with TP had a median ascites adenosine deaminase (ADA) level of 139 U/L (range, 25 to 303U/L). Peritoneal involvement (wet peritonitis) was seen in all the cases. Following 6-month administration of combined anti-TBC treatment, mean serum CA-125 levels were within the normal range among patients who had previously higher serum CA-125 level. Mortality rate in the total cases was 4.6%.

Conclusion: Peritoneal tuberculosis should be considered in the differential diagnosis of exudative ascites in eastern Turkey. A high level of suspicion is required, especially in high-risk populations living in rural areas. ADA seems to be a sufficient, safe, and inexpensive method to perform the diagnosis of peritoneal tuberculosis. Serum CA-125 levels may play a key role to support the diagnosis as well as disease management of TP.

Keywords: Tuberculous peritonitis, adenosine deaminase, eastern Turkey, serum CA-125

INTRODUCTION

Tuberculosis (TB) has become a public health problem worldwide. The rates of TB continue to rise throughout the world, causing 6% mortality (1). According to WHO data, Turkey is a country with low prevalence in terms of TB (27/100,000) (2). Tuberculous peritonitis (TP) is an extremely rare form of tuberculosis. The absence of characteristic clinical features of the disease often makes its diagnosis difficult and elusive. So, it can be easily mixed with other intraabdominal diseases. On the other hand,

tuberculosis of the peritoneum and gastrointestinal system is less frequently seen in developed countries, as compared to less developed regions (3). The worldwide incidence of TP for all forms of TB is reported as 0.1% and 0.7% (4). Therefore, we reviewed 21 TP cases in the current study.

MATERIALS AND METHODS

Twenty-one TP cases over 14 years of age who were admitted and followed up in the Gastroenterology and

Adress for Correspondence: Sevdegül Karadaş, Department of Emergency Medicine, Yüzüncü Yıl University Faculty of Medicine, Van, Turkey E-mail: sevdegulkaradas@yahoo.com.tr

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Emergency Departments of Yuzuncu Yil University Medical School Education and Research Hospital from January 2004 to October 2008 were retrospectively evaluated in this trial. Approval of the ethics committee of the Faculty of Medicine was obtained from Yuzuncu Yil University of Medical Sciences.

Patients were evaluated in terms of socioeconomic level, demographic characteristics, localization of involvement, symptoms, disease history, presence of underlying diseases, physical examination, PPD positivity, laboratory findings, characteristics of ascites, radiological characteristics, treatment regimens, treatment side effects, and mortality. Data were entered in a trial page of Microsoft Excel.

Diagnostic criteria in cases with TP were determined as follows: determination of ARB in peritoneal fluid and tissue samples with EZN staining, isolation of *M. tuberculosis* with Löwenstein-Jensen and radiometric method as a rapid diagnostic method (BACTEC), >38 U/L ADA level in ascites fluid; <1.1 mg/dL serum ascites-albumin gradient; presence of lymphomonocytosis in the cell count of ascites, determination of granuloma with or without caseification in the histopathological examination of tissue samples and positive tuberculin skin test, clinical and radiological findings specific for tuberculosis infection, and response to tuberculosis treatment.

Treatment was initiated with INH 300 mg/day, RIF 600 mg/day, PZA 15-30 mg/kg/day (or morfozinamide 25-50 mg/kg) and SM 1 gr/day or EMB 15-25 mg/kg/day. In the first 2 months of treatment, quadruple antituberculosis treatment was administered, and a 6-month treatment schedule was completed by administration of INH+RIF for 4 months. During hospital stays and follow-up stages in the outpatient clinic, patients were evaluated monthly in a gastroenterology clinic for treatment side effects.

Among major characteristics, descriptive statistics for characteristics with categorical features were given as figures and percentages, while continuous characteristics (variables) were indicated as mean and standard deviation. Pearson correlation coefficient was used for determination of (linear) correlation between continuous variables, and significance level was accepted as 5% and 1%. All calculations were performed in SPSS (ver 16).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago, Illinois, USA). While descriptive statistics were implied for continuous variables as average, standard deviation, and minimum and maximum values, categorical variables were signified as number and percentage.

RESULTS

Sociodemographic data

A total of 21 patients, followed up from October 2004-October 2008 (4 years), were enrolled in this trial. The age range of patients was 18-60 (mean 30 ± 12 SD). While 17 of patients were women, 4 were men. Fifteen patients were residing in rural regions (71%), and 6 patients were living in urban regions (29%). Past history of pulmonary TB was present in 3 patients (14%). Fifteen patients indicated that they consumed unpasteurized local dairy products (e.g., cheese with various herbals) at least 3 times a week.

Pulmonary tuberculosis findings were found in 8 patients (38%). In 2 cases (9%), active pulmonary TB was determined. As underlying diseases, liver cirrhosis in 1 patient (5%), chronic renal failure in 2 patients (10%), and colon adenocarcinoma in 1 patient (5%) were determined. No case of alcohol-induced liver parenchyma disease was detected among our patients. Mean duration of symptoms prior to diagnosis was 2.6 months (2 weeks-8 months). Abdominal pain was present in all cases (100%). The main characteristic features of the patients are presented in Table 1.

Laboratory findings

Anemia was present in 45% of cases (mean hemoglobin: 11.1 g/dL); 42% presented with microcytosis (mean MCV: 74); 10% with leukocytosis (mean WBC: $7280/\text{mm}^3$), and 45% with thrombocytosis (mean PLT: $391,000/\text{mm}^3$). Sedimentation was high in 95% of patients (mean sedimentation rate: 42 mm/hour), and CRP was determined as high in 90% (mean CRP: 85

Table 1. Initial symptoms of signs of patients at referral

Referral Symptoms	Number of Patients	%
Abdominal pain	21	100
Abdominal distention	19	90
Weight loss	18	85
Anorexia	18	85
Night sweats	14	66
Cough	8	38
Findings		
Ascites	19	90
Fever	13	61
Hepatomegaly	12	57
Abdominal tenderness	9	45
Splenomegaly	5	23
Peritonitis	2	9
Intestinal obstruction	2	9

Table 2. Age and laboratory parameters of patients

	n	MEAN±SD	St. Error	St. Deviation	Min	Max.
Age (year)	21	29.86±2.53	2.525	11.573	18	60
MCV (fl)	21	75.10	2.035	9.327	54	87
ESR (mm/hour)	21	41.24	4.106	18.817	4	80
CRP (U/L)	21	84.38	13.250	60.719	11	251
Serum albumin (mg/dL)	21	3.35	1.500	6.875	2.3	4.4
SAAG (mg/dL)	21	0.67	0.649	2.972	0.2	1.4
Ascites ADA (U/L)	21	140.33	12.197	55.892	29	229
Ascites albumin (mg/dL)	21	2.66	1.125	5.153	1.4	3.6
Ascites WBC (/mm ³)	21	4303.33	787.353	3608.104	1100	15800
Ascites lymphocyte (/mm ³)	21	2579.05	425.476	1949.774	600	7000
Ascites CA-125 (U/L))	21	427.57	18.883	86.532	182	500
Ascites Glucose (mg/dL)	21	76.38	3.938	18.046	46	110
Ascites LDH (U/L)	21	792.71	163.843	750.825	264	3874
PPD (mm)	21	14.14	0.433	1.982	10	18
Serum globulin (mg/dL)	21	4.31	1.573	7.210	2.6	5.6
Hemoglobin x 10 (g/dL)	21	11.61	3.606	16.525	8.5	15.4
WBC (/mm ³)	21	7507.14	857.337	3928.813	3700	21000
PLT x 100 (/mm ³)	21	412.86	25.234	115.634	211	655

*Characteristics are indicated as mean and standard error.

MCV: mean corpuscular volume; ESR: sedimentation; CRP: c-reactive protein; SAAG: serum ascites-albumin gradient; ADA: adenosine deaminase; WBC: white blood cell ; LDH: lactate dehydrogenase; PPD: purified protein derivative; PLT: platelet

U/L). Serum albumin level was low in 57% of cases (mean albumin: 3.3 g/dL), and serum globulin level was high in 90% of patients (mean globulin level: 4.2 g/dL). Albumin/globulin ratio was determined as 0.78.

Analysis of ascites

Unguided or ultrasound-guided diagnostic paracentesis was performed in all cases. Mean diagnostic parameters in ascites were as follows: albumin: 2.65 mg/dL, leukocytes: 4295/mm³, lymphocytes: 2577/mm³, CA 125:427 U/L, glucose: 76 mg/dL, and LDH: 792 IU/L. Domination of lymphomonocytosis in ascitic fluid was found in 19 cases (90%). Serum ascites-albumin gradient was 0.72 mg/dL. Mean ascitic ADA level was 139 U/L. Except in one case, ADA values were found to be over 35 U/L in all patients. Laboratory features of the study patients are depicted in Table 2.

Radiology

Among study patients, 18 patients (85%) were evaluated by thorax CT. In 7 patients (33%), pulmonary fibrocalcification and fibrosis were determined, while pleural effusion was found in 8 cases (38%).

Abdominal ultrasonography was performed in all cases, and abdominal tomography was performed in 19 patients (90%). Ascites was determined in 21 cases (100%), while omental thickening was found in 17 cases (81%), peritoneal thickening in 12 cases (57%), and intraabdominal lymphadenopathy in 7 cases (33%). Hepatomegaly was present in 12 patients (57%), and splenomegaly was detected in 5 patients (24%).

Tuberculin test

PPD test was performed in 15 cases, and the test was positive in 8 patients (53%) (positivity with >12-mm endurance).

Laparoscopy or laparotomy

Laparoscopy or laparotomy was planned for all patients. For 6 patients (28%) with informed consent for the procedure, laparotomy was performed with a midline incision, 5 cm below the umbilicus. In 4 of these cases, diagnosis was histopathologically confirmed in the obtained samples.

Microbiological examinations

Ascitic fluid samples of 15 patients were forwarded to the microbiology department for MT culture. Growth was detected

Table 3. Diagnostic Methods of Tuberculosis in Our Patients

Concurrent histology and positivity of culture	3	14%
Histology only	3	15%
Culture only	3	14%
Response to TBC treatment or other findings (ADA, PCR etc.)	12	57%

ADA: adenosine deaminase; PCR: polymerase chain reaction

in 6 samples (29%) in 4-8 weeks, and diagnosis was microbiologically confirmed. In 2 patients, diagnosis was confirmed by Polymerase Chain Reaction (PCR) evaluation of ascitic material samples. Diagnostic methods of tuberculosis in our patients are shown in Table 3.

Treatment and prognosis

During first 2 months of treatment, RIF, INH, and PZA were administered to all patients, with addition of EMB in 8 cases. RIF and INH were administered for 4 months during the maintenance phase (6 months in total). Treatment was completed in 19 patients (90%). Two patients, one case of metastatic colon cancer and another case with sepsis due to intestinal perforation (10%), died during the treatment phase. Apart from two fatal cases, post-treatment serum CA-125 levels were determined in 10 of 19 patients (8 women, 2 men). Mean pre-treatment CA-125 value of these patients was 279 U/L, and mean CA-125 level in ascites was 532 U/L. Following 6-month administration of combined anti-TBC treatment, mean serum CA-125 level was determined as 15 U/L (normal: <35 U/mL).

Asymptomatic LFT disturbance developed in 4 patients, which did not exceed 3 times the upper level of normal values. In 2 cases, LFT disturbance exceeded 5 times the upper level of normal values. In the latter group, standard treatment regimen was discontinued, followed by re-initiation of treatment with sequential regimen. In one of these patients, streptomycin 1 gr/day and levofloxacin 1000 mg/day were initiated upon re-occurrence of liver toxicity, and the patient was treated successfully. No complications developed. Nausea and anorexia developed in 6 cases (28%).

DISCUSSION

Epidemiology

In developing countries, tuberculosis is an important cause of mortality and morbidity (5). In Turkey, no trial investigating the incidence of TP has been conducted up to this date.

Liver cirrhosis was determined in 62% of TP cases, especially due to underlying alcoholic liver disease (6). In our trial, the rate of patients with liver cirrhosis was only 4%. Besides, most TBS cases, which have dramatically increased in recent years, are associated with the HIV/AIDS pandemic. In the current trial, HIV

test was implemented in all patients with no detected case of HIV infection. This result may be due to the rare occurrence of HIV infection in our region (7).

Active concurrent pulmonary disease in the presence of TP is evident in approximately 14% of cases (3). Coexistence of active pulmonary tuberculosis and TP was determined as 32% and 9% in various studies conducted in Turkey (8,9). Among our patients, pulmonary fibrocalcification with fibrosis was determined in 7 cases (33%), and pleural effusion was indicated in 8 cases (38%). The number of cases with active pulmonary tuberculosis was indicated as 4 (19%). Non-existence of active pulmonary TBC in most of our cases is inclined to confirm the correlation between the disease and consumption of unpasteurized dairy products.

Symptoms and signs

The most common clinical features are: abdominal distention (82%), clinical ascites (79%), abdominal tenderness (76%), fever (74%), weight loss (62%), abdominal pain (58%), and diarrhea (16%) (3).

The most common examination findings reported in publications in our country are fever, ascites, and hepatosplenomegaly (8-11).

In our trial, the mean duration of symptoms prior to diagnosis was 2.6 months (2 weeks-8 months). Abdominal pain was found in all patients (100%). Other symptoms were: abdominal distention (90%), weight loss (85%), anorexia (85%), night sweats (66%), and cough (38%). Findings in the physical examination, in order of frequency, were: ascites (90%), fever (61%), hepatomegaly (57%), and splenomegaly (23%). The rate of cases with hepatosplenomegaly was higher, as compared to other series.

Laboratory findings

In a trial conducted in the UK on 36 patients, the most common laboratory findings were determined as low hemoglobin and high CRP levels (12).

In our trial, the mean values of leukocyte count were determined as normal, and leukocytosis was observed in only 10% of cases. As observed in the current trial, the laboratory characteristics of TP were nonspecific and exhibited features that only raised a suspicion of a chronic infectious disease.

Examination of ascitic fluid

Among our patients, ascitic fluid exhibited exudative features (with low albumin gradient) and was mainly lymphocytic in character. On the other hand, glucose levels were normal (mean: 76 mg/dL). In TP cases, pre-treatment serum

values were shown to be higher than in ovarian cancer patients (13,14).

In all of our cases, ascitic CA-125 levels were found to be increased, and no gynecological malignancy was determined in any patient. However, since ascitic CA-125 levels also increase in other diseases with peritoneal involvement, this may be considered as a tumor indicator, only indicating a suspicion index for TP (15). Among 10 of our patients who were successfully treated and had post-treatment serum CA-125 levels, serum CA-125 values were determined to be normalized following treatment. This finding indicates that the monitoring of CA-125 levels is beneficial in the evaluation of treatment success.

High LDH levels are also seen in peritoneal carcinomatosis, cirrhosis, pancreatic ascites, and congestive heart failure (16). In a trial conducted in our country, mean LDH values in TP patients were determined as 574 IU/L (17). In all of our cases, LDH levels were found to be high (mean 792 IU/L).

Adenosine deaminase

Adenosine deaminase is an aminohydrolase that inverts adenosine to inosine, and its activity is high in T lymphocytes. In TP cases, ADA levels in ascitic fluid increase, due to stimulation of mycobacterial antigens (18).

Ongoing difficulties in TP diagnosis, the relatively long durations required for culture examinations, and less widespread use of rapid diagnostics methods, like PCR, with high cost have led to investigations for a rapid and alternative non-invasive test for diagnosis. Provided that the limit value is selected as 33 U/L or 35 U/L, the sensitivity and specificity were determined as 100% and 97%, respectively (19).

Activity of ADA is a measure of immune responses. Cirrhotic patients typically have weak reticuloendothelial system function and exhibit abnormal T cell response. In trials published in our country, ADA positivity rates in ascetic fluid in TP patients were reported as 90% and 100% (11,17).

In the current trial, ADA levels were determined in all patients. Relatively high values of mean ADA level among our patients and increased values in all cases, except one patient, are in accordance with the literature. However, mean values were higher, as compared to levels reported in the general literature. In one patient with low ADA values, underlying liver cirrhosis was found, in accordance with the literature data. In our trial, determination of ADA levels was regarded as critical for diagnosis, especially for patients who did not consent to laparoscopy.

PPD

In a trial conducted in our country, PPD positivity among TP patients was reported with varying rates as 42% and 71% (11,17).

In the current trial, PPD test was found to be positive in 53% of our cases.

Microbiological diagnosis

Rates of EZN staining of ascitic fluid and positivity of culture are 5% and 20-83%, respectively (20). In the current trial, ascitic fluid of 15 patients was forwarded to the microbiology department for MT culture. Other samples could not be sent for culture analysis, due to technical reasons. In 6 samples (40%), growth was observed in 4-8 weeks, and diagnosis was microbiologically confirmed. No patient was diagnosed with EZN.

Another diagnostic method used in this trial was PCR. While test sensitivity was determined as 95% in smear-positive patients, it decreased to 48% in smear-negative cases (21). In only 2 cases (10%), diagnosis was confirmed by PCR examination of ascitic fluid.

Radiology

Tuberculous peritonitis ascitic fluid has high attenuation values, due to high protein content. In one trial, fine septae and debris in ascitic fluid were reported as characteristic features (22).

In addition, mesenteric involvement, leading to patchy or widespread increase in the density and presence of stellate appearance, is indicated in CT. In the same trial, presence of disperse lymph nodes, omental thickening leading to omental cake appearance, and presence of fibrotic layer surrounding the omental line were detected (23).

In the current trial, ascites with septation was determined in all patients. This was followed by common CT findings of omental thickening (81%), peritoneal thickening (57%), and intraabdominal lymphadenopathy (33%).

Laparoscopy

In a trial, laparoscopic biopsy was performed in 84% of cases, and in 60% of these patients, diagnosis was confirmed histopathologically (17).

In various publications, laparoscopy is reported to be superior to laparotomy and unguided percutaneous peritoneal biopsy, and provided that it is used in combination with targeted biopsy of the peritoneal cavity through laparoscopic appearance, TP is indicated to be diagnosed with a rate of 80-95% with this method (24).

In the current trial, laparoscopic biopsy was performed in 8 cases (38%). In 6 of these cases (75%), histopathological diagnosis was confirmed. Epithelioid cell granulomas with caseification necrosis were determined in these patients. The rate of com-

plications due to laparoscopy, like intestinal perforation and intraabdominal hemorrhage, is reported as 2.7% (25). In our trial, intraperitoneal hemorrhage developed in only one case (4.7%) and recovered by surgical treatment.

Treatment

The treatment schedule for most adult patients who were not treated previously is initiated with INH, RIF, PZA, and EMB for 2 months. This is followed by a maintenance phase of 4 months with administration of INH and RIF. Treatment periods longer than 6 months are not recommended (26,27).

In a series of approximately 800 patients, an evaluation of overall results revealed a mortality rate of 19% (24).

The mortality rate in our trial was determined as 10% (2 patients). In one of our remaining 19 patients, second-generation anti-TBC drugs were required. Based on these results, we may indicate that resistance to TP treatment is not high in our region, though we did not perform a resistance trial. One of the fundamental issues in TP treatment is the hepatotoxic effect of anti-TBC drugs. Asymptomatic increased levels of ALT and AST are observed in 20% of cases (26). The rate of hepatotoxicity among our patients was 28% (6 patients). In 2 of these cases (approximately 10% of all patients), treatment was discontinued, and monitorization was required.

Finally, a high level of suspicion is required, especially in high-risk populations living in rural areas. ADA seems to be a sufficient, safe, and inexpensive method to perform the diagnosis of peritoneal tuberculosis. Serum CA-125 levels may play a key role to support the diagnosis of TP as well as disease management.

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