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# Pooled analysis of 163 published tuberculous peritonitis cases from Turkey

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**Background/aim:** Tuberculous peritonitis may be difficult to diagnose due to its insidious and variable clinical manifestations as well as characteristics similar to malignancy. In this study, case reports from Turkey over the last 10 years were reviewed systematically using pooled analysis.

**Materials and methods:** Thirty-four suitable articles were found and 163 tuberculous peritonitis cases were included in the study.

**Results:** The mean age was 34.1 years (17–79 years), and 146 (98.6%) of the patients were female and 17 (10.4%) were male. The most common complaints of these patients were abdominal pain (77.4%) and abdominal distention (73.5%). Ascites in the abdomen (75%), fever (42%), abdominal tenderness (33%), and abdominal distention (30.7%) were the most common physical examination findings. The mean adenosine deaminase level was 120.3 IU/L. In the subsets of patients with relevant data, acid-fast bacilli were found in 23.3%, culture was positive in 22.2%, and *Mycobacterium tuberculosis* polymerase chain reaction was positive in 20%. In abdominal imaging, ascites was reported in 92%. Elevated serum CA-125 was reported in 96.7% of the patients. Of 105 patients with data available following the antituberculous therapy prognosis, four (3.8%) died and the other 101 (96.2%) showed good treatment response.

**Conclusion:** Tuberculous peritonitis should be kept in mind during the differential diagnosis of patients admitted with the triad of ascites, fever, and abdominal distention.

**Key words:** Tuberculosis, peritonitis, adenosine deaminase, Turkey

## 1. Introduction

Although the global incidence of tuberculosis is decreasing, it remains among the top ten causes of death worldwide. There is an upward trend in the proportion of extrapulmonary tuberculosis patients both in Turkey and abroad (1–4). Peritoneal tuberculosis is a common form of abdominal tuberculosis. During primary infection, bacilli spread by lymphohematogenous dissemination from a pulmonary focus to peritoneum. These latent bacilli can reactivate at any time, causing peritoneal tuberculosis. In females, it is also possible for tubercle bacilli to spread from the fallopian tubes to the peritoneal space (5,6). Tuberculous peritonitis may be of the serous or plastic type. The more common clinical presentation is the serous type, which is characterized by ascites formation. The plastic type, without ascites, is less common. Ascites likely develops due to peritoneal lymphatic obstruction (6,7). The lack of specific signs and symptoms of the disease and its insidious course can make diagnosis challenging. Noticing the clinical course of tuberculous peritonitis is even more difficult in patients who also have cirrhosis or are undergoing peritoneal dialysis. A substantial number of patients receive a preliminary diagnosis of malignancy because serum CA-125 levels are usually elevated in tuberculous peritonitis and the conditions may share similar clinical features. Bacteriologic confirmation is difficult and time-consuming, and as a result of this, tuberculous peritonitis is usually diagnosed histopathologically. While the risk of tuberculous peritonitis increases in the presence of cirrhosis, diabetes, HIV infection, malignancy, antitumor necrosis factor (anti-TNF) therapy, steroid use, and dialysis for conditions like chronic kidney disease, the disease can also emerge in patients with none of these risk factors (7–9).

The aim of this study was to analyze the clinical, radiological, and laboratory findings of tuberculosis peritonitis case reports from Turkey published in national and international journals over the last 10 years.

## 2. Materials and methods

Two national databases (the ULAKBİM Turkish medical literature database and http://www.turkishmedline.com)

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and two international databases (PubMed and Science Citation Index-Expanded) were screened in February 2016 for tuberculous peritonitis case reports from Turkey published in national and international journals over the last 10 years. The key words "tüberküloz peritonit" and "peritoneal tüberküloz" were used when searching Turkish databases. When searching international databases, the keywords "tuberculous peritonitis in Turkey" and "peritoneal tuberculosis in Turkey" were used. Pediatric case reports and cases of tuberculous peritonitis within extrapulmonary tuberculosis series were not included in the analysis because they did not contain the requisite details.

The tuberculous peritonitis cases were analyzed in terms of the following: age, sex, symptoms, physical examination findings, time from symptom onset to diagnosis, concomitant diseases, routine laboratory findings, pulmonary imaging findings, purified protein derivative (PPD) tuberculin skin test positivity, serum CA-125 levels, ascitic fluid characteristics and adenosine deaminase (ADA) level, radiologic findings (abdominal ultrasonography [US]/computed tomography [CT]), diagnostic procedures (laparotomy, laparoscopy, percutaneous needle biopsy), diagnostic methods (pathology, azide-resistant bacteria [ARB], culture, polymerase chain reaction [PCR]), any preliminary diagnoses preceding definitive diagnosis, and prognosis.

Statistical analysis was performed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). The clinical, laboratory, and imaging data from the case reports and the case series were pooled and descriptive analyses were presented using percentages, median, min–max, means, and standard deviations.

**3. Results**

A search of four databases using the specified keywords yielded 163 tuberculous peritonitis cases from 34 accessible reports (10–43). Of those cases, 146 (89.6%) patients were female and 17 (10.4%) were male; mean age was 34.1 years (17–79 years).

Concomitant disease data were available for 106 of the patients. Nine of the patients were infertile, six had chronic renal failure, four had chronic HBV infection, two had cirrhosis, one had malignancy, one was using steroids due to rheumatoid arthritis, and one patient was pregnant. The remaining 77% of the patients had no risk factors for tuberculous peritonitis.

Of 96 patients with available data, the mean time between symptom onset and diagnosis was 10 weeks (1–24 weeks).

The most common complaints at admission were abdominal pain (77.4%), abdominal bloating (73.5%), weight loss (48.7%), and night sweats (27.1%); other symptoms included fever (15.5%), diarrhea (5.8%), and constipation (2.6%). It was noted that nine patients were being tested due to infertility.

Physical examination findings were noted for 88 patients. The most common findings were abdominal ascites in 66 patients (75.0%), fever in 37 patients (42.0%), abdominal and pelvic tenderness in 29 patients (33.0%), abdominal distention in 27 patients (30.7%), and palpable mass in the abdominal or pelvic area in 12 patients (13.6%) (Table 1).

Of the patients with routine laboratory test data, mean hemoglobin was 10.8 ± 1.3 g/dL, serum albumin was 2.94 ± 0.52 g/dL, C-reactive protein (CRP) was 74.7 ± 61.8 mg/L, and leukocyte count was 7520 ± 3074 /mm$^3$ (Table 1).

Lymphocytes were the predominant cell type in the ascitic fluid of 95% of 88 patients with available data. All of these patients had exudative ascites and their serum ascites-albumin gradient was less than 1.1. Mean ascitic fluid ADA level, assessed in 39 patients, was 120.3 IU/L (10–171 IU/L).

In terms of bacteriologic analysis, 46 of 60 patients (76.6%) tested as ARB-negative and 14 of 60 (23.3%) were ARB-positive. Mycobacterial culture of ascitic fluid was negative in 56 of 72 patients (77.7%), while isolates were obtained from 16 of 72 patients (22.2%). Ascitic fluid mycobacterial PCR analysis was positive for eight (20%) of the 40 patients tested. Mycobacterial culture from peritoneal tissue and mycobacterial tissue-PCR were done for 10 patients; three (30%) were culture-positive and five (50%) had positive PCR results. The patients' microbiologic findings are shown in Table 2.

Histopathologic examination of the peritoneum was done for 129 patients; calcified granulomatous inflammation was reported for 67 (52%) patients and granulomatous inflammation for 62 (48%) patients. Peritoneal biopsy was performed by laparotomy in 51 patients, laparoscopy in 59 patients, US-guided percutaneous needle in 17 patients, and endoscopic needle in three patients. For one patient who underwent US-guided percutaneous needle biopsy, insufficient material was reported as the pathology result.

Analysis of diagnostic methods revealed that tuberculous peritonitis was diagnosed based on histopathology in 102 cases, microbiology in 9, and both histopathology and microbiology in 27, while 25 patients were diagnosed based on clinical findings (Table 3).

Serum CA-125 levels were assessed in 122 patients, 118 (96.7%) of whom had high CA-125 levels based on a threshold of 25 U/mL.

Of 53 patients tested, PPD test results were positive in 27, negative in 23, and anergic in three patients.

Findings on pulmonary imaging were noted for 136 patients. Imaging was normal in 89 patients, 10 patients

**Table 1.** Patients' physical examination, radiology (ultrasonography and/or computed tomography), and laboratory findings.

| Physical examination findings (n = 88) | |
|---|---|
| Ascites | 75.0% |
| Fever | 42.0% |
| Abdominal tenderness | 33.0% |
| Abdominal distention | 30.7% |
| Palpable mass | 13.6% |
| Radiologic findings (n = 150) | |
| Ascites | 92% |
| Thickened peritoneum | 55% |
| Pelvic mass | 40% |
| Lymphadenopathy | 14% |
| Laboratory findings | |
| Hemoglobin, g/dL (mean ± SD) | 10.8 ± 1.3 |
| Serum albumin, g/dL (mean ± SD) | 2.94 ± 0.52 |
| CRP, mg/L (mean ± SD) | 74.7 ± 61.8 |
| Blood leukocytes, /mm$^3$ (mean ± SD) | 7520 ± 3074 |

**Table 2**. Microbiologic findings.

| | Positive patients (%) |
|---|---|
| Acido-resistant bacteria (ARB) (n = 60) | 14 (23.3%) |
| Mycobacterial culture (ascitic fluid) (n = 72) | 16 (22.2%) |
| Mycobacterial PCR (ascitic fluid) (n = 40) | 8 (20%) |
| Mycobacterial culture (tissue) (n = 10) | 3 (30%) |
| Mycobacterial PCR (tissue) (n = 10) | 5 (50%) |

**Table 3.** Diagnostic method.

| | Patients (%) |
|---|---|
| Histopathology | 102 (62.5%) |
| Microbiology | 9 (5.5%) |
| Histopathology and microbiology | 27 (16.5%) |
| Clinical | 25 (15.4%) |

showed signs of active tuberculosis, and three showed signs of tuberculosis sequelae. Pleural effusion was the most common pathology among the patients with abnormal imaging results.

Abdominal US and/or CT examination findings were recorded for 150 patients. Of these, ascites was noted in 139 patients (92%), peritoneal thickening in 83 (55%), pelvic mass in 61 (40%), and lymphadenomegaly in 21 (14%) (Table 1).

Of 105 patients with data following the antituberculous therapy prognosis, four (3.8%) died and the other 101 (96.2%) showed good treatment response.

According to the institutions listed for the studies' first authors, most cases were reported from gynecology/obstetrics and gastroenterology clinics. A substantial proportion of the patients with preliminary diagnoses had undergone a procedure due to a prediagnosis of malignancy.

## 4. Discussion

Although it typically affects the lungs, tuberculosis is a disease that can involve all organs and tissues. According to 2013 data from the Turkish Ministry of Health, extrapulmonary tuberculosis accounted for 36.8% of all cases. The same report cited the proportion of gastrointestinal/peritoneal tuberculosis as 5.5%, comprising 4.7% of female and 35.3% of male patients (http://tuberkuloz.thsk.saglik.gov.tr/).

The patients included in our analysis were 89.6% female and 10.4% male with a mean age of 34.1 years. These results indicate that peritoneal tuberculosis predominantly affects young women.

The incidence of tuberculous peritonitis is higher among patients with underlying diseases that compromise immunity. However, some patients may have no obvious risk factors (7–9). Of the patients in this study, 77% had no risk factors, while the others had concomitant conditions such as chronic renal failure, cirrhosis, malignancy, steroid use, chronic HBV infection, pregnancy, or infertility. Three patients with infertility were asymptomatic and were diagnosed while attempting to identify the etiology of their infertility. This indicates that in countries where tuberculosis is common, peritoneal and genitourinary tuberculosis should be considered for young women with infertility (44).

Peritoneal tuberculosis manifests with a subacute clinical course and no specific symptoms. Patients' presenting symptoms are usually nonlocalized abdominal pain, abdominal bloating, weight loss, night sweats, and fever (7–9). In the present study, the most common complaints at presentation were abdominal pain (77.4%), abdominal bloating (73.5%), weight loss (48.7%), and night sweats (27.1%); other symptoms were fever (15.5%), diarrhea (5.8%), and constipation (2.6%).

In a study investigating the etiology of polyserositis, 5% of patients were diagnosed with tuberculous peritonitis (45). In a study from Tunisia investigating the etiology of exudative ascites, tuberculous peritonitis was detected in 51 of 90 patients (46). In another study, 152 of 305 patients

with exudative ascites were diagnosed with tuberculous peritonitis (47). These studies highlight the need to include tuberculosis in the differential diagnosis of exudative ascites. In peritoneal tuberculosis, ascites is usually exudative with a predominance of lymphocytes. Neutrophils may predominate in patients undergoing peritoneal dialysis due to the more acute course (7,8,48). All of the patients in this analysis with available data had exudative ascites and, with the exception of 4 patients undergoing peritoneal dialysis, lymphocytes were the predominant cell type.

Particularly in women, peritonitis may manifest as a result of genital tuberculosis. In females, enlargement of the mesenteric lymph nodes and tubo-ovarian abscesses are sometimes evaluated as pelvic masses, leading to a prediagnosis of ovarian cancer (6,49). The most common findings in the present study were abdominal ascites (75%), fever (42%), abdominal and pelvic tenderness (33%), abdominal distention (30.7%), and palpable mass in the abdominal or pelvic area (13.6%) (Table 1).

The insidious clinical course of the disease prolongs the time between symptom onset and diagnosis (7–9). Among the 96 patients in this study with available data, this time was 10 weeks (1–24 weeks). The length of this period is important in terms of prognosis. It was reported that mortality was higher in patients diagnosed more than 6 weeks after symptom onset. Particularly for patients undergoing peritoneal dialysis or with conditions like cirrhosis, the condition is usually initially evaluated as bacterial peritonitis; tuberculosis is considered after the patient shows no treatment response.

Routine laboratory tests have limited value in peritoneal tuberculosis. Patients often exhibit anemia, hypoalbuminemia, and elevated CRP level, while leukocyte count is usually normal (7–9). Similarly, notable findings in the patients analyzed in this report were anemia, hypoalbuminemia, and elevated CRP.

In peritoneal tuberculosis, the ADA level in the ascitic fluid is high. Therefore, a high ascitic fluid ADA level can be considered an indirect indicator for tuberculosis diagnosis. ADA is an enzyme that functions in the catabolism of purine bases in lymphoid cells and is necessary for their maturation. Levels of ADA are increased when mycobacterial antigens stimulate T lymphocytes (6,7,9). A metaanalysis indicated that when using a threshold of 39 IU/L, the test had specificity of 97% and sensitivity of 100% (50). According to the results of metaanalyses, a finding of elevated ADA in addition to the patient's clinical presentation may justify the initiation of empiric antitubercular therapy while waiting for culture and biopsy results (50–52).With the exception of two patients, the ADA level was elevated (using a threshold of 39 IU/L) in all patients in the current study for whom data were available. The assessment of ADA level is simple, fast, and inexpensive, but levels may appear normal due to active cellular immunity in cases of HIV coinfection or cirrhosis.

Culture remains the diagnostic gold standard for tuberculosis. However, because of the low density of bacilli, ascitic fluid ARB and culture positivity rates are low (7–9,53). One report noted ARB positivity in 3% and culture positivity in 35% of a large patient series (9). In a Turkish study including cases of extrapulmonary tuberculosis, 12% of patients diagnosed with peritonitis tested positive for ARB and 9% had positive cultures (54). Culturing with conventional media takes 3–8 weeks, though automated systems may reduce this time to 1–3 weeks. PCR can return results within hours, but PCR sensitivity varies in parallel to culture and smear positivity (9,55). In the present study, positivity rates were 23.3% among those tested for ARB and 22.2% for those with culture data. This ARB positivity rate is high compared to the literature. Positive results were obtained for 20% of patients with ascitic fluid PCR data and 5 of 10 patients with tissue-PCR data. Our high ratio of ARB-positive patients may be related to the high sensitivity of PCR. In clinically suspicious cases, mycobacterial PCR analysis of both ascitic fluid and peritoneal tissue may facilitate the diagnosis.

The possible finding of elevated serum CA-125 levels causes this disease to be mistaken for ovarian cancer at initial evaluation. There are many studies that challenge the value of high CA-125 levels as an indirect marker for tuberculous peritonitis (56–60). The consensus of these studies is that due to its potential elevation in both malignant and benign conditions, an elevated CA-125 level has limited diagnostic value in peritoneal tuberculosis but may be useful when monitoring treatment response. Consistent with the literature, 96.7% of the patients in our analysis exhibited high CA-125 levels, which returned to normal following treatment.

The PPD test positivity rate is also low in tuberculous peritonitis. For this reason, a negative/anergic test result cannot be used to exclude a tuberculosis diagnosis. In the present study, 50% of those tested had positive PPD test results. In countries like Turkey where the chance of encountering tubercle bacilli is high and BCG vaccination is performed, PPD test results should be evaluated in the context of other findings.

Peritoneal tuberculosis may occur with active pulmonary tuberculosis. Findings of active tuberculosis were noted in the pulmonary imaging of 10 patients in our case series.

CT and US have limited diagnostic value because certain findings may suggest peritoneal tuberculosis but are not specific. Ascites, thickened peritoneum and mesentery, lymphadenomegaly, and omental involvement are common imaging findings. Fine septations in the ascitic fluid are a finding that suggests tuberculosis (61,62). Enlarged lymph

nodes may appear as hypodense areas on CT due to central calcification. This appearance is sometimes described as multiple masses (62). The most commonly reported radiologic findings in this analysis were peritoneal thickening, pelvic mass, and lymphadenomegaly.

Because it may have features similar to malignancy and bacteriologic confirmation is difficult and time-consuming, tuberculous peritonitis is usually diagnosed histopathologically (7–9,63). The results of our analysis were consistent with this, revealing that 102 patients (62.5%) were diagnosed histopathologically, 25 (15.4%) clinically, 9 (5.5%) bacteriologically, and 27 (16.5%) both bacteriologically and histopathologically. The low number of patients with bacteriologically confirmed diagnosis may also be due in part to the low rate of microbiologic sampling. Culture is important both for confirming diagnosis as well as providing an opportunity to study drug resistance.

Peritoneal tissue specimens may be obtained by percutaneous needle biopsy, laparoscopy, or laparotomy. Percutaneous needle biopsy is of limited diagnostic value due to the possibility of not being able to obtain tissue from the appropriate area. Because laparotomy is invasive, it is only recommended in cases where laparoscopy is technically difficult. The consensus in many studies is that laparoscopy is the best diagnostic procedure for peritoneal biopsy (7,9,63). Laparoscopy allows the acquisition of suitable tissue while visually examining the peritoneum. The characteristic appearance of the peritoneum on laparoscopy includes peritoneal thickening, hyperemia, and scattered yellowish nodules with central calcification. In studies of large patient groups, evaluation of the laparoscopic appearance of tuberculous peritonitis together with biopsy results had a sensitivity of 80%–94% (63). While waiting for bacteriologic confirmation, laparoscopic appearance and histopathologic examination can accelerate the diagnostic process and facilitate earlier initiation of treatment. Laparotomy was the diagnostic procedure used in 31% of the cases included in our analysis, which can be explained by these patients' prediagnosis of malignancy.

There are some limitations of our report. In studies conducted with pool analysis, not all reports contained all the target parameters, which is one limitation of our study. A substantial proportion of the reports did not include sufficient data regarding treatment and as a result of this we were unable to evaluate that aspect in the present study. Other limitations were the inability to detect possible double reports of patients and not including congress abstracts in the study. However, to our knowledge, our analysis includes the largest dataset to be reported from Turkey to date.

To summarize, suspecting tuberculosis is the most important step in diagnosis. Most of the cases in this study were reported from gynecology and obstetrics or gastroenterology clinics, and some of those patients underwent unnecessary invasive procedures due to a preliminary diagnosis of malignancy. Tuberculosis should be considered in the differential diagnosis of patients presenting with the triad of ascites, fever, and abdominal distention.

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