



Evaluation of Forty-Nine Patients with Abdominal Tuberculosis

Abdominal Tüberkülozlu Kırk Dokuz Hastanın Değerlendirilmesi

Forty-Nine Cases of Abdominal Tuberculosis

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Özet

Amaç: Abdominal tüberküloz ekstrapulmoner enfeksiyonun nadir bir formudur. Bu çalışmada, abdominal tüberkülozun spesifik olmayan klinik prezentasyonlarını ve tanısız zorluklarını vurgulamayı amaçladık. **Gereç ve Yöntem:** 2003 ve 2014 yılları arasında abdominal tüberküloz tanısı konan 49 hastanın klinik özellikleri, tanı yöntemleri ve tedavi sonuçları retrospektif olarak analiz edildi. **Bulgular:** Hastalar peritoneal (28), nodal (14), intestinal (5), ve solid organ tüberkülozu (2) olarak sınıflandırıldı. En sık görülen belirtiler karın ağrısı, karında şişkinlik ve yorgunluk idi. Asit en sık klinik bulgu olarak ortaya çıktı. Asit ve büyümüş karın lenf nodları ultrasonografi ve tomografide en sık bulguları. Abdominal tüberküloz tanısı, esas olarak asit sıvısının ve periton, karın lenf nodları veya kolonoskopik biyopsilerin histopatolojisine dayalı idi. İlaç tedavisini bırakan veya devam eden semptom ve bulguları olan 8 hastada 9-12 aylık uzatılmış tedavi gerekirken 40 hasta standart 6 aylık tedavi ile iyileşti. Bir hasta yaygın enfeksiyon nedeniyle tedavi süresi içinde öldü. **Tartışma:** Abdominal tüberküloz tanısı farklı klinik prezentasyonlar nedeniyle genellikle zordur. Asit varlığı, kişisel/aile/temas öyküsü ve eşlik eden aktif ekstraabdominal tüberküloz tanıda en önemli işaretlerdir. Tanısız laparoskopi ve doku örnekleme abdominal tüberküloz için en iyi tanısız yaklaşım gibi görünmektedir.

Anahtar Kelimeler

Karın Tüberkülozu; Tanı; Tedavi; Tüberküloz

Abstract

Aim: Abdominal tuberculosis is an uncommon form of extrapulmonary infection. In this study, we aimed to highlight the nonspecific clinical presentations and diagnostic difficulties of abdominal tuberculosis. **Material and Method:** Clinical features, diagnostic methods, and the therapeutic outcomes of 49 patients diagnosed as abdominal tuberculosis between 2003 and 2014 were retrospectively analyzed. **Results:** The patients were classified into four subgroups including peritoneal (28), nodal (14), intestinal (5), and solid organ tuberculosis (2). The most frequent symptoms were abdominal pain, abdominal distention and fatigue. Ascites appeared to be the most frequent clinical finding. Ascites and enlarged abdominal lymph nodes were the most frequent findings on ultrasonography and tomography. Diagnosis of abdominal tuberculosis was mainly depended on histopathology of ascitic fluid and biopsies from peritoneum, abdominal lymph nodes or colonoscopic materials. Forty patients healed with standart 6-month therapy while extended treatment for 9-12 months was needed in 8 whom had discontinued drug therapy and had persistent symptoms and signs. One patient died within the treatment period due to disseminated infection. **Discussion:** The diagnosis of abdominal tuberculosis is often difficult due to diverse clinical presentations. The presence of ascites, personal/familial/contact history of tuberculosis, and coexisting active extraabdominal tuberculosis are the most significant marks in diagnosis. Diagnostic laparoscopy and tissue sampling seem to be the best diagnostic approach for abdominal tuberculosis.

Keywords

Abdominal Tuberculosis; Diagnosis; Treatment; Tuberculosis

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Introduction

Tuberculosis (TB) remains a major public health problem with 1.3 million/year deaths globally [1]. Although extrapulmonary TB is less frequent than pulmonary TB, its incidence has been increasing worldwide due to various factors such as HIV infection, multidrug resistance and certain genetic variations in mycobacteria. Abdominal tuberculosis (ATB), as a rare manifestation of extrapulmonary tubercular disease, contains the types of gastrointestinal, peritoneal, nodal and solid organ TB. ATB poses a significant diagnostic challenge due to its variable presentations and lack of specific symptoms. No single diagnostic method is sufficient in the diagnosis of ATB. Since it can be easily confused with other clinical conditions, delay in diagnosis is not rare. Therefore, a high index of clinical suspicion should be required for correct diagnosis of this uncommon disease which carries good prognosis if promptly diagnosed and treated.

Material and Method

Patients and study design

The records of 49 patients diagnosed with ATB between January 2003 and December 2014 were analyzed 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' characteristics such as age, gender, past history of TB, comorbid diseases, initial clinical symptoms and findings, duration of symptoms were recorded. Laboratory investigations including complete blood counts, routine biochemistry analysis, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), pretreatment and post-treatment serum CA-125 were also noted. All diagnostic tests including purified protein derivative (PPD) skin test (positivity is >12 mm induration), chest X-ray, abdominal ultrasound (US), acid-fast basille (AFB) staining of ascitic fluid, mycobacterial culture and adenosine deaminase (ADA) levels of ascites, polymerase chain reaction (PCR) analysis for *M. tuberculosis* complex expression, paracentesis findings and results of biopsy obtained by laparoscopy, laparotomy or colonoscopy were analysed. A microbiological diagnosis was attempted in all cases; however, in patients who could not diagnosed microbiological, the histopathological finding of caseating granulomas or multinucleated giant cells were accepted as a definite evidence of TB. Only one patient was diagnosed by response to anti-TB therapy because of failure in all diagnostic methods. Patients were classified into four subgroups: Intestinal, nodal, peritoneal and solid organ TB. All patients were also evaluated in terms of coexisting pulmonary TB, with chest X-ray and culture of respiratory secretion.

Anti-TB therapy

All patients were treated with isoniazid (5 mg/kg day, max. 300 mg/day) and rifampicin (10 mg/kg day, max. 600 mg/day) for 6 months. In the first 2-month period, pyrazinamide (20-30 mg/kg day, max. 2 g/day) and streptomycin (15 mg/kg day, max. 1 g/day) or ethambutol (15-20 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 full 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 analysis

The Statistical package for social science (SPSS 15.0) IL-Chicago- USA standard version was used for data analyses. Descriptive analysis was done for demographic, clinical and radiographic features and results are presented as mean \pm SD/percentages for continuous variables and number/percentage for categorical variables. Chi-square (χ^2) test, Fisher's Exact test and Mann Whitney U test were used to test for the significance of association between the two anti-TB treatment groups (patients who healed with standart anti-TB therapy for 6 months and those who needed extended therapy of 9-12 months). Significance level was accepted as $p < 0.05$.

Results

Demographic and clinical characteristics of the patients

Among the 1603 TB patients, 55 (3.4%) ATB cases were found during a period of eleven years. Six of those were excluded from the study due to the irregular medical records, and therefore data of 49 patients were analyzed. Median age of the patients with ATB was 41.5 (range 18-75 years). Of the 49 cases, 33 (67.3%) was female and 16 (32.7%) was male. More than half of the patients (28, 57.1%) were diagnosed as peritoneal TB. The remaining patients had nodal (14, 28.5%), intestinal (5, 10.2%), and solid organ TB (one patient with liver TB and one patient with liver + spleen TB, 4%) (Figure 1). Basic patient characteristics are presented in Table 1.

The most frequent symptoms were abdominal pain (65.3%), abdominal distension (61.2%) and fatigue (32.6%). Ascites appeared to be the most frequent clinical finding (63.2%) (Table 2).

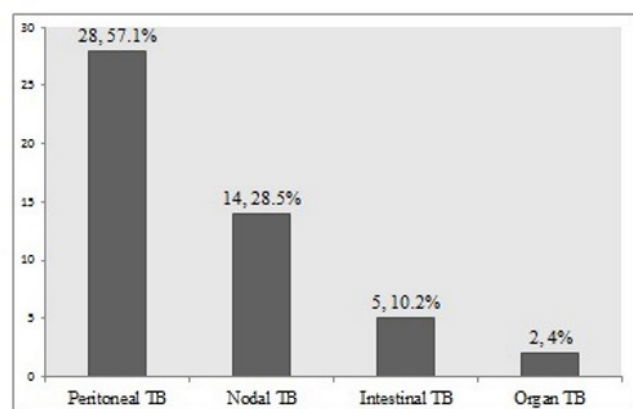


Figure. The classification of patients with ATB according to the primary involvement site

Diagnostic algorithm

Various radiological and experimental methods were used in the diagnostic algorithm, but 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 34.6% ($n=17$) and 28.5% ($n=14$) of patients, respectively. Decreased hemoglobin levels (<10 g/dL) were found in 55.1% ($n=27$) of patients.

Table 1. Demographic data and baseline clinical characteristics of patients (n=49)

Patient characteristics	n
Age (y)	41.5±15.7 (18-75)
Gender	
Male	16 (32.7%)
Female	33 (67.3%)
Immundeficiency conditions	
Malignancy	4 (8.1%)
Diabetes mellitus	2 (4.08%)
Chronic HCV carriers	2 (4.08%)
Chronic renal failure	2 (4.08%)
Crohn disease	2 (4.08%)
Intravenously drug use	2 (4.08%)
Amiloidosis	1 (2.04%)
History of pulmonary TB	9 (18.3%)
Familial history of TB	14 (28.5%)
Contact history	17 (34.6%)
Extrapertitoneal TB sites	
Pleural TB	17 (34.6%)
Genital TB	10 (20.4%)
Pulmonary TB	7 (14.2%)
Cervical lymph node TB	4 (8.1%)
Duration of symptoms (d)	63.8±42.4 (5-180)

Age and duration of symptoms were presented as mean±SD (range); other variables were presented as number (%). y: year, d: day

Table 2. Presenting symptoms and findings (n= 49)

Symptoms	n	%	Findings	n	%
Abdominal pain	32	65.3	Clinically apparent ascites	20	40.8
Abdominal distension	30	61.2	Fever	12	24.4
Fatigue	16	32.6	Weight loss	8	18.3
Loss of appetite	14	28.5	Genital discharge	6	12.2
Nausea and vomiting	14	28.5	Diarrhea	3	6.1
Cough and sputum	12	24.4	Peripheric LAP*	2	4.1
Night sweats	9	18.3	Peritonitis	2	4.1

LAP*: Lymphadenopathy

Tuberculin skin test was positive in 16 of 19 patients (84.2%). However, of these 16 patients, 14 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). Approximately

Table 3. The sonographic and tomographic findings of the patients with ATB (n=49)

Abdominal US	n/%	Abdominal CT	n/%
ascites	26/63.2%	ascites	29/59.1%
enlarged abdominal lymph nodes	15/30.6%	t.*peritoneum/mesentery/ omentum	19/38.7%
t.*peritoneum/mesentery/omentum	14/28.5%	enlarged abdominal lymph nodes	18/36.7%
genital TB findings**	9/18.6%	genital TB findings**	10/20.4%
hepatosplenomegaly	4/8.1%	hepatosplenomegaly	8/16.2%
hepatic nodule	2/4.0%	hepatic nodule	2/4.0%
splenic nodule	1/2.0%	splenic nodule	1/2.0%
normal	5/10.2%	normal	2/4.0%

t*: thickened, genital TB findings **: tubo-ovarian mass, irregular endometrial lining, and etc.

half of the patients (n=21, 42.8%) had normal chest X-ray. The other findings on chest radiography were pleural effusion (n=20, 40.8%), radiopacity/lesion (n=7, 14.2%), and sequel TB findings (n=4, 8.1%). On ultrasonographic (US) examination, ascites was the most frequent finding (31/49 cases, 63.2%). Additionally, enlarged abdominal lymph nodes were found to be the second most frequent sonographic finding (17/49 cases, 34.6%).

Diagnosis of ATB was mainly depended on histopathology of ascitic fluid and biopsies from peritoneum, abdominal lymph nodes or colonoscopic materials. All of the patients with intestinal TB (n= 5) were diagnosed by colonoscopic biopsy. Paracentesis could be performed in 20 patients (40.8%), and low SAAG was seen in all. However, lymphocytic predominance (n=16, 80%), decreased glucose levels and elevated LDH levels were obtained in 16 (80%), 15 (75%), and 14 (70%) patients, respectively. AFB staining of ascitic fluid was found to be positive only in one (5%). On the other hand, high ascitic ADA (>35 U/L) and CA125 (>35 U/ml) levels were detected in a ratio of 85% and 90% respectively. The measurement of serum CA125 was used only in six patients with TBP. 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.

Biopsy from peritoneum or abdominal enlarged lymph nodes via laparoscopy (n=30) or laparotomy (n=2, due to emergency condition) was performed in 32 patients. The histopathologic examination of peritoneal/nodal biopsy was positive for TB in 29 patients (95.4%). Of the biopsy specimens, 95.2% (n=20) revealed caseating granulomas, while 4.8% (n=1) was non-caseating. All tissue samples were also evaluated by Ziehl-Neelsen staining, and AFB positivity was seen in the minority of cases. Cultures of ascites and peritoneal/nodal/colonoscopic biopsy were examined in 20 and 39 patients, respectively. Diagnostic yield of all the investigations are presented in Table 4.

Table 4. Diagnostic yield of the tests used in diagnosis

Diagnostic method	n	Yield of diagnostic method
ADA in ascites (mean 144.4±79.3, range: 21-292)	20	17/85%
CA125 in ascites (mean 433.2±268.7, range 22-808)	20	18/90%
PCR analysis of ascites	8	3/37.5%
AFB positivity of ascites	20	1/ 5%
AFB positivity of peritoneal/nodal/colonoscopic biopsy	39	4/10.2%
Histopathology of peritoneal/nodal/colonoscopic biopsy	39	36/92.3%
Culture of peritoneal/nodal/colonoscopic biopsy	39	17/43.5%
Culture of ascites	20	7/35%

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 biopsy via laparotomy or laparoscopy.

Treatment and follow-up

All patients received standard anti-TB therapy for 6 months. Forty (81.6%) patients healed with standard 6-month therapy while extended treatment for 9-12 months was needed in 8 (16.3%) whom had discontinued drug therapy and had persistent symptoms and signs. There were no statistical differences between the patients who healed with standard 6-month anti-TB therapy and the patients who needed extended treatment, in terms of clinicopathological features ($p > 0.05$). One patient died within the treatment period due to disseminated infection. Two patients developed recurrence during the follow up period, and were treated with anti-TB therapy of 8 months (2H3R3Z3E3S3 + 1H3R3Z3E3 + 5H3R3E3). No recurrence was observed during their follow-up periods.

Discussion

Although TB is a common disease worldwide, ATB is an unusual manifestation of extrapulmonary TB [2]. ATB poses significant diagnostic and management challenge. Unfortunately, delay in diagnosis is a common entity in daily practice because of the variable clinical presentations. Abdominal pain, weight loss, abdominal distension and fever are the most common symptoms in patients with ATB. Additionally, ascites is the most clinical finding as was in our study [3,4]. The term, ATB, contains various variants including nodal, peritoneal, gastrointestinal and solid organ TB. In many studies, peritoneal and nodal forms are the most common types of ATB [5-7]. In our study population, more than half of the cases had only peritoneal form. However, the nodal form was the second most type of ATB. Cases of gastrointestinal and solid organ tuberculosis are less common conditions and are usually found as small series in the literature [8-11]. It is well known that gastrointestinal TB often involves the ileocecal region. The other sites such as stomach, duodenum, colon, liver and spleen are extremely rare. Hepatic TB occurs as the following types: Micronodular, macronodular, mixed, and isolated tubercular abscess [12]. Splenic tuberculosis may manifest as isolated splenomegaly, micronodular, or macronodular form. In our study, five patients had intestinal TB (four ileocecal and one colon), one patient had hepatic TB, one patient had both hepatic and splenic TB. Hepatic TB was micronodular in our two cases. Similarly, there was only one patient with micronodular splenic TB in our study. Hepatosplenomegaly is a common physical finding as in our cases with hepatosplenic TB. Tubercular infection often spreads to the solid abdominal viscera hematogenously. However, the other route is contiguously spread from TB salpingitis. Therefore, the patients who are suspected for ATB, should be always questioned about their past histories of TB and concomitant extra abdominal TB. For this reason, a chest radiography should be one of the main tool of the diagnostic algorithm in such patients. In a study, up to half of the patients with abdominal TB had extra abdominal involvement [7]. Khan et al. [5] also found radiological evidence of pulmonary TB in two thirds of patients with abdominal TB. In our study, approximately half of the cases had active extra abdominal TB including TB salpingitis, pleural and pulmonary TB. This condition demonstrates the importance of anamnesis and physical examination for correct diagnosis. Diagnostic delays lead to significant morbidity and mortality

in the patients with ATB [13]. Unfortunately, current diagnostic tests including Mantoux tuberculin skin test, US, barium X-Rays and CT have limited diagnostic value. Furthermore, radiological findings of ATB can mimic various diseases. Most of the patients with ATB suffer from abdominal pain, ascites and fever. Rarely, these patients may be presented with acute abdomen findings. In this condition, the physicians can be easily fall into diagnostic failure, and unnecessary surgery can be performed as a result. However, the presence of ascites, history of TB and a detailed examination can prevent unnecessary operations and related risks. For the patients presenting with acute abdomen findings, laparoscopic evaluation may be the most appropriate diagnostic approach. Diffuse white peritoneal plaques, enlarged lymph nodes, ascites, 'violin string' fibrinous strands, and omental thickening are the most frequent operative signs of ATB. Rarely, enlarged abdominal mass due to intestinal TB can mimic a malignant lesion. Emergency surgery for ATB should be needed for acute complications such as ongoing gastrointestinal bleeding, intestinal obstruction and hollow viscus perforation. In patients with peritoneal TB, ascitic fluid is usually in exudative character with elevated lymphocyte count, decreased glucose level, elevated lactate dehydrogenase (LDH) and total protein. Additionally, high (>35 IU/L) ascitic ADA levels and low (<1.1) serum ascites albumin gradient are the characteristic features. However, due to the poor diagnostic accuracy, these tests often need to be confirmed by other diagnostic tools such as positive AFB staining, positive culture or PCR analysis for *M. Tuberculosis*. Among those, AFB staining of peritoneal fluid can detect only a minority of cases [14]. Similarly, we performed paracentesis in 20 patients, and positive AFB staining was obtained from only one of those. However, high ADA levels were obtained in 17 of 20 patients. Although the high diagnostic value of ascitic ADA measurement in peritoneal TB has been shown in many studies, it is not only a specific marker for this disease [15,16]. The other diagnostic tool, PCR analysis of ascitic fluid, is also a rapid test to reach the diagnosis of TB, but the low accuracy rate and high cost limit its general use.

It is well known that identification of TB basile in any material is the gold standard diagnostic method. However, approximately four weeks are needed for culture of *Mycobacterium tuberculosis*, meaning high morbidity and mortality rates. Moreover, negative result of culture cannot exclude the diagnosis of TB. Therefore, tissue biopsy via laparoscopy is generally considered as a gold standard diagnostic method for ATB [17-19]. In our study, laparoscopic approach was used in 20 patients with ATB and correct diagnosis was obtained in all cases. Additionally, colonoscopy provided accurate diagnosis in all cases with intestinal TB. However, the other diagnostic methods generally showed less accuracy in diagnosis of ATB.

In conclusion, no single test is sufficient for diagnosis of ATB, and a high index of suspicion is essential to reach the correct diagnosis. Additionally, past history of TB, presence of ascites and unknown fever should be questioned in all patients with a suspicion of ATB. Diagnostic laparoscopy and tissue sampling seem to be the best diagnostic approach for ATB, and emergent surgery is usually required for acute complications. Laparoscopy can be also used to rule out other intraabdominal pathologies.

Competing interests

The authors declare that they have no competing interests.

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