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Clinical and pathological features of three types of peritoneal tuberculosis: a single centre in China.

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Abstract

Background: Tuberculosis (TB) is a crucial communicable disease worldwide. Peritoneum tuberculosis (TBP) is a common type of extra-pulmonary tuberculosis.
Aim: To investigate clinicopathological features of three different types of TBP.
Methods: This retrospective, observational study was conducted from 2009 to 2014 in the hospitalized patients with TBP. Based on the clinical data and surgical records, patients were divided into: wet-ascitic, fibrotic-fixed, and dry-plastic types. Categorical data were analysed using the Chi-square test or a two-tailed Fisher's exact test.
Results: Of the 91 patients (50 male, 41 femalemale to female ratio=1.22) enrolled, 48 (52.7%) were wet-ascitic, 33 (36.3%) were fibrotic-fixed and 10 (11.0%) were dry-plastic types. The frequency of haematogenous dissemination of pulmonary TB was significantly higher in the dry-plastic type than in fibrotic-fixed type (P=0.0498). The frequency of abdominal pain was significantly lower in the wet-ascitic than in the other two types (P=0.000 and P=0.017). Patients (30 (90.9%)) of fibrotic-fixed type had ileus. The Langhans giant cells were observed more in the wet-ascitic type than in fibrotic-fixed type (P=0.006). All slices in the dry-plastic type were observed with granulomatous inflammation (P=0.040). The hospital stay prolonged in the fibrotic-fixed type and the dry-plastic type than the wet-ascitic type (P=0.006 and P=0.003).
Conclusion: The fibrotic-fixed and dry-plastic types TBPs presented more rate of abdominal pain. Most of the fibrotic-fixed type patients have ileus. The Langhans giant cells were observed more in the wet-ascitic type. All specimens of the dry-plastic type were observed with granulomatous inflammation. All dry-plastic type could be diagnosed through histopathology, but fibrotic-fixed type could not.

Keywords: Peritoneal tuberculosis, Mycobacterium tuberculosis, Clinicopathological features.

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Introduction

Tuberculosis (TB) is a major health concern throughout the world. A reported World Health Organization in 2013, there were 9 million people suffered with tuberculosis and 1.5 million deaths worldwide. China is one of the major prevalent regions in the world [1-3] and more than 1.3 million new cases reported annually. Although steps have been taken in the attempt to control TB by the Chinese government tuberculosis-related death still ranks the top mortality among the 37 noticeable communicable diseases related death in China [3,4].

Besides lung TB, peritoneum is one of the favourable infection sites of the tubercle bacillus [5]. Peritoneal tuberculosis may present a variety of symptoms and signs that may confuse with other common and rare diseases. The microbiological tests for peritoneal TB (TBP) are usually time consuming and inadequate to make the diagnosis. The ultrasonography (US) and computed tomography (CT) findings are non-specific. Therefore, it remains difficult to make a prompt diagnosis of the disease [5,6].

The peritoneal tuberculosis can be divided into three types: wet-ascitic type, fibrotic-fixed type, and dry-plastic type. The wet-ascitic type is most common type in the clinical practice and is characterized by free or loculate ascites. The fibrotic-fixed type is less common and is characterized by large omental masses, matted and tethered bowel loops and mesentery. The dry or plastic type is rare and characterized by caseous nodules, fibrous peritoneal reaction, and dense adhesions [7,8].

Several studies for the detection of TBP have been carried out worldwide [9-12]. But the detailed clinicopathological features are not clear, and the diagnostic yield of various methods was inconsistent. Therefore, we retrospectively studied the peritoneal tuberculosis cases with pathological results in our hospital in recent 5 years. The clinical and pathological features of these patients were here in extracted.

Patients and Methods

Study design and setting

This retrospective observational study was conducted at PLA 309th Hospital, one of the largest tertiary referral centres specific for tuberculosis in Beijing, China. The study was approved the Ethic Committee of the PLA 309th Hospital. The enrolled patients were selected from the inpatients of the PLA 309th Hospital from January 2009 to December 2014. All the patients were aged more than 16 years old and were diagnosed as peritoneal tuberculosis histologically. The peritoneal specimens were obtained by either ultrasound-guided peritoneal biopsy or surgery.

The diagnosis was made if any of the following criteria was fulfilled [10-13]: (1) Histological evidence of TB was confirmed by examination of peritoneal specimens; (2) Positive smear for acid fast bacilli from ascitic fluid/dialysate solution or peritoneal specimen; (3) Positive detection of Mycobacterium tuberculosis by Polymerase Chain Reaction (PCR) in the biopsy specimens; (4) Patients were sensitive to anti-tuberculosis therapy and the therapy continued for at least 6-months. Two physicians from the tuberculosis department independently evaluated the type of peritoneal tuberculosis based on the clinical data and surgical records.

Laboratory investigations

Serum antibody against TB (TB-Ab) was investigated by rapid gold immuno-assay test triplicated using kits from 3 different company: the Aupu TB IgG Colloidal Gold Test kit (Shanghai Aupu Biotechnology Co., Shanghai, China), the Aetna TB IgG Colloidal Gold Test kit (Aetna agents seized Beijing in diagnostic technology company, Beijing, China), the SD rapid TB IgG Test kit (Standard Diagnostics Inc., Korea) [14,15]. TB specific effector T cell population was evaluated by T-SPOT test using diagnosis kit for Mycobacterium tuberculosis infection (Oxford Immunotec Ltd.UK).

The sample tissue sections were evaluated by two pathologists independently to reveal the clinicopathological features. TB DNA in paraffin-embedded tissue was tested by Mycobacterium tuberculosis DNA kit (DAAN Gene Co., Guangzhou, China).

Statistical analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). The results were expressed as mean ± standard deviation. Continuous variables were compared using the One-way ANOVA or the Kruskal-Wallis test. SNL-q test was used to compare data in different types. Categorical data were analysed using the Chi-square (χ^2) test or a two-tailed Fisher's exact test. P value <0.05 was considered statistically significant.

Results

Demographic data, disease history and relative extra peritoneal tuberculosis

A total of 91 patients were enrolled for the experiment, of which 50 (54.9%) were male and 41 were female (45.1%) with a mean age of 35.66 ± 15.46 years (range, 16–77 years). The study included, 48 patients (52.7%) were of wet-ascitic type, 33 (36.3%) were fibrotic-fixed type and 10 (11.0%) were of dry-plastic type.

Patients represented a history of underlying diseases such as 4 patients were operated for appendectomy, 3 patients underwent caesarean operation within 6 months and 1 patient was operated for fallopian tube recanalization within 3 months. Others included, 3 patients with rheumatoid arthritis (two of them has taken prolonged corticosteroids), 2 patients with diabetes mellitus, 1 patient with primary biliary cirrhosis and ankylosing spondylitis, 1 patient with coronary atherosclerotic cardiopathy, 2 patients with virus B hepatitis and 1 patient with primary hypertension. Risk factors were identified in 4 patients (4.4%) with close contact to TB patients and 3 patients (3.3%) with tuberculosis history. There were no statistically significant differences among the 3 types with respect to age, gender and disease history. The details of patient's demography and the distribution of relative extra peritoneal tuberculosis in 3 types of peritoneal tuberculosis are shown in Table1.

Table 1: *Demographical features and relative extra-peritoneal tuberculosis distribution in different types of peritoneal tuberculosis.*

	wet-ascitic (n=48)	fibrotic-fixed (n=33)	dry-plastic (n=10)	P value
Age(years)	36.79 ± 16.31	36.12 ± 14.92	28.70 ± 12.09	0.293
Sex(male: female)	28:20:00	16:17	6:04	0.643
Pulmonary tuberculosis	22 (45.8%)	18 (54.5%)	5 (50%)	0.743
haematogenous disseminated pulmonary tuberculosis	2 (4.2%)	0	2 (20%)	0.026

Intestinal tuberculosis	0	4 (16.7%)	3 (30%)	0.003
Tuberculosis Pleuritis	21 (43.8%)	10 (30.3%)	5 (50%)	0.37
Data represented as Mean ± SEM or n (%)				

All patients received chest X-ray or CT. 45 patients (49.5%) were diagnosed for pulmonary TB which was not significantly different among the three types. On the whole, 4 patients (4.4%) were diagnosed with haematogenous dissemination of pulmonary tuberculosis and its frequency was significantly higher in the dry-plastic type than in fibrotic-fixed type (2/10 patients (20%) vs. 0/33 patients (0); P=0.0498). Eventually, 36 patients (39.6%) had tuberculosis pleuritis, and there was no statistically significant difference among the 3 types. 7 patients (7.7%) were with intestinal tuberculosis and the frequency was significantly higher in the dry-plastic type than in fibrotic-fixed type and wet-ascitic type (0/48 patients (0) vs. 4/33 patients(12.1%,), 3/10 patients (30%); P=0.025, P=0.004).

Symptoms

All 48 patients (52.7%) suffered with fever and no statistically significant difference was observed among the 3 types. However, dry-plastic type patients suffered with high fever (temperature 39-40°C) than the fibrotic-fixed type (6/10 patients (60.0%) vs. 5/33 patients (15.2%); P=0.010). The difference was not seen in the medium and low fever. More than half of the patients (61 (67.0%)) presented with symptoms of abdominal pain but with significantly lower frequency in the wet-ascitic type than in the fibrotic-fixed and the dry-plastic type (23/48 patients (47.9%) vs. 29/33 patients (87.9%), 9/10 patients (90.0%); P=0.000, P=0.017). The other commonly appearing symptoms were abdominal distension (71 (78.0%)), night sweating (18 (19.8%)), anorexia (20 (22.0%)), nausea or vomiting (24 (26.4%)), body weight loss (23 (25.3%)) and no statistically significant differences were observed between the 3 types for the above mentioned symptoms. The symptoms of each type of TBP are summarized in Table 2.

Table 2: *Symptoms in different types of patients.*

	wet-ascitic (n=48)	fibrotic-fixed (n=33)	dry-plastic (n=10)	P value
Fever	26 (54.2%)	14 (42.4%)	8 (80.0%)	0.109
High fever (39-40)	16 (33.3%)	5 (15.2%)	6 (60.0%)	0.018
Medium fever (38-39)	2 (4.2%)	4 (12.1%)	2 (20.0%)	0.192
Low fever (37-38)	8 (16.7%)	5 (15.2%)	0	0.385
Abdominal pain	23 (47.9%)	29 (87.9%)	9 (90.0%)	0.000
Abdominal distention	38 (79.2%)	26 (75.8%)	7 (70.0%)	0.809
Night sweating	7 (14.6%)	7 (21.2%)	4 (40.0%)	0.179
Anorexia	8 (16.7%)	9 (27.3%)	3 (30.0%)	0.426
Nausea/vomiting	11 (22.9%)	9 (27.3%)	4 (40.0%)	0.531
Body weight loss	13 (27.1%)	9 (27.3%)	1 (10.0%)	0.500
Ileus	0	30 (90.9%)	3 (30.0%)	0.000
Data represented as n (%)				

A total of 33 (34.1%) fibrotic-fixed type patients presented with intestinal obstruction and of these, 30 had ileus, which were significantly higher compared to the wet-ascitic type and dry-plastic type (30/33 patients (90.9%) vs. 0/48 patients (0%); 3/10 patients (30.0%); P=0.000, P=0.000). While the other 3 had no clinical symptoms of intestinal obstruction, but adhesions were found in the omentum and parietal peritoneum during laparoscopy for pelvic tuberculosis. Moreover, the frequency of intestinal obstruction was significantly increased in the dry-plastic type when compared to the wet-ascite type (3/10 patients (30.0%) vs. 0/48 patients (0%); P=0.004).

Lab data, CT and histopathological findings

A total of 75 patients were tested for the presence of serum antibody to Mycobacterium tuberculosis (TB-Ab) by 3 different types of colloidal gold diagnostic kits. Serum Aupu TB-IgG was positive in 15 (20.0%) patients. Serum Aetna TB IgG was positive in 22 (29.3%) patients. These 2 types of TB IgG did not differ significantly among the three types. Serum SD TB IgG was positive in 55 (73.3%) patients, and the patients of wet-ascitic type were statistically significant than the fibrotic-fixed type (P=0.009). Serum T-SPOT.TB was positive in 44 (62.0%) patients, and was significantly higher in

the dry-plastic type when compared to the wet-ascitic type (P=0.007). Almost 88 patients received abdominal CT. CT results showed peritoneum thickening in 60.2% patients. The frequency of peritoneum thickening was statistically significant in the wet-ascitic type and the fibrotic-fixed type than the dry-plastic type (66.0% P=0.012 and 64.5%, P=0.026 vs. 30.0%. Patients indicated encapsulated ascites (47.7%) and enlarged lymph node (44.3%) with no statistically significant differences among the three types.

A total of 91 patients were pathologically examined. The Langhans giant cells were observed in the pathologic slices of 25 (27.5%) patients, and was found to be more common in the wet-ascitic type than in the fibrotic-fixed type (P=0.006). Though, the Langhans giant cells were observed more in the wet-ascitic type than that in the dry-plastic type, but no significant difference was found due to small sample size. The granulomatous inflammation was observed in pathologic slices of 71 (78.0%) patients. All slices in the dry-plastic type were observed in the granulomatous inflammation, and was statistically significant when compared to the fibrotic-fixed type (100% vs. 63.6%; P=0.040). The caseous necrosis was observed in pathologic slices of 38 (41.8%) patients, and its presence could not differentiate among the three types. In addition, the positive rate of acid fast stain (AFS) was 32.2% patients, with no significant difference among the three types. TB DNA in paraffin-embedded tissues was positive in 37 (59.7%) patients with no significant difference among the three types. On the whole, the specimen histopathology was positive for TB in 92.3%.The frequency of positive specimen histopathology in the wet-ascitic type was significantly higher than that of the fibrotic-fixed type (97.9% vs.81.8%; P=0.017). The frequency of positive specimen histopathology in the dry-plastic type was increased when compared with that of the fibrotic-fixed type, but there were no statistically significant differences. The special lab examination for TB, abdominal CT and histopathology findings of each type of peritoneal tuberculosis are summarized in Table 3.

Table 3: *Special lab examination for TB, abdominal CT and histopathological findings of each type of peritoneal tuberculosis.*

	Wet-ascitic	Fibrotic-fixed	Dry-plastic	P value
Special lab Examination for TB				
Serum Aupu TB IgG	6/40 (15%)	5/25 (20%)	4/10 (40%)	0.210
Serum Aetna TB IgG	11/40 (27.5%)	8/25 (32%)	3/10 (30%)	0.926
Serum SD TB IgG	34/40 (85%)	13/25 (52%)	8/10 (80%)	0.012
T-SPOT.TB	17/36 (47.2%)	19/27 (70.4%)	8/8 (100%)	0.011
Abdominal CT				
Peritoneum Thickening	31/47 (66.0%)	20/31 (64.5%)	2/10 (20%)	0.022
Encapsulated ascite	25/47 (53.2%)	13/31 (41.9%)	4/10 (40%)	0.544
Enlarged lymph node	22/47 (46.8%)	14/31 (45.2%)	3/10 (30%)	0.619
Histopathology findings				
Langhans giant Cells	20/48 (41.7%)	4/33 (12.1%)	1/10 (10%)	0.006
Granulomatous inflammation	40/48 (83.3%)	21/33 (63.6%)	10/10 (100%)	0.022
Caseous necrosis	18/48 (37.5%)	15/33 (45.5%)	5/10 (50%)	0.663
AFS	15/48 (31.3%)	9/32 (28.1%)	4/10 (40%)	0.778
TB DNA	21/32 (65.6%)	12/22 (54.5%)	4/8 (50%)	0.600
Positive histology	47/48 (97.9%)	27/33 (81.8%)	10/10 (100%)	0.018

Data represented as positive number/total number (positive rate).

Management

The hospital times were increased in the fibrotic-fixed type and the dry-plastic type than that of wet-ascitic type, but no significant differences were observed among the three types. The hospital stay was significantly prolonged in the fibrotic-fixed type and the dry-plastic type when compared to that of the wet-ascitic type (P=0.006 and P=0.003). Among the 48 wet-ascitic patients, 3 underwent laparoscopy/laparotomy (1 patient underwent hepatic resection, 2 patients went for pelvis operation), ultrasound-guided peritoneal biopsies were carried out in the rest of the patients. Among the 33 fibrotic-fixed patients, 31 underwent laparoscopy/laparotomy, multiple peritoneal biopsies was carried out in 2 patients. All of the 10 dry-plastic type patients underwent laparoscopy/laparotomy, 1 patient had intestinal fistula and 1 patient had rectovaginal fistula. On the whole, only 1 patient in the fibrotic-fixed type

died due to tubercular meningitis. The hospitalization and surgery for each type of peritoneal tuberculosis are summarized in Table 4.

Table 4: Hospitalization and surgery for each type of peritoneal tuberculosis.

	Wet-ascitic	Fibrotic-fixed	Dry-plastic	P value
Hospital Times	1.21 ± 0.46	1.55 ± 0.97	1.60 ± 0.84	0.139
Hospital stay (days)	30.58 ± 16.15	43.58 ± 25.33	49.20 ± 2.72	0.034
Surgery Rate	6.25%	93.9%	100%	0.000
Data represented as Mean ± SEM or positive rate				

Discussion

In this study cohort, the number of male patients was more than female (male to female ratio=1.22), which was consistent with the previous reports [10-12]. More patients with fibrotic-fixed and dry-plastic types were enrolled due to the necessity of the pathological results for certain records. Since most of the wet-ascitic type could be diagnosed through symptoms, lab tests and image examination, without biopsy. However, most of the fibrotic-fixed and the dry-plastic types have to undergo surgery. The previous articles published on peritoneal tuberculosis were all about the wet-ascitic type with rare description of the fibrotic-fixed and the dry-plastic types8. Peritoneal tuberculosis can affect any age group, but people of 21-45 years range are more prone to it. The mean age of the patients enrolled for the study was 35.66 ± 15.46 years (range, 16–77 years), which was similar to other reports [11-16]. In the current study, 3 (3.3%) patients had undergone caesarean operation within 6 months of the study which might lead to reduced immunity against infection. Therefore, caesarean operation was a possible risk factor for TBP. Noticeably, there were no demonstrable risk factors in most of the patients.

In this study, 49.5% patients had been diagnosed for pulmonary TB and 3.3% patients were confirmed to be positive for sputum AFS and mycobacterial culture [17]. No significant difference was observed among the three types. There were more haematogenous spread pulmonary tuberculosis patients in the dry-plastic type than the wet-ascitic type. The hematogenous spread pulmonary tuberculosis has plenty of Mycobacterium that are spread into blood which maybe results in heavier type of peritoneal tuberculosis-the dry-plastic type. In our study, fever appeared in 52.7% patients and 60% dry-plastic type patients suffered with high fever (temperature 39-40°C) due to its severe nature. Abdominal fullness (78.0%) is the most common symptom rather than abdominal pain (67.0%), which is unusual from the previous reports [10,11]. 87.9% fibrotic-fixed type patients and 90% dry-plastic type patients presented abdominal pain. Most of the fibrotic-fixed type patient had ileus and were operated for enterolysis (see Table 4, Surgery rate).

In our study, 3 different companies of colloidal gold diagnostic kit was used to test the serum TB IgG. The positive rate of 3 companies TB IgG was 20.0%-73.3%. Serum SD TB IgG had higher positive rate compared with Aupu TB IgG and Aetna TB IgG. But, there was no statistically significant difference among the three types. Immune-based tests are potentially suitable for use in low-income countries such as China. But, in a systematic review conducted by Karen R. Steingart, commercial antibody detection tests for extrapulmonary tuberculosis have no role in clinical care or case detection [18]. T-SPOT.TB is a quantitative test that assesses the cell-mediated immune response against Mycobacterium tuberculosis. It is based on the detection of interferon-gamma (IFN-γ) released by activated T lymphocytes. In our study, the total positive rate of T-SPOT.TB was 63.4% and 100% in dry-plastic type. So, T-SPOT.TB may be a useful ancillary method for the rapid diagnosis of TBP. In addition, some cytokines are correlated with TBP, such as Interleukin-33 (IL-33). Soluble ST2 (suppression of tumorigenicity 2) is a decoy receptor for IL-33. Tuberculosis can enhance the activation of IL-33/ST2 biochemical pathways. Therefore, sST2 can become a reliable biomarker in the evaluation of such patients [19].

CT can highlight the ascite, peritoneal, or lymph node involvement [20,21]. CT was also done by assessing exudative ascites pathogenesis for differential diagnosis of primary tumour. The dry-plastic type has lower rate of peritoneum thickening than the wet-ascitic type and the fibrotic-fixed type. Thus, patients with suspending peritoneal tuberculosis without peritoneum thickening must be cautioned, as they have dry-plastic type tuberculosis. Ha et al. [13] reported 69% sensitivity, in the diagnosis of peritoneal tuberculosis by CT scan, which is similar to the findings of this study.

The Langhans giant cells were observed more in the wet-ascitic type, as it is relatively early stage of the peritoneal tuberculosis. All specimens of the dry-plastic type were observed with the granulomatous inflammation. In our study, the positive rate of acid fast stain (AFS) was 32.2% (28/90 patients), which is in accordance with the previous reports 3-25% [21-23].

Thus, we can infer that the conventional microbiological techniques with direct detection of pathogens were not sufficiently sensitive and hence TB DNA was employed for the diagnosis. The TB DNA in paraffin-embedded tissues is supposed to be less complicated, less time consuming, cost-effective method to diagnose the Mycobacterium tuberculosis.

In our study, the positive rate of TB DNA was 59.7%, which is lower than that reported by Gupta et al. (80.95%) [24]. The specimen histopathology was positive for TB in 92.3%. The dry-plastic type positive rate in histopathology is 100%. However, the fibrotic-fixed type positive rate is only 81.8% (27/33 patients), which might be due to the intake of anti-TB drugs by 6 negative patients in fibrotic-fixed type. As most of the fibrotic-fixed patients were operated for enterolysis and more surgical success rates were obtained for the patients with non-active TB. So, we conclude that taking TB treatment may decrease the specimen histopathology positive rate.

Increased hospital times and the hospital stay was present in the fibrotic-fixed type and the dry-plastic type compared with that of the wet-ascitic type, which also suggests that the severity and complicated nature of the fibrotic-fixed type and the dry-plastic type. Thus, more emphasis should be provided on these two types. The ultrasound-guided peritoneal biopsy was done in most of the wet-ascitic patients. Also, presented a high diagnostic rate without any complications and eventually, serves as a best method to be recommended for the non-known ascite diagnosis. Laparoscopy/laparotomy was performed in most of the fibrotic-fixed type and the dry-plastic type patients, which was considered as treatment rather than diagnosis. So, we can conclude that the surgical treatment must be considered for the fibrotic-fixed and the dry-plastic types. In current study, only 1 patient died in hospital contributing to mortality rate of 1%. Possible explanations for the lower mortality rate in this study are adequate and long-term drug (9-12 months) therapy and timely surgical treatments are warranted.

Limitations

The study was retrospective rather than prospective which has some unavoidable limitations, including the relatively small number of cases and incomplete examination in all patients. Longer follow-up is needed in future epidemiological studies to help correlate data about the 3 different types of TBP. However, we hope that these findings may contribute to the future diagnosis and treatment.

Conclusions

The study reported that hematogenous dissemination of TBP patients was more likely to have the dry-plastic type TBP. If TBP patients had abdominal pain then they are more likely to have the fibrotic-fixed and dry-plastic type TBPs. In this study, most of fibrotic-fixed type patients had ileus. In pathological examination, The Langhans giant cells were more observed in the wet-ascitic type. All specimen of the dry-plastic type were observed with the presence of granulomatous inflammation. All dry-plastic type could be diagnosed through histopathology, but fibrotic-fixed type could not. Compared with the wet-ascitic type, the fibrotic-fixed type and the dry-plastic type had more hospital times and longer hospital stay in.

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