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Original Article

Disseminated peritoneal tuberculosis simulating advanced ovarian cancer: A retrospective study of 17 cases

Chen-Hsuan Wu, Chan-Chao ChangChien, Chih-Wen Tseng, Hung-Yaw Chang, Yu-Che Ou, Hao Lin*

Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

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Abstract

Objectives: The abdominopelvic cavity is one of the common sites for extrapulmonary tubercular infections. The rate of preoperative misdiagnoses between peritoneal tuberculosis (TB) and ovarian cancer is high because of overlapping nonspecific signs and symptoms. We attempted to analyze the experience within our hospital so as to establish the best means of discriminating between peritoneal TB and advanced ovarian cancer.

Methods: Seventeen patients diagnosed as having peritoneal TB between July 1986 and December 2008 at the Obstetrics and Gynecology Department of our hospital with the initial presentation simulating advanced ovarian cancer were retrospectively reviewed and evaluated.

Results: Patients' ages ranged from 24 years to 87 years (median, 38 years). Ten of 17 patients (60%) were younger than 40 years. All patients except one had elevated serum cancer antigen-125 levels with a mean of 358.8 U/mL (range, 12–733 U/mL). Computed tomographic (CT) scans showed ascites with mesenteric or omental stranding in all (100%), enlarged retroperitoneal lymph nodes in six (35.3%), and an adnexal mass in three (17.6%). Abdominal paracentesis was performed in seven cases, in which the findings revealed lymphocyte-dominant ascites without malignant cells. Surgical intervention by laparotomy was performed in 13 cases (76%) and by laparoscopy in three cases (18%), and a CT-guided peritoneal biopsy was performed in one case (6%). A frozen section was taken from 16 patients but not the patient who received a CT-guided peritoneal biopsy, and all revealed granulomatous inflammation. A final pathological examination confirmed a diagnosis of peritoneal TB. All patients responded to anti-TB treatment.

Conclusions: In view of these data, a clinical diagnosis of peritoneal TB should be considered in a relatively young female with nonspecific symptoms of abdominal distension and wasting, as well as lymphocytic ascites without malignant cells. Laparoscopy or a minilaparotomy to obtain tissue samples for frozen-section analysis may be the most direct and least-invasive approach for a diagnosis, thus avoiding unnecessary extended surgery in these patients.

Keywords: Ascites; CA-125; Extrapulmonary tuberculosis; Ovarian cancer; Peritoneal tuberculosis

Introduction

According to the US Centers for Disease Control and Prevention, nearly one-third of the world's population is infected with tuberculosis (TB), which kills almost 2 million people per year [1]. With the development of effective anti-TB agents and improvements in environmental hygiene and immunity, active TB cases decreased year by year from 1950 to 1980. However, increasing population migration, use of more potent immunosuppressant therapies, the presence of an acquired immunodeficiency syndrome epidemic, and the appearance of highly virulent multidrug-resistant strains of *Mycobacterium tuberculosis* resulted in a resurgence of this disease worldwide after 1980 [2].

* Corresponding author. Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, No.123, Ta-Pei Road, Niao-Sung District, Kaohsiung City 883, Taiwan.
E-mail address: haolin@adm.cgmh.org.tw (H. Lin).

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Extrapulmonary TB is less common than pulmonary TB, and the peritoneum is one of the most common extrapulmonary sites of tuberculous infections. The postulated mechanisms by which the tubercular bacilli reach the peritoneal cavity are by hematogenous spread or by direct spread from the contiguous infected small intestine, lymph nodes, and fallopian tubes [3]. The most common symptoms and signs of female patients with peritoneal TB are abdominal pain, wasting, fever, loss of appetite, abdominal distension with ascites, and elevation of the serum cancer antigen (CA)-125 level; these symptoms overlap with those of advanced ovarian carcinoma [3,4].

Diagnosing this disease remains a challenge because of its insidious nature, the variability of its clinical presentation, and the limitations of available diagnostic tools. Fortunately, the treatment regimens for tuberculous peritonitis use the same principles as those for pulmonary TB. A good prognosis is expected with an early diagnosis, except for patients at an advanced age and with a poor medical condition, such as renal failure and liver cirrhosis [5]. Therefore, in this study, we attempted to analyze the experience within our hospital so as to establish the best means of discriminating between peritoneal TB and advanced ovarian cancer.

Materials and methods

We retrospectively examined the medical records of patients with peritoneal TB that mimicked advanced ovarian cancer who were managed at the Obstetrics and Gynecology Department of Chang Gung Memorial Hospital—Kaohsiung Medical Center, Taiwan, over a period of 22 years between July 1986 and December 2008. In total, 27 patients were diagnosed as having peritoneal TB according to pathology reports, and 17 of them presented with initial symptoms and signs that were similar to those of advanced ovarian cancer. Patients diagnosed as having peritoneal TB but not simulating advanced ovarian cancer were not included in the present study. We analyzed those 17 patients' clinical presentations; findings on pelvic examination; laboratory results; CA-125 levels; chest radiographic findings; examination of ascites; imaging studies, such as ultrasonography and computed tomography (CT); and diagnostic procedures. The diagnosis was confirmed on the basis of at least one of the following criteria, as advocated by Pauslian et al [6]: (1) histological evidence of caseating granulomatous inflammation; (2) acid-fast bacilli identified in tissue specimens or ascitic fluid; (3) tissue or ascitic fluid culture yielding *M tuberculosis*; (4) positive polymerase chain reaction (PCR) for *M tuberculosis* DNA on tissue specimens or ascitic fluid; or (5) a good therapeutic response to anti-TB agents in patients with clinical evidence of peritoneal TB. All data were obtained from patients' files and pathology reports. This study was approved by the Research Ethics Committee of Chang Gung Memorial Hospital (Institutional Review Board No. 98-2016B).

Results

In total, 17 patients with a documented diagnosis of peritoneal TB simulating advanced ovarian cancer were identified. All of our patients were Taiwanese women with a median age of 38 years (range, 24–87 years). More than half of the peritoneal TB (10 of 17, 59%) was found in patients aged between 20 years and 40 years, and most patients (82.4%) were multiparous, whereas only three patients (17.6%) were nulliparous.

Clinical features

Abdominal pain and pronounced weight loss appeared to be the most common presenting features among these 17 patients, and three of them (17.6%) also reported fever and night sweats (Table 1). All patients had a clinical evidence of ascites, along with thickening or ill-defined nodularities in the Douglas pouch and/or in the adnexal areas on a pelvic examination, but only three (17.6%) had the suggestion of an adnexal mass of around 4–6 cm in diameter. Five patients received a lower gastrointestinal series examination because of symptoms of bowel habit change, but only one patient had a clinical evidence of bowel obstruction. The possibility of peritoneal TB was suspected at presentation in only three patients (17.6%).

Laboratory findings

Changes in hematological indices were nonspecific except for mild normochromic, normocytic anemia with a mean hemoglobin level of 10.7 g/dL noted. All patients except one

Table 1
Characteristics of the 17 cases with peritoneal tuberculosis

Clinical parameters	No.	%
Clinical symptoms/signs		
Abdominal pain/fullness, wasting	17	100
Fever	3	17.6
Chest X-ray findings		
Normal	10	58.8
Pleural effusion	5	29.4
Suspected pulmonary TB	2	11.8
CT image findings		
Ascites & mesenteric/omental stranding	17	100
Adnexal mass	3	17.6
Enlarged retroperitoneal nodes	6	35.3
Diagnostic approach		
Laparotomy	13	76.5
Diagnostic laparoscopy	3	17.6
CT-guided biopsy	1	5.9
Frozen section[a]	16	
Granulomatous inflammation	16	100
Acid-fast bacilli on permanent section	17	
Positive	12	71
Negative	5	29
PCR assays for *Mycobacterium tuberculosis*	2	
DNA in ascites		
Positive	0	0
Negative	2	100

[a] Among 17 patients, only one received CT-guided biopsy, and all the other 16 underwent surgical intervention.
CT = computed tomography; PCR = polymerase chain reaction; TB = tuberculosis.

(94.1%) had elevated levels of CA-125 with a mean value of 358.8 U/mL (range, 12–733 U/mL).

Chest radiography, abdominal ultrasound, and CT scan

Abnormal chest X-ray signs, such as pleural effusion and increased infiltration, were seen in seven patients but were specific for pulmonary TB, such as fibrocalcification lesions, in only two patients (11.8%). The sputum specimens in these two patients were negative for acid-fast stain for *M tuberculosis*.

Transabdominal and transvaginal ultrasound studies showed abnormalities in all patients: pelvic ascites in all and a tubo-ovarian mass in three. All patients underwent abdominopelvic CT, and separated ascites with peritoneum thickening and mesenteric and omental stranding were demonstrated in all patients (100%), an ovarian mass with a heterogeneous nature in three patients (17.6%), and retroperitoneal lymphadenopathy in six patients (35.3%, Table 1). The CT images of one patient are shown in Figs. 1 and 2.

Analysis of peritoneal fluids

Abdominal paracentesis was performed in seven patients, in whom the findings were felt to be most inconclusive for a diagnosis of ovarian cancer; this revealed a clear exudative fluid with benign lymphocytic cells being predominant (in a range of around 60–70%). Staining for acid-fast bacilli (Ziehl-Neelsen) and culture for TB from the ascitic fluid were performed in these seven cases, and all revealed negative findings. Two patients also received PCR assays for *M tuberculosis* DNA, and both were negative.

Diagnostic procedures

An exploratory laparotomy was performed in 13 cases (76%), a diagnostic laparoscopy in three cases (18%), and a CT-guided peritoneal biopsy in one case (6%). Of the 13 patients who had a laparotomy, four underwent extended surgery, including a total hysterectomy and/or bilateral salpingo-oophorectomy, owing to the coexisting uterine or ovarian pathology. A rather pathognomonic picture of miliary TB with peritoneal thickening, omental cake formation, and adhesion was discovered throughout the peritoneal cavity in all patients. A peritoneal biopsy for a frozen section under direct visualization was performed in 13 patients during the laparotomy and in three during diagnostic laparoscopy (Fig. 3). The frozen-section reports of these 16 patients who underwent surgery revealed granulomatous inflammatory changes. The final pathological examination of all patients confirmed a diagnosis of TB, and 12 patients (71%) were also positive for acid-fast staining (Table 1).

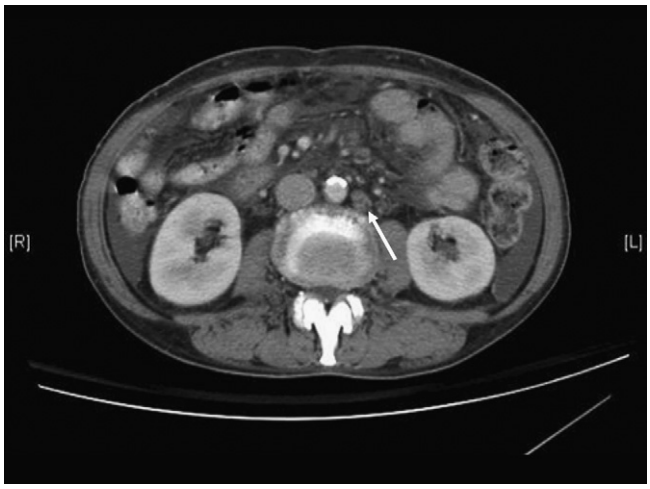

Fig. 2. Computed tomography image of a patient with peritoneal tuberculosis showing retroperitoneal lymphadenopathy of the para-aortic lymph node (arrow).

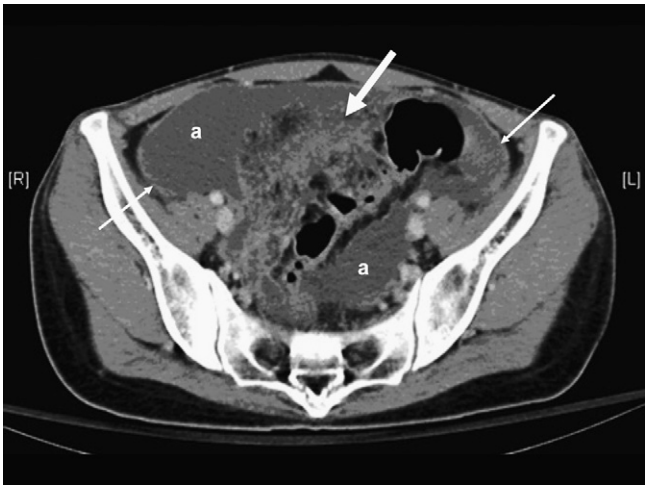

Fig. 1. Computed tomographic image of a patient revealing moderate and separated ascites with a thickened mesentery and peritoneum lining (small arrows), prominent strands in the omentum, and a sigmoid mesocolon (large arrow). a = ascites.

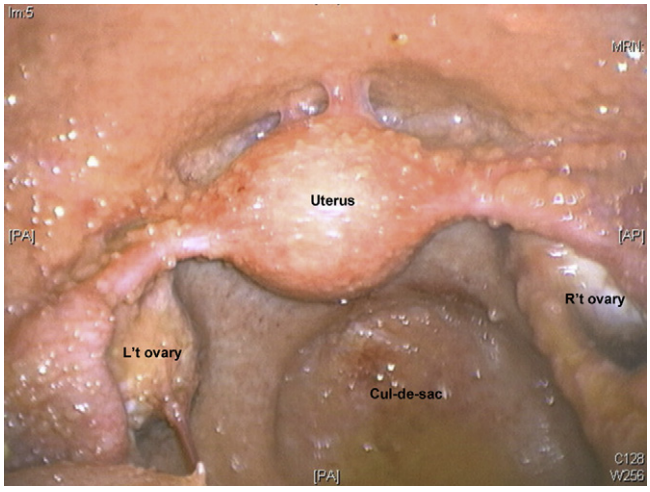

Fig. 3. Laparoscopic finding of a patient with peritoneal tuberculosis revealing multiple whitish nodules and tubercles studding the uterine surface and pelvic peritoneum.

Treatment and outcomes

Postoperatively, all patients had uneventful courses, and these 17 patients were subjected to quadruple anti-TB therapy for at least 6 months. The CA-125 levels of 16 patients in whom preoperative levels were elevated returned to a normal range (0–35 U/mL) during the anti-TB treatment and remained so after completion of the treatment course. We followed up these patients for 12–24 months, and all patients were alive and free of the disease at the end of follow-up.

Discussion

Peritoneal TB tending to present with nonspecific features and the insidious nature of this disease render the diagnosis a great challenge. Risk factors for peritoneal TB include liver cirrhosis, renal failure with peritoneal dialysis, diabetes mellitus, malignancy, AIDS, and administration of systemic corticosteroids. About 12% of patients with peritoneal TB have no risk factors, and thus, it is increasingly difficult to diagnose this disease [5]. Peritoneal TB in female patients may present with many nonspecific clinical symptoms and signs, such as pelvic pain, abdominal fullness, elevation levels of serum CA-125, ascites, and/or an adnexal mass, which can mimic advanced ovarian cancer [3,4,7,8]. There are still no ideal tools that can be used to rapidly and accurately diagnose tuberculous peritonitis. The laboratory tests are not helpful, such as elevation in CA-125 serum levels, negative results for tuberculin skin tests, Ziehl-Neelsen staining of the ascites, and culture growth of *Mycobacterium* sp. of the ascitic fluid, as confirmed by this report. Although an elevation in CA-125 serum level is not helpful in differential diagnosis of peritoneal TB, it may be regarded as a useful marker for the efficacy of anti-TB treatment.

However, ovarian cancer is rare before the age of 40 years and peaks at age 65–75 years, but pelvic TB most often occurs in patients between the ages of 20 years and 40 years, as reported by our study [9–11]. In addition, most patients with peritoneal TB in our study were multiparous (82.4%), unlike patients with ovarian cancer who are often nulliparous.

Although the gold standard for diagnosis is culture growth of *Mycobacterium* sp. in ascitic fluid or a peritoneal biopsy, the delay of 4–6 weeks before a culture result is obtained may increase the mortality rate of this disease [12]. Chow et al [5] reviewed 60 patients with tuberculous peritonitis within 12 years, and they reported a mortality rate of 53% and 84% of those patients died within 6 weeks of presentation, often before the results of the mycobacterial culture were available. Therefore, the utility of ascitic fluid cultures for *M tuberculosis* is questionable, because early diagnosis is a very important issue. Direct preparation of ascitic fluid in peritoneal TB, which reveals a dominance of lymphocytes without malignant cells, can provide a hint. In our study, seven patients underwent an examination of the peritoneal fluid, and all had relatively lymphocytic pleocytosis. Many studies showed the usefulness of adenosine deaminase in various biological fluids for diagnosing TB. It is an alternative rapid test with reported sensitivity and specificity levels of >90% with cutoff values of 36–40 IU/L [13,14]. Unfortunately, this test has decreased sensitivity in patients with liver cirrhosis because of poor humoral and T-cell-mediated responses in them [15]. A molecular diagnosis of TB using PCR amplification of the IS6110 sequence in ascitic fluid was also reported. It has a higher sensitivity and may be a useful diagnostic tool, especially in patients with smear-positive ascitic fluid for *M tuberculosis* [16,17]. However, there is still no study concerning the accuracy of using PCR to diagnose patients with peritoneal TB. In addition, another approach using a serum-ascites albumin gradient of <1.1 g/d also has a high sensitivity for analyzing ascites associated with peritoneal TB, although the specificity remains low because it is frequently seen in patients with underlying liver or renal disease [12].

An abdominal CT in patients with peritoneal TB may show separated or particulate ascites, strands of omentum, and no apparent adnexal mass in the mesentery, accompanied by a thickened peritoneum and retroperitoneal lymphadenopathy, as presented in most of our patients. The widespread miliary nodules of the peritoneal surface in these cases can cause multiple adhesions and thickening of the peritoneum, possibly leading to intestinal obstruction, as in one of our cases. After beginning anti-TB therapy, the prolonged obstruction in these patients spontaneously resolved.

Diagnosing this disease usually requires a peritoneal biopsy performed under direct visualization [18,19]. It can provide the highest diagnostic accuracy and help in optimizing the selection of anti-TB therapy. Open laparoscopy or a minilaparotomy peritoneal biopsy can be chosen [20]. A visually guided biopsy is recommended because blind peritoneal biopsies have a low diagnostic rate and are associated with complications, including death [21,22]. Typically, multiple whitish nodules or tubercles studding the visceral and parietal peritoneum, enlarged lymph nodes, "violin-string" fibrinous strands, and omental thickening are the preferred sites for a biopsy [23]. The intraoperative frozen-section analysis seems to be a gold standard in the differential diagnosis and a fundamental management tool to avoid extended surgery. The pathological findings of targeted biopsies in our study revealed granulomatous inflammation in up to 100% of patients, and 71% of patients were positive for acid-fast bacilli, which are similar to the data reported by Manohar et al [18]. Some authors suggested that a tissue biopsy by laparoscopy is a safe tool for diagnosing such patients to prevent extended surgery [7,23,24]. However, laparoscopy is not suggested by gynecologic oncologists because of a probable increased risk of laparoscopic port-site metastasis in ovarian cancer patients [25].

Conclusions

Our data indicate that a high index of suspicion for peritoneal TB is needed in relatively young females with nonspecific symptoms of abdominal distension and wasting as well as lymphocytic ascites without malignant cells. We suggest that the clinical features in conjunction with a less-invasive laparoscopic visually guided peritoneal biopsy for frozen-section analysis can be used to diagnose peritoneal TB

and to avoid unnecessary extended surgery. CA-125 levels may be useful in following up the treatment response in these patients.

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