MAJOR ARTICLE

Tuberculous Peritonitis–Associated Mortality Is High among Patients Waiting for the Results of Mycobacterial Cultures of Ascitic Fluid Samples

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We identified 60 cases of tuberculous peritonitis during the past 12 years at our health care center. Most of the patients had severe underlying medical conditions, such as cirrhosis, renal failure, diabetes mellitus, and malignancy. Abnormal chest radiograph findings, ascitic fluid lymphocytosis, and biochemical findings for exudates could only identify 33%, 37%, and 53% of the cases, respectively. On the other hand, peritoneal biopsy allowed early definitive diagnosis for 9 patients. Thirty-one patients died, 26 of whom died ⩽6 weeks after their initial presentation, often before the result of mycobacterial culture was available. Only 8 patients died of advanced disease after antituberculous therapy was started. Univariate analysis showed that advanced age, underlying diagnosis, and delayed initiation of therapy were associated with higher mortality rates. Standard antituberculous chemotherapy is highly effective. However, conventional microbiologic diagnostic methods are slow and not sensitive enough for establishing a diagnosis of tuberculous peritonitis.

Despite the introduction of effective antituberculous chemotherapy, the mortality rate associated with tuberculous peritonitis has remained high and has probably been underreported [1–3]. The reported mortality rates for the antibiotic era have ranged from 15% [1, 2] to 31% [3]. The high mortality for tuberculous peritonitis is explained, at least in part, by its highly variable and often nonspecific clinical presentation and the practical difficulties in establishing an early bacteriologic diagnosis [4–9].

With the global resurgence of tuberculosis, it is timely to improve the characterization of this potentially lethal disease. After all, much of our knowledge about tuberculous peritonitis originated from 4 large series published before the 1980s [1, 10–12]. We report the findings of a single-center study of the clinical features and outcome of tuberculous peritonitis.

PATIENTS, MATERIALS, AND METHODS

Patient selection. We identified all patients in the clinical database of Prince of Wales Hospital in Hong Kong who had tuberculous peritonitis diagnosed during the period of January 1989 through December 2000. The accuracy of the database was ensured by a thorough audit of all ascitic fluid specimen requests, autopsy results, and our computerized diagnosis-coding system.

The diagnosis of tuberculous peritonitis was established on the basis of either culture of ascitic fluid specimens that yielded *Mycobacterium tuberculosis* or pathological proof of tuberculosis within the peritoneal cavity. Clinical data were obtained from hospital rec-

Received 26 December 2001; revised 27 March 2002; electronically published 17 July 2002.

Financial support: This work was supported in part by The Chinese University of Hong Kong research account 6901031.

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Clinical Infectious Diseases 2002; 35:409–13

1058-4838/2002/3504-0010$15.00

ords, clinic visits, and telephone interviews; the data included demographic characteristics at the time of presentation, coexisting medical problems, clinical features, treatment received, and survival information as of 1 April 2001.

Statistical analysis. Data analysis was performed using SPSS for Windows, version 9.0 (SPSS). Results are expressed as mean values ± SD, unless otherwise stated. Data were compared using the χ^2 test, Fisher's exact test, or Student's *t* test, as appropriate. Univariate analysis was performed to explore the association between clinical factors and tuberculosis-related mortality. All probabilities were 2-tailed. The level of statistical significance was set at .05.

RESULTS

Clinical data. Sixty patients (35 male and 25 female) with tuberculous peritonitis were identified from the 12-year period. They were observed for a total of 115 patient-years. The mean age at presentation was 55 ± 18 years (range, 17–91 years). Twenty-three patients (38%) had underlying liver cirrhosis; 8 of these patients (13% of the total) had alcoholism, 16 patients (27% of the total) had chronic hepatitis B infection, and 1 patient (2% of the total) had hepatitis C infection. Another 20 patients (33%) had advanced renal failure that required peritoneal dialysis. There were 16 patients with diabetes mellitus (27%), and 11 patients (18%) had underlying malignancy. Six patients (10%) were receiving systemic corticosteroid therapy at the time of presentation. One patient (2%) had AIDS. Only 12 patients (20%) had none of the aforementioned risk factors.

Common symptoms included abdominal swelling (56 patients [93%]), abdominal pain (44 [73%]), and fever (35 [58%]). Three patients (5%) presented with intestinal obstruction; 3 patients (5%) presented with worsening of hepatic encephalopathy; and another 2 patients (3%) presented with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Most of them had mild to moderate normochromic normocytic anemia. The mean hemoglobin level at presentation was 9.9 ± 2.5 g/dL. Only 20 patients (33%) had old tuberculous scars visible on chest radiographs.

Diagnostic tests. The diagnosis of tuberculous peritonitis had been difficult to make in our series. We subjected all sterile fluid and tissue specimens to direct Ziehl-Neelsen staining on-site on the same day, and the results were reported within 24 h. Examination of the ascitic fluid specimens by Ziehl-Neelsen staining could only identify the presence of acid-fast bacilli in 2 patients (3%). Similarly, only 32 patients (53%) had an ascitic fluid protein concentration of >25 g/L (mean protein concentration, 37.3 ± 17.2 g/L). The serum-ascites albumin gradient was 0.66 ± 0.56 g/dL. Nine (40%) of the 23 cirrhotic patients had >250 polymorphonuclear leukocytes per cubic millimeter of ascitic fluid and were initially classified as having spontaneous bacterial peritonitis. Lymphocytosis of ascitic fluid (defined as >30% leukocytes in the total ascitic fluid cell count [13]) was present in 18 of the 40 patients who did not have renal failure, whereas only 4 of the 20 patients who had renal failure had lymphocytosis of the peritoneal dialysis effluent ($P < .001$, by the χ^2 test).

For 9 patients, peritoneal biopsy was performed, either by laparotomy (7 patients) or laparoscopy (2 patients). All of the biopsy specimens revealed caseating granuloma on examination, and acid-fast bacilli were present in 6 patients (67%). Regardless of the Ziehl-Neelsen stain results, mycobacterial cultures of ascitic fluid and tissue samples were performed. All samples were centrifuged and then inoculated onto a pair of solid culture media (1 Lowenstein-Jensen–glycerol slope and 1 Lowenstein-Jensen–pyruvate slope) and tested with the BACTEC radiometric system (Becton Dickinson), as described elsewhere [14]. Solid media were observed weekly for visible growth for a total of 8 weeks. The BACTEC 12B cultures were tested for growth index according to the manufacturers' recommendation. The growth index was determined twice per week for the first 3 weeks, then weekly until the sixth week. A growth index of ⩾100 was considered to indicate positive growth. Fifty-five patients (92%) had positive results of mycobacterial cultures of ascitic fluid samples. The mean time from primary inoculation to culture positivity was 27.0 days (range, 9–56 days) in our series. All positive results were immediately reported via a computer reporting system. For 11 (48%) of the 23 cirrhotic patients, compared with 6 (16%) of the 37 noncirrhotic patients, the diagnosis of tuberculous peritonitis was established after the patient's death ($P = .016$, by the χ^2 test).

All mycobacterial isolates were sent to reference laboratory for identification (by conventional biochemical methods) and drug susceptibility analysis (by the absolute concentration method [15]). Of the 55 culture-positive cases, the mycobacterium isolated was resistant to isoniazid in 4 cases; rifampicin, in 1; pyrazinamide, in 6; ethambutol, in 1; and streptomycin, in 2. A multidrug-resistant mycobacterium, which was defined as one with resistance to at least isoniazid and rifampicin, was isolated in 1 case.

Treatment and outcome. For 16 patients (27%), a positive ascitic fluid mycobacterial culture was available only after the patient died. For another 5 patients (8%), the diagnosis of tuberculous peritonitis could only be confirmed by autopsy examination of the peritoneal membrane. Antituberculosis chemotherapy was implemented in the other 39 patients (65%). The median time interval between the onset of symptoms and the initiation of treatment was 23 days (mean, 30 ± 38 days). All of these patients received directly observed therapy with 4 antituberculous agents, which were isoniazid, rifampicin, pyrazinamide, and a fourth agent (either ethambutol or streptomycin). The duration of treatment ranged

from 9 to 18 months. All treated patients responded to treatment and had at least probable cure, according to the recommended definition of the World Health Organization [16].

The overall attributable mortality rate for tuberculous peritonitis was 52%. However, the observed mortality rate was 60% among patients for whom treatment was not started within 30 days after presentation. In fact, 26 of the 36 deaths occurred within the first 6 weeks after the initial presentation; 8 patients died after the initiation of antituberculous therapy, all because the disease was far too advanced by the time of initiation of therapy. Univariate analysis showed that patients who died of tuberculous peritonitis were older and more likely to have underlying cirrhosis (table 1). Patients who had antituberculous therapy initiated within 6 weeks after the onset of symptoms and patients who had diagnostic peritoneal biopsy performed were more likely to survive than were the other patients (table 1).

DISCUSSION

The findings of our present study argue for prompt diagnosis and treatment of tuberculous peritonitis. However, early diagnosis of tuberculous peritonitis is often difficult to make. As illustrated in the present series and in previous studies [1, 3, 12, 17–19], the symptoms of tuberculous peritonitis are generally nonspecific. Radiologic imaging techniques are not sensitive or specific for diagnostic purposes [20–22]. Despite the advances in molecular medicine [23, 24], bacteriologic identification of the *Mycobacterium* species depends on conventional microbiologic culture [25, 26]. However, direct microscopic smear detection of acid-fast bacilli in the ascitic fluid is insensitive, with reported sensitivity ranging from 0% [18, 27] to 6% [11, 17, 28].

More importantly, conventional mycobacterial culture takes up to 8 weeks to achieve results [17], whereas our present series found that, for >80% of the patients, the condition deteriorated and/or the patient died within 6 weeks after their initial presentation. Patients who died of tuberculous peritonitis had a significantly longer time lag from symptom onset to initiation of treatment than did the survivors (table 1). In fact, similar difficulty in making an early definite diagnosis has also been highlighted in many other reports [29, 30]. The mean time interval between the onset of symptoms and diagnosis of tuberculosis among our subjects concurs with the figures that have recently been reported from elsewhere in our region [3, 31]. We believe that alternative means of obtaining clinical specimens are crucial for reducing the time from symptom onset to initiation of treatment.

Examination of peritoneal biopsy specimens appeared to be an attractive method for early diagnosis of tuberculous peritonitis. Previous studies of peritoneal biopsy performed by laparoscopic guidance, minilaparotomy, or exploratory laparotomy reported a diagnostic yield of 85%–95% for tuberculous peritonitis [17, 32–35]. In our present series, the peritoneal biopsy method reduced the time to achieve a correct diagnosis,

Table 1. Comparison of patients who survived and patients who died of tuberculous peritonitis.

Variable	Patients who survived (n = 28)	Patients who died (n = 31)	P[a]
No. of male/no. of female patients	14/14	21/10	.20
Age, mean years ± SD	46 ± 17	60 ± 16	.001[b]
Coexisting diseases or therapy received			
Diabetes mellitus	5 (18)	11 (35)	.11
Cirrhosis	6 (21)	16 (52)	.01
Alcoholism	6 (21)	2 (6)	.16[c]
Renal failure on dialysis	10 (36)	8 (26)	.46
Malignancy	6 (21)	6 (19)	.33
Corticosteroid therapy	2 (7)	4 (13)	.44[c]
Previous tuberculosis	3 (11)	2 (6)	.61[c]
Concurrent tuberculosis			
Pulmonary	9 (32)	12 (39)	.54
Extrapulmonary	9 (32)	7 (23)	.45
Peritoneal biopsy performed	9 (32)	0 (0)	.001[c]
Treatment initiated ⩽6 weeks after presentation	20 (71)	8 (26)	.001

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Determined by use of the χ^2 test, unless otherwise indicated.

[b] Determined by use of Student's t test.

[c] Determined by use of Fisher's exact test.

which probably explains the lower mortality rate for the patients for whom this procedure was done. The advantage of peritoneal biopsy would be particularly prominent for cirrhotic patients, in whom tuberculous peritonitis is often not recognized.

Our finding of high mortality associated with tuberculous peritonitis in cirrhosis was consistent with the findings of previous reports [3, 36]. The excess mortality was probably the result of nonspecific clinical presentation as well as late diagnosis. It is not uncommon for cirrhotic patients with tuberculous peritonitis to have polymorphonuclear leukocyte–predominant ascites (i.e., >50% of total nucleated cells; for example, 40% in our series), and, not unexpectedly, these patients would be initially treated as if they had bacterial infection. In fact, there is often much diagnostic difficulty because of the similarity in the findings of ascitic fluid analysis for tuberculous peritonitis and spontaneous bacterial peritonitis or "culture-negative neutrocytic ascites," which are more common in cirrhotic patients than they are in patients with tuberculous peritonitis [37, 38].

A limitation of this observational study is that we were unable to eliminate the potential biases. For example, there might have been a tendency to perform invasive procedures, such as peritoneal biopsy, in lower-risk patients who could tolerate abdominal surgery and anesthesia. Therefore, the benefit of examination of peritoneal biopsy specimens might have been overestimated. Nevertheless, because such investigative procedures have a very low rate of complication [11, 12, 17, 33, 39–41], we suggest performing early diagnostic peritoneal biopsy for patients with unexplained ascites, especially in localities where tuberculosis is prevalent.

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