Original Article

Tuberculosis Peritonitis in Negara Brunei Darussalam

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Abstract

Introduction: Tuberculosis peritonitis (TBP) is uncommon and symptoms can be non-specific. Local data are lacking and our aim is to review our local experience with TBP. Materials and Methods: Between the period of 1996 to 2004, there were 10 [male: 6; mean age, 48 ± 18.5 years (range, 26 to 73)] cases of histologically documented TBP. Comparisons were made with pulmonary tuberculosis (PTB) patients. Results: The overall prevalence ranged from 0% to 1.01% of all TB infections. The median duration of symptoms before diagnosis was 2 months (range, 3 days to 24 months). Five patients (50%) had comorbid conditions and 3 patients (30%) had a history of positive contact. Presenting symptoms were abdominal distension (70%), abdominal pain (60%), fever (60%), anorexia (60%) and weight loss (40%). Two patients had pulmonary symptoms: cough/dyspnoea (n = 1) and cough (n = 1). Chest x-ray changes consistent with PTB were seen in 30%. TBP was diagnosed by laparoscopy (n = 6), laparotomy (n = 3) and blind peritoneal biopsy (n = 1). Adverse effects of TB drugs occurred in 80%, consisting of hepatitis (n = 4), nausea/vomiting (n = 2), rash (n = 1) and encephalopathy (n = 1). Haemoglobin ($P = 0.026$) and serum albumin levels ($P = 0.002$) were significantly lower in TBP patients. There was a significantly greater number of adverse effects ($P < 0.001$). There were no significant differences between TBP and PTB with regard to age, non-specific symptoms (weight loss, anorexia and fever) and erythrocyte sedimentation rate. All were treated with standard regimes and there were no mortalities. Conclusions: TBP is uncommon in our population. TBP patients had significantly lower haemoglobin and serum albumin levels. They also experienced more adverse events during treatment. There were no differences in non-specific symptoms between TBP and PTB.

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Key words: Characteristics, Prevalence, Pulmonary tuberculosis, Treatment outcome

Introduction

There has been a resurgence of tuberculosis (TB) in many countries, including developed nations, especially with the HIV pandemic and the increase in immigration.[1,2] In underdeveloped and developing nations, this infectious disease is still very common. TB peritonitis (TBP) is rarely encountered and is estimated to occur in 0.1% to 3.5% of those with active pulmonary TB (PTB) and represents 4% to 10% of all extrapulmonary TB.[1] TBP, like TB infections involving other organs, is easily treated. However, it is often misdiagnosed as carcinomatosis peritonitis or diagnosed at a later stage, leading to a delay in treatment or inappropriate treatment.[3,4] This can lead to significant morbidity and even mortality.[5-7] We present a review of the local experience with TBP, looking at the clinical characteristics, investigations and treatment outcomes. Comparisons were made with PTB patients.

Materials and Methods

Between 1995 to December 2004, 10 patients (male: female ratio, 6:4) were diagnosed with TBP and treated at the TB Coordinating Centre, Negara Brunei Darussalam. All patients had histological diagnoses consistent with TB [positive for caseating granuloma with or without positive smear for acid-fast bacilli (AFB), or positive for TB in other organs]. All patients were treated with standard TB therapies. Between these periods, 2 standard regimes were used. Up till 1997, the first-choice regime was the SRIP (streptomycin-

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15 mg/kg/day, rifampicin-10 mg/kg/day, isoniazid-5 mg/kg/day and pyrazinamide-30 mg/kg/day). After 1997, all patients were started on the quadruple regime of RIPE (rifampicin, isoniazid, pyrazinamide and ethambutol-20 mg/kg/day) for the first 2 months, followed by rifampicin and isoniazid for a further 4 to 9 months. Pyridoxine (vitamin B6) was routinely given to prevent peripheral neuropathy secondary to isoniazid.

Patients were placed on directly observed therapy (DOT) surveillance and followed up regularly; initially once every 1 to 2 weeks and then monthly if their condition was stable and improving. Patients who were at risk of or had experienced adverse events were routinely followed more closely until events had settled. Patients and family members were advised to seek medical attention if patients experienced adverse symptoms. Side effects of TB drugs were considered if the events or symptoms had begun after anti-TB medications were started, other causes were absent and there was resolution of these side effects upon reducing or stopping the suspected medication. These ranged from non-specific gastrointestinal symptoms such as nausea, vomiting and abdominal pain, to known complications such as hepatitis. Significant hepatitis was considered when serum alanine aminotransferase rose to more than 2 times the baseline or 3 times the upper limit of normal. Patients were observed closely and treatment restarted either sequentially or altogether if patients' symptoms had resolved. Alternative regimes were used if a particular medication could not be restarted. Alternative medications included the use of fluoroquinolone (ciprofloxacin) or a compromised regime for a longer duration. Ophthalmological and otological evaluations were done for patients treated with ethambutol and streptomycin respectively. After the completion of treatment, patients were followed up for a further 12 months to exclude the possibility of relapse.

Clinical records of patients were retrospectively reviewed and data on clinical presentations, comorbid conditions, particularly those associated with immune compromised state [diabetes mellitus, renal failure, malignancies, chronic pulmonary diseases], laboratory [full blood counts, liver function tests and serum erythrocyte sedimentation rate (ESR)], histological, operative and treatment outcomes were extracted. PTB patients (n = 163) treated in 2003 served as control for comparison.

Data were entered into the SPSS (Version 10.0, Chicago IL, USA). Continuous variables were compared using the Mann-Whitney test and categorical variables were compared using Fisher's exact test. Level of significance was taken as $P < 0.05$.

Results

All patients were local Malays except for a Nepalese soldier who had arrived in Brunei from the United Kingdom 6 months prior to diagnosis. He had previously been well and had no history of contact. The median duration of symptoms prior to diagnosis was 2 months (range, 3 days to 24 months). The median duration of delay between presentation and diagnosis of TBP was 5 days (range, 3 days to 29 days). There were significantly more Malays with TBP compared to PTB ($P = 0.016$). The demographic data is shown in Table 1. All were negative for HIV serology. The annual incidence of peritoneal TB over a period of 7 years (1997 to 2003) is shown in Table 2.

Presenting complaints are shown in Table 3. Two patients had pulmonary symptoms: cough/dyspnoea (n = 1) and cough (n = 1). Both had chest radiography changes. Chest radiography changes consistent with PTB were seen in 3 patients; right upper zone fibrosis (n = 1) and pleural effusions (n = 2). Only 3 patients had clinical evidence of ascites.

One patient, who presented with right iliac fossa pain

Table 1. Demographic of Patients with Tuberculous Peritonitis

Age (y)	48 ± 18.5 (range, 26 to 73)
Gender	
Male	6
Female	4
Race	
Malay	9 (90%)
Nepalese	1 (10%)
Weight (kg)	57 (range, 47 to 76)
Contacts	
Positive	3 (30%)
Negative	3 (30%)
Unknown	4 (40%)
Comorbid conditions*	5 (50%)

* Associated comorbidities were mentally subnormal (1), diabetes/hypertension (1), pituitary tumour (1), end-stage renal failure on dialysis (1) and myelodysplasia syndrome (1)

Table 2. Total Cases of Tuberculosis (TB) and TB Peritonitis Reported (Data from the National TB Coordinating Centre)

	TB		TB peritonitis	
Year	Annual incidence	per 100,000 population	Annual incidence	per total TB cases
2003	203	55.5	1	0.49
2002	220	61	1	0.45
2001	207	59	2	0.97
2000	308	91	0	0
1999	266	80	0	0
1998	198	61	2	1.01
1997	149	48	1	0.67

Figures for 1995 to 1996 and 2004 were not available

Table 3. Clinical Presentations Prior to Diagnosis

Symptom	n (%)
Abdominal distension	7 (70)
Abdominal pain	6 (60)
Fever	6 (60)
Loss of appetite	6 (60)
Loss of weight	4 (40)
Cough	2 (20)
Diarrhoea	1 (10)
Dyspnoea	1 (10)

suggestive of acute appendicitis, underwent laparoscopic appendectomy. Three patients with symptoms of bowel obstruction underwent laparotomies. One patient (a 73-year-old male), who had TB involvement of the oesophagus, stomach and duodenum, underwent diversion surgery. The other 2 patients (a 33-year-old female and a 69-year-old female) were suspected of having underlying malignancies until laparotomy was performed. These showed matted bowels and dense adhesions. All patients who had laparoscopy (n = 6) and laparotomy (n = 3) showed typical white nodules representing granuloma involving the peritoneum. One patient had diagnosis confirmed by blind peritoneal biopsy for assessment of ascites. AFB smears were positive in 5 patients (50%) in their histology.

All patients were treated with a standard regime. All patients responded to treatment (median, 6 months; range, 6 to 12 months). Side effects of TB drugs were seen in 8 patients (80%), and these consisted of hepatitis (n = 4), nausea/vomiting (n = 2), rash (n = 1) and encephalopathy (n = 1). The encephalopathy was attributed to isoniazid (no other causes and encephalopathy settled with withdrawal of isoniazid). Fortunately, these adverse effects were mild. Medications needed to be altered in 6 patients. There were no deaths attributable to TBP.

TBP patients had significantly lower haemoglobin levels ($P = 0.026$) and serum albumin ($P = 0.002$). They also had more comorbid conditions that can lead to immuno-compromised state, but this did not reach statistical significance ($P = 0.099$). There was a significantly greater occurrence of side effects of TB drugs in TBP patients ($P < 0.001$). There were no differences in terms of age and prevalence of non-specific symptoms; fever ($P = 0.288$), weight loss ($P = 0.526$) and loss of appetite ($P = 1.000$). This is shown in Table 4.

Table 4. Comparisons Between Tuberculous Peritonitis and Pulmonary Tuberculosis

Parameter	TB peritonitis	Pulmonary TB	*P* value
Age (y)*	48.0 ± 18.5	42.4 ± 17.0	0.314
Gender			
Male	60%	58.9%	0.945
Ethnic group			
Malay	90%	50.3%	0.016
Comorbid†	50%	26%	0.099
Non-specific symptoms‡			
Fever	60%	42.4%	0.288
Weight loss	40%	50.6%	0.526
Anorexia	60%	60%	1.000
Blood investigations*			
Haemoglobin (gm/dL)	10.7 ± 2.5	12.6 ± 2.0	0.026
Haematocrit (%)	33.9	37.5	0.083
ESR (mm/h)	72 ± 16	57 ± 37	0.240
Albumin (gm/dL)	27.5 ± 3.4	33.7 ± 6.7	0.002
Adverse events‡	80%	18%	<0.001

ESR: erythrocyte sedimentation rate

* Mann-Whitney test

† Comorbid conditions associated with immunocompromised state (diabetes mellitus, renal failure, malignancies and chronic pulmonary diseases)

‡ Fisher's exact test

Discussion

TB is an easily treated infection but remains the leading infectious cause of death worldwide,[2] particularly in underdeveloped and developing nations. There has been a worldwide resurgence of TB, particularly with the HIV pandemic and the increase in immigration. Delay in the diagnosis of TB or misdiagnosis can lead to delay in treatment, leading to significant morbidity and even mortality.[5,6] This is particularly true for extrapulmonary TB, which can be quite difficult to diagnose without a high level of suspicion. Pulmonary changes of old PTB may be seen only in 20% to 30% and have been reported to be even less in those with active TB[7,8] in patients with tuberculosis of the peritoneum/peritonitis. The presence of pulmonary changes often heightens clinical suspicion and helps in making early diagnosis. Changes consistent with PTB were seen in only 3 of our patients.

TBP is the second commonest manifestation of gastrointestinal TB after ileocaecal involvement. In Negara Brunei Darussalam, a developing nation, the incidence of TBP has remained the same over this period (1997 to 2003). As TB infection is known to affect almost any organ, it is possible that many patients with peritoneal involvement were not identified. This is because the treatment of TB is essentially the same; hence the identification of TB infections, particularly PTB or that occurring in another organ, often leads to treatment without further investigations being required unless indicated.

AFB can often be very difficult to isolate from pleural and ascitic fluids. The literature shows that the positive rates are disappointingly low but can be raised by increasing the amount of fluid analysed.[5,9-11] Culture positivity varies from 7.7% to 83%.[5,6,9,12,13] Unlike the findings in published

literature, only 3 of our patients had clinical evidence of ascites.[13-16] This perhaps indicates an earlier spectrum of TBP compared to previous studies.

Laparoscopy with biopsy is currently considered the gold standard for diagnosing TBP, with low complications and a reported sensitivity of up to 100%.[11,13,14,17-19] However, this is invasive and may not be widely available in many countries. Non-invasive tests such as adenosine deaminase have been shown to be useful in TB.[20] Again, these are not widely available. Our yield of 50% positive smear for AFB is attributable to the directed sampling during laparoscopy or laparotomy. Blind peritoneal biopsy has been reported to give a low yield and can be complicated by viscera perforation and even death.[13,14] In our only patient who had a blind peritoneal biopsy, AFB was seen in the histology. After the biopsy, his course was complicated by a pyogenic peritoneal abscess that required percutaneous drainage. Sepsis continued and he required surgical drainage. There was no evidence of any overt perforation during surgery. The intra-abdominal abscess is likely to represent an infection from a possible micro perforation from the initial procedure or from the translocation of bacteria from the gut.

Often, the presence of TB infections indicates the presence of underlying conditions that compromise host immunity. This is true in developed nations, where most cases of TB are associated with conditions such as HIV infections, diabetes, and end-stage liver and end-stage renal diseases.[18] However, in underdeveloped and developing nations, this may not be true. TB infections can occur even in patients without any significant premorbid conditions. Only half of our patients had comorbid conditions that could have contributed to the infection or reactivation of previous infections. Up to the present, there had only been one documented case of TB infection (a patient with PTB) and HIV co-infections in Negara Brunei Darussalam [personal communication – Dr Badesab (Epidemiology unit, Ministry of Health)].

In our experience, TBP patients have significantly lower serum albumin and haemoglobin levels. These may indicate a more severe spectrum of TB infection compared to PTB. Non-specific symptoms are also common in patients with TBP. However, these were not significantly different from PTB cases. In addition, side effects of TB drugs were significantly more common in TBP patients, and the increased susceptibility of these patients again suggests a more severe spectrum of disease. The majority of these adverse events were hepatotoxicity. Despite most of these adverse events being self-limiting, it is important that they are recognised early to avoid any complications that may affect the outcomes of treatment. Hence, family members need to be well informed.

The treatment of TBP is essentially the same as the treatment of active PTB, with standard triple or quadruple therapy for 2 months initially, followed by dual therapy for a further 4 to 7 months. Existing therapies are very effective and it is important to make an early diagnosis to avoid unnecessary delay in treatment. Currently, there has been no case of multi-resistant TB documented in our local setting. However, it is important to make an accurate diagnosis as treatment is prolonged and associated with side effects. An aggressive approach, with visualisation of the peritoneum and a targeted biopsy, has been recommended for making an early diagnosis of TBP.[21] Therefore, TB should always be considered in patients presenting with abdominal symptoms and non-specific constitutional symptoms, particularly in young patients. Fortunately, there was not much diagnostic delay in our patients. This is probably due to the presence of coexisting pulmonary changes of PTB and the acute presentations of some of the patients requiring urgent interventions. Incidental findings of TBP during surgery/laparoscopy for other suspected pathologies led to the diagnosis.

There are limitations in our study. Firstly, the retrospective nature is inherently associated with many limitations, particularly in assessing the prevalence of symptoms. Secondly, the small size of our patients sample may affect the results. Despite this, our results are comparable to those published in the literature.

Conclusions

Our local experience shows that TBP is very uncommon and predominantly occurs in the Malays. TBP patients had significantly lower haemoglobin and serum albumin levels and experienced more adverse events during treatment. There were no differences in the prevalence of non-specific symptoms. Although uncommon, TBP should be considered, particularly in patients presenting with abdominal distension, pain and non-specific constitution symptoms. Associated pulmonary changes should be looked for and inspection of the peritoneum, particularly with laparoscopy and a targeted biopsy, should be utilised early.

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