ORIGINAL ARTICLE

Differences in Patient Profiles of Abdominal and Pulmonary Tuberculosis: A Comparative Study

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SUMMARY

Objectives: Tuberculosis remains a common infection and is often associated with non-specific constitutional symptoms or laboratory investigations regardless of site of manifestations. This study compares the profiles of abdominal tuberculosis (ATB) and pulmonary tuberculosis (PTB).

Methods: Patients with ATB (n=34, male-21, mean age 43.3 ± 16.0 years) diagnosed over a nine year period were identified from the National Tuberculosis registry and retrospectively reviewed. Comparisons were made with patients treated for PTB (n=163).

Results: The most commonly affected sites were the ileocecal regions, peritoneum and hepatobiliary system. Common clinical presentations were abdominal pain (61.8%), anorexia (44.1%), weight loss (55.9%), fever (41.1%) and abdominal distension (29.4%). Four patients had concomitant active PTB. Compared to PTB, patients with ATB had significantly lower serum haemoglobin (11.6 ± 2.4 vs. 12.6 ± 2.0 gm/dL, p=0.036) and higher rate of adverse events of anti-tuberculous treatment (50% vs. 15.4%, p<0.001). There were no difference in prevalence of constitutional symptoms (fever, weight loss and anorexia), platelet level, albumin, total protein and erythrocyte sedimentation rate. Importantly, there was no difference in the treatment response. More patients with ATB and concomitant active PTB had reported weight loss (100% vs. 36.7%, p=0.017).

Conclusion: There are differences in the profiles of ATB and PTB. Awareness of such differences can help to improve the understanding and management of this infection.

INTRODUCTION

Tuberculosis remains an important cause of morbidity and mortality especially in the underdeveloped and developing nations [1]. There is a resurgence of this infection in many countries including the more developed nations especially with the Human Immunodeficiency virus (HIV) pandemic and increase in immigrations [2, 3]. It remains a major public health issue in the South-East Asia region. World Health Organisation estimated that there were 4.88 million prevalent cases and an annual incidence of 3.17 million TB cases in the South-East Asia region in 2008 [4]. This represented one-third of the global burden of tuberculosis. Most cases occur in the age group of 15-54 years, with males being disproportionately affected with a ratio of 2:1 among newly detected cases. Importantly, with the introduction of directly observed therapy, the deaths associated with tuberculosis have declined. Despite this, the estimated prevalence and incidence in the region between 2004 and 2007 have remained static [4].

Pulmonary tuberculosis (PTB) remains the most common manifestation. Abdominal tuberculosis (ATB) is the sixth most commonly affected system [5-8]. Certain clinical manifestations are more common than others depending on the system or organ involved but can also be non-specific [5-11]. Pulmonary symptoms will be prominent in PTB, abdominal pain or distension in ATB, bone pain and joint movement restrictions in osteoarticular involvement and neurological symptoms in those with neurological involvement. However, constitutional symptoms such as fever, loss of weight and anorexia are common to all tuberculosis infections [12]. Similarly, certain laboratory investigations such as erythrocyte sedimentation rate (ESR), hypoalbuminemia, anaemia and thrombocytosis are non-specific and are common manifestations. This study compares the profiles of ATB and PTB, specifically looking at the non-specific manifestations, laboratory investigations and outcome of treatment.

MATERIALS AND METHODS

Patients treated for ATB over a nine year period (1995 to 2004) were identified from the National Tuberculosis registry and retrospectively reviewed. Diagnoses of tuberculosis were based on consistent histology (granuloma with or without caseation, giant epitheloid cell and Langerhan's cells), positive Ziehl Neelsen staining for acid fast bacilli (AFB) or positive culture for Mycobacterium tuberculosis. Investigations that led to the diagnosis included endoscopy, surgery (laparotomy or laparoscopy) and imaging guided percutaneous biopsies. Response to treatment in the absence of AFB being isolated was used to confirm the diagnosis in a minority of patients. All patients were checked for HIV.

Patients were placed on the directly observed therapy surveillance. Patients were treated with standard regime consisting of streptomycin 15mg/kg/day, rifampicin 10mg/kg/day, isoniazid 5mg/kg/day and pyrazinamide 30mg/kg/day before 1997 and rifampicin, isoniazid, pyrazinamide and ethambutol 20mg/kg/day after 1997. After two months of quadruple therapy, patients were continued for four to seven months with rifampicin and isoniazid. Pyridoxine (10 to 20mg/day) was routinely given to reduce

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risk of isoniazid neurotoxicity. Patients were followed up for a further 12 months to monitor relapse before being discharged back to their primary physicians. Patients were considered to have responded to treatment when there was clinical improvement (i.e. weight gain, lysis of fever and improvement of gastrointestinal symptoms), normalisation of serum erythrocyte sedimentations rate (ESR) and improvement of blood investigations.

During treatment, all patients were monitored for adverse events and liver profiles were done regularly. Medications were withheld if there was any evidence of adverse events directly related to the medications. Alternatives regimes were used if a particular medication/s cannot be restarted. In all tested sample, there were no resistance to any of the anti-tuberculous medications used.

Data collected included demographic features, laboratory and radiological data at clinical presentations, treatment and outcomes from detailed case notes review. Weight loss was quantified by weight measurement on presentations and comparison with previous documented measurements either in the case notes or from patients' recollection of previous stable weight.

Comparisons were made with 163 patients diagnosed and treated for PTB in 2003. Detailed case note reviews were carried out. Comparisons between patients treated for PTB in 2003 to those treated for PTB in 2001 (n=187), 2002 (n=183) and 2004 (n=153) showed no significant differences in the demographic (age and gender).

All data were entered into the Statistical Program for Social Sciences (SPSS Version 10.0, Chicago, Il, USA) for analysis. Data are expressed as mean, standard deviation and range. The Mann-Whitney test was used to compare the age and the different blood investigations. Chi-squared test was used to compare the different gender and clinical symptoms. Level of significance is taken when $p<0.05$.

RESULTS

There were 34 patients diagnosed with ATB. The patients' demographic are shown in Table I. All patients were negative for HIV serology. There was a mean delay of 7.5 months (0 to 60) before diagnosis. Clinical presentations were abdominal pain (61.8%), loss of appetite (44.1%), weight loss (55.9%), fever (41.1%), abdominal distension (29.4%), diarrhoea (8.8%) and constipation (2.9%). Four patients (11.8%) had respiratory symptoms. Ten patients (29.4%) had radiological changes consistent of PTB, four of which had positive sputum for AFB indicating active PTB.

The site of involvements is shown in figure 1. Four patients had multiple site involvements. Diagnoses were made through endoscopy in 13 patients (38.2%), laparoscopy or laparatomy in 14 patients (41.2%) and seven patients (20.6%) with percutaneous biopsy of suspected lesions.

All except for two had completed their treatment, two of which had gone back to their homeland. Adverse events were seen in 50% of patients (16/32): hepatotoxicity (mild, n=4 and severe, n=2), gastrointestinal complaints, mainly nausea and vomiting (n=5), rash/pruritus (n=4) and encephalopathy secondary to isoniazid (n=1).

Compared to patients with PTB, patients with ATB had significantly lower serum haemoglobin ($p=0.036$) and significantly more adverse events of treatment ($p<0.001$). However, there was no difference with significant adverse events (18.8% vs. 0.0%, $p=0.166$). Most adverse events were self-limiting. There were no significant differences in the prevalence of constitutional symptoms, serum platelets level, serum total protein, albumin, erythrocyte sedimentation rates and treatment response (Table II).

Patients with concomitant active PTB (n=4) had significantly more weight loss (100% vs. 36.7%, $p=0.017$) and marginally non-significant anorexia (100% vs. 50%, $p=0.059$) and serum albumin (25.7 ± 1.5 vs. 32.1 ± 7.6 gm/dl, $p=0.057$). There were no difference in fever (75% vs. 36.7%, $p = 0.143$), serum haemoglobin (11.1 vs. 11.6 gm/dL, $p=0.692$), ESR (71 vs. 44 mm/hr, $p=0.120$) and adverse events (46.4% vs. 50%, $p=0.893$).

DISCUSSION

Tuberculosis remains a common infection and important cause of death worldwide [1]. Despite improvement in the knowledge, diagnostics and availability of effective treatment, tuberculosis related death is still substantial. In 2009, it was estimated that 1.7 million people died from this infection [13]. Therefore, it is important to diagnose and initiate appropriate treatment early.

Overall, the sites of involvements and clinical manifestations among our patients with ATB are consistent to what have been reported in the literature [5-11, 14-19]. The ileocecal region was the most commonly affected site (62%) followed by the peritoneum and the hepatobiliary system. Four patients (11.8%) had multiple site involvements. Similarly, the clinical presentations were also comparable to those reported in the literature with abdominal pain being the most common, followed by weight loss, anorexia and fever. Abdominal distension was present in only 29% and is consistent with the prevalence of peritoneal involvement. Generally, the reported prevalence of symptoms varied between studies due to differences in the prevalence of various organs involvements reported. Some reported more peritoneal involvements whilst others with reported more gastrointestinal involvement [5-11, 14-19]. It is very likely that certain symptoms are more common than others depending on the organs involved and the stage of disease.

Common to all tuberculosis infection, non-specific constitutional symptoms are common. To our knowledge, no studies have previously compared the prevalence of these non-specific symptoms between organs involvements. In ATB, the prevalence of constitutional symptoms reported in the literature ranged from a third to more than 80% [5-11, 14-19]. Among our patients with ATB, up to 50% had experienced constitutional symptoms. Compared to patients with PTB, there was no difference in the overall prevalence of constitutional symptoms. This is not unexpected considering

Table I: Patients' demographic at diagnosis

Mean age (years old)	**43.3 ± 16.0**
Gender	
Male	21 (61.8)
Female	13 (38.2)
Racial	
Malay	25 (73.5)
Chinese	2 (5.9)
Indigenous	1 (2.9)
Others	6 (17.6)
Tuberculosis contact	
Positive	9 (26.5)
Negative	10 (29.4)
Unknown	15 (44.1)
Co-morbid conditions	8 (23.5)

‡ Expressed in mean, standard deviation and range (bracket)
Data presented in parenthesis are percentages

Table II: Comparison between Abdominal TB and pulmonary TB at presentation

	Abdominal TB (n=34)	**Pulmonary TB (n=163)**	**P value**
Age (years)	43.30 ± 16.02	42.39 ± 18.96	0.621
Gender (male)	21 (61.8)	96 (58.9)	0.757
Constitutional symptoms			
Fever	14 (41.4)	67 (41.1)	0.881
Anorexia	19 (55.9)	78 (47.9)	0.488
Weight loss	15 (44.1)	78 (47.9)	0.828
Laboratory investigations			
Hemoglobin (gm/dL)	11.6 ± 2.4	12.6 ± 2.0	0.036
MCV	79.3 ± 8.7	80.2 ± 7.2	0.144
Platelets (109/L)	385 ± 140	384 ± 126	0.843
ESR (mm/hr)	46 ± 28	57 ± 39	0.305
Albumin (gm/dL)	31.7 ± 7.7	33.7 ± 6.8	0.091
Total protein (gm/dL)	74.0 ± 11.7	78.7 ± 8.2	0.097
Treatments			
Response	34 (100)	160 (98.2)	0.454
Adverse events*	16 (50)	25 (15.4)	<0.001

* 32 patients completed treatment

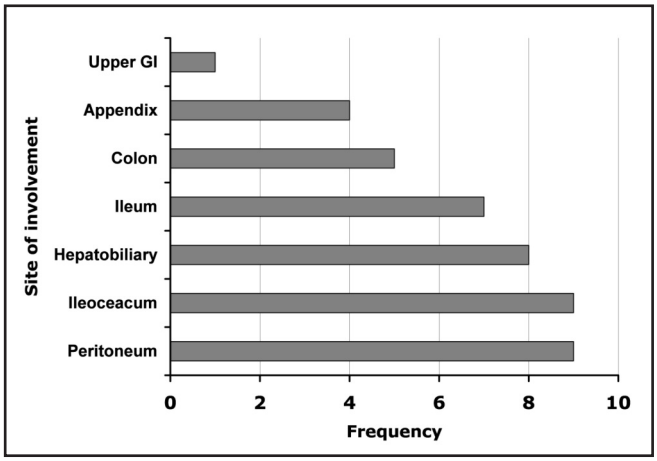

Fig. 1: Site of involvements.

these constitutional symptoms are secondary to the complex inflammatory processes that are common to all tuberculosis infections. However, significantly more patients with ATB with concomitant active PTB reported weight loss compared to those without active PTB. They also had higher prevalence of fever and anorexia, although not statistically significant. This may be due to the severity of illness in patients with multi-system involvements or the direct consequence of gastrointestinal involvements. Patients with ATB already experience many gastrointestinal complaints and coupled with luminal pathologies affecting intake, digestion and absorption can further exacerbate their symptoms. These can further worsen anorexia and precipitate malnutrition and further weight loss.

Generally, blood investigations such as ESR, serum haemoglobin, and albumin are non-specific but can also be considered as marker of disease severity especially the latter two. Among our patients, the serum haemoglobin level was significantly lower compared to those with PTB. The serum albumin and protein were lower in our patients with ATB but these were not statistically significant. Among our patients with ATB with concomitant active PTB, there was also a trend towards significance for lower serum albumin level compared to those without concomitant PTB. Lower serum heamoglobin level may be due to severity of illness, marrow infiltrations or blood loss from gastrointestinal tract. Similarly, mucosal involvements can also lead to mucosal loss or malabsorption of protein. Presence of multi-system

involvement generally will lead to a greater catabolic state and greater negative nitrogen balance. Hence lower serum nutritional markers.

Importantly, there was no difference in the treatment response between patients ATB and PTB, even among patient with concomitant ATB and active PTB. However, significantly more patients with ATB experienced more adverse events of treatment, both the significant and non-significant adverse events. This is not unexpected for various reasons. First, patients with ATB already experience many gastrointestinal symptoms and this may increase their risk for gastrointestinal side effects of medications. Second, patients with hepatobiliary involvement may be particularly at increased risk for side effects due to impaired hepatic metabolism, not just the hepatotoxic adverse events. Fortunately, most of the adverse events encountered by our patients were self-limiting. Despite this, it is important for clinicians to be aware of this and monitor their patients carefully.

Whether such differences seen among our patients can also be seen when compared to other extra-pulmonary tuberculosis such as osteoarticular, urogenital or neurological tuberculosis is unknown. To our knowledge, apart from the current study, there have been no reports of direct comparisons between PTB and the various extra-pulmonary manifestations. In osteoarticular tuberculosis, common constitutional symptoms were reported by 38.4%; that included fever (24.2-44%), anorexia (38%), night sweats (38.5%) and weight loss (50%) [20-22]. Similarly in neurological and gynaecological tuberculosis, non-specific constitutionals symptoms are also common [23, 24]. Similarly, investigations, treatment responses and the side effects profiles of other extra-pulmonary tuberculosis are also comparable. Despite the lack of studies with direct comparisons, it very likely that there are differences between different site involvements. However, these will require confirmation.

In conclusion, this study showed that there were no significant difference between the prevalence of constitutional symptoms and treatment response. However patients with ATB were more likely to have lower serum haemoglobin and experience adverse effects of treatment. Patients with ATB and concomitant active PTB were more likely to have more severe disease as evident by lower serum albumin and higher proportion with weight loss. Awareness of such differences can help to improve our understanding and the management of this infection.

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