Prevalence, Clinical Profile, and Treatment Outcomes of Adult Patients Diagnosed with Disseminated Tuberculosis seen at University of the Philippines Manila-Philippine General Hospital Tuberculosis Directly Observed Treatment Short Course (TB-DOTS) Clinic

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ABSTRACT

Objective**.** To determine the prevalence, demographic, clinical profile, diagnostic and treatment outcomes of adult patients diagnosed with disseminated tuberculosis

Methods**.** This is a cross sectional study of patients referred to the UP-PGH TB DOTS clinic with a diagnosis of disseminated TB from January 2011 to December 2015.

Results. The prevalence of disseminated tuberculosis was 1.7 %. Mean age at diagnosis was 33.9 years (range 19-64 years) with a male: female ratio of 1:1. The most common comorbidity was HIV (5.8%). The mean duration of symptoms before initial consult was 281 days (SD 510.7). The most common presenting symptoms were abdominal pain (19%), back pain (13%), and abdominal enlargement (11%). The lungs (86%) are still the most commonly involved site, followed by the gastrointestinal tract (22%) and the vertebra (27%). Majority were started with Category I treatment regimen (54%, 37 patients). Of the 68 patients, only 16% (11 patients) continued follow-up at PGH; all had documented treatment completion.

Conclusion. Patients with disseminated tuberculosis are young and majority had no comorbid illness. They have long latency of symptoms prior to diagnosis, and usually present with non-pulmonary symptoms despite high evidence of pulmonary involvement. To date, this is the largest local study on disseminated TB known to the authors.

Key Words: Disseminated Tuberculosis, Tuberculosis

Introduction

Tuberculosis is a major public health problem in the Philippines. Based on the 2005 Philippine health statistics, it was ranked sixth among the ten leading causes of mortality in the country.[1] Pulmonary tuberculosis (PTB) comprised 98.9% of all TB cases notified; extra-pulmonary TB (EPTB) composed the remaining 1.1%.[2] The low case detection for EPTB in the Philippines may be due to the limited capability of primary care facilities to diagnose these cases, and in part this relates to its being less common, therefore, less familiar to most clinicians. Disseminated tuberculosis is presumed to result from the inability of the host defenses to contain the infection leading to multi-organ involvement. Because of the multisystem involvement in disseminated tuberculosis, the clinical manifestations are variable. Presenting symptoms and signs are generally nonspecific hence are harder to detect. Treatment can also be complicated depending on the site involved and the presence of an underlying immunocompromised state. In recent years, focus has been placed on TB-HIV co-infection and the challenges it brings in terms of treatment. With the increase in number of people living with HIV (PLHIV), cases of extra-pulmonary and disseminated TB are likely to be more prevalent.

The objective of this study was to describe the prevalence, clinical profile, and treatment outcomes of patients diagnosed with disseminated tuberculosis and referred to the TB DOTS center of the UP-Philippine General Hospital (UP-PGH), one of the biggest tertiary hospitals in the country. With information obtained from this study, the investigators aimed to contribute to a more accurate picture of tuberculosis in the country and to the improvement of national policies.

Literature review

The TB Burden

In 2014 alone, the World Health Organization (WHO) has reported that around 9.6 million people were newly diagnosed with tuberculosis (TB) worldwide. Almost 60% of cases of TB reported were found in the South-east Asia and Western Pacific regions.

The Philippines is among one of the 22 high-burden countries that account for 80% of TB cases worldwide.[1] From 2003-2010, a total of 1.3 M cases of TB have been identified.[2] It remains to be one of the leading causes of morbidity and mortality in the country. In 2013, the

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economic burden of this disease was estimated at around Php 8 billion. Since the 1960s efforts have been made to control the disease and improve treatment outcomes in patients. The National TB Control Program (NTP) has served as the policy making body of the Department of Health (DOH) for TB, in compliance with standards set by the World Health Organization (WHO) and the International Standard of TB Care.[3]

TB DOTS

The main strategy of the NTP is implementation of the directly observed treatment short course (DOTS). [3] In the hospital setting, TB-DOTS centers such as that in the University of the Philippines-Philippine General Hospital (UP-PGH), may serve as "referring" centers. All TB cases identified at the outpatient department and wards must be referred to the hospital DOTS center according to NTP guidelines. The DOTS center facilitates provision of drugs to admitted TB patients. Upon discharge, the hospital will refer the patient to a local DOTS facility for continuity of care. With this approach, the main objective is improvement in case detection and treatment success rates, the major indices used in tracking TB control programs.

Disseminated tuberculosis

There is no globally accepted definition of disseminated tuberculosis. Shandera and Merchant reviewed 31 papers on extra-pulmonary TB (EPTB).[4] They concluded that disseminated TB and miliary TB were not clearly distinguished from isolated forms of EPTB in most of the papers. Studies limited to disseminated TB have used varying definitions as well, combining mostly bacteriologic, radiographic, and histopathologic evidence of multi-organ involvement. Examples of definitions used by Wang et al are as follows:

- *Isolation of M* tuberculosis *from blood, bone marrow, liver biopsy specimen of 2 noncontiguous organs*[5]
- *Isolation of M tuberculosis from 1 organ and histologic demonstration of caseating granulomatous inflammation from the bone marrow, liver biopsy specimen, or another noncontiguous organ*[5]
- *Isolation of M tuberculosis from 1 organ and radiographic finding of miliary lung lesions*[5]

Miliary pattern on chest radiograph are considered by most as indicative of hematogenous spread resulting in disseminated infection. One study included clinical symptoms of TB along with a positive tuberculin skin test in their definition.[6] The absence of an international definition of disseminated TB, especially by one supplied by TB control programs implies the under recognition of this disease state.

Disseminated TB is presumed to result from the inability of the host defenses to contain the infection leading to multi-organ involvement.[7] HIV and other causes of immunosuppression usually predispose to the development of disseminated disease. Identifying cases of disseminated TB is more difficult. For one, it is less common and physicians are less familiar with its presentation. Symptoms may be very nonspecific, such as fever, weight loss, anorexia, and weakness or may depend on which organs are involved. Bacteriologic confirmation of disseminated tuberculosis is also more difficult as obtaining samples from extra-pulmonary sites is more challenging, is usually invasive, and has lower bacteriologic burden. Furthermore, prevalence of disseminated tuberculosis may be underreported because once confirmation of TB in one site is achieved further investigation of other involved sites are no longer pursued.[7]

A study done in Duke University from 1989 to 1999 identified only 52 patients with disseminated TB.[8] Most cases were found in immunocompromised patients: patient with HIV, alcohol dependence, diabetes mellitus, or cancer. Twenty-one percent of the patients died within one month of presentation. Low hemoglobin and low albumin were among the laboratory derangements identified, suggesting chronic disease and malnutrition.

A 10-year study in Taiwan reported 164 cases.[9] Similar to the US study, most patients were immunocompromised, had hypoalbuminemia and anemia. Some patients also had hypercalcemia and hyponatremia. Miliary pattern on chest radiograph was a common finding. The lungs were still the most commonly affected site followed by musculoskeletal and urogenital involvement. Thirty-one percent died within a one-year period, with 14% of the deaths being directly attributable to TB. They found that combined cultures and histopathologic studies resulted in higher diagnostic yields.

Several studies described the clinical profile of patients with military TB, diagnosed by chest radiograph. Similarly, an immunocompromised state was found in majority of patients identified.[9-12]

A local study done in the University of Sto. Tomas described 13 cases of disseminated TB over a 10-year period until 1997.[6] Eight patients (61%) had a history of TB exposure from their family members. Eight patients also received prior BCG vaccination. Only one patient received prior anti-tuberculosis medications. Three patients had a low body mass index. Majority of patients had pulmonary involvement. Pulmonary with hepatobiliary and pulmonary with adenopathy were the most common patterns of organ involvement. Four patients had involvement of 3 organs. Eight patients had miliary TB. Fever, night sweats and abdominal pain, were the most common presenting symptoms. No additional local studies have been published on the profile of patients with disseminated TB patients despite the high TB burden in the Philippines.

The small number of cases identified support the idea that disseminated tuberculosis is not a common disease. However it may also imply that case detection and reporting programs are not yet in place. All the studies mentioned describe the high variability in clinical presentation and the

challenges in achieving a definite diagnosis of disseminated tuberculosis. Treatment outcomes and mortality data on disseminated TB is still lacking.

General objective

To describe the epidemiology of patients diagnosed with disseminated tuberculosis and referred to the TB-DOTS center of the UP-PGH.

Specific objectives

- Determine the prevalence of disseminated TB among patients referred to the UP-PGH TB DOTS Center.
- Describe the demographic profile and clinical characteristics of patients diagnosed with disseminated TB.
- Determine the common sites involved in disseminated TB.
- Describe the diagnostic test results of patients with disseminated TB.
- Describe treatment outcomes of patients with disseminated TB.

Definition of terms

The definitions below are consistent with international and local definitions of TB cases set by the World Health Organization and the National TB Control Program [3,13]

- Pulmonary tuberculosis (PTB) - refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree
- Extra-pulmonary tuberculosis (EPTB) - refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, eg, pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges. Histologically diagnosed EPTB through biopsy of appropriate sites will be considered clinically diagnosed TB.
- Disseminated tuberculosis –refers to any bacteriologically confirmed or clinically diagnosed case of TB involving two or more non-contiguous sites. TB adenitis of the cervical lymph nodes with concomitant pulmonary TB is considered as one site and does not fall into disseminated tuberculosis. The presence of miliary TB is considered as disseminated TB.
- Miliary tuberculosis – "millet" seed pattern on chest radiograph representing 1-2 mm granulomas resulting from hematogenous spread of *M tuberculosis*
- Bacteriologically confirmed - A TB patient from whom a biological specimen is positive by smear microscopy, culture or rapid diagnostic tests (such as Xpert MTB/RIF).
- Clinically diagnosed – A PTB patient who does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to pursue TB treatment. This definition includes cases diagnosed on the basis of radiologic abnormalities or suggestive histology, and extrapulmonary cases without laboratory confirmation.
- Category I treatment – Patients are subjected to 2 months of intensive phase with isoniazid/rifampicin/pyrazinamide/ethambutol (HRZE) and 4 months maintenance phase with isoniazid and rifampicin (HR)
- Category Ia treatment - Patients are subjected to 2 months of intensive phase with isoniazid/rifampicin/pyrazinamide/ethambutol (HRZE) and 10 months maintenance phase with Isoniazid and Rifampicin (HR)
- Category II treatment - Patients are subjected to 2 months of isoniazid/rifampicin/pyrazinamide/ethambutol/streptomycin (HRZES), 1 month of HRZE, and 5 months of isoniazid, rifampicin, ethambutol (HRE)
- Category IIa treatment - Patients are subjected to 2 months of isoniazid/rifampicin/pyrazinamide/ethambutol /streptomycin (HRZES), 1 month of HRZE, and 9 months of isoniazid, rifampicin, ethambutol (HRE)

Treatment outcomes

- Cured – A patient with bacteriologically-confirmed TB at the beginning of treatment and who was smear- or culture-negative in the last month of treatment and on at least one previous occasion in the continuation phase
- Treatment completed – A patient who completes treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable
- Treatment failed – A patient whose sputum smear or culture is positive at 5 months or later during treatment
- Died – A patient who dies for any reason during the course of treatment
- Lost to follow up – A patient whose treatment was interrupted for 2 consecutive months or more
- Not evaluated – A patient for whom no treatment outcome is assigned. This includes cases transferred to another DOTS facility and whose treatment outcome is unknown
- Isoniazid preventive therapy – Isoniazid prophylaxis (10mg/kg) given to children without TB but with TB exposure from household contacts, and to people living with HIV (PLHIV) regardless of age for 6 months.

Methods

Study design and population

We conducted a retrospective chart review of all patients referred to the UP-Philippine General Hospital (UP-PGH) TB-DOTS center from January 2011 to December 2015

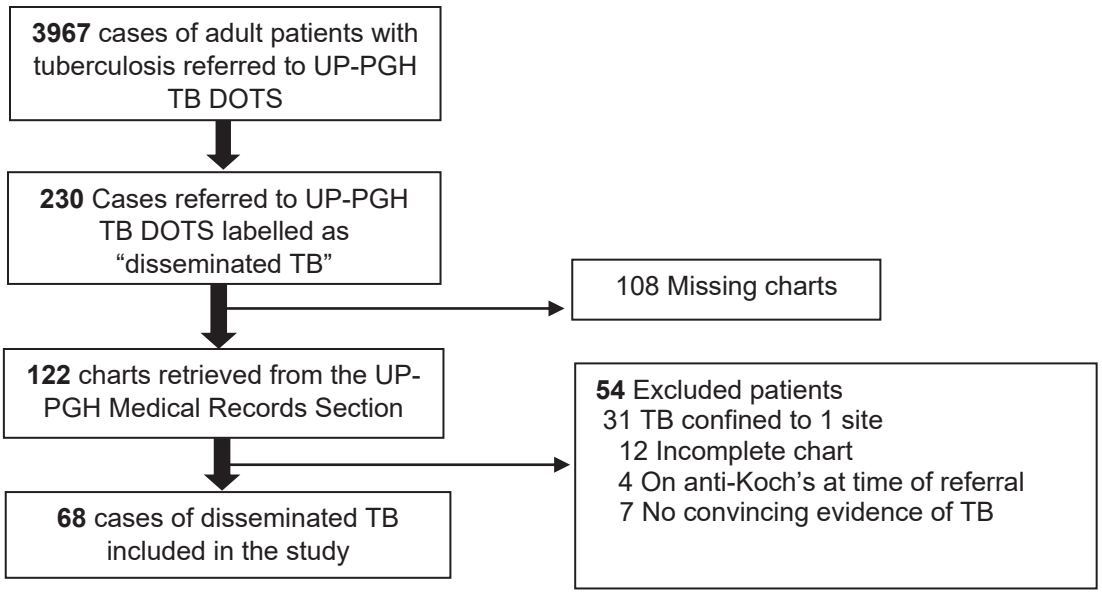

Figure 1. Study population.

for disseminated TB. Patients included were 19 years old and above with newly diagnosed active disseminated TB documented through any of the following:

1. At least two bacteriologically confirmed sites
2. At least one bacteriologically confirmed site and one clinically diagnosed site
3. At least two clinically diagnosed sites, with at least one site having typical radiologic and/or histologic findings highly suggestive of TB based on literature
4. Miliary TB on chest radiograph.

This inclusion criteria were decided upon taking into account the socioeconomic background of majority of the patients seen in UP-PGH and the limited resources of the hospital that factor into how referring physicians decide to work-up and treat diagnosed TB patients. Charity and pay patients either in-patient or out-patient were all included. Excluded patients were those less than 19 years old and those whom upon review of the referral form or the patient's chart did not have evidence of TB in at least 2 non-contiguous sites (eg, isolated pulmonary TB mislabeled as disseminated TB). Patients were also excluded if their charts could not be retrieved or were incomplete, if the diagnosis of disseminated TB was made in a different institution, and if the patient was already receiving anti-Kochs prior to being seen at PGH. Each case was discussed, and a consensus was reached prior to including/excluding each patient.

The study was conducted after obtaining approval from the ethics and research committee of the UP-PGH from May 2016 to October 2016. The authors manually screened all referral forms submitted to the TB-DOTS clinic of UP-PGH between January 2011 and December 2015. Patients *labeled* as disseminated TB and milliary TB on the referral forms were obtained, and were assigned with patient identification number. Medical records of included patients were retrieved and chart review was performed.

Baseline demographic, clinical profile, laboratory parameter and TB related information (diagnostics, treatment category, TB-DOTS acceptance, treatment outcome) of included patients were obtained using data extraction sheet (Appendix A). We attempted to complete missing data by cross-referencing with records from the Department of Laboratories and Pathology and Radiology, and by contacting the patients or their family members. All data obtained were encoded using Microsoft Excel 2010.

Results

Prevalence

From January 2011 to December 2015, a total of 3967 referrals to UP-PGH TB DOTS clinic were recorded. Of these, a total of 231 cases were labelled as "disseminated TB", only 122 charts were available for review, 54 patients were excluded, and a total of 68 cases were included in the study (Figure 1). Thus, the estimated prevalence of disseminated tuberculosis is *1.7 %* (68 of 3967 TB cases).

Demographics

The mean age at diagnosis was 33.9 years (range, 19-64 years) with equal sex distribution (Table 1). Majority of them reside in Luzon (n=63) and the greater Manila area. Referring departments included Medicine, Orthopedics, OB-Gyne, Neurology, and Surgery. Predisposing conditions were found in 16 patients (23%), the most common being co-infection with HIV (4 patients, 5.8%),

liver cirrhosis (3 patients, 4.4%), and alcoholism (3 patients, 4.4%). There were only fourteen patients who had their anthropometrics recorded and eight patients had history of TB exposure from household or family members. None of the patients were asked about history of BCG vaccination and prior isoniazid therapy.

Table 1. Baseline characteristics of 68 patients with disseminated tuberculosis

Baseline characteristics (N=68)	
Age (in years, mean)	33.97
Sex	
M (%)	50
F (%)	50
Recipient of immunosuppressive drugs (%)	1.4
History of TB exposure (%)	11.7
With comorbid illness (%)	23
HIV infection	5.8
Diabetes	1.4
Malignancy	1.4
Connective tissue disorder	1.4
Liver cirrhosis	4.4
Chronic kidney disease	2.9
Alcoholism	4.4
Congestive heart failure	1.4

Clinical features

The mean duration of symptoms before initial consult was 281 days (range, 1-3600days). Patients with Pott's disease, intestinal, and cutaneous tuberculosis usually had prolonged presentation of symptoms (>360days) prior to consult. The most common presenting symptom for patients with disseminated TB was abdominal pain (19%), followed by back pain (13%), abdominal enlargement (11%), and a mass (10.2%) (Table 2).

Table 2. Common presenting symptoms of disseminated tuberculosis (N total=68)

Symptom	N	(%)
Abdominal pain	13	19
Back pain	9	13
Abdominal enlargement	8	11
Mass	7	10.2
Dyspnea	6	8
Generalized weakness	4	5
Cough	4	5
Joint pain	3	4
Others	13	19

Diagnosis

There were almost equal proportions of patients diagnosed with disseminated tuberculosis using the authors' case criteria (Table 3). The most commonly involved site for disseminated TB is still the lungs (86%), followed by intestinal (32%), spinal or Pott's (27%), and pelvic/genital TB (19%) (Table 4). The different foci of multi-organ involvement found in 68 patients with disseminated TB are summarized in Table 5.

Table 3. Number of cases diagnosed with disseminated TB fulfilling the authors' case definition

Case definition	No. of patients	(%)
1. 2 Bacteriologic	20	29.4
2. 1 Bacteriologic, 1 clinical	23	33.8
3. 2 Clinical with at least 1 radiologic/ histopathologic finding	25	36.8
4. Miliary TB	5	7.3

Table 4. Involved sites for diagnosis of disseminated tuberculosis

Site	No. of cases (n)
Lung	59
Intestinal	22
Vertebral (Pott's)	19
Pelvic/genital	13
Hepatobiliary	9
Urinary	9
Psoas/ retroperitoneal abscess	6
Lymph node	5
Cutaneous	5
Joint	5
Others (eg, pericardial, esophageal, CNS)	13

Table 5. Different foci of 68 patients with disseminated tuberculosis

Sites	Number of cases (n)	Percentage
Pulmonary + Intestinal	9	13.2
Pulmonary + Vertebral	6	8.8
Pulmonary + Pelvic	6	8.8
Pulmonary + Hepatobiliary	4	5.9
Pulmonary + Intestinal + Pelvic	3	4.4
Hepatobiliary + Urinary	3	4.4
Pulmonary + Pericardial	2	2.9
Pulmonary + Vertebral + Psoas abscess	2	2.9
Pulmonary + Intestinal + Urinary	2	2.9
Pulmonary + Hepatobiliary + Urinary	2	2.9
Pulmonary + Adenopathy + Cutaneous	2	2.9
Others	27	39.7

Diagnostic findings

A complete blood cell count, serum creatinine, and transaminases were commonly requested at baseline for patients (Table 6). Among those with available results, most had anemia, an elevated WBC, hypoalbuminemia, high-normal calcium, and hyponatremia. Transaminases were normal at baseline.

Specimens submitted for mycobacteriologic studies and the results are summarized in Table 7 and Appendix B. Acid-fast bacilli (AFB) smears and imagining studies were the most commonly utilized. Data were aggregated by patient and sample type. For example, if 1 of the sputum AFB smear samples was positive, then the results of sputum AFB smear were recorded as positive. Sputum was the most common submitted specimen for microscopy but was only positive in 39% of patients. Stool, urine and gynecologic samples for AFB microscopy also have high positivity results (Table 8).

Table 6. Baseline laboratory results of patients with disseminated tuberculosis

Laboratory Test	n	Reference	Mean (SD)
Hemoglobin (g/dL)	57	120-180	110.64 (20)
WBC (x 10^9/L)	55	4-11	17.24 (42)
Platelet (x 10^9/L)	53	150-450	413.52 (172)
Albumin (g/dL)	35	34-50	26.5 (7)
Aspartate aminotransferase (U/L)	59	15-37	41.43 (30)
Alanine aminotransferase (U/L)	59	30-65	29.82 (20)
Creatinine (mg/dL)	54	53-115	57.19 (84)
Adjusted calcium (mmol/L)	31	2.12-2.52	2.51 (0.51)
Sodium (mmol/L)	41	135-145	133 (7)

Table 7. Diagnostics tests used to document involvement per site

Site	Diagnostic test
Lung	Sputum AFB, Sputum Gene Xpert, chest X-ray
Pelvic/Genital	Endometrial tissue/blood AFB, transvaginal ultrasound, endometrial/adnexal biopsy
Hepatobiliary	Bile AFB smear, abdominal ultrasound and CT scan, liver biopsy
Intestinal	Stool AFB, intestinal ulcer/mucosal biopsy
Spinal	Spinal X-ray, MRI
Peritoneum	Ascitic fluid AFB, abdominal ultrasound and CT scan
Urinary	Urine AFB, kidney/urinary tract ultrasound
Lymphnode	Lymph node biopsy, abdominal/chest CT scan
Cutaneous	Abdominal/Chest CT scan, cutaneous biopsy AFB and histopathology
Joint	Synovial fluid AFB, joint X-ray
Psoas abscess	Abdominal ultrasound and CT scan, aspirate AFB
Pericardium	2D echo, pericardial fluid AFB
Central nervous system	Cranial CT scan with IV contrast, CSF AFB
Esophageal/ retropharyngeal	Aspirate AFB

Table 8. Results of specimen AFB smear microscopy for 68 patients with disseminated tuberculosis

Site	Number of patients (Smear positivity/tested)	% of positive specimens
Lung	23/58	39
Intestinal	14/14	100
Urinary	9/9	100
Pelvic/genital	4/5	80
Joint	3/3	100
Psoas/retroperitoneal	2/2	100
Cutaneous	1/2	50
Central nervous system	0/2	0
Hepatobiliary	1/1	100

Treatment

The mean time from presentation to initiation of therapy was 22 days (range, 1–150 days). Category I treatment regimen was started in 54% of patients (37 patients), while 10.7% were started on Category Ia (7 patients), 19% on Category II (13 patients), and one patient on Category IIa.

Among admitted patients diagnosed with disseminated TB, four patients (5.88%) died. Mortality rates of those seen on out-patient basis could not be obtained. Among all those referred, the UP-PGH TB DOTS center was able to document referral and acceptance of twenty-nine percent (18 patients) to their local TB DOTS facilities. Only 16% (11 patients) continued follow-up in PGH, and were documented to have completed their treatment. Outcomes of patients who continued treatment in their local facilities could not be obtained. Continuity and outcome of treatment for the remaining 68% (48 patients) is unknown.

Discussion

Prevalence and associated factors

To our knowledge, this report represents the largest study on disseminated TB in the Philippines. Our results estimate the prevalence of disseminated TB at 1.7 %, which is higher than a local cases series done at University of Santo Tomas in 1997 (prevalence of 0.6%). (6) This is still likely to be an underestimate of the true prevalence, as records of more than a hundred suspected cases could not be retrieved.

Our results also revealed that patients with disseminated TB were young adults, with mean age of 33 years. There was no observed gender predisposition for the disease (1:1 male-to-female ratio). In contrast, an international study done in Taiwan[5] revealed a male preponderance (male-to-female ratio 2.6:1) while a study in Pakistan[9] showed female preponderance (1:1.4). Gender preponderance appears to be varied in different countries.

Disseminated tuberculosis is thought to develop in immunocompromised individuals, when host defenses are unable to contain the infection in a single site. It is interesting to note that only 23% of our patients have comorbid illnesses. HIV was the most common comorbidity, seen in 5.8% of the total patients included. This is significantly lower from previous studies where comorbidities were found in 42-87% of study population.[8,9] This difference may be due to suboptimal workup for underlying immunosuppression (eg, HIV screening) or under-recognition or under-reporting of established risk factors for disseminated TB such as malnutrition, alcohol abuse, liver disease, and drug dependence.[15] On the contrary, our results may also imply that disseminated TB can and should be suspected even in patients without predisposing conditions.

Prior TB exposure is a well-established risk factor for development of tuberculosis prompting the need to screen for latent TB. Sixty percent of patients (8 of 13) in the earlier local series had documented TB exposure.[6] In our study, only 11% had exposure to relatives or household contacts with TB. Information on prior isoniazid therapy and BCG status was also not elicited from any of the patients in the present study. Pursuing household contacts of TB patients and TB preventive strategies seem to be neglected in the evaluation of patients with disseminated TB.

Consistent with other studies,[8,9] the common laboratory abnormalities in patients with disseminated TB

were anemia, hyponatremia, and hypoalbuminemia. These findings are non-specific for TB, and may reflect a chronic inflammatory process. Malnutrition based on body mass index was detected in 23 percent of disseminated TB cases in an earlier study.[6] In PGH, very few had their anthropometrics measured at baseline (20%), suggesting that malnutrition as a predisposing factor is often neglected.

Sites of involvement

Pulmonary TB is still the most commonly affected site in disseminated TB. Gastrointestinal TB (intestine, peritoneum, and hepatobiliary) was the second most common site. Proposed pathogenic mechanisms for development of GI TB were swallowing of sputum with direct seeding or hematogenous spread.[16] Interestingly however, cough as the presenting symptom was only seen in a few patients. In our study, the most common presenting symptoms were gastrointestinal and musculoskeletal in origin (abdominal pain, abdominal enlargement, back pain). Thus for cases of disseminated TB, patients seem to be bothered by and consult due to their extra-pulmonary symptoms. Patients with disseminated TB also have less pulmonary symptoms despite pulmonary involvement.

Diagnosing disseminated TB

The duration of symptoms prior to seeking first consult was long, with a mean of around 9 months, and this was consistent with earlier reports.[5,6] However, it ranged from 1 to 3600 days, reflecting the varied presentation of disseminated TB. The duration prior to consult is likely associated with which sites were involved. Patients with Pott's disease usually had back pain for years, which they ignored or attributed to prior injuries, and only sought consult when they developed alarming symptoms like weakness and numbness. This also reflects the indolent course of disseminated TB, suggesting that means for earlier detection, especially when it is still isolated to a single site, should be explored.

Bacteriologic evidence was still sought in majority of the patients; two-thirds of patients had at least 1 bacteriologically confirmed site. For pulmonary involvement, sputum AFB was still the most commonly requested test to confirm bacteriologic involvement. Xpert, PCR, and TB cultures were seldom requested, likely due to its cost. In our study, sputum AFB was only positive in 39% of those with pulmonary involvement (23 of 58 patients). In the WHO surveillance report on isolated pulmonary TB in the Philippines from 2003 to 2011, 54% of cases were smear-positive.[14] Hence, the nature of pulmonary involvement appears to be different when it is the sole site involved as compared to being a composite site in disseminated TB. We hypothesize that cases of disseminated TB may have started as undetected latent pulmonary TB before spreading to other sites. Pulmonary involvement in disseminated TB may have a pauci-bacillary nature similar to extra-pulmonary tuberculosis. For the sputum AFB negative cases, diagnosis of pulmonary TB was made through chest xray. Only 8% of those with pulmonary involvement had a milliary pattern on CXR, markedly lower than the 61% documented in an earlier local study.[6] This underscores the observation that disseminated TB does not seem to require severe pulmonary involvement.

Compared to pulmonary TB, extra-pulmonary TB is less studied and the recommendations for work-up are weaker. Clinical samples for bacteriologic confirmation of extra-pulmonary TB can be difficult because of relatively inaccessible sites and poor-yield leading to lower sensitivity. According to the local clinical practice Guidelines for Tuberculosis in Adult Filipinos 2016 Update,[17] Xpert is recommended for CSF, lymph node tissue, and gastric lavage but has limited evidence for other sites. Cultures remain specific, but results take weeks limiting its use. AFB smear microscopy of organ-specific specimens was still the most utilized test by physicians in our institution. Stool and urinary specimens had the highest yield, with all samples sent being positive. Xpert and TB cultures were rarely sent, even for CSF samples.

Because of the challenges with bacteriologic confirmation, imaging and/ or histopathologic examination was widely utilized to detect extra-pulmonary involvement. Skoura et al described the imaging modalities of choice for extra-pulmonary TB.[18] For musculoskeletal TB, MRI is the preferred imaging modality with findings ranging from demineralization of endplates and vertebral collapse, to gibbus deformity. Similarly, in our study, this was requested among majority of the patients with a consideration of Pott's disease in addition to plain spinal radiographs. Contrast-enhanced MRI best detects central nervous system involvement. In the present study however, cranial CT scan was the only imaging modality performed to document CNS involvement. Abdominal CT scan was found to be sensitive for hepatobiliary tuberculosis while liver biopsy was more specific.[19] In this study, abdominal ultrasound was more popularly ordered. Colonoscopy was also utilized in our institution to document TB colitis.

Overall, in our institution, cost and availablity of different diagnostic tests (radiologic, bacteriologic, and histopathologic) appear to be important factors that determine the approach of physicians to diagnosing disseminated TB. Given these limitations, a high index of suspicion was probably the most important tool of our physicians. Despite the wide range of clinical presentation, we observed that most physicians in the PGH setting were able to consider tuberculosis at the onset. Hence, in resource-limited but high-TB burden areas like the Philippines, the value of clinical experience and knowledge truly play an important part in the diagnosis of disseminated TB.

Treatment

Our study showed that it took an average of 3 weeks from first consideration of disseminated TB to initiation of therapy. This is likely due to delays in work-up due to logistical constraints of the institution (ie, scheduling of MRI, delayed release of results) and financial constraints of the patients. It was also observed that initiation of anti-TB medications were mostly left to the Infectious Disease (ID) service. Hence despite strong evidence of TB when seen by other specialties (e.g. Orthopedics), treatment was delayed until the patient was seen and referred to ID. This has bearing on infection control, as delays in initiating treatment prolongs the period the patient remains contagious.

Most patients were first-time TB patients and were thus started on Category I treatment. Very few continued consult at PGH until completion of therapy (16% of patients), reflecting the role of the UP-PGH DOTS as a referring center. Among those who completed treatment in PGH, cure was documented mostly clinically by resolution of symptoms or of radiologic and histologic findings. Microbiologic cure was not well documented. Outcomes of those who continued treatment in their local facilities could not be obtained, underscoring the need to enhance tracking of these patients. From our data, it is hard to make conclusions on the lethality of disseminated TB.

As a referring center, UP-PGH DOTS refers patents with TB to their local TB DOTS facilities for continuity of care. However acceptance to these facilities was properly documented in only 29% of patients. Improvements in record-keeping is needed.

Limitations and future directions

Missing and incomplete records were the major limitations of our study. Enhanced record-keeping and documentation both by physicians and the UP-PGH DOTS Center is encouraged.

Our data are a stepping stone to better understand disseminated TB and how it is related to or differs from isolated pulmonary or extra-pulmonary TB. The emergence of disseminated TB allows us to reflect on how we currently monitor and manage single-site tuberculosis. Our data may be used to improve on local TB control programs on latent and active pulmonary TB.

Future studies on disseminated TB are required. Studies on risk factors for disseminated TB (ie,. HIV, malnutirtion, prior TB exposure) are needed as most physicians neglect this on intitial encounter. More studies are also needed on the sensitivity and specificity of different diagnostics for extra-pulmonary sites to arrive with stronger recommendations to guide physicians. Treatment outcomes and mortality of disseminated TB also need to be studied.

Conclusion

The Philippines is considered a high-burden country in terms of tuberculosis (TB) and TB remains to be a major cause of death. Disseminated TB is under-recognized and very little is known since it was last studied in 1997. We found that patients with disseminated TB are relatively young, and majority had no comorbid illness or immune disorder. They have long latency of symptoms prior to diagnosis, and usually presents with non-pulmonary symptoms despite high evidence of pulmonary involvement. Due to its varied presentation, a high index of suspicion is required to detect disseminated TB. A combination of microbiologic studies, imaging, and histopathologic examination with close correlation with clinical presentation is utilized in most cases to confirm a diagnosis. Majority of patients have never been treated, and are started on Category I treatment. Our data highlighted the need to improve record-keeping and to encourage treatment follow-up of patients with disseminated tuberculosis to ensure treatment compliance, completion, and documentation of cure.

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

All authors declared no conflict of interest.

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Appendix A

DATA COLLECTION FORM
Patient Number: _____
PGH Case Number: _____

General Information

1. Age (in yrs)		5. Date referred to TB DOTS (MM/DD/YY)	
2. Gender	Male Female	6. Date of first consult for TB (MM/DD/YY)	
3. Hometown	Luzon Visayas Mindanao Province:	7. Contact number of patient	
4. Referring physician	Department: Medicine Surgery Ortho OB Gyne ORL Ophtha Neurology Rehab Psychiatry Subspecialty:		

*indicate if N/A

Clinical Profile

Height	_____ m	Baseline laboratories at time of diagnosis	
Weight	_____ kg	Hgb(g/dL)	
BMI	_____ kg/m2	WBC (109/L)	
Comorbidities	Diabetes mellitus Malignancy, specify site: Connective tissue disease, specify type: Post-transplant, specify: Alcoholism Chronic kidney disease, specify stage: Chronic liver disease* Congestive heart failure, specify functional class: HIV/AIDS, CD4 count:	Platelet (109/L)	
		Albumin (g/dL)	
		AST (U/L)	
		ALT (U/L)	
		Creatinine (mg/dL)	
		Adjusted calcium (mmol/L)	
Medications	Immunosuppresants: No Yes, specify: *duration	Sodium (mmol/L)	
Others:	Recipient of isoniazid prophylaxis: YES NO		
	History of BCG vaccination: YES NO		

*documented CLD with laboratory/ clinical/ histopathologic confirmation
**indicate if N/A

Tuberculosis profile

Site	Bone marrow Muskuloskeletal, site: Hepatobiliary Intestinal Lymph node Lung, with effusion Lung, without effusion Genital Urinary CNS Peritoneum Pericardium Cutaneous Blood Others:		Confirmatory diagnostics	AFB smear: Specimen: Results:
				TB culture: Specimen: Results
				TB PCR Specimen: Results:
				Gene Xpert Specimen: Results:
				Histopathology Specimen: Histopath #: Results:
Presenting symptom			Additional Diagnostics	Xray
Associated symptoms	Fever Weight loss Night sweats Dyspnea Back/joint pains Changes in sensorium Seizures Abdominal distension GI bleeding Others:	Malaise Poor appetite Cough Myalgia Dysuria Headache Abdominal pain Diarrhea Nodes		CT scan MRI Ultrasound Others:
Duration of symptoms before consult (days)			Treatment started	No, reason:
Duration from diagnosis to starting treatment (days)				Yes, regimen: 2HRZE/ 4 HR 2 HRZES/ 1 HRZE/ 5 HRE Others:
Duration of treatment (months)				
Treatment outcome	Cured Completed Failure Relapse Death Lost to ff-up			

*indicate if N/A

Appendix B

Diagnostic findings in patients with disseminated TB

	Total No. of patients with involved site	AFB Smear		Radiologic		Histopathologic	
		No. of specimens examined	No. (% from samples sent*) Positive	No. of specimens examined	No. (%*) positive	No. of specimens tested	No. (%*) positive
Lung	59	58	23 (39)	52	44 (85)	-	-
Intestinal	22	14	14 (100)	-	-	5	4 (80)
Spinal (Pott's)	19	-	-	19	19	-	-
Pelvic/Genital	13	5	4 (80)	12	12	5	3 (60)
Hepatobiliary	9	1	1	9	9	2	2
Urinary	9	9	9	1	1	-	-
Psoas/retroperitoneal	6	2	2	4	4	-	-
Lymph node	5			2	2	2	2
Cutaneous	5	2	1 (50)	1	1	1	1
Joint	5	3	3	2	2	-	-
Peritoneum	3	1	1	3	3	-	-
Central nervous system	3	2	0 (0)	3	3	-	-
Esophageal/ Retropharyngeal	2	1	1	-	-	-	-
Pericardium	2	-	-	2	2	-	-

* those with no % specified have 100% positivity