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Disseminated Tuberculosis among Adult Patients Admitted to Hamad General Hospital, Qatar: A Five Year Hospital Based Study

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Abstract

Objectives: To describe the demographic, clinical features, diagnostic and procedure results, organ involvement and outcomes in patients with disseminated tuberculosis (TB).

Patients and methods: This retrospective observational study was conducted at Hamad general hospital in Qatar. It involved all patients 15 years of age or older who were admitted to Hamad general hospital with disseminated TB from January 1, 2006 to December 31, 2010.

Results: We enrolled 100 patients. There were 74 (74%) males and the mean age (±SD) of patients was 31.3±12.2. The most common presenting symptom was fever (95%). Fifteen (15%) patients had other underlying medical conditions; the most common being diabetes mellitus 7 (7%), while two patients had human immunodeficiency virus (HIV) infection. The tuberculin skin test was positive in 42 (42%) patients. Sputum and gastric lavage examination were performed in 84 (84%) and 9 (9%) patients respectively while bronchoscopy was performed on 32 (32%) cases.

Most patients 94 (94%) completed their treatment in Qatar whereas (3%) left the country before completion. The in-hospital mortality rate was 3% (3 patients). Systemic corticosteroids were prescribed for 36 (36%) cases and 15 patients had complications, the most being tuberculoma 9/23 (39.1%). Drug toxicity was noted in 17 (17%) patients, including hepatitis, optic neuritis and hyperurecemia. Only presence of underlying medical conditions was found to be an independent predictor of mortality.

Conclusions: Disseminated TB has a non-specific clinical picture, gives rise to high morbidity and mortality and therefore demands a high index of suspicion to promptly diagnosis and initiate timely treatment.

Keywords: Tuberculosis; Disseminated; Mliary shadow; Bone marrow; Bronchoscopy

Introduction

Disseminated TB is defined as having two or more noncontiguous sites resulting from hematogenous dissemination of *Mycobacterium tuberculosis*, which may occur during the course of primary tuberculosis, immediately after the post-primary period, or at a time for remote from the post-primary period as late generalized tuberculosis [1].

Now-a-days, the term miliary TB is also used to denote all forms of progressive, widely disseminated hematogenous tuberculosis even if the classical pathologic or radiologic findings are absent. Although disseminated tuberculosis is increasingly recognized to be an important cause of morbidity and mortality in developing countries, it has become more common in most developed countries due to the advent of HIV infection, chronic noninfectious diseases and immunosuppressive drugs and treatments [2]. Disseminated TB accounts for about 1-2% of all cases of tuberculosis and about 8% of all forms of extrapulmonary tuberculosis in immunocompetent individuals [3].

In Qatar, disseminated TB is accounting for 2.6% of all extrapulmonary tuberculosis [4]. The purpose of this study was to describe the demographic and clinical features, diagnostic test and procedure results, organ involvement and outcomes in patients with disseminated TB.

Methods and Patients

Design and setting

This retrospective observational study was conducted at Hamad general hospital, Qatar, which is a tertiary center that covers all specialties except for cardiology, hematology-oncology and obstetrics.

Patients and data source

This study involved all patients 15 years of age or older who were admitted to Hamad general hospital with disseminated TB from January 1, 2006 to December 31, 2010.

Patients were identified by three methods: hospital discharge records, microbiology laboratory records and the tuberculosis unit database. Then the records of these patients were reviewed retrospectively to retrieve data on patients' demographics, sign-symptoms, underlying medical conditions, investigations, procedures, therapy offered and outcomes.

The chest x-ray films were independently reviewed retrospectively by two radiologists in order to confirm the radiological findings.

Diagnostic Criteria

Inclusion criteria

Disseminated TB was diagnosed if the patient had any of the following conditions [2]. Isolation of *Mycobacterium tuberculosis* from bone marrow, liver biopsy specimen or ≥ 2 noncontiguous organs; Isolation of *M. tuberculosis* from one organ and histopathological demonstration of caseating granulomas from the bone marrow, liver biopsy specimen or another noncontiguous organ; Isolation of *M. tuberculosis* or histopathological identification of caseating granulomas from one organ and radiographic finding of miliary lung lesions.

Exclusion criteria

The followings were excluded from the study [2]. Tuberculosis patients with sole organ involvement were excluded from the study; A patient with isolated tuberculous hepatic abscess or tuberculoma rather than diffuse hepatic involvement was not included in the study; The dual sites involvement of cervical lymph node and lung was regarded as a loco-regional disease rather than disseminated disease; The dual site involvement of the lung and pleura and/or gastrointestinal tract was regarded as a loco-regional disease rather than disseminated disease.

Data analysis

Quantitative variables were expressed as mean ± standard deviation (SD) and range. Univariate logistic regression was performed to determine the probable predictors of mortality among patients with disseminated TB.

All potential risk factors significant at the 0.1 level in the univariate analysis were entered in the multiple logistic regression to identify the independent predictors of mortality at $P < 0.05$. Data analysis was performed with SPSS software (v 17.0; IBM Corp, Armonk, NY, USA).

Research Committee Approval

The study was approved by the research committee at Hamad Medical Corporation; a waiver of informed consent was obtained from the research committee.

Results

Demography

During the study period, 100 patients were diagnosed with disseminated TB. There were 74 (74%) males and 26 (26%) females. The mean age (±SD) of patients was 31.3±12.2 (range: 15-67 years). Table 1 describes the demographic data of our patients.

Variable	Number of patients%
Gender	
Male	74 (74)
Female	26 (26)
Age (Mean± SD)	31.3±12.2 (15-67 years)
Age group	
15-24	32 (32)
25-34	44 (44)
35-44	12 (12)
≥ 45	12 (12)
Nationality	
Nepalese	46 (50.0)
Indian	17 (9.3)
Ethiopian	5 (9.3)
Pakistani	4 (5.6)
Qatari	7 (3.7)
Filipino	4 (3.7)
Indonesian	7 (3.7)
Sri Lankan	1 (3.7)
Bangladeshi	6 (1.9)
Somali	1 (1.9)
Kenyan	1 (1.9)
Kyrgyzstani	1 (1.9)
History of contact	13 (13)

Table 1: Distribution of socio-demographic characteristics among disseminated tuberculosis patients presented at Hamad general hospital, Qatar during 2006 to 2010.

Clinical Features

The mean duration of symptoms prior to presentation was 41.3±39.1 days (range 4 - 180 days) and the most common presenting symptoms were fever 95 (95%), cough 80 (80%) and anorexia 73 (73%).

Of the 100 patients, 15 (15%) patients had underlying medical conditions, the most common being diabetes mellitus 7 (7%) and two patients had human immunodeficiency virus (HIV) infection.

Table 2 summarizes the clinical features on admission, underlying medical conditions and complications of 100 patients involved in this study. A history of contact with tuberculosis cases was present in 13% (13) of the patients, usually immediate family members 61.5% (8/13). No patient had a prior history of tuberculosis. The involved organs are shown in Table 3.

Variable	Number of patients%
Duration of symptoms	41.3±39.2 (5-180 days)
Clinical features	
Fever	95 (95)
Cough	80 (80)
Anorexia	73(73)
Night sweats	56 (56)
Weight loss	57 (57)
Hemoptysis	9 (9)
Dyspnea	21 (21)
Chest pain	17 (17)
Weakness	52 (52)
Mental changes	12 (12)
Headache	32 (32)
Abdominal pain	24 (24)
Diarrhea	12 (12)
Vomiting	27 (27)
Pleural effusion	10 (10)
Ascites	10 (10)
Hepatomegaly	23 (23)
Splenomegaly	23 (23)
Meningeal signs	16 (16)
Rales	33 (33)
Lymphadenopathy	15 (15)
Others	21 (21)
Underlying medical conditions	
Diabetes mellitus	7 (7)
Hypertension	4 (4)
Epilepsy	2 (2)
ESRD	2 (2)
Alcoholics	2 (2)
HIV	2 (2)
Chronic liver disease	2 (2)
Renal transplantation	2 (2)
Liver transplantation	1 (1)
Stroke	1 (1)
Complications	
Adrenal insufficiency	5 (5)
ARDS	8 (8)
Stroke	8 (8)
Tuberculoma	9 (9)
Pneumothorax	5 (5)
Hydrocephalus	5 (5)
Intestinal perforation	1 (1)
Seizures	1 (1)
Subdural abscess	1 (1)
Ophthalmoplegia	1 (1)
Hypercalcemia	1 (1)
Hospital stay	26.0±24.5 (4-150 days)

Table 2: Clinical characteristics of disseminated tuberculosis patients presented at Hamad general hospital, Qatar during 2006 to 2010.

Organ involved	Number of patients%
Lungs	
Miliary pattern	77 (77)
Non-miliary pattern	20(20)
Bones, joints and muscles	
Bones	12 (12)
Joints	2 (2)
muscles	2 (2)
Reticuloendothelial System	
Lymph nodes	17 (17)
Liver	2 (2)
Bone marrow	6 (6)
Serosal membranes	
Pleura	10 (10)
Peritoneum	10 (10)
Menings	23 (23)
GI system	
Intestine	3 (3)
stomach	1 (1)
Urogenital system	

Kidney	2 (2)
Epididymis	2 (2)
Testis	1 (1)
Prostate	1 (1)
Adrenal gland	2 (2)

Table 3: The frequency of involved organs in disseminated tuberculosis patients presented at Hamad general hospital, Qatar during 2006 to 2010.

Investigations and Procedures

Tuberculin skin tests were positive in 42% (42) of the cases and erythrocyte sedimentation rate ranged between 2 and 137 mm/h (mean 49.42±30.60 mm/h). Table 4 summarizes the main hematological findings in our patients. Sputum and gastric lavage examination was performed in 84% (84) and 9% (9) respectively. Bronchoscopy was performed on 32 (32%) cases. Tables 5 and 6 describe the cytological and microbiological characteristics of different fluids and specimens.

Variables	Mean ± SD (range)/ N (%)
WBCs (/µl)	7836.29 ± 4072.24 (5000-23600)
Leucopenia (<4000/ µl)	8 (8)
Leucocytosis (>11000/ µl)	17 (17)
Hemoglobin (g/dl)	11.49 ± 1.97 (6-16)
Platelets (/µl)	276240 ± 123170 (15000-635000)
Thrombocytopenia (<150,000/ µl)	14 (14)
ESR (mm/h)	49.42 ± 30.60 (2-137)

Table 4: Hematological findings for patients with disseminated tuberculosis presented at Hamad general hospital, Qatar during 2006 to 2010.

Treatment, Outcome and Complications

Treatment was initiated for all patients except for one, who died before the diagnosis had been made. Initially all except two patients received a combination of isoniazid, rifampicin, pyrazinamide and either ethambutol or streptomycin. The exceptions were two patients with chronic liver disease, which were treated with second line drugs. An additional patient with INH and rifampicin resistance was ultimately shifted to second line therapy. Most patients, 94 (94%), completed their treatment in Qatar, while 3 (3%) left the country before completion. In-hospital mortality was 3% (3), as shown in Table 7. Of the 94 patients who completed their therapy in Qatar, 49 (52.1) demonstrated a good clinical response to the six-month treatment as described in Table 7. Systemic corticosteroids were prescribed for 36 (36%) cases, including 23 (23%) meningitis patients, 8 (8%) with acute respiratory distress syndrome (ARDS) and 5 (5%) with adrenal insufficiency. Fifteen patients had complications, the most common being tuberculoma 9/23 (39.1%) as shown in Table 2. Drug toxicity was noted in 17 (17%) patients, including hepatitis, optic neuritis and hyperurecemia. Table 7 lists the side effect of antituberculous therapy.

In-hospital Mortality Predictors

Univariate analysis showed the following factors as probable predictors of in-hospital mortality: male sex, non-Qatari patients, altered mental status and presence of underlying medical conditions. Only the presence of underlying medical conditions (adjusted OR=0.07, 95% CI =0.007-0.92, P = 0.04) was found to be an independent predictor of mortality by multivariate logistic regression analysis.

Discussion

Demography

In this study we observed a significant increase in the number of patients with disseminated TB as compared with the previous study [5]. This may be explained by the fact that the population in Qatar has grown significantly in recent years, with laborers from TB endemic areas being the dominant group. Usage of advanced diagnostic facilities also may have contributed rise in cases. Most of our patients, 88 (80%), were less than 45 years old. The mean age of the population in this study (31.3±12.2 years) was younger than that mentioned in other reports, [6-10] but similar to that found in two hospital-based studies in Iran and Philippine [11,12].

Clinical features

The clinical presentation of disseminated TB is nonspecific and patients usually present with symptoms and signs referred to various organ systems ranging from anorexia, pyrexia of unknown origin to even multi-organ failure. Therefore the diagnosis of this disease is generally difficult and usually there is a delay in seeking medical help for more than one month by more than 50% of patients. This delay was noted here in addition to several other reports [2,5-12]. Fever was the most common presenting symptom in many studies [2-10] as well as in our series. Disseminated TB can involve many organs, with the lungs being the commonly involved [2-12]. The lungs were involved most frequently in our study, followed by meninges. Meningitis was found in 23 (23%) of our patients, which falls within the range of 10-30% mentioned in the literature [3,13,14]. Choroidal tubercles are pathognomonic of disseminated TB and offer a valuable clue to the diagnosis [14,15]. In our patients, there was no mention of the frequency of choroidal tubercles since funduscopic examinations were not routinely performed.

Underlying medical conditions

The relationship between underlying medical conditions such as an impaired immune response due to alcoholism, diabetes mellitus, end stage renal disease (ESRD) or HIV and tuberculosis, including disseminated TB, has been mentioned in many reports [3]. In the current report, 15% of the patients had underlying medical conditions,

the most common being diabetes mellitus 7/100 (7%) see Table 2, and there were no demonstrable associated medical conditions in 85% of the patients, which challenges our clinical suspicion to consider disseminated TB in the differential diagnosis, especially in the setting of the non-specific clinical features of this disease.

Investigations and procedures

Although abnormalities were present, basic hematologic and biochemical tests were not specific for the diagnosis of disseminated TB. Hypercalcemia has been described in 13.4% of the patients with disseminated TB, [2] in our study it was found only in 1/100 (1%) patient. In our series tuberculin skin tests were positive in 42% of the cases, which falls within the range of 20-70% mentioned in the literature [14]. Skin testing is frequently unreliable and of no help in excluding or confirming the disease. Miliary infiltrates (on chest radiograph or CT) were present in 77 (77%) of our patients, which falls within the range of 29–89% reported in different studies [2,3,5-12].

To confirm the diagnosis in patients with suspected disseminated TB, selection of appropriate tissue and body-fluid samples, which depends on the extent of organ-system involvement, is needed [6,14]. Detailed history, physical examination and appropriate imaging studies (chest and abdomen contrast-enhanced computed tomography (CT) and Magnetic resonance imaging (MRI)) may help in determining the best approach for such patients. Diagnostic modalities are useful in identifying miliary lesions at occult extrapulmonary sites. For example, an abdominal CT scan can detect intra-abdominal lymphadenopathy, cold abscesses and lesions in the liver, spleen, mesentery and peritoneum [3,14].

In patients with suspected disseminated TB with pulmonary involvement, sputum is commonly sent for study to confirm the disease. It must be subjected to smear and mycobacterial culture examination. The sensitivity of sputum acid-fast smear was 6-36%, [2,5,7,10] while the frequency of a positive sputum culture for M. tuberculosis was 27-97% [2-12]. In our study, sputum smear showed acid fast bacilli in 43% (36/84), and culture was positive in 91.6% (77/84) of the cases. If patient cannot give sputum, endotracheal secretions and gastric lavage can also be used to confirm the diagnosis. Fiberoptic bronchoscopy (FBS), bronchoalveolar lavage (BAL), bronchoscopic aspirate, brushings, washings, and transbronchial biopsy (TBB) are important diagnostic procedures in patients with suspected disseminated TB whose sputum specimens were negative for smear [14]. The combination of the various bronchoscopy samples increased the diagnostic yield to 46-92% [14,16]. In our study, FBS with BAL, bronchial wash and TBB was performed in 32 patients; the overall diagnostic yield of these procedures for disseminated TB was 78.2%, which falls within the above mentioned range.

As noted in the current series, the diagnostic yield of lymph node biopsy or FNA was high. Therefore, significant lymphadenopathy must be specially looked for, as it may often coexist. In agreement with many reports, [2-14] pleural fluid, ascitic fluid, cerebrospinal fluid (CSF), synovial fluid, urine, and tissue biopsy specimens had all been employed in our study to confirm the diagnosis of disseminated TB with inconsistent diagnostic yields.

When the above mentioned diagnostic workup fails, samples from systemic sites such as blood, bone marrow and liver should be obtained to support the diagnosis of disseminated TB [6]. Mycobacterial blood culture was found to be as sensitive as bone marrow culture and performing mycobacterial blood culture instead of bone marrow culture was recommended by some authors when disseminated TB was suspected [6]. In current study, none had been diagnosed on blood culture examination.

Bone marrow aspiration and biopsy have been found to be useful for diagnosis of disseminated TB if subjected to smear and mycobacterial culture and histopathology examination [6,14]. The combined tests increased the diagnostic yield between 50% and 93% [2,17]. In our study, the sensitivity of bone marrow studies for disseminated TB (smear: 7.7%, mycobacterial culture: 23.1%, histopathologic examination: 57.1%, combined: 85.7%), falls within this range. On the other hand, several reports showed a high sensitivity of liver biopsy to granulomas between 91% and 100% [17,18]. However, a serious and potentially life-threatening bleeding complication is estimated to occur in approximately 10% of cases. In our series, we found liver biopsy was sensitive to granulomas in 50% (2/100) of the cases and no complications had been reported.

Spacemen	AFB smear positive (%)	TB culture positive (%)
Sputum	36/84 (42.9)	77/84 (91.6)
Gastric lavage	1/9 (11.1)	6/9 (66.6)
BAL	8/32 (25)	22/32 (68.75)
BA wash	10/32 (31.25)	24/32 (75)
Endotracheal secretions	1/5 (20)	5/5 (100)
CSF	2/23 (8.70)	23/23 (100)
Ascites	0/11 (0)	9/11 (81.8)
Pleural fluid	0/7 (0)	5/7 (71.4)
Prostate aspirate	1/1 (100)	1/1 (100)
Muscle aspirate	1/2 (50)	2/2 (100)
Urine	1/2 (50)	2/2 (100)
Synovial fluid	1/2 (50)	2/2 (100)

Table 5: Results of mycobacterial smear and culture for different specimens from disseminated tuberculosis patients presented at Hamad general hospital, Qatar during 2006 to 2010.

Treatment, outcome and complications

Although there is no consensus regarding the optimum duration of treatment in patients with disseminated TB, [14] early initiation of therapy in cases of disseminated TB is associated with a significant improvement in outcomes [19]. In general, antituberculous therapy for disseminated TB is the same as pulmonary infection; however, longer duration of therapy may be appropriate for high organism burden, slow clinical response, immune suppression, CNS infection and in certain patients with bone and joint involvement, where a surgical approach is sometimes mandatory [20]. Adjunct corticosteroid treatment can be given in tuberculosis meningitis, pericardial tuberculosis, pleural tuberculosis and adrenal insufficiency [14]. The current guidelines for treatment of disseminated TB at Hamad medical corporation (HMC) include administration of the "four-drug regimen", which consists of two phases, rifampicin, isoniazid (INH), pyrazinamide and ethambutol/ streptomycin were given daily for the first two months and then treatment is continued with rifampicin and

isoniazid for a further four months. As noted in this study, 52.1% (49/94) of the patients who completed their therapy in Qatar showed a good clinical response to the six month treatment. The duration was extended to 9, 12, and 18 months in 19, 24, and 2 patients respectively. Consistent with many reports, [2,3,8] steroids were used mainly for treating patients with meningitis, in critically ill patients with ARDS and in adrenal insufficiency (Table 6).

Variable	Number of patients%
Treatment regimen	
Four drugs	97 (97)
Second line	3 (3)
Treatment duration	7.4±2.8 months
Mean±SD (range)	(1-18 months)
No treatment	1 (1)
< 6 months	5 (5)
6 months	49 (49)
9 months	19 (19)
12 months	24 (24)
18 months	2 (2)
Side effects	
Hepatitis	15 (15)
Hyperurecemia	1 (1)
Optic neuritis	1 (1)
Patients received steroids	36 (36)
INH resistance	5 (5)
Rifampicin resistance	1 (1)
Outcome	
Died	3 (3)
Cured	94 (94)
Left	3 (3)

Table 6: Treatment and outcome of patients with disseminated tuberculosis presented at Hamad general hospital, Qatar during 2006 to 2010.

In-hospital mortality predictors

Despite advances in the supportive care and therapy of patients with disseminated TB, mortality is still high, ranging from 25% to 30% [3]. For reasons unclear, the mortality rate in our study was much lower than expected at only 3%.

Many predictors of mortality associated with disseminated TB are mention in the literature, such as meningismus, increasing age, liver cirrhosis, leucopenia, leucocytosis, increasing age, presence of underlying disease, altered mental status and night sweats [3]. Only the presence of underlying disease was found to be independent predictor of mortality in our study (Table 7).

Biopsy	Caseating granuloma (%)	AFB smear positive (%)	TB culture positive (%)
Bone marrow	8/14 (57.1)	1/13 (7.7)	3/13 (23.1)
Transbronchial	14/23 (60.9)	4/6 (66.7)	4/6 (66.7)
Liver	1/2 (50)	0/1 (0)	0/1 (0)
Lymph node	5/5 (100)	2/2 (100)	2/2 (100)
Lymph node FNA	10/12 (83.4)	9/10 (90)	9/10 (90)
Pleural	6/6 (100)	2/2 (100)	2/2 (100)
Peritoneal	1/1 (100)	0/1 (0)	0/1 (0)
Gastric	1/1 (100)	ND	ND
Intestinal	3/5 (60)	2/2 (100)	2/2 (100)

Table 7: Histopathological and microbiological results for different biopsies from disseminated tuberculosis patients involved in this study during 2006 to 2010.

Study Limitations

This study was limited by virtue of being retrospective and based in a single hospital. However, the frequency of various clinical presentations and the diagnostic yield of differing sample types are still valid and should be taken into consideration when choosing methods of diagnosis and in improving one's general awareness of disseminated TB.

Conclusion

In conclusion, disseminated TB is an important health problem in Qatar associated with significant morbidity and mortality burden. The diagnosis is difficult due to its non-specific clinical picture and inability to detect easily miliary changes on a simple chest X-ray. Therefore, high index of suspicion is needed to make the diagnosis. Patients with immunosuppression (HIV patients, patients with organ transplantation and chronic liver diseases) and patients coming from endemic areas, who are most likely to have disseminated TB, should be targeted with more aggressive efforts to diagnose and treat this disease as early as possible.

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