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Extrapulmonary Tuberculosis: A retrospective review of 194 cases at a tertiary care hospital in Karachi, Pakistan

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Abstract

Objective: To describe the types and treatment outcomes of the extra-pulmonary tuberculosis (EPTB) cases in a tertiary care hospital in a high burden tuberculosis country.

Method: A retrospective case series study was conducted at Liaquat National Hospital (LNH), the largest private tertiary care hospital in Karachi, Pakistan. All cases diagnosed and treated as EPTB between November 2005 and February 2007 were included. Data was retrieved from medical records on demographics, clinical, laboratory, and outcome status.

Results: A total of 194 patients treated for EPTB were identified. Mean age of patients was 34 ± 16.4 years, and 75% of patients were female. Lymph nodes and spine were the most common sites involved (60%). The cure rate was 40.7%. There was no difference in cure rate of males and females (p=0.99).

Conclusion: EPTB is an important clinical problem in Pakistan. Due to lack of guidelines for diagnosis and duration of treatment in EPTB most physicians in Pakistan treat patients based on clinical symptoms and for prolonged duration of 12, to even as long as 24 months. The National TB Program, and chest and infectious disease societies must develop standardized guidelines for the diagnosis and treatment of EPTB.

Introduction

Mycobacterium tuberculosis has existed in human populations since ancient times; however it was in the seventeenth century that pathological and anatomical descriptions of tuberculosis (TB) disease began to appear.[1] When the World Health Organization (WHO) declared TB a global health emergency in 1992, it was prevalent in almost all countries of the world.[2] Despite the accelerated efforts to control the disease for decades, it remains the seventh leading cause of death globally.[3] WHO estimated a total of 9.27 million new cases worldwide in 2007 with 13.7 million prevalent cases and 1.3 million deaths with >90% in developing countries.[4] In the same year 0.5 million multidrug resistant tuberculosis (MDR-TB) cases were reported.[4] Interaction of HIV with TB, income inequality, and emergence of MDR-TB are the key drivers to re-emergence of tuberculosis in developing countries.[5-7] Asia is home to 55% of the global case burden followed by Africa with 31%.[4] Addressing the global threat of TB, the Millennium Development Goals (MDGs) include halving the prevalence of TB disease and deaths by 2015.[7,8]

In 2007 there were an estimated 181/100,000 new cases and 223/100,000 prevalent cases in Pakistan. Based on the incident cases in 2007 globally, WHO ranked Pakistan eighth in the list of high burden countries. Although pulmonary TB is the most common presentation of TB disease, it can involve any organ in the body. Extrapulmonary Tuberculosis (EPTB) is defined as the isolated occurrence of TB in any part of the body other than lungs. Mycobacteria may spread to any organ of the body through lymphatic or haematogenous dissemination and lie dormant for years at a particular site before causing disease. Manifestations may relate to the system involved, or simply as prolonged fever and non specific systemic symptoms.[9] Hence diagnosis may be elusive and is usually delayed.

The proportion of EPTB among all TB cases varies from country to country. The extrapulmonary manifestation of TB is prevalent in 10-34% of non-HIV cases while it occurs in 50-70% of patients co-infected with HIV.[10] In Pakistan, WHO estimates that 34,000 (15%) of newly reported cases in 2007 were extra-pulmonary.[11] EPTB reports in the country range from a quarter of all TB patients presenting to a hospital in Rawalpindi[12] to a third of TB patients visiting GP clinics in Karachi.[13] This study reviews the general spectrum of cases diagnosed with EPTB at a large private sector hospital in Karachi and presents their key demographics, dominant infection sites and the treatment outcomes.

Methods

A retrospective audit of 205 patients under treatment for extrapulmonary TB was conducted at the Department of Infectious Diseases at Liaquat National Hospital. Patients

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registered from November 2005 to February 2007 were included in the case series and their demographic, diagnostic, and clinical data were obtained from the departmental medical record system. Patients who were mobile and did not require hospitalization were treated and followed as outpatients. Those with intracranial, pericardial or musculoskeletal TB were hospitalized for the initial phase of the disease and continued to be followed in the outpatient department of the hospital.

Extrapulmonary TB was defined as patients with TB of organs other than lungs such as lymph nodes, abdomen, genitourinary system, musculoskeletal and meninges. An extrapulmonary TB case with multiple organ involvement was classified based on the site representing the most severe form of disease. As per WHO guidelines[9] a patient with both pulmonary and extrapulmonary tuberculosis was labelled as pulmonary and therefore excluded from the study. The case definition of MDR-TB included patients who had active tuberculosis with bacilli resistant to isoniazid (INH) and rifampicin (RIF).

Obtaining material for culture confirmation in extrapulmonary TB is often challenging because of a) smaller number of bacteria which produce poor yield on culture, and b) it is difficult to access organs such as retroperitoneal tissue, mediastinal glands and occasionally a non approachable window in the spine. Despite these disadvantages, every effort was made to obtain evidence-based criteria for diagnosis. Fine needle aspiration of neck, axillary glands and breast, and CT guided aspiration of spinal abscess were attempted and examined for histopathology, smears and culture. Microscopic description of granulomas with caseation and necrosis was acceptable provided other clinical criteria were met. In cases of abdominal TB, ultrasonographic or CT description of "thickened bowel loops" was acceptable. Exudative fluids with lymphocytic pleocytosis in synovial, peritoneal, pleural, pericardial and cerebrospinal fluids (CSF) were considered tuberculous unless proven otherwise. CT evidence of brain "tuberculoma" was considered sufficient evidence for initiating treatment. Culture was considered to be the gold standard for diagnosis. Culture yields were highest from pus or fluid taken from deep tissue from bones, joints, lymph glands and terminal ileum at laparotomy. Where these were not possible, the physician's justification of "strong clinical evidence", exclusion of other possible causes of the disease pathology, and satisfactory clinical response to treatment with anti-tuberculosis chemotherapy was considered to be acceptable for a diagnosis of extra-pulmonary tuberculosis. In all the cases of EPTB, chest radiographs were used to investigate the involvement of lung parenchyma.

Standard treatment of all cases included use of a four drug regimen: isoniazid, rifampicin, ethambutal and pyrazinamide for initial phase of 2 months, followed by 4-8 months of continuation phase with isoniazid and rifampicin. TB adenitis was treated for the shorter duration while TB of meninges, bones, joints, spine and abdomen were of longer duration. All doses were weight -based. Adjunctive steroids were used in cases of meningeal and pericardial TB for the initial 2-3 weeks. Drug susceptibility testing for the first line drugs was conducted for patients who did not respond to treatment and regimens were changed based on the susceptibility results or strong clinical suspicion of unresponsiveness. Treatment outcome was reported as either cured (culture negative in the last month of treatment), treatment completed (no culture results available), treatment failed, defaulted or died.

The protocol was approved by the Institutional review Board at Interactive Research and Development, Karachi. Data was double entered and analyzed using Stata (StataCorp LP, College Station, TX) and SPSS (SPSS Inc. Chicago, Illinois). A descriptive analysis was performed to explore the general characteristics while the chi-square test was used to compare the proportions.

Results

From November 2005 to February 2007, a total of 205 patients were treated for extra pulmonary TB. Ten cases were excluded due to incomplete or missing data while one case was removed due to associated pulmonary infection. Final analysis was performed on 194 cases. The demographics of patients and out come of treatment are described in Table-1. The overall male to female ratio was 1:3 (49/145). The mean age of patients was 34.1 ± 16.3 years, in males (35.3 ± 17.3 years) slightly older than females (33.4 ± 16.0 years). Of all the EPTB cases 25 (12.9%) had a known history of TB exposure, of which 10 (40%) had a known household contact. The common infection sites were lymph nodes and spine accounting for more than 60% of the EPTB cases followed by CNS, abdominal and musculoskeletal system (Table-2). Among lymph nodes, the cervical region was most commonly affected (70%), followed by axillary lymph nodes (20%). Thoracic region (49%) was the dominant site involved in spinal TB where as in abdominal TB, intestine (42%) was the most common. Fourteen patients (7.2%) with EPTB had multi-organ involvement. The cure rate for females did not differ from males (40.7% vs. 40.8%; p=0.99).

A total of 33 (17%) cases were classified as drug resistant

Table-1: General Characteristics & treatment outcomes of EPTB patients presenting to a private hospital in Karachi (Nov 2005-Feb 2007).

Characteristic	Number (n=194)			
	Total	Female	Male	Percent
Gender	194	145	49	100.0
Age (years)				
0-14	15	13	2	7.7
15-29	73	52	21	37.6
30-44	56	44	12	28.9
45-59	33	25	8	17.0
60-74	15	11	4	7.8
75-89	2	0	2	1.0
Past history of TB				
Yes	25	17	8	12.9
Diagnostic criteria				
Histopathology	91	68	23	46.9
Radiology	45	33	12	23.2
Microbiology	17	12	5	8.8
Clinical only	16	15	1	8.3
Compatible biochemistry*	15	11	4	7.7
Others	10	6	4	5.1
Outcome				
Cured	79	59	20	40.7
Treatment Complete	37	27	10	19.1
Treatment Failure	10	5	5	5.2
Defaulted	67	54	13	34.5
Died	1	0	1	0.5

*Elevated protein, low glucose, lymphocytic pleocytosis in CSF, ascitic, pleural, pericardial and synovial fluids.

Table-2: Distribution and diagnosis of EPTB cases by site of infection.

Site	Number, (%)	Diagnosis based on*					
	n=194	H	R	M	C	B	O
Lymph nodes	69 (35.6)	44	16	4	3	0	2
Spine	51 (26.3)	25	13	3	5	0	5
CNS	18 (9.3)	0	3	2	1	11	1
Abdomen	18 (9.3)	4	5	3	4	1	1
Musculoskeletal	18 (9.3)	8	6	0	1	2	1
Pericardial	3 (1.6)	2	0	0	1	0	0
Breast	3 (1.6)	2	0	1	0	0	0
Pleural	2 (1.0)	1	0	1	0	0	0
Eye	1 (0.5)	0	0	0	1	0	0
Skin	1 (0.5)	1	0	0	0	0	0
Miliary	1 (0.5)	0	0	1	0	0	0
Others	9 (4.6)	4	2	2	0	1	0

*H=Histopathology, R=Radiology, M=Microbiology, C=Clinical, B=Biochemical, O=Others.

cases (Table-3). Mean age for these patients was 36 years. The dominant site of infection in the drug resistant cases was lymph nodes (n=18; 54%) followed by musculoskeletal (n=5; 15%) and spine (n=4; 12%) cases. Four patients with MDR TB had history of household TB contact. Drug susceptibility tests showed resistance to both INH and RIF. Susceptibilities to second line drugs were not available in our laboratory.

Table-3: Treatment outcome of drug resistant TB cases.

Site	N	Diagnosis*		History of	Outcome‡			
		Clinical	Cultural	TB contact	C	T	F	D
Lymph nodes	18	7	3	3	4	6	1	7
Musculoskeletal	5	1	1	1	0	1	1	3
Spine	4	2	2	2	3	1	0	0
CNS	3	-	-	0	0	1	0	2
Other	3	-	1	1	0	0	1	2
Total	33	10	7	7	7	9	3	14

*missing data for few observations

‡ C=cured, T=treatment completed, F=treatment failure, D=defaulter

While none of the study cases tested reported to have Human Immunodeficiency Virus (HIV), other co-morbidities did exist such as chronic lung disease (n=3; 1.6%), diabetes mellitus (n=18; 9.3%), hepatitis (n=3; 1.6%) and hypertension (n=7; 3.6%). Only one death (0.51%) was observed during the study period, in a 20-year-old male with TB of the cervical lymph nodes.

Discussion

This is a case series of 194 EPTB patients over a 16 months period at a tertiary care hospital in Karachi. Our study shows higher number of female EPTB cases than males (145 vs. 49), a ratio consistent with other studies.[14,15] We did not study lifestyles, socioeconomic status or body mass indices of these women, however we postulate that possible reasons for female disease preponderance may be the social exclusion of younger women who are generally homebound and have poorer nutritional status than their male counterparts, social stigma associated with TB which discourages women from seeking early medical care,[16] and Vitamin D deficiency due to poor dietary intake as well as inadequate exposure to sunlight because of poor housing and the culture of wearing burqas. Several studies have shown Pakistani women to have low levels of serum 25-hydroxyvitamin D.[17-19] There is growing evidence of a strong association between TB and Vitamin D deficiency.[20,22] Macrophages infected with mycobacterium tuberculosis require 25-hydroxyvitamin D to initiate the immune response. When serum levels of 25-hydroxyvitamin D fall below 20 ng/ml, macrophages fail to trigger an immune response. This phenomenon probably explains the relation between TB and Vitamin D deficiency.[7] Vitamin D supplementation is now recommended for patients with TB.[23,24]

TB primarily begins in the lung parenchyma or hilar glands and spreads through lymphatics or blood to other

body organs. The microorganism may remain dormant for variable lengths of time and reactivate when conditions are optimum. Clinical manifestations depend upon the site and burden of infection and host response. Hence more than one organ may be infected simultaneously but not necessarily detected in all organs for lack of accurate testing. In our series we diagnosed multi-organ involvement in 14 cases (7.2%). The frequency of EPTB cases by site was highest in lymph nodes (35.6%), followed by spine (26.3%). Studies from Nepal,[14] and the Netherlands[15] have also reported high number of cases with lymph node involvement. The high incidence of spinal TB in our series could be due to bias because of frequent referrals from the active neurosurgery and invasive radiology departments within the hospital where the study was conducted. The hospital received suspected TB spine cases from across the city, as well as other parts of the Sindh and Balochistan provinces.

The diagnosis of EPTB was based upon several parameters referred to in the methodology. In all cases, clinical follow up and response to anti-tuberculous drugs were closely monitored. In at least one case of "granulomatous hepatitis" the diagnosis of sarcoidosis was confirmed a year later and the patient was then excluded from our series.

Cure rates strictly denote bacteriologic cure which is difficult to assess in EPTB. A total of 116 patients completed treatment while 10 failed to respond. Possible reasons for failure were missed diagnosis of drug resistance, non tuberculous mycobacteria, and late diagnosis of patients with TB meningitis or pericarditis who suffered complications. A close relationship between patient and physician generally ensures continuity of care and good adherence to treatment. This practice was adhered to in principle at the study center, visits were regular and adverse events were monitored. Despite this a default rate of 34.5% (67 patients), considered high, was mainly due to long distance travel. Many patients had to travel from remote and difficult to access places in interior Sindh and Baluchistan provinces, or returned to care of physicians in their locality after initial consultations at the study center. Pakistan is still categorized as 'concentrated epidemic country with HIV prevalence among the general population currently less than 1%.[25] Therefore it was not considered cost effective to test for HIV antibodies on all TB patients.

EPTB is an important clinical problem in Pakistan. Most physicians in the country treat patients with EPTB based on clinical symptoms. There are no established national guidelines for the duration of treatment for EPTB. WHO recommends the same duration of severe EPTB as for Diagnostic Category 1 pulmonary TB. For TB meningitis a 6 month regimen with rifampicin throughout was shown to be as good as 8-12 month regimen.[9] Adjunctive steroids are recommended for initial treatment against meningeal and pericardial TB. They do, however, concede that there is paucity of controlled studies and that there is a need for studying this issue.[9] In actual practice most physicians tend to prescribe longer courses empirically.

A comprehensive research plan is required to estimate the disease burden country-wide. Women of child bearing age seem to be the most vulnerable for EPTB. This group should be targeted for further study to find the cause/s and intervention for disease prevention. Health care providers must remain cognizant of emerging issues such as increasing drug resistance and HIV prevalence in the country. Furthermore, recommendations should be made to maximize attempts to obtain tissue for histopathology and culture with drug sensitivity testing which is particularly important with the rising trend of drug resistance. Empiricism must be avoided unless one has no other option but to treat with antituberculous medication. In every case, close observation for response or otherwise is the cornerstone of good management. Finally, since there seems to be no consensus on length of treatment of EPTB in various sites, it is recommended to conduct large scale studies to determine effective duration of treatment of EPTB.

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