



EXTRA-PULMONARY TUBERCULOSIS AT TERTIARY HEALTH CARE CENTER: A REVIEW

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Abstract-

Introduction- Tuberculosis (TB) continues to be a major global health problem. Extra-pulmonary TB (EPTB) manifests with protean symptoms and establishing a diagnosis is more difficult than pulmonary TB (PTB).

Objective- To describe the types and treatment outcomes of Extra-pulmonary TB (EPTB) cases in Tertiary care teaching Hospital, Ahmedabad in a high burden tuberculosis country.

Material and Methods- A retrospective study was conducted at one of the largest government tertiary care teaching hospital in Ahmedabad, India. All cases diagnosed and treated as EPTB from January 2011 to December 2012 were included. Data was retrieved from medical records on demographics, clinical, laboratory and treatment outcome status.

Results- A total 204 patients treated for EPTB were identified. Out of total 204 patients, 134 (65.69%) were females and 70 (34.31%) were males. Extra-pulmonary TB is more common in age group of 20-39 years. The common infection sites were lymph nodes and spine accounting for more than 60% of the EPTB cases. The cure rate was 41.2%. There was no difference in cure rate of males and females.

Conclusion- EPTB is an important clinical problem in India. Due to lack of guidelines for diagnosis and duration of treatment in EPTB most physicians in India treat patients based on clinical symptoms and for prolonged duration of 12 months, 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.

Keywords- Extra Pulmonary Tuberculosis (EPTB), Pulmonary Tuberculosis, Mycobacterium Tuberculosis, Human Immunodeficiency Virus (HIV)

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Introduction

Tuberculosis, MTB, or TB is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* [1]. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air [2]. Most infections are asymptomatic and latent, but about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected.

Tuberculosis (TB) is an ancient killer disease that can heavily affect both HIV positive and HIV negative individuals. It remains a major challenge worldwide both in terms of disease burden and resistance to conventional antibiotic therapy [3]. When the World Health Organization (WHO) declared TB a global health emergency in 1992, it was prevalent in almost all countries of the world [4].

Despite the accelerated efforts to control the disease for decades, it remains the seventh leading cause of death globally [5].

The classic symptoms of active TB infection are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss (the latter giving rise to the formerly prevalent term "consumption"). Infection of other organs causes a wide range of symptoms. Diagnosis of active TB relies on radiology (commonly chest X-rays), as well as microscopic examination and microbiological culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) and/or blood tests. Treatment is difficult and requires administration of multiple antibiotics over a long period of time. Social contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in multiple drug-resistant tuberculosis (MDR-TB) infections. Prevention relies on screening programs and vaccination with the bacillus Calmette-Guérin vaccine.

In 2007, there were an estimated 13.7 million chronic active cases

globally [6]. while in 2010, there were an estimated 8.8 million new cases and 1.5 million associated deaths, mostly occurring in developing countries [7]. The absolute number of tuberculosis cases has been decreasing since 2006, and new cases have decreased since 2002 [7]. The distribution of tuberculosis is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5-10% of the United States population tests positive [7]. More people in the developing world contract tuberculosis because of compromised immunity, largely due to high rates of HIV infection and the corresponding development of AIDS [8]. Extrapulmonary tuberculosis has become chronic and presents several complications for the patient. Some illnesses such as meningitis and peritonitis may be dangerous for the patient life from the beginning. It requires diagnosis and urgent treatment. In the past, node, tonsillar, bone and gut tuberculosis was caused by consumption of unpasteurized milk, infected by a virus similar to Koch bacillus. Today, however, by milk pasteurization, this risk has decreased considerably.

About 5-10% of those without HIV, infected with tuberculosis, develop active disease during their lifetimes [9]. In contrast, 30% of those co-infected with HIV develop active disease [9]. Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis) [10]. Extrapulmonary TB occurs when tuberculosis develops outside of the lungs. Extrapulmonary TB may coexist with pulmonary TB as well [10]. General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue [9], and significant finger clubbing may also occur [9].

The clinical manifestations of TB are of two types: Pulmonary and Extrapulmonary forms of TB (EPTB), the former being the commonest. In EPTB highly vascular areas such as lymph nodes, meninges, kidney, spine and growing ends of the bones are commonly affected. The other sites are pleura, pericardium, peritoneum, liver, gastro-intestinal tract, genito-urinary tract and skin. The definition of EPTB disease under the RNTCP follows the international classification [11]. Diagnosis of EPTB is based on one culture-positive specimen from the extrapulmonary site; or histological evidence; or strong clinical evidence consistent with active EPTB disease followed by a medical officer's decision to treat with a full course of anti-TB therapy. Patients suspected of having EPTB should also have their sputum examined for AFB if they have chest symptoms, irrespective of the duration of these symptoms. A patient diagnosed with both pulmonary and EPTB is classified as a case of pulmonary TB. The problem of EPTB is still high, both in developing and developed countries. In India, EPTB forms 10 to 15 percent of all types of TB, in comparison to 25 percent in France and 50 percent in Canada, partly due to the dual infection of TB with human immunodeficiency virus (HIV) [12,13]. Since 1987, EPTB has been accepted as an AIDS defining disease [14]. Lymph node TB (LNTB) is the commonest form of EPTB. Most studies in peripheral LNTB have described a female preponderance, while pulmonary TB is more common in adult males [15]. In the era before the HIV pandemic, and in studies involving immunocompetent adults, it was observed that EPTB constituted about 15 to 20 percent of all cases of TB in general practice. HIV infected persons are at markedly increased risk for primary or reactivation TB and for second episodes of TB from exogenous re-infection. In some settings, EPTB can account for up to 53 to 62 percent of cases of TB in HIV-positive individuals [16-19].

Pulmonary

If a tuberculosis infection does become active, it most commonly involves the lungs (in about 90% of cases) [20]. Symptoms may include chest pain and a prolonged cough producing sputum. About 25% of people may not have any symptoms (i.e. they remain "asymptomatic"). Occasionally, people may cough up blood in small amounts, and in very rare cases, the infection may erode into the pulmonary artery, resulting in massive bleeding (Rasmussen's aneurysm). Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs. The upper lung lobes are more frequently affected by tuberculosis than the lower ones. The reason for this difference is not entirely clear. It may be due either to better air flow or to poor lymph drainage within the upper lungs.

Extrapulmonary

In 15-20% of active cases, the infection spreads outside the respiratory organs, causing other kinds of TB [21]. These are collectively denoted as "extrapulmonary tuberculosis" [22]. Extrapulmonary TB occurs more commonly in immunosuppressed persons and young children. In those with HIV, this occurs in more than 50% of cases [22]. Notable extrapulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (in Pott's disease of the spine), among others. When it spreads to the bones, it is also known as "osseous tuberculosis" [23] a form of osteomyelitis. Sometimes, bursting of a tubercular abscess through skin results in tuberculous ulcer [24]. An ulcer originating from nearby infected lymph nodes is painless, slowly enlarging and has an appearance of "wash leather" [25]. A potentially more serious, widespread form of TB is called "disseminated" TB, commonly known as miliary tuberculosis. Miliary TB makes up about 10% of extrapulmonary cases [26].

Extrapulmonary tuberculosis affects people with weak immune system, diabetes, HIV, or malnourished people, very young children or elderly, those undergoing prolonged treatment with chemotherapy or cortisone. Among the most common forms of extrapulmonary tuberculosis are node tuberculosis, osteo-articular, renal and skin tuberculosis. Meningitis may accompany pulmonary tuberculosis or be an independent disease. Commonly it occurs in children between one and five years and affects the elderly people too.

It is manifested by fever, headache, nausea, dizziness, subsequent neurological symptoms and coma. Tuberculous meningitis may be confused with meningitis caused by other microbes and is diagnosed by isolation of Koch bacillus in the cerebrospinal fluid. Node tuberculosis involves in particular, the nodes in the neck, which increase in volume, become slightly painful and untreated in time, can cause skin ulcers and fistulas. Injuries caused by node chronic tuberculosis require surgery and leave scarring.

WHO estimates a total of 8.7 million new cases of tuberculosis (13% co-infected with HIV) worldwide in 2011 and 1.4 million people died from TB [27]. Globally almost 60,000 cases of MDR-TB were notified to WHO in 2011 which represented 19% (only one in five) of the estimated 3,10,000 cases of MDR-TB [27]. Interaction of HIV with TB, income inequality, and emergence of MDR-TB are the key drivers to re-emergence of tuberculosis in developing countries [28-30]. Geographically, burden of TB is highest in Asia and Africa. Asia is home to 59% of global case burden followed by Africa with

26%. India and China together account for almost 40% of world's TB cases [27].

In 2011 there were an estimated 181/100,000 new cases and 249/100,000 prevalent cases in India [27]. 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 [31]. Hence diagnosis may be elusive and is usually delayed. Extrapulmonary tuberculosis has a broad spectrum of clinical manifestations that may be referable to almost any organ system and should be considered in the differential diagnosis of bone, joint, genitourinary tract and central nervous system (CNS) disease [32]. This study reviews the general spectrum of cases diagnosed with EPTB at a tertiary care teaching hospital, Ahmedabad and presents their key demographic and epidemiological pattern, dominant infection sites and the treatment outcomes.

Material and Methods

A retrospective study of 204 patients under treatment for extra-pulmonary TB was conducted at Tertiary care Teaching Hospital, Ahmadabad, Gujarat. Patients registered from January 2011 to December 2012 were included in the case study 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.

Extra-pulmonary TB was defined as patients with TB of organs other than lungs such as lymph nodes, abdomen, genitourinary system, musculoskeletal and meninges. An extra-pulmonary TB case with multiple organ involvement was classified based on the site representing the most severe form of disease. As per WHO guidelines [31] a patient with both pulmonary and extra-pulmonary tuberculosis was labeled as pulmonary and therefore excluded from the study. Multidrug resistant tuberculosis (MDR-TB) was defined as resistance to at least 1 and/or 2 important drugs, isoniazid (INH) and/or rifampicin (RIF). Defaulter was defined, in accordance with the World Health Organization, as a patient who did not collect medication for 2 months or more any time after registration.

Result and Observations

From January 2011 to December 2012, a total of 204 patients were treated for extra pulmonary TB. The demographics of patients and outcome of treatment are described in [Table-1]. Out of total 204 patients, 134 (65.69%) were females and 70 (34.31%) were males. [Chart-1] Extrapulmonary TB is more common in age group of 20-39 years. [Chart-2] Of all the EPTB cases 28 (13.73%) had a known history of TB exposure [Chart-3].

Out of total 204 patients, 48.04% patients were diagnosed by Histopathology, followed by Radiology (23.53%) and Microbiology (8.83%) [Chart-4].

Out of total 204 patients, 84 (41.18%) patients were completely cured from TB, 39 (19.12%) patients have completed treatment but not cured completely. While treatment failure occurs in 10 (4.90%)

patients and 70 (34.31%) were defaulter. Only one death (0.50%) was observed during the study period, in a 30 year old male with TB of the cervical lymph nodes [Chart-5].

Table 1- General Characteristics & Treatment outcome Of EPTB patients presenting to a Tertiary Care Teaching Hospital in Ahmedabad (January 2011 To December 2012)

Characteristic	Number (n=204)			Percent
	Male	Female	Total	
Gender	70 (34.31%)	134 (65.69%)	204	100%
Age (Years)				
0-14	3	13	16	7.84%
15-19	2	10	12	5.88%
20-29	18	32	50	24.52%
30-39	14	40	54	16.47%
40-49	9	28	37	18.14%
50-59	6	12	18	8.82%
60-69	4	10	14	6.86%
70-79	2	0	2	0.98%
>80	1	0	1	0.49%
Past History of TB				
Present	9	19	28	13.73%
Absent	61	115	176	86.27%
Diagnostic Criteria				
Histopathology	26	72	98	48.04%
Radiology	13	35	48	23.53%
Microbiology	5	13	18	8.83%
Clinical Only	2	14	16	7.84%
Compatible Biochemistry*	4	10	14	6.86%
Others	4	6	10	4.90%
Treatment Outcome				
Cured	22	62	84	41.18%
Treatment Completed	11	28	39	19.12%
Treatment Failure	5	5	10	4.90%
Defaulter	16	54	70	34.31%
Died	1	0	1	0.50%

**Elevated Protein, Low Glucose and Lymphocytic Pleocytosis in CSF, ascitic, pleural, pericardial and synovial fluids.*

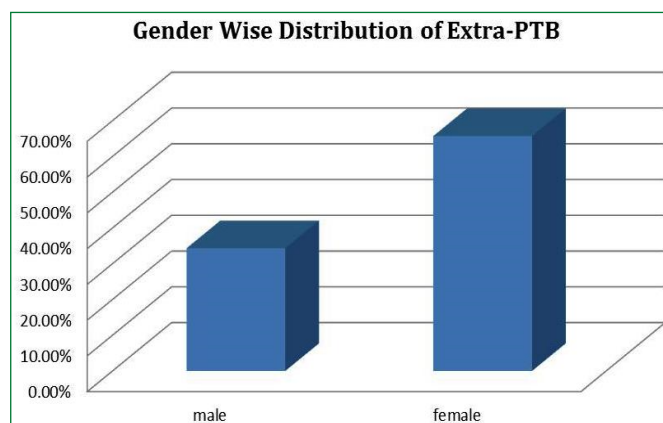


Chart 1- Gender wise Distribution of Extrapulmonary Tuberculosis

The common infection sites were lymph nodes and spine accounting for more than 60% of the EPTB cases followed by abdominal, CNS, pleural and musculoskeletal system [Table-2] [Chart-6]. Among lymph nodes, Cervical region was most commonly affected (70%), followed by supraclavicular and axillary lymph nodes. [Chart -7] Thoracic region (49%) was the dominant site involved in spinal TB where as in abdominal TB, intestine (40%) was the most common. Sixteen patients (7.84%) with EPTB had multi-organ involvement.

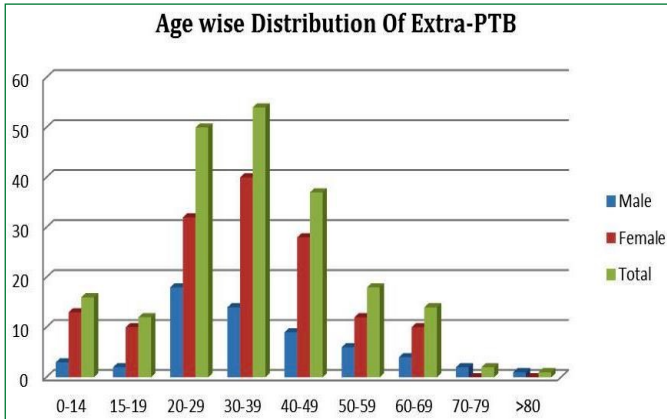


Chart 2- Age wise Distribution of Extrapulmonary Tuberculosis

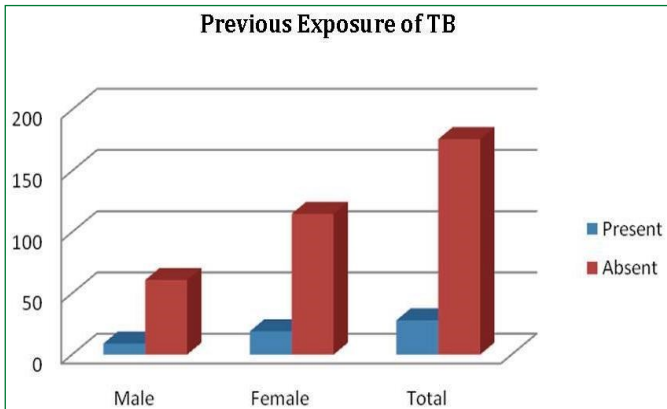


Chart 3- Previous Exposure of TB

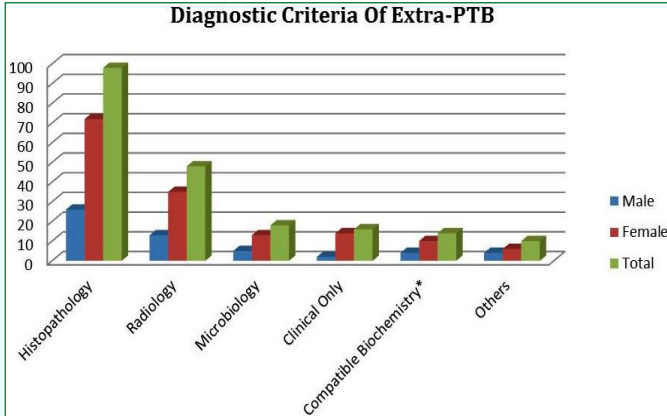


Chart 4- Diagnostic Criteria of Extrapulmonary Tuberculosis

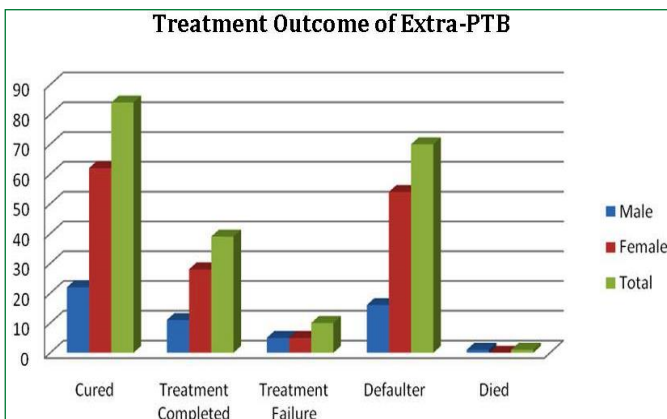


Chart 5- Treatment Outcome of Extrapulmonary Tuberculosis

Table 2- Distribution and Diagnosis of EPTB cases by site of Infection

Site	Diagnosis based on						Total, (%) n=204
	H	R	M	C	B	Others	
Lymphnode	51	20	7	5	0	2	85 (41.67%)
Cervical	40	14	4	3	0	0	61 (30%)
Supraclavicular	5	2	2	1	0	0	10 (4.90%)
Axillary/Mediastinal	2	1	1	1	0	0	5 (2.45%)
Mixed	4	3	0	0	0	2	9 (4.41%)
Spine	15	19	1	4	0	3	42 (20.60%)
Abdominal	4	6	2	2	1	1	16 (7.84%)
CNS	1	3	2	1	7	1	15 (7.35%)
Pleural	4	8	2	0	0	0	14 (6.86%)
Musculoskeletal	5	2	0	1	1	1	10 (4.90%)
Pericardial	3	0	2	0	0	0	5 (2.45%)
Breast	3	0	1	0	0	0	4 (1.96%)
Eye	0	0	0	1	0	0	1 (0.49%)
Skin	1	0	0	0	0	0	1 (0.49%)
Miliary	0	0	1	0	0	0	1 (0.49%)
Others	5	2	2	0	1	0	10 (4.90%)
Total	92	60	20	14	10	8	204 (100%)

H-Histopathology, R-Radiology, M-Microbiology, C-Clinical, B-Biochemistry

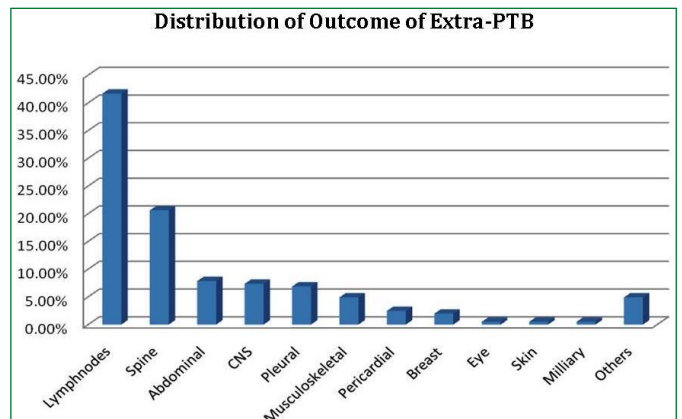


Chart 6- Distribution of Extra-PTB

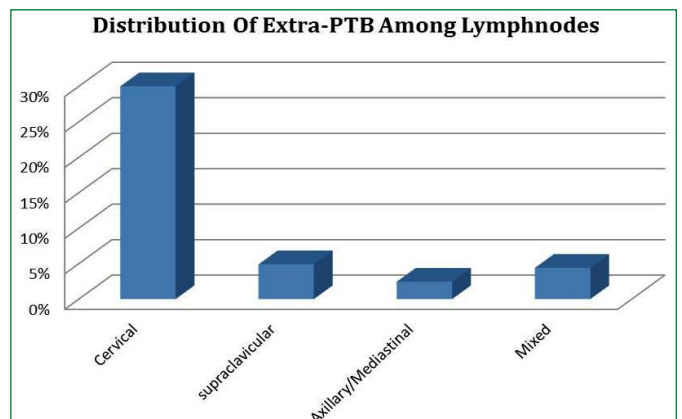


Chart 7- Distribution of Extrapulmonary Tuberculosis Among Lymphnodes

A total of 35(17%) cases were classified as drug resistant cases [Table-3]. Dominant site of infection in the drug resistant cases was lymph nodes (n=19; 54%) followed by musculoskeletal (n=5; 14%) and spine (n=5; 14%) [Chart-8].

Table 3- Treatment Outcome of Drug Resistant TB cases.

Site	Outcome				Total
	Cured	Treatment complete	Treatment Failure	Defaulter	
Lymphnode	4	7	1	7	19
Musculoskeletal	0	1	1	3	5
Spine	3	1	0	1	5
CNS	0	1	0	2	3
Others	0	0	1	2	3
Total	7	10	3	15	35

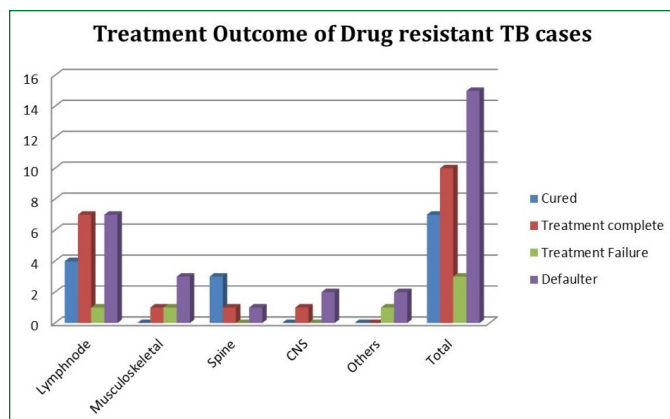


Chart 8- Treatment Outcome of Drug resistant TB Cases

Discussion

This is a case series of 204 EPTB patients over a 24 months period at a tertiary care teaching hospital in Ahmedabad. Our study shows higher number of female EPTB cases than males (134 vs. 70), which is consistent with other studies [33,34]. 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, [35] and Vitamin D deficiency due to poor dietary intake as well as inadequate exposure to sunlight. There is growing evidence of a strong association between TB and Vitamin D deficiency [36,37]. 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 [30]. Vitamin D supplementation is now recommended for patients with TB [38,39].

Over the last 2 decades, the incidence of extra-pulmonary tuberculosis in developed countries has remained relatively constant, despite a progressive fall in the number of reported cases of pulmonary tuberculosis [40-42]. Tuberculosis is still a major public health problem in India. 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 16 cases (7.84%). The frequency of EPTB cases by site was highest in lymph nodes (41.67%), followed by spine (20.6%). Studies

from Nepal [33], and the Netherlands [34] have also reported high number of cases with lymph node involvement. Moreover, extra-pulmonary tuberculosis rapidly progresses by nature, and is potentially fatal but usually treatable condition. Therefore, diagnostic procedures should seek earlier detection in any suspected cases, before final diagnosis.

Cure rates strictly denote bacteriologic cure which is difficult to assess in EPTB. A total of 123 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 34.31% (70 patients), considered high, was mainly due to long distance travel, poor knowledge about the disease, its treatment and cure rate. Many patients had to travel from remote and difficult to access places in interior India or returned to care of physicians in their locality after initial consultations at the study center.

EPTB is an important clinical problem in India. 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 [31]. 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 [31]. In actual practice most physicians tend to prescribe longer courses empirically.

Conclusion

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 anti-tuberculous 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. Due to lack of guidelines for diagnosis and duration of treatment in EPTB most physicians in India treat patients based on clinical symptoms and for prolonged duration of 12 months, 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.

References

- [1] Kumar V., Abbas A.K., Fausto N., Mitchell R.N. (2007) *Robbins Basic Pathology*, 8th ed., Saunders Elsevier, 516-522.

- [2] Konstantinos A. (2010) *Australian Prescriber*, 33(1), 12-18.
- [3] Eltringham I.J., Drobniewski F. (1998) *Br. Med. Bull.*, 54, 569-78.
- [4] World Health Organization (1988) *Highlights of Activities from 1989 to 1998*, *World Health Forum*, 9, 441-56.
- [5] World Health Organization (2004) *The Global Burden of Disease: 2004 Update*, WHO, Geneva, Switzerland.
- [6] World Health Organization (2009) *Epidemiology*, 6-33.
- [7] World Health Organization (2011) *The Sixteenth Global Report on Tuberculosis*.
- [8] Lawn S.D., Zumla A.I. (2011) *Lancet*, 378(9785), 57-72.
- [9] Gibson P.G., Abramson M. (2005) *Evidence-based Respiratory Medicine*, 1st ed., Oxford, 321.
- [10] Gerald L. Mandell, John E. Bennett, Raphael Dolin (2010) *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, 7th ed., Churchill Livingstone/Elsevier Philadelphia, PA, 250.
- [11] World Health Organization (2003) *Guidelines for National Programmes*, 3rd ed., Geneva, Switzerland, 313.
- [12] Sudre P., Hirschel B.J., Gatell J.M., Schwander S., Vella S., Katlama C., Ledergerber B., d'Arminio Monforte A., Goebel F.D., Pehrson P.O., Pedersen C., Lundgren J.D. (1996) *Tuber. Lung. Dis.*, 77(4), 322-8.
- [13] Stelianides S., Belmatoug N., Fantin B. (1997) *Rev. Mal. Respir.*, 14(5), S72-87.
- [14] Pitchenik A.E., Cole C., Russell B.W., Fischl M.A., Spira T.J., Snider D.E. Jr. (1984) *Ann. Intern. Med.*, 101(5), 641-5.
- [15] Balasubramanian R., Ramachandran R. (2000) *Indian Journal of Pediatrics*, 67, S34-S40.
- [16] Fanning A. (1999) *Canadian Medical Association Journal*, 160, 1597-603.
- [17] Sharma S.K., Mohan A. (2004) *Indian J. Med. Res.*, 120, 316-53.
- [18] Mohan A., Sharma S.K. (2001) *Tuberculosis*. Jaypee Brothers Medical Publishers, New Delhi, 14-29.
- [19] Corbett E.L., Watt C.J., Walker N., Maher D., Williams B.G., Raviglione M.C., Dye C. (2003) *Arch. Intern. Med.*, 163, 1009-21.
- [20] Behera D. (2010) *Textbook of Pulmonary Medicine*, 2nd ed., New Delhi, Jaypee Brothers Medical Pub., 457.
- [21] Jindal S.K. (2011) *Textbook of Pulmonary and Critical Care Medicine*, New Delhi, Jaypee Brothers Medical Publishers, 549.
- [22] Golden M.P., Vikram H.R. (2005) *American Family Physician*, 72(9), 1761-8.
- [23] Vimlesh Seth, Kabra S.K. (2006) *Essentials of Tuberculosis in Children*, 3rd ed., Jaypee Bros. Medical Publishers, New Delhi, 249.
- [24] Alexis Thomson, Carlos Pestana, Alexander Miles (2008) *Manual of Surgery*, Kaplan Publishing, 75.
- [25] Burkitt H. George (2007) *Diagnosis & Management*, 4th ed., 34.
- [26] Thomas M. Habermann, Amit K. Ghosh (2008) *Mayo Clinic Internal Medicine: Concise Textbook*, Mayo Clinic Scientific Press, Rochester, 789.
- [27] World Health Organization (2012) *Global Tuberculosis Report*.
- [28] Ilgazli A., Boyaci H., Basyigit I., Yildiz F. (2004) *Arch. Med. Res.*, 35, 435-41.
- [29] Yang Z., Kong Y., Wilson F., Foxman B., Fowler A.H., Marrs C.F., Cave M.D., Bates J.H. (2004) *Clin. Infect. Dis.*, 38(2), 199-205.
- [30] Broekmans J., Caines K., Paluzzi J.E. (2005) *Investing in Strategies to Reverse the Global Incidence of TB*, UN Millennium Project, United Nations Development Programme, London.
- [31] World Health Organization (2003) *Treatment of Tuberculosis: Guidelines for National Programmes*, WHO, Geneva, Switzerland.
- [32] Alvarez S., McCabe W.R. (1984) *Medicine (Baltimore)*, 63, 25-55.
- [33] Sreeramareddy C.T., Panduru K.V., Verma S.C., Joshi H.S., Bates M.N. (2008) *BMC Infect. Dis.*, 8, 8.
- [34] Lowieke A.M., te Beek, Marieke J. van der Werf, Clemens Richter and Martien W. Borgdorff (2006) *Emerging Infectious Diseases*, 12(9), 1375-82.
- [35] Begum V., de Colombani P., Das Gupta S., Salim A.H., Hussain H., Pietroni M., Rahman S., Pahan D., Borgdorff M.W. (2001) *Int. J. Tuberc. Lung Dis.*, 5, 604-10.
- [36] Davies P.D. (1985) *Tubercle*, 66, 301-6.
- [37] Wilkinson R.J., Llewellyn M., Toossi Z., Patel P., Pasvol G., Lalvani A., Wright D., Latif M., Davidson R.N. (2000) *Lancet*, 355, 618-21.
- [38] Martineau A.R., Honecker F.U., Wilkinson R.J., Griffiths C.J. (2007) *J. Steroid Biochem. Mol. Biol.*, 103, 793-8.
- [39] Nursyam E.W., Amin Z., Rumende C.M. (2006) *Acta Med. Indones*, 38, 3-5.
- [40] Farer L.S., Lowell A.M., Meador M.P. (1979) *Am. J. Epidemiol.*, 109, 205-17.
- [41] Dwyer D.E., MacLeod C., Collignon P.J., Sorrell T.C. (1987) *Australian & New Zealand Journal of Medicine*, 17, 507-11.
- [42] Rieder H.L., Snider D.E., Cauthen G.M. (1990) *Am. Rev. Respir. Dis.*, 141, 347-51.