Original article:

A retrospective study of drug resistant osteoarticular tuberculosis

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Abstract:

Introduction: Osteoarticuar tuberculosis comprises 1-4.3% of all tuberculosis cases and 10-15% of all extra pulmonary tuberculosis cases.The diagnosis of osteoarticular tuberculosis is mainly clinico-radiological and presents a greater diagnostic challenge due to less liberation of bacilli.Drug resistant form of osteoarticular tuberculosis has very rare prevalence and less commonly studied. This study presents a series of drug resistant osteoarticular TB cases, their clinic-radiological as well as drug resistence profile.

Material methods: This was a retrospective study in patients attending outpatient/in patient department at P. D. Hinduja National Hospital Mumbai between August 2005-2014. Total 25 patients were included.Data retrieval system of the institute was used to retrieve the demographic and clinical data of the patients diagnosed to have tuberculosis. All patients were subjected to telephonic interview including answers to a set of questionnaire. Collected data was analyzed statistically.

Results: In our study the average age of patients having drug resistant osteoarticular tuberculosis was 24.92 years. Drug resistant tuberculosis of spine was seen in 21.62% cases, calcaneum osteomyelitis in 10.81% cases and SI joint, foot, tibia, ankle joint were involved in 8.11% cases each.total 37 different sites of osteoarticular system involved and multifocal tuberculosis (>1 bone involved) was seen in 7 patients (28%), Single bone involved in 18 patients (72%).18 patients were MDR strains (72%), 1 had XDR strain (4%) and 5 patients had monoresistance (20%) and 1 patient was resistant to 2 drug (non MDR) (4%).

Conclusion: This study highlights the growing threat posed by the development of resistance to antituberculous drugs in the management of osteoarticular tuberculosis. Delay in diagnosis of drug resistance can lead to further complications and non response to standard antitubercular treatment.

Key words: Osteoarticular TB, MDR TB, Non MDR TB

Introduction:

Tuberculosis has plagued mankind worldwide for thousands of years. John Bunyan (Nov.28, 1628–Aug 31, 1688)[1]. In 1993, the WHO declared TB a global emergency in recognition of the large increase in the number of notified cases worldwide. The last few decades have seen a remarkable increase in incidence of drug resistance in Mycobacterium tuberculosis. From single drug resistance we have reached the era of multidrug resistance and extensive drug resistance and other increasingly important epidemiological factors that continue to fuel the tuberculosis epidemic[2]. Extra pulmonary tuberculosis (EPTB) constitutes about 15-20% of all cases of tuberculosis and more cases of EPTB in HIV positive individuals[3].Osteoarticuar tuberculosis comprises 1-4.3% of all tuberculosis cases and 10-15% of all extra pulmonary tuberculosis cases.[4]Osteoarticular TB represents a greater diagnostic challenge than pulmonary TB because it presents with less frequency and occurs with less liberation of bacilli, as

well as the fact that it is localized in sites that are difficult to access.[4]The diagnosis of osteoarticular tuberculosis is clinico-radiological, particularly in the endemic regions. The typical lesion can be diagnosed clinicoradiologically with support of newer imaging modalities like computed tomography/magnetic resonance imaging (CT/MRI); however, tissue diagnosis is a must when there is a slightest doubt[5]. The emerging drug resistant strains are posing a threat to cure the tubercular lesion hence the mycobacterium should be isolated and subjected to drug susceptibility test[5].However in oeteoarticular tuberculosis culture is only positive in 20-50% cases.[5,6]

Drug resistant form of osteoarticular tuberculosis is ill reported in the literature[7]. The diagnosis, management thus remains a challenge to the treating surgeon. The study include a series of cases that are drug resistant osteoarticular TB on the basis of clinico-radiological findings and Evaluation with further investigations (including cultures for mycobacteria, as well as histopathological findings) used to assess pattern of drug resistance, and favorable outcome. With the help of our study we highlight the key to successful elimination of TB by 'optimum treatment' of cases. This study tried to assess these critical issues of this "relatively less studied condition".

Material and methodology:

This was a retrospective study to analyze the demographics of drug resistant osteoarticular tuberculosis in patients attended outpatient/in patient department at P. D. Hinduja National Hospital Mumbai between August 2005-2014. 25 patients who were diagnosed to have drug resistant osteoarticular tuberculosis on the basis of their drug sensitivity testing patterns were studied. Hospital ethics committee clearance and waiver consent was taken before proceeding on this study. Patients with clinical and radiological diagnosis of osteoarticular tuberculosis and those drug sensitivity pattern shows resistance to at least 1 antitubercular drug were included in the study. Those who had negative culture on biopsy, doubtful diagnosis and drug sensitive osteoarticular tuberculosis were excluded from the study.

Data retrieval system of the institute was used to retrieve the demographic and clinical data of the patients diagnosed to have tuberculosis. All patients were subjected to telephonic interview including answers to a set of questionnaire required to complete the data retrieval. Demographic data including the age, sex, profession, and regional address of the patient were noted. Prior history or contact to a known case of tuberculosis/MDR-TB was recorded to drive insight into the endemic problem of this morbid disease.Medical history and previous drug history pertinent to antituberculosis chemotherapy was noted to determine the drug interactions. Response to previous chemotherapy in terms of symptomatic relief was quantified. Clinical data including symptoms and signs (systemic and neurologic) were noted. Pertinent relief/worsening over the period of time as regards with previous drug history was noted to cite the importance of early

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diagnosis and drug sensitivity pattern of resistant tuberculosis. Laboratory investigations were studied to note drug-related complications and to monitor the progression/regression of disease state.Radiologic images including roentgenograms and magnetic resonance imaging scan of the affected region were retrieved. These included the images before treatment and in due course of ongoing chemotherapy and if possible after completion of therapy.All the patients were evaluated by infectious disease specialist or chest physician working with our hospital. Individualized treatment regimens were instituted as per the needs of individual cases according to their previous history and their drug susceptibility testing patterns. Due to lack of data on drug-resistant osteoarticular tuberculosis, we followed the WHO norms regarding management of pulmonary MDR-TB. The treatment charts were carefully reviewed for the number of antitubercular drugs used, changes made in the regimen, and a record of the side effects. Surgical history and details were noted for cases that underwent surgery for various indications. Surgical parameters including indication for surgery, perioperative parameters were noted to establish any difference from drug sensitive tuberculosis cases. Information pertinent to the complete information retrieval according to set proforma was collected, if required final follow-up arranged for further clinical and radiologic assessment. Favorable outcome defined as disease fully healed and no pain/minimal pain in affected part and good/acceptable functional outcome, acceptable residual deformity. Unfavorable outcome defined as disease cured but persistent pain in affected part, poor functional outcome and unacceptable deformity.

Result &discussion:

Osteoarticular tuberculosis its dismal outcomes in the pre-antibiotic era have improved significantly because of potent antitubercular drugs and advances in surgical treatment[8].In our study the average age of patients having drug resistant osteoarticular tuberculosis was 24.92 years (5-64yrs). Another study done by Litao Li et al[9]the average age was 36.5 years (4–62yrs).Spinal tuberculosis is most common form of skeletal tuberculosis. Followed by hip, knee, foot, elbow, hand, shoulder, bursal sheaths and other.[10,11,12] In our study , Drug resistant tuberculosis of spine was seen in 21.62% cases, calcaneum osteomyelitis in 10.81% cases and SI joint, foot, tibia, ankle joint were involved in 8.11% cases each. Elbow joint, hip joint, knee joint, ulna, femur were involved in 5.41% cases, and shoulder joint, illium, gluteal abscess were involved in 2.7% cases.Incidence of multifocal tuberculosis higher among children because With poor nutritional status, widespread acute and chronic pyogenic infections, worm infestations, high tubercular prevalence, the immune system of children in developing countries is constantly under attack, such that quiescent secondary tubercular complexes flare up[13]. In our study total 37 different sites of osteoarticular system involved and multifocal tuberculosis (>1 bone involved) was seen in 7 patients (28%), Single bone involved in 18 patients (72%). 5 out of 7 patients of multifocal osteoarticular tuberculosis were less than 20 years of age.Litao Li et al[9]found past history of Pulmonary tuberculosis (25.7%)in drug resistant spinal tuberculosis and none had HIV infection. Out of 25 patientsPawar et al[7]found past history of pulmonarytuberculosis in 4 ; 2 patients were immunocompromised with HIV infection; and rest of the patients did not have any other comorbidities. In our study, past history

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ofpulmonary tuberculosis was seen in 28% cases, and past history of pulmonary + lymphnode TB, pott's spine, tubercular meningitis was seen in 4% cases each, 60% cases were seen in our study with no previous history of tuberculosis, Contact history of tuberculosis was seen in 3 cases (12%), history of immunosuppression present in total 2 patients (8%), 1 case of hodgkins lymphoma, 1 case was on chemotherapy and radiotherapy and rest of the patients did not have any othercomorbidities, no patient with HIV. In our study most cases 76% were subjected to formal open biopsy in order to obtain adequate representative tissue, while CT/USG guided biopsies/ arthroscopic drainage was used in 24% patients. In Mohan K et al [14] Samples were obtained through open surgeries in 72 (64.8%) patients while CT/USG guided biopsies/drainage was used in 39 (35.1%) patients. Histopathological diagnosis of osteoarticular TB has been reported in the range of 53-100%.[5,15,16], specimens histopathological positivity in our series was 100%.Pawar et al[7]reportedat presentation all patients had radiographic evidenceof tuberculosis of the spine, similar in our study all patients had radiographic evidence of tuberculosis.In our study Out of the 25 drug-resistant cases, 18 patients were MDR strains (72%), 1 had XDR strain (4%) and 5 patients had monoresistance (20%) and 1 patient was resistant to 2 drug (non MDR) (4%). Among the first-line drugs, maximum resistance was found to isoniazid (96%) followed by rifampicin (76%), pyrazinamide(56%) and streptomycin (52%), Relatively least resistance was found against ethambutol (48%). Among the second-line drugs, maximum resistance was found against ethionamide (32%) and ofloxacin (16%) followed by PAS (12%), moxifloxacin (12%). Least resistance was against kanamycin (4%), amikacin (4%). No isolate was found to be resistant to clofazamine and capreomycin. There was a mean delay of 14.2 months between making the diagnosis and starting of appropriate treatment for drug resistant osteoarticular tuberculosis. Our pattern of drug resistance comparable with studies done by Litao Li et al[9]and Lan Xu et al[17]butdiagnostic delay found higher in our study.

The WHO–IUAT global drug resistance surveillance carried out in India between 1996 and 2002 reported the median prevalence of primary and acquired MDR- pulmonary TB to be 3.4% (1.8%–5.7%) and 25% (7.3%–52.3%), respectively. These studies were conducted in different states mostly in institutions and tertiary care centers and they do not reflect the overall status of drugresistance problem in India[18]. Similarly Almeda*et al* highlighted an alarmingly high percentage of multidrug-resistant *M. tuberculosis* isolates in an urban center(Mumbai-India) (51%) as compared with that at the rural center (2%).[19]There is paucity of data on prevalence of drug resistant osteoarticular system, only few study on drug resistant spinal tuberculosis. To the best of our knowledge there is no literature on this topic. While host genetic factors may contribute to the development of primary MDR-TB, incomplete and inadequate treatment is the most important factor leading to secondary drug resistance development, suggesting that it is often aman made tragedy.[20] The sources are many and the causes multifactorial.The treating physician, by his lack of knowledge regarding dosages, varied drug regimens followed by surgeons, side effects and standard regimens, andfrequent change of brand names contributes to the problem.[21] In one of the studies where prescriptions of 449 physicians were analyzed, 75% of the

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physicians werefound to have made some prescription error.

Noncompliant patients due tomonetary lack, lack of information, side effects of drugs, and social myths and misconceptions, often do not adhere to treatment. Comorbid conditions like diabetes, HIV infection, psychiatric conditions, the habits of smoking and alcoholism make the patient more vulnerable. To sum up, drug resistant osteoarticular tuberculosis usually results from inadequate drug therapy, inadequate knowledge of the prescribing physician/surgeon, difficulty in obtaining drugs by poor patients due to lack of financial resources or social insurances, frequent shortage of second line antituberculous drugs by poor management and/or financial constraints, use of drugs or fixed drug combination (FDC) of drugs with unproven bioavailability, lack of motivation at the beginning of treatment and inadequate self-administration of drugs without direct observation in the intensive phase of therapy[21]. The most common method of detecting drug resistant strains of tuberculosis is culture. This is not easily available in many countries and hence used only in patients with no response to the initial standard treatment regimen.[22] Therefore, detection of drug resistance is attempted only when there is a clinical suspicion of drug resistance. In 1 study, delay in starting appropriate MDR treatment after pulmonary TB diagnosis was 8 months if the drug susceptibility pattern of the source case was not considered.[23] Even in the present study a diagnostic delay of 14.2 months was noted The general treatment principles for MDR-TB according to the WHO criteria for pulmonary tuberculosis were followed which include: (*a*) Drug sensitivity testing, available from a reliable laboratory, should be used to guide therapy; (*b*) Regimens should consist of minimum 4 new drugs not used previously; (*c*) An injectable aminoglycoside should be used for a minimum period of 6 months; (*d*) Never add a single drug to a failing regimen-"Addition Syndrome"; (*e*) Treatment should be for a minimum duration of 18 to 24 months[24,25,26]. Patients on second line drugs need to be monitored carefully for side effects. Gastrointestinal side effects are the most common. Drug induced neuropathies form a considerable group to the extent that pyridoxine should be an integral part of the regimen from the outset. Therefore the importance of regular and long-term follow-up to ensure compliance, to assess drug side effects and development of further resistance should be emphasized to the patient.[27,28]Sufficient data, again from pulmonary MDR-TB emphasize the fact that treatment of MDR-TB is difficult, complicated, much costlier, challenging, needs experience and skills of a specialized physician.

Conclusion:

In conclusion, our study highlights the growing threat posed by the development of resistance to antituberculous drugs in the management of osteoarticular tuberculosis. Complications arise due to delays in diagnosis and by inappropriate administration of drugs. Based on our findings, we recommend:-

(1) Having a high index of suspicion for the presence of drug resistance. Routine biopsy, culture and drug sensitivity testing of all patients.

(2) Use of drug susceptibility patterns wherever available to guide selection of appropriate second-line drugs.

(3) Consideration to be made to relative drug toxicities, efficacy and compatibility when selecting second-line drugs.

(4) Importance of regular and long-term follow-up

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to ensure compliance, to assessdrug side effects and development of further resistance should be emphasized to the patient.

(5) Council and encourage patients not to stop treatment despite all its discomforts to prevent morbidity, mortality, and transmission of drug resistance.

References:

1.Daniel TM. The history of tuberculosis: past, present and challenges for the future. Respiratory Medicine (2006) 100, 1862 –1870.

2. DyeC,Williams BG. The population dynamics and control of tuberculosis. Science2010; 328:856–61.

3.Sharma S.K and Mohan A. Extrapulmonary tuberculosis. Ind J Med Res 2004;120:316-353.

4.Garcia-Elorriaga G, Gracida-Osorno C, Carillo-Monster G, Gonzalez-Bonilla C. Clinical usefulness of the nested polymerase chain reaction in the diagnosis of extra pulmonary tuberculosis. SaludPublicaMex 2009; 51:240-245.

5.Lakhanpal VP, Tuli SM, Singh Hardas, Sen PC. The value of histology, culture and guinea pig inoculation examination in osteoarticular tuberculosis. ActaOrthopScand 1974;45:36-42.

6.Agashe*et al* Osteoarticular tuberculosis – diagnostic solutions in a disease endemic region *J Infect DevCtries*2009;April 3(7):Page511-516.

7.PawarUday M. et al, Multidrug-Resistant Tuberculosis of the Spine—Is it the Beginning of the End?? Euro. J Spine, Volume 34, Number 22, pp E806– E810.

8.Jain AK (2010) Tuberculosis of the spine: a fresh look at an old disease. J Bone Joint Surg Br 92(B):905–913.

9.Litao Li et al Management of drug-resist ant spinal tuberculosis, International Orthopaedics (SICOT) (2012) 36:277–283.

10.Tuli SM. General principles of osteoarticular tuberculosis. ClinOrthopRelat Res 2002;(398):11–19.

11.Grosskopf I, Ben David A, Charach G, Hochman I, Pitlik S. Bone and joint tuberculosis—a 10-year review. Isr J Med Sci 1994;30:278-83.

12. Watts HG, Lifeso RM. Tuberculosis of bones and joints. J Bone Joint Surg Am 1996;78:288-98.

13. Eid A, Chaudry N, el-Ghoroury M, Hawasli A, Salot WL, Khatib R. Multifocal musculoskeletal cystic tuberculosis without systemic manifestations. Scan J Infect Dis 1994;26:761–4.

14. Mohan K. et al Drug resistance patterns in 111 cases of drug-resistant tuberculosis spine, Eur Spine J, jan 2011, vol 20, (1).

15.Jain AK et al. Evaluation of clinico-radiological, bacteriological, serological, molecular and histological diagnosis ofosteoarticular tuberculosis, IJO 2008,Volume 42,Issue 2, 173-77.

16. Saxena PS, Sharma RK. Value of histopathology, culture and guinea pig inoculation in osteoarticular tuberculosis. IntSurg 1982;67:540-2.

17. Lan Xu et al, Int. surg 2013;98:175-80

18. Paramasivan CN, Venkataraman P. Drug resistance in tuberculosis in India. Indian J Med Res2004;120:377–86.
19. Almeida D, Mehta A, Rodriques C, et al. Comparison of drug resistance of tuberculosis from rural area Sakawar and urban tertiary care centre. Presented at: 110th General Meeting of ASM; May 21–25, 2002; Los Angeles, CA. Abstract U58.
20. Sharma SK, Mohan A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. *Chest* 2006;130:261–72.
21. Prasad R. MDR TB: current status. Indian J Tuberc2005;52:121–31.
22. Udwadia ZF. Indias multi-drug resistant tuberculosis crisis. Ann NY AcadSci2001;953:98–105.
23. Schaaf HS, Shean K, Donald PR. Culture confirmed multi-drug resistant tuberculosis: diagnostic delay, clinical features and outcome. Arch Dis Child 2003;88:1106–11.
24. Crofton J, Chaulet P, Maher D. *Guidelines for the Management of Drug Resistant Tuberculosis*. Geneva, Switzerland: WHO; 1997. Document WHO/TB/96: 210.
25. Mukerjee JS, Rich ML, Socci AR, et al. Programmes and principles in treatment of multi-drug resistant tuberculosis. *Lancet* 2004;363:474–81.
26. Central TB division, Director General of Health Services. *Revised NationalTuberculosis Programme*. NirmanBhavan, New Delhi: DOT plus.
27. Dhingra VK, Rajpal S, Mittal A, et al. Outcome of Multi-drug resistant tuberculosis cases treated by individualized regimens at a tertiary level clinic. Indian J Tuberc2008;55:15–21.
28. Prasad R. Management of multi-drug resistant tuberculosis: Practitioners view. Indian J Tuberc. 2007;54:3–11.

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