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LONG-TERM OUTCOME OF ORBITAL AND ADNEXAL TUBERCULOSIS IN NON- HIV INFECTED PATIENTS

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ABSTRACT **BACKGROUND-** To present 5 years' data on clinical profile and treatment outcomes of orbital TB in patients seronegative for HIV. **METHODS-** A retrospective review was performed on records of 123 patients of orbital TB who had continuous 5 years' follow-up. ELISA for HIV was done to select seronegative patients. Orbital TB was diagnosed on clinico-radio-pathological basis. All patients were treated with ATT as per DOTS Category I in accordance with RNTCP guidelines. Patients were followed for a minimum period of 12 months. Drug defaulters were excluded. Treatment response was statistically analysed using paired T-test. **RESULTS-** Periocular discharging sinus mass was most common presentation, followed by periocular mass (non-eyelid). Mantoux skin test was positive in all patients. Histopathology was positive in 100% while CB-NAAT was positive in 87% isolated samples for tubercular infection. Other tests showed variable level of positivity. Patients were followed up monthly till disease remission, then three and six monthly till 5 years. All patients had clinical resolution at average 3.6 weeks following start of ATT. No recurrences were seen till last follow-up ($P < 0.001$). **CONCLUSION-** The study establishes DOTS Category I treatment as an effective therapeutic treatment protocol for orbital TB in non-HIV infected patients.

KEYWORDS : adnexal tuberculosis, cicatricial ectropion, orbital cold abscess, orbital tuberculosis, pus discharging sinus

INTRODUCTION

The average prevalence of all forms of tuberculosis (TB) in India is estimated to be 5.05 per thousand. [1] Worldwide, TB is the most common serious opportunistic infection among people with human immunodeficiency virus (HIV) infection.[2] Co-infection of TB and HIV frequently causes extra-pulmonary infection.[3] However, extra-pulmonary TB, including orbital TB, may also be seen in non-HIV patients. The incidence of ocular and orbital TB ranges from 1.4% to 18% in various studies.[4,5] Hematogenous spread from the lungs is the primary mechanism by which TB affects the orbit and eyes, but TB can also spread via direct local extension.[6,7] Tuberculosis can affect any orbital or extra-ocular tissue.[8]

The purpose of the study is to present 5 years' experience of the clinical presentation and response to therapy of orbital TB in non-HIV patients.

METHODS

The study was conducted in accordance with the Declaration of Helsinki after approval from the institutional review board. An informed voluntary consent for treatment was obtained from all the study subjects.

A retrospective review of records was performed to isolate 123 patients of orbital and adnexal TB, who had completed continuous 5-year follow-up. Patient data analysed included the clinical presentation, investigations done, treatment given, response to treatment and follow-up. Drug defaulters and patients with a follow-up period of less than one year were excluded from the study. Diagnosis was made on the basis of clinico-radiological evidence and confirmed by microbiological and molecular evidence. ELISA for HIV was done for all the patients and only the seronegative patients were selected for the study.

Orbital TB was clinically suspected on the basis of long standing orbital/ adnexal disease with poor response to conventional antibiotic or anti-inflammatory therapies, positive history of treated/ partially treated/ untreated TB and other symptoms like cough with sputum, low grade fever and weight loss. Induration of 15 mm or more on Mantoux skin test was considered positive for active TB. Chest radiograph was done in patients with active cough to rule out pulmonary disease. Orbital computerized tomography (CT) was done in all patients. Tissue aspirate or biopsy, wherever available, was subjected to histopathology to look for caseating granuloma and microbiological staining with acid-fast bacilli (AFB) stain and culture. Aspirates were also sent for Cartridge Based Nucleic Acid Amplification Test (CB-NAAT) for diagnosis of tuberculosis. Sputum AFB and culture were done for cases with a positive history of cough with sputum.

Positively diagnosed patients were started on Anti-tubercular treatment (ATT) as per DOTS Category I in accordance with the latest Revised National Tuberculosis Control Programme (RNTCP) guidelines. [2] Patients underwent a baseline ocular exam prior to starting ATT, which included visual acuity testing, pupillary reaction, intraocular pressure, colour vision, anterior and posterior segment evaluation, and was also done on every follow up visit DOTS treatment was given from home district DOTS centres. Surgical debridement was done in cases of discharging sinus with partial response to treatment. Scar revision was done for cicatricial lid changes. Relief from presenting symptoms were considered as evidence of resolution and was divided into early (two weeks or less), intermediate (between two weeks and one month) and delayed (more than a month). Patients were followed monthly till disease remission, then three and six monthly till 5 years. Evaluation for progression or regression and monitoring for drug toxicity was done in each subsequent visit. The course of the disease and the response to treatment were noted and statistically analysed using paired T test.[9]

RESULTS

A total of 123 patients diagnosed with orbital and adnexal TB were included in the study out of which 79 (64.2%) were male and 44 (35.8%) were female. The mean age of presentation was 22 years.(range 6- 71 years). Most common clinical presentation was periocular discharging sinus with or without cicatricial ectropion (27.6%), followed by periocular mass (non-eyelid) (22.8 %) Other clinical presentations were in the form of displaced eyeball (18.7%), eyelid mass (15.4%), proptosis (15.4%), and unexplained visual loss (0.8%). No patient was diagnosed with TB at the time of first consultation. Orbital periostitis was the most common radiological finding and was observed in patients with pus discharging sinus (27.6%), followed by inflammatory lacrimal gland involvement (26%). The distribution of clinical presentations of the patients is given in Table 1 and the distribution of clinico-radiological presentations of orbital TB is described in Table 2.

No cases of multidrug resistant (MDR) TB were encountered. The latency between onset of symptoms and the diagnosis ranged from two to six months (average of 4.2 months). No age predilection was identified. ELISA for HIV was negative for all the patients. Mantoux skin test was used as screening test and was positive in all the patients, with induration ranging from 18 to 23 mm. Seven cases had ulceration at the test site. The diagnostic tests performed for orbital TB are illustrated in Table 3. Co-existing pulmonary disease was found in 14 patients, which was confirmed on chest X-ray and presence of AFB in sputum. .Sample from the pus discharging sinus was also subjected to

culture for AFB. Four out of 34 (3.3%) patients having discharging sinus were AFB positive. Pus aspirate was isolated from 46 patients (discharging sinus and eyelid cold abscesses) and 40 cases confirmed *M. Tuberculosis* on CB-NAAT. Tissue samples were isolated for histopathological evaluation in 70 out of 76 patients who had either eyelid/orbital mass, lacrimal gland or lacrimal sac involvement, and all cases confirmed presence of caseating granulomas and giant cells suggestive of tuberculosis infection. Six cases in whom biopsy samples could not be taken were situated deep within the orbit. Non granulomatous inflammation was not encountered in any patient. Four patients with pus discharging sinus and clinically evident non-response to treatment were taken up for surgical debridement and removal of sequestrum. The excised tissues were sent for HPE and culture for acid fast bacilli (AFB). Cultures were negative for AFB while HPE showed caseating granuloma in all the samples.

All patients were administered DOTS category one for minimum six months. Evidence of clinical resolution at an average of 3.6 weeks was observed in all patients, following start of ATT. Time period between start of ATT and symptomatic relief is illustrated in table 4. Four patients suffered from toxic optic neuropathy and seven patients had deranged liver function tests (LFT) for which the drug doses had to be modified accordingly. No patient reported with recurrence within the study period ($P < 0.001$). Cosmetically acceptable scars were formed in 27 cases cases of treated discharging sinus. Seven patients had cicatricial ectropion causing functional lagophthalmos that required surgical correction.

DISCUSSION

According to the Centers for Disease Control and Prevention (CDC), approximately one third of the world's population is infected with TB. However, only 10% of those infected will develop clinical manifestations of the disease.[10] Of these, 16–27% have extrapulmonary manifestations, which includes those with orbital and external eye disease.[11] About 2.5 million people or 0.4% adult population in India are HIV seropositive and 50% of them have developed TB as opportunistic infection.[12]

Extraocular TB is reported to have resurfaced in HIV positive patients.[4] However, in our experience, periocular TB appears to be common in non-HIV patients as well. This could be attributed to the endemicity of TB in the region.[13] [8]

Amongst the 123 patients that were enrolled in the study, none was diagnosed or suspected as suffering from TB at the time of the primary ophthalmic consultation. The current study analysis revealed that males are predisposed to the disease (approximately 64%). Majority worked in crowded settings with poor ventilation. This could attribute to the greater chances of being infected due to exposure.

Orbital and adnexal TB poses a challenge for the clinician on account of rarity of the condition.[14-17] Also there is a wide spectrum of clinical presentations that can occur due to TB.[7] In our study, clinical features include periocular pus discharging sinus with or without cicatricial ectropion (Figure 1), periocular mass, displaced eyeball (Figure 2 and 3), eyelid mass (Figure 4) and proptosis (Figure 5). The latency between the onset of symptoms and the diagnosis (average time being about 4 months) further corroborates the above. Thus, there is a need for a high index of suspicion for an early diagnosis.

Periorbital bones are the sites of predilection. Our analysis shows that frontal bone was the most commonly involved in periocular discharging sinus. The predisposition of the flat bones of the body is documented in literature. [18] Several previous studies have reported draining sinus tracts with radiographically confirmed bony changes with the involvement of the frontal, sphenoid, and zygomatic bones.[19-22] Other common presentations in our practice were inflammatory involvement of the lacrimal gland, the eyelids as well as the orbital soft tissue. Previous reports have documented tubercular involvement of lacrimal gland in the form of dacryoadenitis unresponsive to conventional antibiotic therapy.[23,24] Also, eyelid lesions in the form of chronic blepharitis or chalazion like nodules have been reported which recur after excision.[25-27] Literature also reports orbital caseating granulomas, soft tissue tuberculomas, and diffuse orbital involvement.[21,28,29] Orbital periostitis was observed to be the commonest radiological finding, which is in accordance to other published data.[7] Rare presentations like lacrimal sac and base of skull granuloma are e also observed in our study (Table 2). Adequate clinico-radiological literature supports the fact that any extraocular structure can be affected with TB.[6,8]

The confirmation of diagnosis of orbital and adnexal TB was based upon previously published guidelines, which establishes diagnosis by one or more of the following criteria: (i) clinico-radio-pathological features suggestive of the orbital TB infection along with associated pulmonary/extra-pulmonary TB (ii) demonstration of AFB on histopathological examination of tissue biopsy specimen. (iii) isolation of mycobacteria on tissue culture and (iv) detection of mycobacterial DNA by PCR of biopsied tissue.[7,30,31] Mantoux test occurred as a useful screening tool, over which additional diagnostic tests in the form of HPE and CB-NAAT were performed for diagnosis. Mantoux skin test was positive in all cases ($P < 0.001$), suggesting it to be very useful in ascertaining the diagnosis. Co-existent pulmonary involvement was a chance finding, which was confirmed on chest X-ray and presence of AFB in sputum. Also, AFB positivity in patients presenting with discharging sinus was also very low (four out of 34 patients), despite full precautions for transportation and staining. This is supported by previously done studies that suggest that the yield of AFB via microscopy or culture of intraocular fluids or biopsied tissue is low.[32,33] Interferon-gamma release assays and PCR analysis were not readily available and thus not done for our patients. The sensitivity of HPE was observed to be 100% and CB-NAAT was 87% in diagnosing orbital and adnexal TB infection. The sensitivity of CB-NAAT is not observed to be 100% due to lower *M. Tb* counts in seronegative patients, as per previous published literature. [34]

DOTS Category one regimen administered to all patients was well tolerated. Patients who had optic neuropathy and hepatotoxicity were detected early and given drug modifications, signifying the importance of a baseline ocular exam prior to starting ATT for assessment of side effects, which can sometimes be confused with worsening ocular TB. [9] Efficacy of treatment was established by relief in symptoms and resolution of signs. This acted as a surrogate confirmation of the diagnosis. Response patterns varied with the presentation, being quicker in smaller lesions of the periocular tissue (Table 4). Such differential patterns in response have not been found mentioned in literature. Clinico-radiological response guided the duration of treatment. Shortest treatment duration of 6 months was adhered to.[35]

Cure rate after full course of ATT was 96.7 % without any recurrence ($P < 0.001$). Cure rates with standard regimen exceed 90%, thus establishing that drug therapy alone is adequate in managing orbital TB.[36,37] Surgical intervention in the form of debriment for non-responders and ectropion correction in treated cases were only required in a small subset of cases. Sequestrum removal is required in non-responders to augment response of therapy.[38] Scars resultant from discharging sinuses are amenable to surgical correction thus providing accepatable cosmesis and functionality.

The management of periorbital TB requires a high index of suspicion, especially in endemic areas. The authors suggest consideration of values more than 15 mm on Montoux test as indiacators of TB. Advanced serological and histopathological tests should be harnessed in confirmation of diagnosis. Targeted DOTS Category I treatment provides adequate therapeutic relief in majority of cases, preventing avoidable complications of eyelid malpositions and corneal scars.

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Figures

Figure 1: Clinical presentation of tubercular cicatricial ectropion without discharging sinus (right upper lid)

Figure 2: (a) Periocular (non-eyelid) mass with inferiorly displaced globe (left side) on clinical presentation and (b) CT scan-axial section showing cold abscess with lateral wall bony erosion in superior orbit (left side).

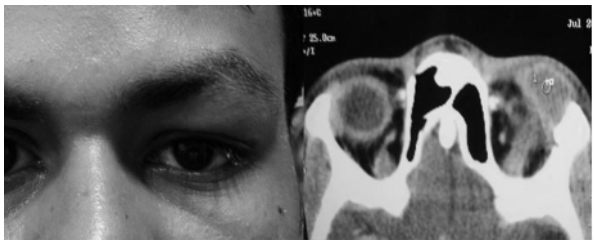

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Figure 3: (a) Periocular (non-eyelid) mass with inferiorly displaced globe (left side) on clinical presentation and (b) CT scan-coronal section showing cold abscess with lateral and superior wall bony erosion in left orbit.

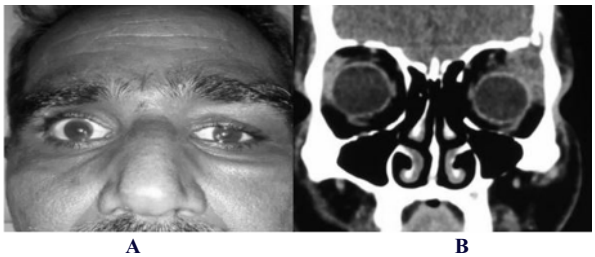

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Figure 4: (a) Clinical presentation of tubercular eyelid mass right upper lid (b) CT scan-axial view showing preseptal lid involvement (right side)

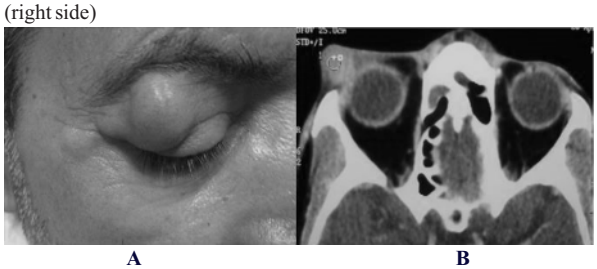

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Figure 5: (a) Clinical presentation of tubercular orbital mass presenting clinically as orbital cellulitis (left side) (b) CT scan-axial view showing heterogenous exctraconal orbital mass resulting inoutward protrusion of left eye.

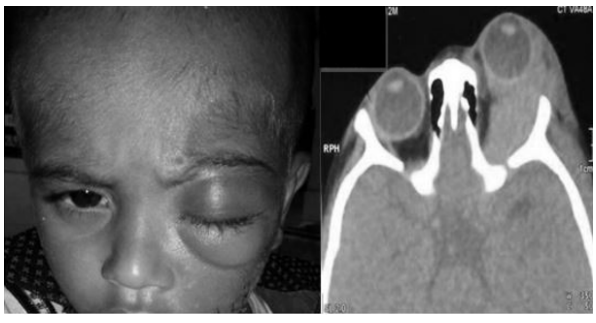

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Table 1: Distribution of clinical presentations among the patients (in decreasing order of frequency)

Presentation	No. of patients	Percentage (out of total)
Periocular discharging sinus	18	14.6%
Periocular discharging sinus with cicatricial ectropion	16	13.0%
Periocular mass	28	22.8%
Displaced eyeball	23	18.7%
Eyelid mass	19	15.4%
Proptosis	18	15.4%
Unexplained visual loss	1	0.8%

Table 2: Distribution of clinico-radiological presentations among the patients

Radiological finding	Clinical presentations	No. of patients	Percentage (out of total)
Orbital periostitis	• Pus discharging sinus with or without cicatricial ectropion	34	27.6%
Lacrimal gland inflammation	• Periocular mass • Displaced eyeball	27 5	22.0% 4.0%
Inflammatory eyelid mass	• Eyelid mass	7	5.6%
Eyelid cold abscess	• Eyelid cold abscess	12	9.7%
Inflammatory orbital mass	• Proptosis • Displaced eyeball	18 18	14.6% 14.6%
Base of skull granuloma invading orbit	• Unexplained visual loss	1	0.01%
Inflammatory lacrimal sac mass	• Periocular mass	1	0.01%

Table 3: Patients showing positive diagnostic tests for TB

Test performed	Positively tested patients (with percentage out of total)	Number of patients tested	Percentage positivity of test
Histopathology	70 (56.9%)	70	100
Cartridge based Nucleic acid amplification test (CB-NAAT)	40 (32.5%)	46	87
AFB culture in discharge	4 (3.3%)	34	11.7
Chest X-ray	14 (11.4%)	14	100
Sputum AFB	14 (11.4%)	14	100
Interferon-gamma release assay	Not done	NA	NA
PCR	Not done	NA	NA

Table 4: Time period between start of ATT and symptomatic relief

Clinico-radio-pathological diagnosis	No. of patients		
	Early relief (2 weeks or less)	Intermediate relief (2 weeks to 1 month)	Delayed relief (more than 1 month)
Periocular discharging sinus	25	5	4
Lacrimal gland inflammation	21	6	5
Eyelid inflammatory mass	3	4	0
Eyelid cold abscess	7	5	0
Orbital inflammatory mass	3	10	23
Base of skull granuloma invading orbit	0	0	1
Lacrimal sac inflammatory mass	1	0	0

REFERENCES

1. Chakraborty A K .Epidemiology of tuberculosis : Current status in India. Indian J Med Res 120 2004:pp 248-276.
2. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis [online]. 2013. Available from URL: http:// www. cdc. gov/ tb/ TB HIV Drugs/ default. htm
3. Sharma S K, Mohan A, Kadhiravan T. HIV-TB co-infection: Epidemiology, diagnosis & management. Indian J Med Res 121 2005: pp 550-567.
4. Sanches I, Carvalho A, Duarte R. Who are the patients with extrapulmonary tuberculosis? Rev Port Pneumol2014; 21 (2):90–3.
5. Yeh S, Sen HN, Colyer M, Zapor M, Wroblewski K. Update on ocular tuberculosis. CurrOpinOphthalmol2012; 23:551.
6. Sharma A, Thapa B, Lavaju P. Ocular tuberculosis: an update. Nepal J Ophthalmol2011; 3 (5):52–67.
7. Mittal, R., Sharma, S., Rath, S., Barik, M. R., & Tripathy, D. (2017). *Orbital tuberculosis: Clinicopathological correlation and diagnosis using PCR in formalin-fixed tissues. Orbit, 36(5), 264–272.* doi:10.1080/01676830.2017.1337169
8. Dalvin A L, Smith W M. Orbital and external ocular manifestations of *Mycobacterium tuberculosis* : A review of the literature. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 2016; 4: 50–57.
9. Nayak B, Hazra A. How to choose the right statistical test? Indian J Ophthalmol 2011; 59(2): 85–86.
10. Gupta V, Gupta A, Rao N A. Intraocular tuberculosis – an update. SurvOphthalmol2007; 52 (6): 561–87.
11. Eurosurveillance editorial team. WHO publishes Global tuberculosis report 2013. Euro Surveill. 2013;18(43):pii=20615. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20615
12. UNAIDS, World Health Organization, AIDS pandemic update. Available at

URL:http://data.unaids.org/pub/EPIslides/2007/2007 epiupdateen.pdf. Accessed on 5/5/20
13. Gupta KB. Challenges in diagnosis and treatment of latent tuberculosis infection. Indian J Tuberc. 2012; 59: 1–5.
14. Helm CJ, Holland GN. Ocular tuberculosis. SurvOphthalmol1993; 38 :229 .
15. Donahue H. Ophthalmologic experience in a tuberculosis sanatorium. Am J Ophthalmol1967; 64: 742.
16. Goldenburg M, Fabricant N D. The eye in the tuberculous patient. Trans Sect Ophthalmol Am Med Assoc1930; 135: 8.
17. Bouza E, Merino P, Muñoz P, Sanchez-Carrillo C, Yáñez J, Cortés C. Ocular tuberculosis. A prospective study in a general hospital. Medicine (Baltimore)1997; 76: 53.
18. John V St. Tuberculosis of the flat bones of the skull. Br J Surg 1921; 9: 228–234.
19. Sen D. Tuberculosis of the orbit and lacrimal gland: a clinical study of 14 cases. J PediatrOphthalmol Strabismus1980; 17 (4): 232.
20. Khurana S, Pushker N, Naik S S, Kashyap S, Sen S, Bajaj M S. Orbital tuberculosis in a paediatric population. Trop Doct2014; 44 (3): 148–51.
21. Pillai S, Malone T, Abad J C. Orbital tuberculosis. OphthalPlastReconstrSurg1995; 11 (1): 27.
22. Narula M K, Chaudhary V, Baruah D, Mathuria M, Anand R. Pictorial essay: orbital tuberculosis. Indian j Radiol Imaging2010; 20 (1): 6–10 .
23. Madhukar K, Bhide M, Prasad C E, Venkatramayya. Tuberculosis of the lacrimal gland. J Trop Med Hyg199; 94 (3): 150.
24. Panda A, Singhal V. Tuberculosis of lacrimal gland. Indian J Pediatr1989; 56 (4): 531.
25. Mocanu C. Tuberculosis of the tarsal conjunctiva. Oftalmologia1996; 40:150–1.
26. Ozdal P C, Codère F, Callejo S, Caissie A L, Burnier M N. Accuracy of the clinical diagnosis of chalazion. Eye (Lond)2004; 18: 135–8.
27. Aoki M, Kawana S. Bilateral chalazia of the lower eyelids associated with pulmonary tuberculosis. ActaDermato-Venereol2002; 82: 386–7.
28. Salam T, Uddin J M, Collin J R, Verity D H, Beaconsfield M, Rose G E. Perioculartuberculous disease: experience from a UK eye hospital. Br J Ophthalmol2015; 99 (5): 582–5.
29. Aversa doSouta A, Fonseca A L, Gadelha M, Donangelo I, Chimelli L, Domingues F S. Optic pathways tuberculoma mimicking glioma: a case report. SurgNeurol2003; 60 (4): 349–53.
30. Mittal, R., Sharma, S., Rath, S., Barik, M. R., & Tripathy, D. (2017). *Orbital tuberculosis: Clinicopathological correlation and diagnosis using PCR in formalin-fixed tissues. Orbit, 36(5), 264–272.* doi:10.1080/01676830.2017.1337169
31. Madge SN, Prabhakaran VC, Shome D, Kim U, Honavar S, Selva D. Orbital tuberculosis: A review of the literature. Orbit 2008; 27(4):267–277.
32. Sen DK. Tuberculosis of the orbit and lacrimal gland: A clinical study of 14 cases. J Pediatr Ophthalmol Strabismus 1980; 17:232–238.
33. Sharma A, Thapa B, Lavaju P. Ocular tuberculosis: an update. Nepal J Ophthalmol2011; 3 (5): 52–67.
34. Gupta A, Gupta V. Tubercular posterior uveitis. IntOphthalmolClin2005; 45 (2): 71–88.
35. Peralta G, Barry P, Pascopella L. Use of Nucleic Acid Amplification Tests in Tuberculosis Patients in California, 2010-2013. *Open Forum Infect Dis*. 2016;3(4):ofw230. Published 2016 Dec 5. doi:10.1093/ofid/ofw230
36. Lee J Y. Diagnosis and Treatment of Extrapulmonary Tuberculosis.TubercRespir Dis 2015;78:47-55.
37. Ormerod L P, Horsfield N. Short-course antituberculous chemotherapy for pulmonary and pleural disease: 5 years' experience in clinical practice. Br J Dis Chest 1987; 81(3): 268-71.
38. Cohn D L, Catlin B J, Peterson K L, Judson F N, Sbarbaro J A. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis.A twice-weekly, directly observed, and cost-effective regimen.Ann. Intern. Med 1990; 112(6): 407-15.
39. Mukopadhaya B. Tuberculosis of Bones and Joints. Ind. J. Tub. 1967;5(2): 35-46.