Original Article

Patterns of extrapulmonary Tuberculosis in Children: A Hospital based study

Hatwal D[1], Chaudhari S[2], Joshi AK[3], Rathaur VK[4]

[1]Assistant Professor, [2]Associate Professor, Pathology, [3]Associate Professor, Orthopedics, [4]Assistant Professor, Pediatrics, VCSGGMS&RI, Sricot,Srinagar,Pauri Garhwal ,Uttarakhand.

Abstract

Background: Extrapulmonary Tuberculosis is an important clinical problem, defined as the isolated occurrence of tuberculosis in any part of the body other than lungs. Aim of the study is to describe the various presentations of extrapulmonary tuberculosis cases in children of Uttarakhand.

Method: The children below 15 years included in the study from the pathology and pediatrics department of VCSG Govt. Medical. Science and Research Institute Srinagar Garhwal, private pathological centers, nursing homes and clinics at Srinagar Garhwal,Uttarakhand , during October 2010 to March 2012. The cases are selected on the basis of cytopathological and histopathological findings suggestive of tuberculosis. Cytologically suggestive cases of tuberculosis were further reviewed for detailed clinical status, conventional tests and response to antitubercular treatment to categorize the different types of extrapulmonary tuberculosis.

Result: Out of 250 suspicious cases, 58 (23.2%) cases were of extrapulmonary tuberculosis. Out of 58 cases, lymph node tuberculosis in 24 (41.3%) was commonest, followed by tubercular meningitis in 22.4%, pleural effusion in13.7%, musculoskeletal in12%,abdominal tuberculosis in 5.2 %, disseminated tuberculosis in 3.4% and cutaneous tuberculosis in only one case (1.7%). Cervical lymphnodes are the most common lymphnode involved (70.8%).Tissue cytology shows high sensitivity for acid fast bacilli on Ziehl- Neelsen staining. Fluid cytology showed high sensitivity (100%) for Adenosine deaminase (ADA) activity. All our cases responded to treatment and recovered well except two cases of tubercular meningitis.

Conclusion: Although microbiological, and cyto-histopathological diagnosis are the gold standard but in our setup the patients having negative diagnostic test with strong clinical, radiographic and hematological investigations indicating tuberculosis were also treated on the line of tuberculosis. The diagnosis in latter was further strengthened by the positive response to the anti-tubercular treatment. Prompt and efficient identification of the source of transmission and application of effective environmental measures are intimately linked to the control of childhood tuberculosis

Key words: Extrapulmonary tuberculosis, Lymphadenitis, Tuberculin test, Adenosine deaminase activity, Ziehl Neelsen.

Introduction:

Despite the accelerated efforts to control the disease for decades, Tuberculosis remains the seventh leading cause of death globally[1]. 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[2]. Contributory factor for current resurgence of all type of tuberculosis are acquired immunodeficiency syndrome (AIDS) epidemic, the emergence of multidrug resistant Mycobacterium strain, poverty, homelessness, inadequate tuberculosis control programmes [3].

Although the pulmonary tuberculosis is the most common presentation, extrapulmonary tuberculosis is also an important clinical problem[4-6]. Tuberculosis involves organs other than the lungs such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges are included in extrapulmonary tuberculosis (EPTB). An estimated 1.3 million cases of tuberculosis and 450000 associated deaths occur annually in children [3].Reliable epidemiological data are lacking regarding the relative contributions of pulmonary and extrapulmonary disease to the total number of tuberculosis cases from India[7]. Of the 9 million cases of tuberculosis worldwide that occur annually, about 1 million cases (11%) occur in children15 years of age. Extrapulmonary tuberculosis account for up to one thirds of all cases[8]. Children have high predisposition to development of extrapulmonary tuberculosis[9] . The impact of extrapulmonary tuberculosis is greatest among infant and young children who tend to develop

Address for Correspondence:
Deepa Hatwal, Assistant Professer, Pathology, VCSGGMS&RI, Sricot, Srinagar, Pauri Garhwal, Uttarakhand.
E-mail: dhatwal@yahoo.com

more severe extrapulmonary disease, especially meningitis and milliary tuberculosis [10, 11].

Very few data regarding extrapulmonary tuberculosis in children of hill are available. Deepener et al in their study found (14.46%) cases of EPTB in age group up to 15 yrs. Extrapulmonary tuberculosis may lead to various complications according to organ involved[12]. The aim of the study was prompt identification of the source of transmission, application of effective environmental measures and early diagnosis and treatment of childhood tuberculosis. This can help in the successful management and in reducing the occurrence of complication.

Material and Method:

The study was conducted by Department of Pathology, VCSG Government medical college, Srinagar - Garhwal, Uttarakhand in association with Department of Peadia VCSG Government medical college, Srinagar - Garhwal, Uttarakhand. Data were also retrieved from private pathological centers, nursing home and clinics at Srinagar. This is prospective study conducted during October 2010 to March 2012. All the cases which arose suspicion of tuberculosis on cytological examination were included in the study .Cytological investigation include fine needle aspiration cytology and fluid cytology (pleural, ascitic, cerebrospinal etc.).The criteria for suspicion of tuberculosis in fine needle aspiration are lymphocytic predominance, epitheliod granulomas, multinucleated giant cells, and necrosis on Geimsa staining .The criteria in fluid cytology were lymphocyte predominance in centrifuged smear on Geimsa staining, exudates fluid and presence of cobweb. The main diagnostic tool for confirmation and categorization of extrapulmonary tuberculosis were kept as demonstration of acid fast bacilli on Ziehl-Neelsen(ZN) staining in 20% H2SO4, Adenosine deaminase (ADA) activity for mycobacterium in fluid, tuberculin test, chest skiagram, detailed clinical history, history of contact, socioeconomic status, physical examination, baseline laboratory investigation, enzyme linked immunoaasay (ELISA) for Human Immunodifficiency Virus (HIV) and response to antitubercular treatment .The cases in which the extrapulmonary tuberculosis was seen along with pulmonary involvement were considered as pulmonary tuberculosis and therefore excluded from the study, as per WHO guidelines a patient with both pulmonary and extrapulmonary tuberculosis is labeled as pulmonary. Diagnosis of extrapulmonary tuberculosis should be based on at least one specimen with confirmed *M. tuberculosis* or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy[13].

Result:

Extrapulmonary tuberculosis was seen in 23.2% (n=250) that include 53.4% female and 46.6% male .Distribution of extrapulmonary tuberculosis according to organs involved was tubercular lymphadenitis in 41.3%, tubercular meningitis in 22.4%, pleural effusion in 13.7%, musculoskeletal in 12%, abdominal tuberculosis in 5.2 %, disseminated tuberculosis in 3.4% and cutaneous tuberculosis in 1.7% (Figure1).

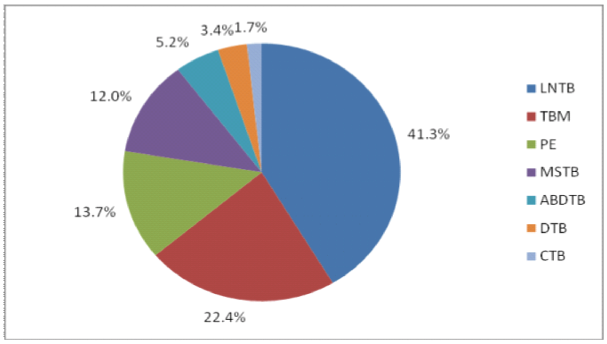

Figure 1 Distribution of Extrapulmonary tuberculosis cases(n=58) by anatomical sites .LNTB -Lymphonode Tuberculosis, TBM= Tubercular Meningitis,PE=Pleural Effusion, MSTB = Musculo Skeletal Tuberculosis,ABDTB=Abdominal Tuberculosis, DTB = Disemmineted Tuberculosis, CTB =Cuteneous Tuberculosis.

Lymphnode tuberculosis (n=24) were the commonest presentation mostly as cervical lymphadenopathy 70.8% followed by axillary 12.5%, Inguinal 8.3% and preauricular 8.3% (figure 2).All cases presented as nontender lump ,varying in size from 2cm to 4cms.The lump were discrete firm and mobile in 13 cases, with central softening in 5 cases and abscess formation in 6 cases. Fine needle aspiration shows suggestive cytology for tubercular lesion in all. Acid fast bacilli on ZN staining seen in 87.5 % of cases. Out of three AFB negative cases two were further confirmed on histopathological examination and one remaining was kept under high index of suspicion .Tuberculin test was positive in 70.8% cases.

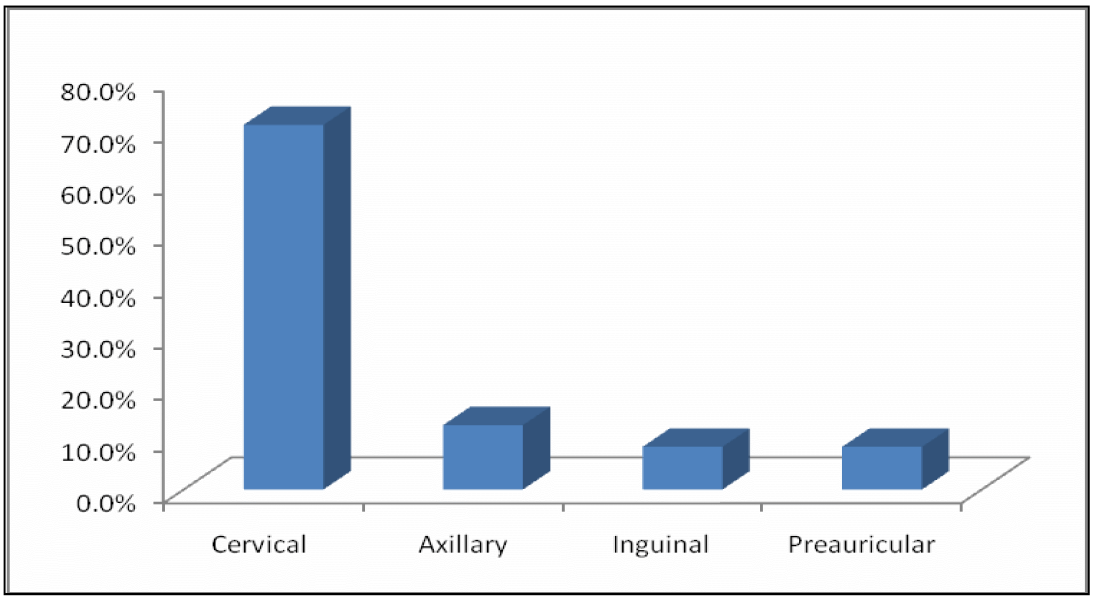

Figure 2: Presentations of extrapulmonary tuberculosis (n=24) in different lymphnode.

In all 13 cases of tubercular meningitis, 8 cases of pleural effusion, and 3 cases of ascitis in abdominal tuberculosis, fluid cytology were strongly suggestive of tuberculosis. Adenosine deaminase activity for mycobacterium was raised in all (100%). Acid fast bacilli on ZN staining seen in two cases of abdominal tuberculosis. Tuberculin test was positive in 38.46% of tubercular meningitis, 75% of pleural effusion, and 33.3% of abdominal tuberculosis.

In cases of musculoskeletal tuberculosis lytic lesion, joint space destruction and periarticular osteoporosis was seen.Cliniclay five patients presented as discharging sinus and two presented as abscess. Of (n=7) Acid fast bacilli seen in 4 (57.1%) cases and one case was confirmed on histopathological examination. Remaining two cases kept under high index of suspicion. Tuberculin test was positive in 85.7%.

In two cases of disseminated tuberculosis, gastric lavage showed acid fast bacilli in one (50%). Single case of cutenous tuberculosis was confirmed histopathologically and was tuberculin positive. Tuberculin test was borderline positive in 3 cases of lymphnode tuberculosis and 1case of disseminated tuberculosis.

All cases presented with constitutional symptoms like fever, anorexia, weight loss malaise and fatigue along with symptoms and signs to related organ. Baseline laboratory investigations show ESR raised in all, 80% cases with anemia, hypoproteinemia in 51.1 %. All the cases were HIV negative. Chest X ray was normal in all cases.

All confirmed as well as the cases with negative test result but strong clinical suspicion of extrapulmonary tuberculosis, supported by radiography and positive hematological tests were treated on the line of EPTB. All cases responded to antitubercular treatment except two cases of tubercular meningitis which shows improvement on repeated cytology but later on expired due to neurological complication.

Discussion

Tuberculosis is one of the measure health problems in India. A nation-wide survey among young children show very high figures of Annual rate of tuberculosis infection in almost all the regions- highest in north zone (1.9%) followed by west zone (1.8%), east zone (1.3%.) and lowest in the south zone (1.0-1.1%)[14]. The results indicate a high rate of transmission of infection due to high load of infectious cases in the community. Uttarakhand is in northern zone with high endemicity for tuberculosis and showing rapidly rising trends of extrapulmonary tuberculosis in area over recent years. Demographic characteristics of extrapulmonary tubercular cases have shown higher detection in females and in patients of young age[15]. The Present study also observes the 23.2% cases of extrapulmonary tuberculosis in children with higher detection in female

which is comparable to other reports (20%-25%) [16]. However the more studies are need to carry out to determine the extrapulmonary tuberculosis and factor responsible for it, but contributory factors may be poor socio-economic status, poor nutrition, lack of awareness, environmental and geographical conditions of hill areas, and onset of HIV era[17]. The importance of these factors is strengthened during early childhood, not only because of the immature immune responses of infants and young children, but also as a result of the economic and social dependence of this group.

Tuberculosis involvement of superficial lymph nodes is common presentation of extrapulmonary tuberculosis in children[18, 19]. The present study also observes the most common presentation as lymphadenitis in 24 (41.3%) cases. Diagnosis of tuberculosis in lymph nodes can be established by demonstrating acid-fast bacilli (AFB) in FNA smears with Ziehl-Neelsen stain or auramine-rhodamine stain, mycobacterium culture or through amplification of bacterial DNA by polymerase chain reaction (PCR) [20, 21]. However, in India, being a developing country, the logistics (cost, equipment and time) involved in other techniques are too much; therefore, demonstration of AFB by Ziehl-Neelsen staining in FNAC smears is the most widely used technique[22].Of the 24, 21 cases (87.5 %) showed acid fast bacilli, which reinforces the necessities and importance of this test in setup like ours where expensive tests like PCR or other technique could not performed either because of high cost or lack of facility.

Infants are more susceptible to undergo severe forms of tuberculosis .Meningitis is common in infants while skeletal and abdominal tuberculosis is more common in older children, indicating age dependent changes in host–pathogen [23]. Tuberculosis meningitis remains the most serious form of extrapulmonary tuberculosis .Thirteen (22.4%) cases in present study had tubercular meningitis most of the child were below the age group of 3 years. Two patients died due to severe neurological complication. Both of these patients did not have BCG vaccination. BCG vaccination is important. Although this did not prevent tuberculosis, but studies have shown that BCG vaccination is helpful in reducing the mortality from severe forms of tuberculosis may be because BCG promotes a T-helper-1 immune response[24, 25].

Adenosine deaminase activity was raised in 100% cases of fluid cytology and all cases responded to antitubercular treatment .Adenosine deaminase (ADA) estimation has been found to be useful in the diagnosis of tuberculosis fluid. Levels rise as a result of stimulation of T cells in response to mycobacterium antigens [26].

Abdominal tuberculosis is caused mostly by mycobacterium bovis and the main route of transmission is the ingestion of infected milk or milk products. In our region people in the remote areas generally consume raw milk. In developing countries abdominal tuberculosis may involve the gastrointestinal tract, peritoneum, lymph nodes or solid viscera; however, peritoneum and abdominal lymph nodes are the most common sites[27, 28]. In this study the age of presentation was similar to the reported in earlier studies (6–11 years) [29]. Abdominal tuberculosis presented with ascitis in all three cases. Acid fast bacilli were demonstrated in 2 cases. All three cases had raised ADA.The

diagnosis was further strengthened by clinical, radiological findings and the response to antitubercular treatment.

Musculoskeletal Tuberculosis is an unusual form of the disease, accounting for 1-5% of all cases of tuberculosis disease and 10-18% of extrapulmonary involvement, as compared to 12.0 % in our study[30-34]. Signs and symptoms are frequently non specific and easily misdiagnosed. The delay in diagnosis may range from months to years in the present study 7 patients had this form of tuberculosis[35]. The most common form involves the vertebral column, followed by the hip, knee, sacroiliac, joint, shoulder, elbow and ankle in order of frequency [36]. However, this study finds tuberculosis in tibia 2 cases, in hip 1 case, in vertebral column 2 cases. Moreover 2 cases of muscle abscess were found. In this study, demonstration of acid fast bacilli in aspiration material were positive in 4 cases and the diagnosis in one patient, was based on histopathological findings. In rest of the cases history of exposure, imaging findings, hematological tests and the response to treatment was considered for diagnosis.

In developing countries where tuberculosis is endemic, and since it is not always possible to identify M. tuberculosis, early treatment should be considered in patients with clinical, radiological and histopathological findings suggesting tuberculosis. Multifocal tuberculosis is rare. There were few reports on multifocal tuberculosis in children and it occurs most commonly in children co infected with Human Immunodeficiency Virus [37]. All our patients were negative for HIV ELISA. In this study anemia was present in 80% of cases, hypoproteinemia in 51.1% of cases.

Childhood tuberculosis reflects the insufficiency of the Public Health System to control and tackle the transmission of infection in the community. Prompt and efficient identification of the source of transmission and application of effective environmental measures are intimately linked to the control of childhood tuberculosis.

Conclusion:

Extrapulmonary tuberculosis is still a measure health problem in childhood. Improving socioeconomic status, effective BCG vaccination, increase awareness about disease, early diagnosis and antitubercular treatment treatment can reduce the mortality and complications. A large scale studies is required to estimate the disease burden in hill region. Children are seemed to be the most vulnerable for EPTB. This group should be targeted for further study to find the cause and intervention for disease prevention.

Author contributios:

Deepa Hatwal – Data, collection, and analysis, manuscript preparation and literature search.

Sheela Chaudhari:- Data collection, analysis and literature search.

Anil Kumar Joshi- Data collection, manuscript preparation, review and literature search.

Vyas Kumar Rathaur- Data collection and review of manuscript.

Reference:

1. World Health Organization, The global burden of disease: 2004 update. World Health Organization, Geneva, Switzerland, 2004.
2. World Health Organization. Global tuberculosis control: surveillance, planning, finances. WHO report 2008. HO/HTM/TB/2008.393. Geneva, Switzerland: WHO, 2008.
3. Raviglione MC, Snider DE Jr, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA. 1995; 273(3): 220-6.
4. Fanning A. Tuberculosis: 6. Extrapulmonary disease. CMAJ. 1999; 160: 1597-603.
5. Iscman MD. Tuberculosis in relation to human immunodeficiency virus and acquired immunodeficiency syndrome. In: Iseman MD, editor. A clinician's guide to tuberculosis. Philadelphia: Lippincott Williams and Wilkins. 2000; 199-252.
6. Dutt AK, Stead WW. Epidemiology. In: Schlossberg D, editor.Tuberculois and nontuberculous mycobacterial infection. Philadelphia: W.B. Saunders Company. 1999; 3-16.
7. Mohan A, Sharma SK. Epidemiology. In: Sharma SK, Mohan A, editors. Tuberculosis. New Delhi: Jaypee Brothers Medical Publishers. 2001; 4-29.
8. Rieder HL, Snider DE Jr, Cauthen GM. Extrapulmonary tuberculosis in the United States. Am Rev Respir Dis. 1990; 141(2): 347-51.
9. Weir MR, Thornton GF. Extrapulmonary tuberculosis. Experience of a community hospital and review of the literature. Am J Med. 1985; 79(4): 467-78.
10. Starke JR. Resurgence of tuberculosis in children. Pediatr Pulmonol Suppl. 1995; 11: 16-7.
11. Smith S, Jacobs RF, Wilson CB. Immunobiology of childhood tuberculosis: a window on the ontogeny of cellular immunity. J Pediatr. 1997; 131(1 Pt 1): 16-26.
12. S.K. Sharma, A. Mohan. Extrapulmonary tuberculosis. Indian J Med. 2004; 316-353.
13. World Health Organization, Treatment of tuberculosis: guidelines for national programmes, World Health Organization, Geneva, Switzerland. 2003.
14. Annual risk of tuberculosis infection in different zones of India. Available from: http://ntiindia.kar.nic.in/docs/ari2000-03/index.html. Accessed December 2, 2009.
15. Rai DK, Bisht RS, Sikarwar V, Upadhyay SK. Clinicoepidemiological trend of tuberculosis in garhwal region. Journal of Pharmacy. 2012; 39-43.
16. Behrman RE, Kliegman RM, Jenson HB. Nelson Textbook of Pediatrics. 17th ed. Philadelphia: WB Saunders. 2004.
17. Gupata P, Rawat J, Sindhwani G, Prasad R, Talekar M. HIV Sero-prevalence and tuberculosis in Uttaranchal. Indian J Tuberc. 2006; 53: 96–100.
18. Narang P, Narang R, Mendiratta DK, Sharma SM, Narang R, NayarS. Field study to evaluate the bacteriological parameters in the diagnosis of lymphnode tuberculosis in children. Indian J Tuberc. 1998; 45:211-4.
19. Aggarwal P, Wali JP, Singh S, Handa R, Wig N, Biswas A. A clinico-bacteriological study of peripheral tuberculous lymphadenitis. J Assoc Physicians India. 2001; 49: 808-12.
20. Raviglione MC, O'Brien RJ. Tuberculosis. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al., editors. Harisson's principles of internal medicine. 14th ed. New York: McGraw-Hill. 1998; 1004-14.
21. Van de Schoot L, Aronson DC, Behrendt H, Bras J. The role of fine-needle aspiration cytology in children with persistent or suspicious lymphadenopathy. J Pediatr Surg. 2001;36:7-11

22. Prasoon D. Acid-fast bacilli in fine needle aspiration smears from tuberculous lymph nodes. Acta Cytologica. 2000; 44: 297-300.
23. Kampmann B, Young D. Childhood tuberculosis: advances in immunopathogenesis, treatment and prevention. Curr Opin Infect Dis. 1998; 11: 331-5.
24. Garly ML, Bale C, Martins CL, et al. BCG vaccination among West African infants is associated with less anergy to tuberculin and diphtheria-tetanus antigens. Vaccine. 2001; 20: 468–74.
25. Roth A, Jensen H, Garly ML, et al. Low birth weight infants and Calmette-Guerin bacillus vaccination at birth: community study from Guinea-Bissau. Pediatr Infect Dis J. 2004; 23: 544–50.
26. Lazarus AA, Thilagar B. Abdominal tuberculosis. Dis Mon. 2007; 53: 32-38.
27. Dinler G, Fiensoy G, Helek D, Kalayc AG. Tuberculous peritonitis in children: Report of nine patients and review of the literature. World J Gastroenterol. 2008; 14: 7235-7239.
28. Basu S, Ganguly S, Chandra P K, Basu S. Clinical profile and outcome of abdominal tuberculosis in Indian children. Singapore Med J. 2007; 48: 900-905.
29. Erkan T, Cam H, Ozkan HC, et al. Clinical spectrum of acute abdominal pain in Turkish pediatric patients: a prospective study. Pediatr Int. 2004; 46: 325-9.
30. Al-Saleh S, Al-Arfaj A, Naddaf H, et al. Tuberculous arthritis: a review of 27 cases. Ann Saudi Med. 1998; 18: 368–9.
31. Garrido G, Gomez-Reino JJ, Fernandez-Dapica P, et al. A Review of Peripheral Tuberculous Arthritis. Sem Arthritis Reum. 1988; 18: 142–9.
32. González-Gay MA, García-Porrúa C, Cereijo MJ, et al. The clinical spectrum of osteoarticular tuberculosis in non-human immunodeficiency virus patients in a defined area of northwestern Spain (1988–97). Clin Exp Rheumatol. 1999; 17: 663–9.
33. Rodríguez NG, Ruán JI, Seoane JL, et al. Tuberculosis extrapulmonar diseminada con afección cutánea, ganglionary ósea. An Med Interna. 1999; 10: 525–6.
34. Meier JL. Mycobacterial and fungal infections of bone and joints. Curr Opin Rheumatol. 1994; 6: 408–14.
35. Evanchik CC, Davis DE, Harrington TM. Tuberculosis of Peripheral Joints: An Often Missed Diagnosis. J Rheumatol. 1986; 13: 187–9.
36. Moore SL, Rafii M. Imaging of musculoskeletal and spinal tuberculosis. Radiol Clin orth Am. 2001; 39: 329-342.
37. Mabiala-Babela JR, Makosso E, Senga P. Retrospective study of 61 cases of multifocal tuberculosis in children in Brazzaville. Congo Med Trop. 2008; 68: 41-4.