EAS Journal of Parasitology and Infectious Diseases
Abbreviated Key Title: EAS J Parasitol Infect Dis
ISSN 2663-0982 (Print) & 2663-6727 (Online) Open Access
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-1 | Issue-5| Sep-Oct-2019 | DOI: 10.36349/easjpid.2019.v01i05.002

Research Article

Cyto-Morphological Response among Extrapulmonary Cervical Tuberculous Lymphadenitis after Two Months of Anti-Tubercular Therapy – A Tertiary Care Center Experience from Remote Indian Island

Dr Samarendra P. Burma[1], Dr Pushpanjali R Ojha[2*], Dr Rakesh kumar[1], and Dr Gulnar Begum[1]

[1]Assistant Professor, Department of Chest and TB, ANIIMS, Port Blair, India
[2]Assistant Professor, Department of Pathology, TRIHMS, Arunachal Pradesh, India

*Corresponding Author
Dr Pushpanjali R Ojha

Abstract: Cervical tubercular lymphadenitis (CTLA) the commonest extrapulmonary tuberculosis which involves human being irrespective of age, sex and race. The disease imparts a global burden because of absence of single confirmatory diagnostic tool in spite of technological advancements, several factors determining the therapeutic response, lack of patient compliance, loss to follow up and absence of definitive single diagnostic tool for follow up. This study is designed to find out a convenient diagnostic tool for confirmatory diagnosis, to analyze the therapeutic response after two months of ATT therapy and to define an algorithm for follow up. This study included 60 cases of adult patients of CTLA and investigated and followed up with FNAC, GeneXpert and MGIT 960 tests. We concluded in our study that cytology can be an easier, cost effective diagnostic tool and can be used to follow up cases after therapy to monitor the response in developing countries with limited resources.

Keywords: GeneXpert, MGIT 960, Therapeutic response (Complete, gradual, incomplete), Post – therapy cytological changes.

INTRODUCTION:

Worldwide extrapulmonary tuberculosis occurs between 10 and 25% of all tuberculosis cases. Cervical Tubercular lymphadenitis (CTLA) is the commonest one among extrapulmonary group of tuberculosis (Biswas *et al.*,, 2018). It affects human beings irrespective of age, sex, race, ethnicity or socio-economic status. The disease has diverse clinical presentation few of them may resemble with primary or secondary neoplastic lesions. These lesions show variation in the therapeutic response at cytological level. CTLA may impart diagnostic and therapeutic challenge because of clinical and cytological diversity and hence need complete cytological follow up including categorization of response. Yogesh Mistry *et al.*, (2012) reported that the conventional methods of diagnosis for tuberculosis like sputum examination of acid-fast bacilli and chest X-ray are fairly accurate in detecting the active pulmonary component of the disease whereas tissue diagnosis is the investigation of choice for extrapulmonary tuberculosis. The cytological confirmation of the cause of lymphadenopathy, differentiation from neoplastic lesions, species identification by culture, categorization of disease according to RNTCP guidelines, initiation of Anti-tubercular therapy (ATT) regimen and the response of therapy after the induction phase (IP) are essential for patient care and prevention of disease spread. Biswas *et al.*, (2018) in their study observed that TBLA may respond slowly to standard ATT with persistent discomfort and thus recommended frequent follow-up during treatment for reassurance and management of local discomfort. They also states that further study is needed as an adjunct to standard antibiotic therapy to improve the otherwise slow response to treatment. Fine Needle Aspiration Cytology (FNAC) is the procedure of choice for the diagnosis and follow ups of patients after IP phase of ATT regimen. ATT regimen includes bacteriostatic and bactericidal drugs that kill the bacteria more effectively. There is rapid change at the tissue level during the course of therapy. This study was conducted with following aims and objectives:-

Quick Response Code

Journal homepage:
http://www.easpublisher.com/easjpid/

Article History
Received: 30.08.2019
Accepted: 05.09.2019
Published: 23.09.2019

- To observe the therapeutic response of ATT at cytological level after induction phase.
- To categorize the therapeutic response on the basis of cytology.
- To prepare an algorithm for further management of the persistent lesions.

MATERIALS AND METHODS:

MATERIALS:

This was a prospective study conducted in the Department of TB and Chest of a newly established Medical college situated at remote Indian Island during the period of June 2016 to December 2018. The study included all the adult patients of age range (18-68 years) who were visited the OPD of TB and Chest Department with persistent neck swelling after taking antibiotics and associated with high suspicion of Tuberculosis. Pediatric patients, patients with pulmonary tuberculosis, Multi-drug resistant tuberculosis, XDR tuberculosis and those with HIV co-infection were excluded from the study. The study included FNAC, GeneXpert and MGIT 960 tests for the diagnosis, follow up and observation of therapeutic response. Ethical clearance from the Institutional Ethical committee was obtained prior to the initiation of study. Informed consent from all the patients was taken before the procedure. There were 1697 enrolments during the study period out of which 79 were followed up after therapy. Among these 79 cases, 19 were excluded because of sample inadequacy (7), death during therapy (4) and loss to follow up (8). Total 60 cases of CTLA were finally counselled and asked about their relevant past, present, family, personal (smoking, tobacco chewing or alcohol intake) and clinical history (Diabetes, Hypertension, HIV, HBV or HCV infection, loss of weight, anorexia, night sweat or fever), were investigated with CXR, sputum examination, CBC, ESR, FNAC, GeneXpert and MGIT 960, categorized under Category I of RNTCP guideline, treated with ATT for two months and followed up with FNAC, GeneXpert and MGIT 960. All the cases with LNs measuring more than 2 x 2 cm in diameter at the time of diagnosis and persistent but reduced in size post – therapy were included and analyzed in the study.

METHODS:

FNAC was performed with 19 – 21 G needle and aspirates were collected. Touch imprints were taken from patients presenting with ulcers or sinuses. At least 1 ml of aspirates were collected, examined grossly and termed as (a) blood mixed (b) grayish brown purulent (c) serous thin fluid and (d) yellowish caseous material. It was divided into two parts- One was sent for GENEXPERT and another was used to prepare air dried smears and stained with Giemsa, H&E and Ziehl-Neelsen stain. Smears were examined and reported as Reactive lymphoid hyperplasia (RLH), Tubercular lymphadenitis (TBLA) and Granulomatous lymphadenitis (GrLA).

GeneXpert test was considered as gold standard in the present study. The test consists of a closed system that is based on real-time polymerase chain reaction (PCR). It can be used by operators with minimal technical expertise, enabling the diagnosis of TB and simultaneous detection of rifampicin resistance within 2 hours (WHO 2011). In 2014, WHO has recommended GeneXpert over the conventional tests (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary tuberculosis. The aspirate material was centrifuged and the sediment was mixed with the sample reagent (1.5ml) supplied with the test in a 3:1 ratio (0.5ml). The mixture was vortexed and incubated at room temperature for 15 minutes. Two ml of the reagent sample mix was then transferred to a cartridge using a Pasteur pipette and the cartridge was loaded onto GeneXpert machine. Results were reported as positive or negative for *M. tuberculosis*, including a semi-quantitative scale based on the quantitative cycle threshold (*Ct*) value of probe A. Rifampicin resistance results were reported as susceptible, resistant or indeterminate (M Tadesse).

MGIT 960 test was done to confirm the diagnosis especially in cases with reactive lymphoid hyperplasia and those were ZN stain negative, to know the bacterial load and their susceptibility to ATT. The principle of this test was based upon that MGIT tube contains an oxygen-quenched fluorochrome, tris 4, 7-diphenyl-1, 10-phenonthroline ruthenium chloride pentahydrate, embedded in silicone at the bottom of the tube. Decontaminated samples were inoculated into MGIT tube (containing 7H9 medium), MGIT 960 non-radiometric automated isolation system (Becton Dickinson, Sparks, MD, USA). During bacterial growth within the tube, the free oxygen is utilized and is replaced with carbon dioxide. With depletion of free oxygen, the fluorochrome is no longer inhibited, resulting in fluorescence within the MGIT tube when visualized under UV light. The intensity of fluorescence is directly proportional to the extent of oxygen depletion. In case of *M. tuberculosis*, at the time of positivity, there is approximately 10^5 – 10^6 colony forming units (CFU) per ml of medium should be present. The instrument declares a tube negative if it remains negative for six weeks (42 days).

Anti-tubercular regimen started in patients those were found to be positive for Tuberculosis either on cytology, GeneXpert or by MGIT 960. After two months of therapy, cytology, GeneXpert and MGIT 960 were repeated to observe the therapeutic response with similar steps as mentioned above. 29 of these cases had no palpable LNs hence USG guided FNAC were performed among these.

All the results were compiled, analyzed and compared with the result of gold standard technique i.e GeneXpert

RESULT:

Out of the 1697 enrolled cases of Tuberculosis in the TB and Chest department during the study period, 60 were followed up for two months post therapy with FNAC, GeneXpert and MGIT 960 tests. Age and sex distribution reflects predominance of cases falling in the age range of 18-28 years and female to male ratio of 1.6:1. The most common presenting complaint was fever followed by weight loss along with disease specific complaint of solitary, firm nontender neck mass followed by neck mass with discharging sinus. On clinical examination solitary enlarged cervical lymph nodes were observed among 47 cases with size ranging between 2.00 to 3.8 cm, 5 cases had sinus tracts with serous discharge, 4 cases had matted hard lymph nodes with strong clinical suspicion of metastatic malignancy and 4 cases had ulcers with caseous material. All of the cases had normal sputum and Chest X – Ray examination thus possibility of pulmonary tuberculosis excluded. Complete blood count (CBC) revealed microcytic hypochromic anemia in 32 cases, neutrophilia in 16 cases and lymphocytosis in 12 cases. Raised ESR was observed in 48 cases. Diagnostic FNAC yielded blood mixed aspirate among 39 cases, grayish brown purulent aspirate among 12 cases, serous thin fluid among 5 cases and yellowish caseous material among 4 cases. The cytological spectrum was grouped into Reactive lymphoid hyperplasia (RLH), Tubercular lymphadenitis (TBLA) and Granulomatous lymphadenitis (GrLA) in the decreasing order of frequency. ZN stain demonstrated AFB in 57.33% cases from purulent aspirate, 45.38% from caseous aspirate, 21.01% from serous fluid and 4.80% from blood mixed aspirates. Cases from RLH and 33.37%of GrLA were ZN stain negative but found positive with GeneXpert and MGIT 960 tests. MGIT 960 test included in the study to increase the confirmative diagnosis of tuberculosis with extrapulmonary tissue material. Mistry *et al.*, reported positive ZN stain in 53.33% cases from pus, 33.33% from cheesy aspirate and 5.88% cases from blood mixed aspirate.

GeneXpert and MGIT 960 results were positive in all cases with bacilli load range 10^4 to 10^{11}. Gautam H *et al.*, 2018 observed detection rates of MTBC by Xpert MTB/RIF and MGIT 960 were 25.71% and 17.85% respectively. The bacilli load was lower in cases of RLH and GrLA and higher in cases of TBLA. On the basis of cytological diagnosis, GeneXpert and MGIT 960 findings, ATT was started and patients were followed up after two months. 29 cases of RLH and 13 cases of GrLA underwent complete response whereas one case of TBLA progressed to MDR. TBLA cases show gradual and incomplete response to ATT. 99% of cases had experienced relief in their systemic symptoms related to the disease like absence of fever and anorexia as well as increase in appetite and weight. Therapeutic response in clinical appearance of LN was described as a spectrum ranging from non-palpable lesion, LN reduced to < 2 cm, granulation tissue, healed scar and unchanged LN. The cytological response was categorized by complete, gradual and incomplete response. Cytological evaluation concluded that RLH lesions were responded very well with 93% normal lymphoid morphology whereas TBLA cases responded least with only 22% normal lymphoid morphology. Spectrum of cytological response was described as normal lymphoid cytology, Occasional granuloma, No granuloma but occasional epithelioid cells, No necrosis with occasional epithelioid cells and MNGs, No necrosis with occasional granuloma, No necrosis but with granulation tissue and occasional MNGs, RLH, TBLA as well as GrLA. Only 23.08% of GrLA and 11.11% of TBLA cases were underwent complete response in the form of as normal lymphoid cytology. 6.90% cases of RLH and 5.08% cases of TBLA show persistence of lesion. The GeneXpert and MGIT 960 findings became negative in all cases of RLH. 13 cases of TBLA and only one case of GrLA appear positive with GeneXpert after therapy. One case of TBLA developed resistance against RIF on GeneXpert with highest bacterial load as observed on MGIT 960.

Table 1 Demographic, Clinical and disease specific parameters

Age range in years	**Female**	**Male**
18 – 28	17	10
29 – 38	12	7
39 – 48	6	4
49 – 58	1	1
59 – 68	1	1
Systemic symptoms	**Number of cases/Percentage**	
Fever	35 / 58.33 %	
Weight loss	16 / 26.66 %	
Anorexia	07 / 11.66 %	
Night sweat	02 / 03.33 %	
Disease specific symptom	**Number of cases/Percentage**	
Solitary, firm, nontender neck mass	47/ 78.33%	
Neck mass with discharging sinus	05/ 08.33%	
Soft, cystic, matted and tender neck mass	04/ 06.66%	
Ulcerative neck mass	04/ 06.66%	

Table 2 Post – therapy clinical and cyto-morphological pattern of Cervical LN tuberculosis

Pre- therapy Diagnosis	Cyto-morphological response (percentage)		Clinical response (percentage)	
RLH (29/60 cases)	Normal lymphoid cytology	93.10%	No palpable LN	72.41%
	RLH	06.90%	Reduction in size of LN	27.59%
GrLA (13/60 cases)	RLH	38.46%	Reduction in size of LN	69.23%
	No granuloma, occasional epithelioid cells	23.08%	No palpable LN	30.77%
	Normal lymphoid cytology	23.08%		
	Occasional granuloma	15.38%		
TBLA (18/60 cases)	No necrosis, occasional epithelioid cells and MNGs	44.44%	Reduction in size of LN	33.33%
	No necrosis, occasional granuloma	11.11%	No palpable LN	22.22%
	No necrosis, granulation tissue and occasional MNGs	11.11%	No discharge, healed scar	22.22%
	RLH	11.11%	No discharge, granulation tissue	16.67%
	TBLA	05.56%	No change in LN	
	GrLA	05.56%		05.56%
	Normal lymphoid cytology	11.11%		

Table 3 GENEXPERT and MGIT 960 Findings in Pre & Post – therapy cases:-

Pre - therapy			Post –therapy			
Cytological diagnosis	**GENEXPERT**	**MGIT 960**	**Cytological diagnosis and response**		**GENEXPERT**	**MGIT 960**
RLH	Positive/RIF sensitive	Positive	**RLH**	Normal lymphoid cytology	Negative	Negative
				RLH	Negative	Negative
GrLA	Positive/RIF sensitive	Positive	**GrLA**	RLH	Negative	Negative
				No granuloma, occasional epithelioid cells	Negative	Negative
				Normal lymphoid cytology	Negative	Negative
TBLA	Positive/RIF sensitive	Positive		Occasional granuloma	Positive/RIF sensitive	Positive
			TBLA	No necrosis, occasional epithelioid cells and MNGs	Positive/RIF sensitive	Positive
				No necrosis, occasional granuloma	Positive/RIF sensitive	Positive
				No necrosis, granulation tissue and occasional MNGs	Positive/RIF sensitive	Positive
				RLH	Negative	Negative
				TBLA	Positive/RIF Resistant	Positive
				GrLA	Positive/RIF sensitive	Positive
				Normal lymphoid cytology	Negative	Negative

Table 4 Degree of therapeutic Response:

	Complete response	Gradual response	Incomplete response	MDR
RLH (29/60)	28/29 (96.55%)	01/29 (03.45%)	00/29 (00.00%)	00/29 (00.00%)
TBLA (18/60)	02/18 (11.11%)	11/18 (61.11%)	04/18 (22.22%)	01/18 (05.56%)
GrLA (13/60)	09/13 (69.23%)	04/13 (30.77%)	00/13 (00.00%)	00/13 (00.00%)

Clinical presentation at the time of diagnosis:

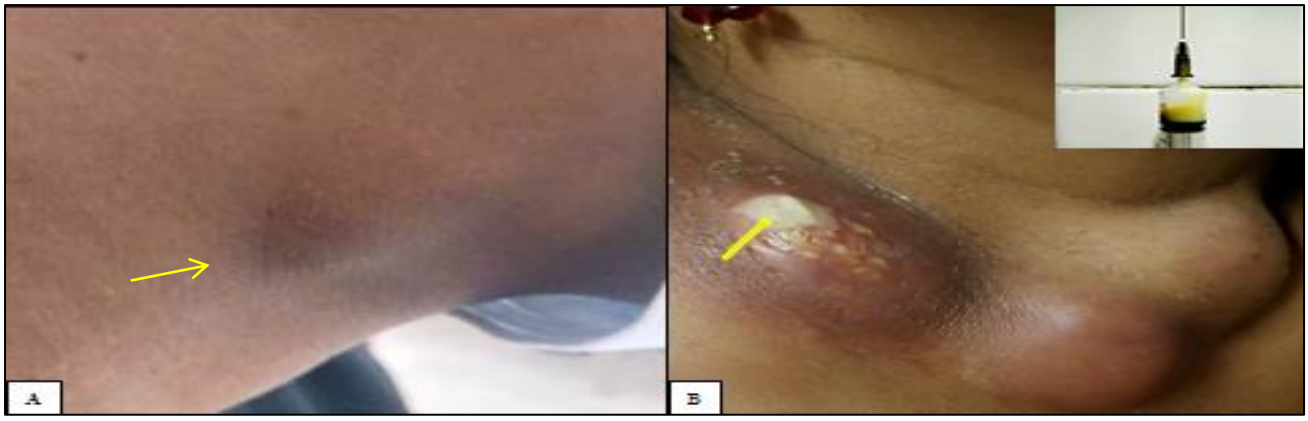

Figure 1 Solitary, painless, enlarged cervical lymph node (yellow arrow) [A] Multiple, tender, matted cervical lymph node with one discharging sinus (yellow arrow) [B].Thick yellowish purulent aspirate from the lesion [inset].

Clinical response of therapy after two months of ATT regimen:

Figure 2 Reduced size of cervical lymph node [A], Persistent matted cervical lymph nodes with one poorly healed lymph node at upper left side [B], Solitary cervical lymph node with evidence of healing [C].

Cytological presentation of cervical tubercular lymphadenitis

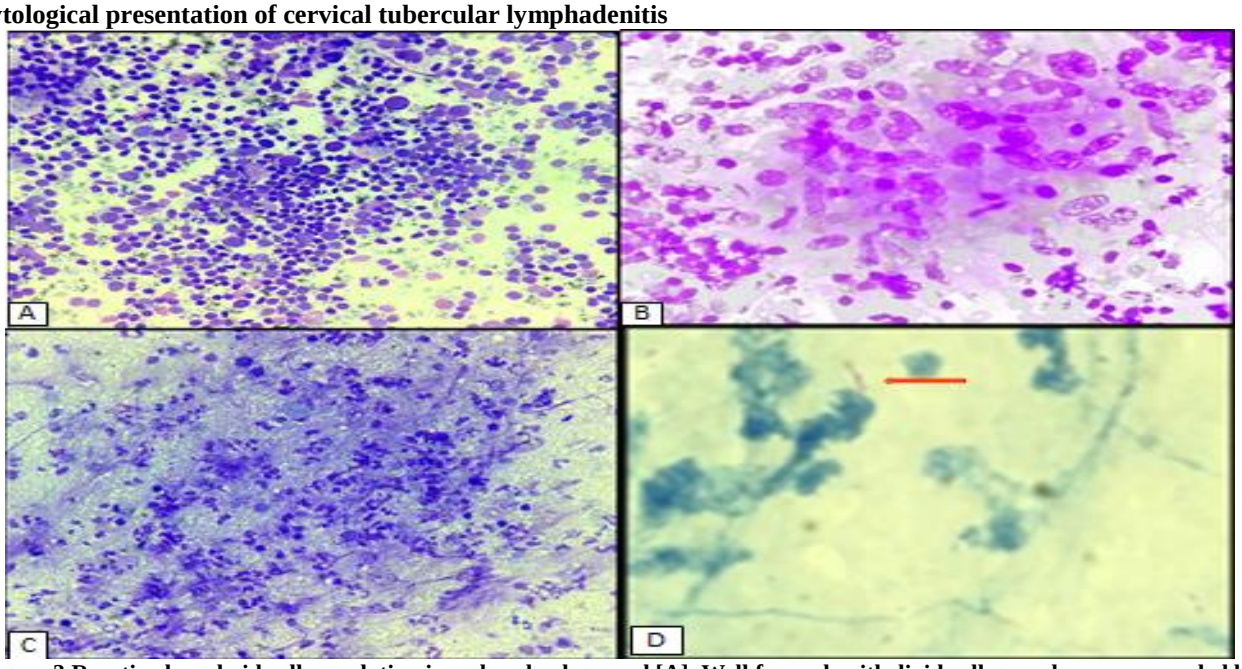

Figure 3 Reactive lymphoid cell population in a clear background [A], Well formed epithelioid cell granuloma surrounded by inflammatory cells in a hemorrhagic background [B], Polymorphonuclear cell population, few lymphoid cells and necrotic cell debris in a dirty background [C], Long, pink, slender and beaded mycobacteria with blunt ends (red arrow) [D].

DISCUSSION:

Worldwide, tuberculosis (TB) is one of the top 10 causes of death and the leading cause from a single infectious agent with an estimated 1.3 million deaths and 10.0 million new cases of TB. India accounts 27% of the total TB cases and 24% of Rifampicin resistant TB (RR-TB) cases (WHO 2018).

Cervical tubercular lymphadenitis is one of the commonest extrapulmonary manifestations of the

disease with marked variation in clinical and cytological patterns as well as in their therapeutic response (Mistry *et al.,* 2012, Biswas *et al.,* 2018). Extrapulmonary TB represents 14% of the 6.4 million incident cases that were notified in WHO 2017 and comprises a fifth of all TB cases (S K Sharma *et al., 2004*). Tubercular lymphadenitis accounts for 20-40% of EPTB cases (P R Gupta 2004).

The disease may affect patients irrespective of their age and sex however this study observed that middle age group was most frequently involved with female predominance which is also supported by the study Gupta V *et al.,* 2018 and Biswas *et al.,* 2018. According to WHO, Eastern Mediterranean, South-East Asia and Western Pacific regions, the TB epidemic is a markedly ageing one, with a progressive increase in the notification rate with age, and a peak among those aged $\geq$ 65 years. TB affects all countries and all age groups, but overall the best estimates for 2017 were that 90% of cases were adults (aged $\geq$15 years) and 64% were male. The present study observed female preponderance which is similar with the study of Gupta V and Bhake A 2018 but in contrast to the WHO reports. Variation among countries in the child : adult and M : F ratios of cases may reflect real differences in epidemiology, differential access to or use of health-care services, or differential reporting practices (WHO 2018).

Over 95% of TB deaths occur in low- and middle-income countries, and it is among the top 5 causes of death among women aged 15-44 years (WHO 2014). Ramanathan VD *et al.,* 1999 reported that this may be due to biological, hormonal, social, environmental and behavioral differences between men and women. Biologically the female immune systems show hormonal influences that can be indicated as the underlying cause for the different pattern of disease. Females leaving in developing countries often have low socio-economic and nutritional status that can affect the immune response to disease.

The spectrum of clinical pattern in the present study will range from solitary painless lymph node enlargement, tender matted mass, suppurative lesion to discharging sinuses. Gupta V *et al.,* 2018 reported that clinical features are influenced by host factors such as age, sex, nutrition, genetics, family history of contact, and the immune competence of the patient. This leads to varied clinical and morphological presentations, with 53.3% presenting with 1 or more constitutional symptoms, with fever being the most prevalent (36.4% of the total cases).58.33% of patients with CTLA were presented with fever in this study. kartikranjan (2014) reported that 55% of patients have lymphadenopathy and 22% have fever. 78.33% patients were presented with solitary lesion.

The cytological spectrum in the study will range from RLH, GrLA to TBLA. The immunological status of patient determines the cytological pattern of disease. Patients with good immunity were found to have RLH, epithelioid granulomas or granulomas without necrosis whereas those with poor immunity develop TBLA with marked necrosis. Reactive lymphoid hyperplasia was the commonest diagnosis similar to that reported by Gupta V *et al.,* 2018. Reactive lymphoid hyperplasia was found in smears made from bloody aspirate and characterized cytologically by presence of mixed lymphoid cell population with predominance of small lymphocytes and variable proportion of centroblasts, centrocytes, immunoblasts, plasma cells, dendritic cells, interspersed pale histiocytes, interdigitating cells, endothelial cells, eosinophils, neutrophils and tingible body laden macrophages. TBLA cases were reported from purulent aspirates and cytologically characterized predominantly by neutrophils, necrotic debris and occasional epithelioid cells. GrLA were characterized cytologically by presence of epithelioid histiocytes forming cohesive clusters and Langhans type of giant cells. Gupta V *et al.,* 2018 states in their study that Real-time PCR for mycobacteria on aspirates proved to be a useful molecular investigative tool in clinically suspected tubercular lymphadenopathy, offering a definitive and comparable diagnosis. Including PCR for mycobacteria in the diagnostic algorithm for the evaluation for tubercular LNs obviates the need for lymph node biopsy and could reduce the burden of TB.

This study grouped the therapeutic response into three categories based on cytological, GeneXpert and MGIT 960 test results after two months of therapy. Complete response was defined as those cases with normal cytological appearance and negative GeneXpert and MGIT 960 results. These patients were followed up and completed the maintenance phase for further four months and declared cured after that. Gradual response was defined as patients showing clinical improvement with reduced but still palpable LN, cytological upgradation like finding of RLH in previously diagnosed GrLA and TBLA. The GeneXpert and MGIT 960 were show reduced but positive bacilli load. These patients were continued with five drug maintenance phase for further four months and tests were repeated. The results were negative hence they declared cured after that. The probable cause behind this was poor nutritional status and compliance of the patient.

Incomplete response was defined as patients which show reduced LN size, mild cytological change and positive GeneXpert and MGIT 960 tests. Out of four of these cases one was found to have MDR/RR – TB. These cases were evaluated further, found to be Rifampicin resistant and hence treated with second line ATT drugs. This may happens probably due to non-compliance of patient leading to the development of drug resistance and poor immunity, warm, humid and overcrowded living environment. Under-diagnosis can occur due to poor geographical and financial access to

health care; lack of or limited symptoms that delay seeking of health care; failure to test for TB when people do present to health facilities; and diagnostic tests that are not sufficiently sensitive or specific to ensure accurate identification of all cases (WHO 2018).

Globally, 3.5% of new TB cases and 18% of previously treated cases had MDR/RR-TB. This study reported 1.67% of MDR/RR – TB in previously treated patients. The latest treatment outcome data show treatment success rates of 82% for TB. Prompt and accurate diagnosis of tuberculosis (TB) and drug-resistant TB, followed by provision of treatment in line with International standards, prevents deaths, limits ill-health among people and further transmission of infection to others. The microbiological detection of TB is critical for infection control because it allows patients to be correctly diagnosed and started on the most effective treatment regimen as early as possible. Globally, TB treatment coverage was 64% in 2017 (WHO 2018).

CAT I ATT regimen was started in all of these cases on the basis of cytological, molecular and clinical diagnosis. Patient's immune system will determine the response of ATT therapy. Patients with good immunity were responded very well as evidenced by improvement in clinical symptoms in the form of increase in appetite, weight gain, absence of fever, anorexia and night sweat, decrease in LN size (11.67%), healing of suppurative lesion by granulation tissue and scar formation. The ulcerated lesions responded with signs of healing with loss of discharge, healthy wound margin and decrease in size. Few of them were replaced by a healed scar. Discharging sinuses were absent.

The cytological response was reported as absence of granuloma in 38.33% cases after two months of therapy. Cytology shows absence of bacilli but they were still positive on CB-NAAT that indicates that these patients need continuation of therapy as the bacilli were reduced in number but still persists within the lesion.

This study aimed to see the response of therapy on lymph node at cellular level and the study effectively observed the alterations. It concludes that there is reduction in the size of affected lymph node on gross examination and reversal of pathology from caseous necrosis towards reactive lymphoid hyperplasia after the induction therapy with ATT.

This study also observed and analyzed the factors influencing the response and found that there were multiple confounding factors that alter the therapeutic response most important among them are socio-economic status, patient compliance toward understanding the disease and drug intake, immunological status, effective drug doses. The study attempted to define therapeutic response in the form of complete, gradual and incomplete based on the cytological, molecular and microbiological finding.

CONCLUSION:-

The study summarizes and defines an algorithm for patients with CTLA as follow:

1. Start empirical therapy for painful and palpable CTLA. Follow it up for two weeks if the size reduced then wait and watch for next two weeks. If there is no change in size or increase in size suspect Tuberculosis and investigate with cytology, GENEXPERT and MGIT 960, start category based ATT regimen and follow the patients after induction phase. If swelling persists but cytologically, molecularly and microbiologically negative continue the maintenance therapy for next four months, stop the regime and follow up the patient for further six months.
2. if patient presents with ulcer or discharging sinus, start empirical therapy along with wound care for two weeks, if there is minimal response or no response investigate with FNAC, GeneXpert and MGIT 960, start ATT both systemic and local for two months and follow up the case for next four months of maintenance phase and six months thereafter.

REFERENCES:

1. Biswas, R. S. R., Chowdhury, M. F. K., & Mamun, S. M. H. (2018). Clinicopathological profile and outcome of 29 lymph node tuberculosis cases. *Journal of the Scientific Society*, *45*(2), 76.
2. Mistry, Y., Ninama, G.L., Mistry, K., Rajat, R., Parmar, R., & Godhani, A. (2012). Efficacy of Fine Needle Aspiration Cytology, Ziehl-Neelsen stain and culture (BACTEC) in diagnosis of Tuberculosis lymphadenitis. National J of Med Res, 2(1), 77-80.
3. Gautam, H., Agrawal, S. K., Verma, S. K., & Singh, U. B. (2018). Cervical tuberculous lymphadenitis: clinical profile and diagnostic modalities. *International journal of mycobacteriology*, *7*(3), 212.
4. World Health Organization: Global tuberculosis report. (2018). Geneva,WHO, 2018. http://www.who.int/mediacentre/factsheets/fs104/en/ (accessed July 26, 2019).
5. Sharma, S.K., & Mohan, A. (2004). Extra pulmonary tuberculosis. Indian J Med Res 120, 4316-4353.
6. Gupta, P.R. (2004). Difficulties in managing lymph node tuberculosis. Lung India, 21, 50-53.
7. Gupta, V., & Bhake, A. (2018). Assessment of Clinically Suspected Tubercular Lymphadenopathy by Real-Time PCR Compared to Non-Molecular Methods on Lymph Node Aspirates. Acta Cytologica, 62, 4-11.
8. World Health Organization. (2014). Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations.

9. Ramanathan, V. D., Jawahar, M. S., Paramasivan, C. N., & Rajaram, K. (1999). A histological spectrum of host responses in tuberculous lymphadenitis. *Indian Journal of Medical Research*, *109*, 212.
10. World Health Organization: Global tuberculosis report. (2016). Geneva,WHO, 2016. http://www.who.int/mediacentre/factsheets/fs104/en/ (accessed August 15, 2016).
11. Kartikranjan, M. (2014). A clincopathological study of cervical lymphadenopathy. Int J Mod Res Rev, 2, 354-357.
12. Khandkar, C., Harrington, Z., Jelfs, P.J., Sintchenko, V., & Dobler, C.C. (2015). Epidemiology of peripheral lymph node tuberculosis and genotyping of *M. tuberculosis* strains: A case-control study. PLoS One, e0132400. (F:M= 2.8:1).
13. World Health Organization. (2011). Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational 'How-to'; practical considerations.