



## Original Research Article

## Cyto-serological correlation in toxoplasma lymphadenitis: Is bypassing biopsy plausible?

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## ABSTRACT

**Objective:** To study ten cases of toxoplasmic lymphadenitis (TL) in which the diagnosis was made by fine needle aspiration cytology and confirmed by subsequent serology.

**Study design:** Retrospective study done over a period of five years. We retrieved ten cases of Toxoplasma lymphadenitis in which fine-needle aspiration cytology (FNAC) of lymph node was done after clinical examination. Serology with electrochemiluminescence was done in all the cases.

**Results:** The cytological features were characterised by microgranulomas, abundance of tingible body macrophages and absence of necrosis. Serologic testing for toxoplasma in all the cases revealed elevated titres.

**Conclusion:** Lymphadenitis due to Toxoplasma infection should be considered in the diagnosis of unexplained lymphadenopathy at all sites, especially the cervical region. Serologic confirmation should be recommended for all suspected cases. FNAC diagnosis can eliminate the need for hospitalization and surgery. To the best of authors' knowledge, this is 5<sup>th</sup> case series of cytodagnosis of TL in the English literature and 2<sup>nd</sup> in the Indian literature. This is the largest case series of cytodagnosis of TL in the Indian literature and 2<sup>nd</sup> largest in the world literature next to the one done by Haque et al.

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### 1. Introduction

Toxoplasma gondii is a ubiquitous coccidian protozoan; definitive hosts are felines like cat, while intermediate hosts are man and other mammals.<sup>1</sup> Toxoplasma infection may be congenital or acquired. The disease is transmitted to humans mostly by intake of undercooked or raw meat containing viable tissue cysts, or by ingesting food or water contaminated with oocyst<sup>2</sup> or through skin inoculation.<sup>3</sup> In acquired infections the disease mostly remains occult until cellular immunity is impaired.<sup>3</sup> The commonest clinical manifestation of the acquired disease is flu like symptoms with lymphadenopathy- also known as Pinner-Kuchinka lymphadenitis.<sup>1</sup>

Diagnosis of toxoplasma lymphadenitis (TL) is important as it can be treated by medical management.<sup>4</sup> Serology is the mainstay of diagnosis.<sup>4</sup> Although prevalence of Toxoplasma infection is high, most of the acquired toxoplasmosis patients who present with lymphadenopathy are usually not suspected. They are advised for fine needle aspiration cytology (FNAC) as their first line investigation. FNAC is widely practiced, safe, simple, and rapid, relatively less painful and minimally invasive technique. Definite diagnosis of TL can be done if tissue cyst or bradyzoites are seen in the FNAC smears; a very

rare finding in clinical practice. Rarely has the demonstration/ identification of the morphologic stages of the parasite been reported.<sup>5,6</sup> However, FNAC smears from lymph nodes affected by toxoplasmosis show some characteristic features in addition to features which are

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present in reactive hyperplasia of lymph node. Careful cognizance of those findings can give the clue of the diagnosis which can be confirmed by serological evidence. Our study was to focus on those criteria which can be helpful for diagnosis of TL, as it is rare to pick up the diagnosis of this entity on FNAC. The study emphasizes consideration of toxoplasmosis in the differential diagnosis of granulomatous lymphadenitis during evaluation of cytospreads of lymph node. A cytodiagnosis of TL followed by serological confirmation helps the patient to get appropriate medical treatment thereby avoiding any surgical procedure. To the best of authors' knowledge, this is 5th case series of cytodiagnosis of TL in the English literature and 2nd in the Indian literature. This is the largest case series of cytodiagnosis of TL in the Indian literature and 2nd largest in the world literature next to the one done by Haque et al.<sup>7</sup>

## 2. Materials and Methods

This is a retrospective study carried over a period of five years, i.e. from August 2009 to August 2014. All cases with lymphadenopathy who reported for FNAC were aspirated using 5cc syringe with 24G needle. Smears were stained with H&E and Papanicolaou stain after fixation in 95% ethanol for 30 min. and pap fixative, respectively. Then they were evaluated based on cytomorphology. Additional special stains such as Z-N and Giemsa were done whenever required. Only the cases with cytological suspicion of TL were included in the study. Following cytomorphological features were evaluated:

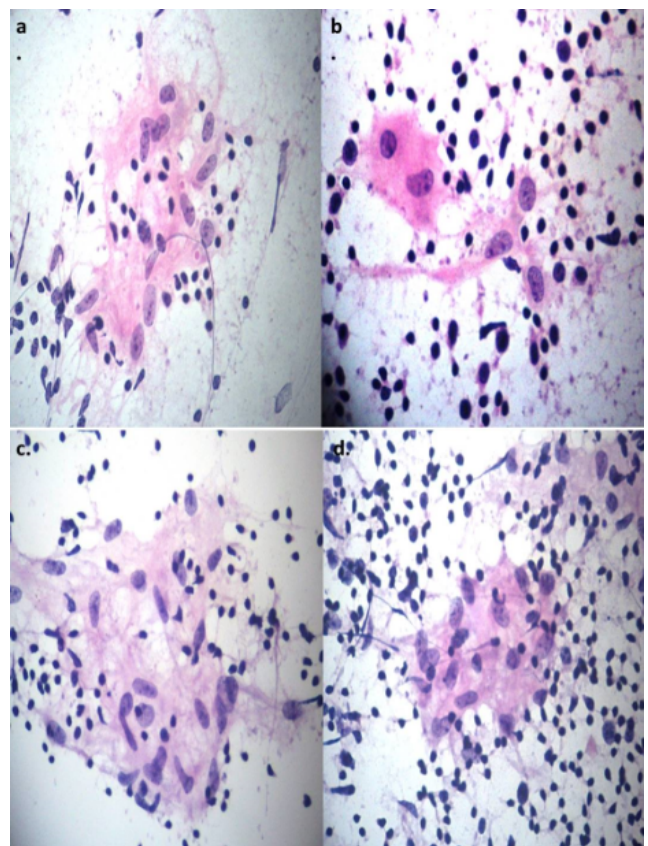
1. Tiny collections of epithelioid histiocytes having abundant cytoplasm. (Micro granulomas)
2. Conspicuous abundance of tingible body macrophages
3. Absence of necrosis and/or more than occasional giant cells.

All patients suspected of TL underwent serological test for *Toxoplasma* IgM and IgG antibodies by electrochemiluminescence. (Roche cobas e 411). The cut off points for positive results for IgM and IgG were >0.65 IU/ml and >8 IU/ml, respectively.

## 3. Result

Ten patients diagnosed as TL on cytology were included in the study and all of them were investigated for serology of anti-*Toxoplasma* antibody by electrochemiluminescence, which confirmed the diagnosis in all these ten patients. Two but all of them were positive for IgM. All of them were positive for IgG. (Table 1)

The age of patients diagnosed finally as TL ranged from 20 to 47 years. Mean age was 34.6 years. Five were males and five were females (M: F = 1:1).



**Fig. 1:** a) to d)- H&E stained cytospreads showing epithelioid cell microgranulomas with cells having abundant eosinophilic cytoplasm, elongated nuclei and prominent nucleoli. 40X

## 4. Discussion

*T. gondii* is a cosmopolitan parasite,<sup>9</sup> higher prevalence is seen in warm and humid climates. A significant population of these areas harbours low titres of antibody.<sup>10</sup> The frequency of such infections varies considerably from country to country and within a country.<sup>11</sup>

As much as 40% of the adult world population is infected with *Toxoplasma gondii*.<sup>6</sup> Seroprevalence average in India is 24.3%, a seroconversion rate of 1.5% had been reported.<sup>12</sup> TL was first recognized in 1950 by Siim<sup>13</sup> and by Gard and Magnussen<sup>14</sup> on tissue section of cervical lymph node. The parasite occurs in three forms namely oocyte, tachyzoites and tissue cysts. Tissue cysts containing bradyzoites are inactive and pseudocysts containing tachyzoites are the active form. *Toxoplasma* infection is acquired by ingestion of viable tissue cyst in a meat or oocyte excreted by cats that contaminate the environment.<sup>11</sup>

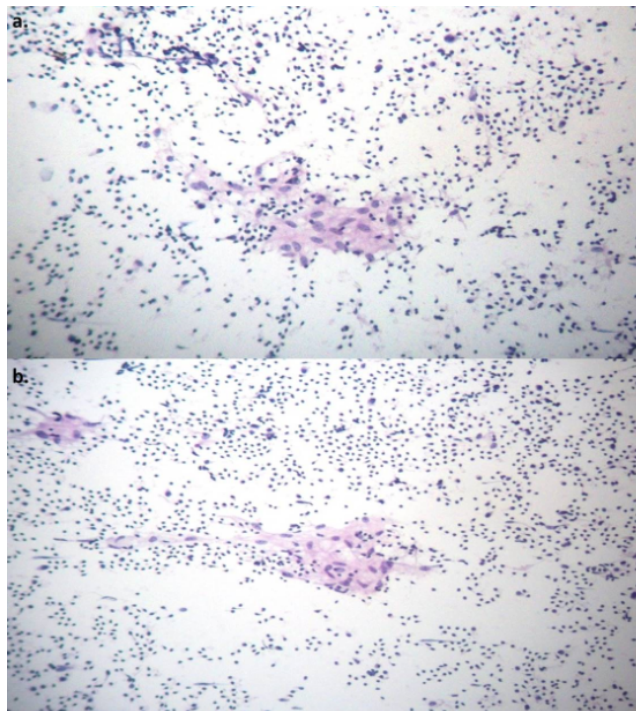
TL is the most common presentation in acquired toxoplasmosis.<sup>11</sup> Manifestations vary, some are asymptomatic, some may present with adenopathy involving multiple sites, and signs & symptoms closely mimicking

**Table 1:** Summary of cases with serology details.

Case No.	Age	Sex	Site	IgG (IU/ml)	IgM (IU/ml)
1	27	Male	Left Submandibular LN	45	4.17
2	35	Male	Right posterior cervical LN	30.4	0.02 (Neg)
3	47	Female	Left posterior cervical LN	>300	6.63
4	25	Male	Left posterior cervical LN	11.89	10.31
5	31	Male	Left posterior cervical LN	>300	5.87
6	42	Female	Submental LN	120.1	7.07
7	42	Female	Right posterior cervical LN	18.17	14.16
8	20	Female	Right Posterior cervical LN	>300	3.85
9	30	Female	Right posterior cervical LN	126	0.39 (Neg)
10	47	Male	Right posterior cervical LN	335.3	67.43

**Table 2:** Previously done cytology studies on TL.

S. No	Study (Year)	No. of cases	Mean age (Yrs.)	M:F ratio	Confirmation
1	Gupta R.K. <sup>8</sup> (1996)	6	28.8	0.16:1	Serology
2	Jayaram N. <sup>3</sup> (1997)	7	41.14	All males	Serology
3	Zaharopoulos <sup>5</sup> (1998)	2	30	All males	Immunocytochemistry for Toxoplasma gondii antigen
4	Haque WS <sup>7</sup> (2018)	22	28.59	1.2:1	Serology
5	Present study	10	34.6	01:01	Serology

**Fig. 2:** a) & b)- H&E stained cytosmears showing epithelioid cell microgranulomas against a background of reactive lymphocytes. 10X

infectious mononucleosis, sometimes lymphoma may also come to differential diagnosis.<sup>10,11</sup> It has been estimated that 15% of unexplained lymphadenopathy is due to toxoplasmosis, usually affecting the cervical lymph nodes. Lymphadenopathy is a typical and sometimes a unique sign of the acquired toxoplasmosis<sup>15</sup> usually soft in consistency, mobile and occasionally painful. Lymphadenopathy usually is encountered in the posterior cervical region (82%), followed by axillary (35%), inguinal (19%), and anterior chest wall (8%). The submandibular nodes are rarely involved (0.45%).<sup>16</sup> In the present study too most common site of involvement is posterior cervical (80%), followed by sub mental (10%) and submandibular (10%) region. In previous studies there was a male preponderance while in our study male and female were affected equally (M: F= 1:1). Mean age ranged from 28.8 years to 41.14 years, in our study mean age us 34.6 years.

There are very few case series on cytology diagnosis of TL confirmed by serology, they're summarized in the table below.(Table 2) A study done by Viguer J.M.<sup>17</sup> used histopathology for confirmation hence is excluded from the comparison since we have not included those cases in our study in which the confirmation was carried out by histopathology. To the best of authors' knowledge, this is 5th case series of cytodagnosis of TL in the English literature and 2nd in the Indian literature. This is the largest case series of cytodagnosis of TL in the Indian literature and 2nd largest in the world literature next to the one done by Haque et al.<sup>7</sup>

FNAC has become an integral part of the initial diagnosis and management of patients with lymphadenopathy.<sup>18</sup> It

is important to diagnose the disease or provide clue to diagnosis in FNAC because it can avoid unnecessary surgery<sup>11</sup> and disease can be totally cured by medical management.

Diagnosis of toxoplasmosis is based on combination of FNAC or tissue biopsy and serological detection of antibody against *Toxoplasma*.<sup>6</sup>

There are very few reports of cervical toxoplasma lymphadenitis cases being diagnosed lymphocytes, and no evidence of necrosis, suppuration or giant cells, on a background of reactive lymphoid hyperplasia.<sup>17</sup> Similar cytomorphology was seen in the cases of present study. (Figures 1 and 2) Very few reports have defined the cytological criteria for a diagnosis of toxoplasma lymphadenitis.<sup>5,6,17</sup>

Argyl et al. Concluded that identification of tissue cyst is very rare in smears.<sup>6</sup> In our study none of the patients had bradyzoites on FNAC. The other FNAC findings were presence of tiny collections of epithelioid cells coupled with abundance of TBMs in a reactive background and absence of necrosis. These cytological findings in our study were appreciated by the pathologists and for confirmation chemiluminescence assay were done. Diagnosis of TL was confirmed after positive serological finding of *Toxoplasma*.

*Toxoplasma* granulomas differ from the granulomas of tuberculosis on cytology. They are tiny comprising of only few epithelioid cells (microgranuloma). The epithelioid cells have abundant dense eosinophilic cytoplasm. They lack necrosis. No or very occasional giant cells. Otherwise background is of reactive lymphoid hyperplasia. No suppuration is seen. In short, one sees epithelioid microgranulomas on a reactive background. Same features are evident in the microphotographs provided, which lack features of tuberculosis.

It is likely that like histology, many cases of *Toxoplasma* are likely to be missed on FNAC. Most of them are reported as Reactive Lymphoid hyperplasia as the microgranulomas are missed and few are reported as tuberculosis although necrosis is not seen. A high degree of suspicion and serological confirmation are quite rewarding and avoid unnecessary biopsy or Anti-tuberculosis drugs. We retrieved ten cases of *Toxoplasma* lymphadenitis in which cytodiagnosis of *Toxoplasma* Lymphadenitis was made on FNAC and which were confirmed with serology by electrochemiluminescence. However, the cases with cytodiagnosis of *Toxoplasma* Lymphadenitis by FNAC (with or without histological diagnosis) without serological confirmation were excluded from the study.

There is no bias for cytodiagnosis of toxoplasma in this study because we have retrospectively selected ten cases in which diagnosis was done on FNAC & confirmed subsequently by serology. We however excluded additional nine cases which were diagnosed on FNAC but could not be confirmed by serology for some reasons. (Although,

histology diagnosis was done in some cases following FNAC).

Serological tests represent the most commonly used method to establish the diagnosis. Documentation of recent seroconversion is the best evidence of recent infection. IgM nosed antibodies to toxoplasmosis are positive within the first week of infection and peak within a month. A negative IgM test almost rules out infection of less than three week's duration in an immunocompetent person. IgG antibodies begin to rise about two weeks after infection and reach a plateau within two months; a steady decline follows over the course of many years.<sup>19</sup>

Toxoplasmosis is not an uncommon cause of lymphadenopathies; in young adults 5-15 % of reactive lymphadenitis may be due to toxoplasmosis.<sup>13,19</sup> It must be considered in the differential diagnosis of lymphadenopathy. Careful attention to evaluate the indicative cytological features in FNAC smears of affected lymph node can raise the suspicion. The

cytological finding, however, must be correlated with positive serological titre, in order to make a definitive diagnosis.

Several reports describe cytological features of TL.<sup>3,5,7,16</sup> In some of them the authors highlight the presence of micro granulomas as the main cytological feature. These micro granulomas are very similar to the one we describe. (Fig.1) The differential diagnoses of TL include reactive lymphadenopathies showing follicular hyperplasia and lymphadenitis with epithelioid granuloma and no necrosis. Concerning other granulomatous disorders, TL rarely shows large, well-formed granulomas or giant cells. Histologically as well as cytologically the clusters are small (usually of <10-15 cells) and composed of polygonal, epithelioid cells with oval rather than spindle nuclei and a few lymphocytes. Due to their small size, most clusters are monolayered. Some are confluent and larger, but they preserve the cellular morphology and show no necrosis or suppurative changes. Therefore, if faced with smears showing numerous large granulomas with spindle, multi-layered cells; vacuolization; and giant cells or showing necrosis or abscess formation, they most probably do not correspond to TL. As stated in Orell's<sup>20</sup> textbook, the initial phase of sarcoidosis, with very few and small granulomas may resemble that of TL. Similarly, lymph nodes draining an area of neoplastic growth may show small, epithelioid granulomas. Nasopharyngeal carcinoma may be associated with granulomas and typically presents as lateroocervical lymph node. In a review of large series of metastatic NPCs, isolated granulomas with similarities to those described for TL were identified.<sup>21</sup> In addition to these micro granulomas, these cases also showed large, well-formed granulomas very different from those described for TL.<sup>22</sup> The presence of neoplastic cells permits reliable differentiation. At low-power examination germinal centres

may resemble the histiocyte clusters of TL. They are more heterogeneous, with several cell types and ill-defined limits. Although tangible body macrophages can be seen in TL micro granulomas, they are almost consistently present in germinal centres.<sup>17</sup>

This study highlights that the presence of characteristic epithelioidmicrogranulomas in an adequate clinical context permits a diagnosis of TL. The cytological diagnosis can be confirmed by serology thereby avoiding biopsy. These patients can then be treated medically and get cured without undergoing any surgical procedure.

## 5. Conclusion

TL is more a reality than it is thought. FNAC smears of lymph node may have adequate clue to its presence which may go unnoticed to an unwary pathologist. FNAC smears of lymph nodes should be carefully examined to detect the features of toxoplasmosis. If findings suggest possibility of TL serology should be done to confirm the diagnosis, especially when microscopic studies alone yield inconclusive results. A cytodiagnosis of TL with serological confirmation helps in appropriate management without any surgical intervention.

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## 8. Conflict of Interest

The authors declare that they have no conflict of interest.

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