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Value of lymph node biopsy in the diagnosis of acquired toxoplasmosis

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Abstract
Toxoplasmic lymphadenitis generally involves a solitary lymph node in the head and neck regions, without systemic symptoms. In order to determine the frequency of toxoplasmic lymphadenitis, we reviewed the histological sections of 731 consecutive patients with reactive lymph node hyperplasia. Amongst 731 patients, 112 had histological features supporting a diagnosis of toxoplasmic lymphadenitis (15.3 per cent). In 80 of these patients (71 per cent), either Indirect Haemaglutination test (IHA), in 37 cases, or the Enzyme-Linked Immunosorbent Assay (ELISA) for detecting toxoplasmic IgG or IgM antibodies, in 43 cases, were performed. In 76 out of 80 patients (95 per cent), histological features correlated well with serological studies. The IHA test was positive in 30 patients with a titre of 1/64 or higher. The IgG-ELISA test was positive in 11 whereas the IgM-ELISA test was positive in 28 patients. These results provide further evidence of the distinctive nature of the histological changes in toxoplasmic lymphadenitis, which should enable the clinician to make a confident diagnosis of acute acquired toxoplasmosis.

Key words: Toxoplasmosis, acquired; Lymph nodes; Biopsy

Introduction

Although mass surveys of serum antibody titres indicate that toxoplasmosis is common in the general population (Elliot *et al.*, 1985; Frenkal, 1985; Seidal, 1985), this diagnosis is rarely considered by physicians (Dorfman and Remington, 1973; McCabe *et al.*, 1987; Sadauddin *et al.*, 1991).

Lymphadenopathy is the most frequent clinical manifestation of acute acquired infections (Gray *et al.*, 1975; Rafaty, 1977; Knobber and Schetzle, 1987; Sauerbrei *et al.*, 1990). Toxoplasmic lymphadenitis generally involves a solitary lymph node in the head and neck regions, without systemic symptoms. The distinctive histopathological changes that occur in the affected lymph nodes of patients with acquired toxoplasmosis are well recognized (Pringer-Kuchinga *et al.*, 1958; Saxen *et al.*, 1958; Stansfeld, 1961). However, many pathologists still appear reluctant to accept the characteristic nature of these changes (Dorfman and Remington, 1973). After requests by us for *Toxoplasma* serological tests in a number of patients whose lymph node biopsies showed changes consistent with toxoplasmic lymphadenitis, a remarkable correlation of the histological findings with serological results was found.

In this present work, we aim to show that toxoplasmosis is not an uncommon cause of lymphadenopathy and the histopathological changes that occur in the affected lymph nodes are evidence of recent infection.

Material and methods

To determine the frequency of toxoplasmic lymphadenitis, we reviewed the histological sections of 731 consecutive patients with reactive lymph node hyperplasia registered at Istanbul University Cerrahpaşa Medical Faculty, Department of Pathology between January 1985 and December 1992. The distinctive histopathological changes consistent with toxoplasmic lymphadenitis were found in 112 cases. Serological tests for *Toxoplasma*, either Indirect Haemaglutination (IHA) (80 patients) or Enzyme-Linked Immunoabsorbent Assay (ELISA) (43 patients) were performed. As a control, the sera of 34 patients with nonspecific reactive hyperplasia but not toxoplasmic lymphadenitis were also studied by using both IHA and ELISA.

In order to determine the frequency of acute and latent *Toxoplasma* infection among the local population, we also reviewed the results of ELISA assay for *Toxoplasma*-specific IgG and IgM antibodies in 3091 consecutive patients registered at the Department of Microbiology between January 1989 and 1992.

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TABLE I
HISTOPATHOLOGICAL FINDINGS IN TOXOPLASMIC LYMPHADENITIS

Histopathological criteria	No. of cases (%)
Follicular reactive hyperplasia	112/112 (100%)
Mitotic figures and numerous stainable-body macrophage containing karyorrhectic debris in germinal centres	97/112 (87%)
Clusters of epithelioid histiocytes within both germinal centres and interfollicular areas	112/112 (100%)
Perisinusoidal cell hyperplasia	106/112 (95%)

Histopathological studies were carried out on tissues fixed in 10 per cent formalin or B5 fixative, embedded in paraffin and stained with Mayer's haematoxylin (H & E). For histopathological interpretation, the criteria described by Pringer-Kuchinga *et al.* (1958) and Saxen *et al.* (1958) which are summarized in Table I were applied. *Toxoplasma* IHA test (Toxo-IHA test, Carter-Wallace, Inc., Caranbury, NJ) and ELISA-IgG, ELISA-IgM antibodies were determined using Platelia Toxo-IgM and -IgG (-Diagnostic-Pasteur, France) as instructed by the manufacturer.

Results

Of the 731 patients diagnosed as having reactive lymphoid hyperplasia, 112 had histological features consistent with toxoplasmic lymphadenitis (15.3 per cent). The majority of patients had presented with cervical lymphadenopathy (60.7 per cent). Other sites of lymphadenopathy were axillary in 42 and inguinal in two patients. Four patients had multiple peripheral lymphadenopathy. The age of the patients ranged from five to 47 years, median age was 27 years. Seventy per cent of patients were less than 30 years of age and 57 per cent were female. The female/male ratio was 1.3:1.

The lymph node sections from all 112 patients showed prominent reactive follicular hyperplasia (Table I). Mitotic figures and numerous stainable body macrophages containing karyorrhectic debris were observed in 87 per cent of cases (Figure 1). Clusters of epithelioid histiocytes were identified

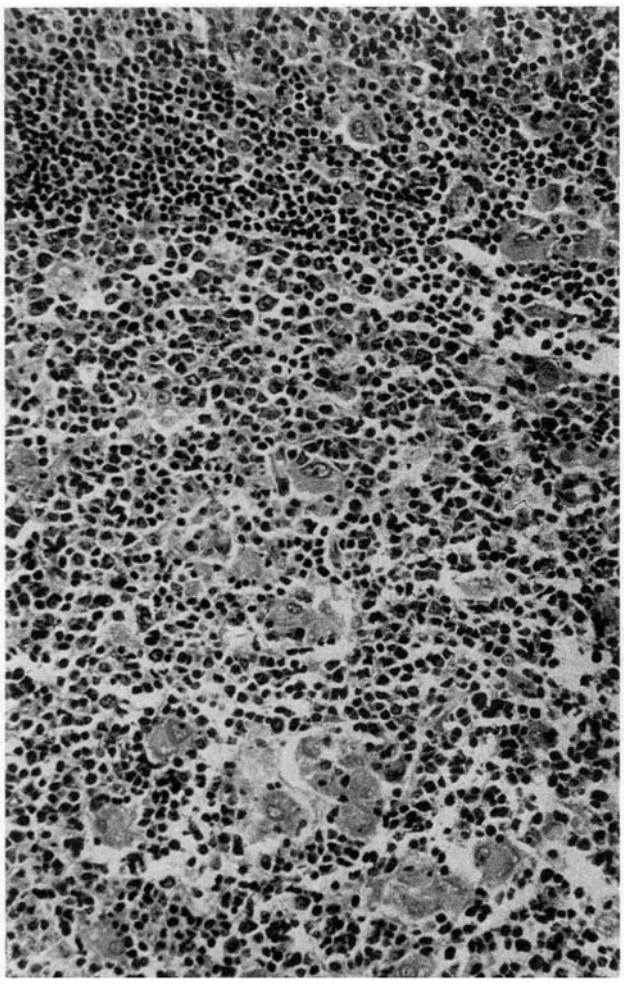

FIG. 1
Germinal centre containing mitotic figures, stainable-body macrophages and epithelioid cells. (H & E; × 200)

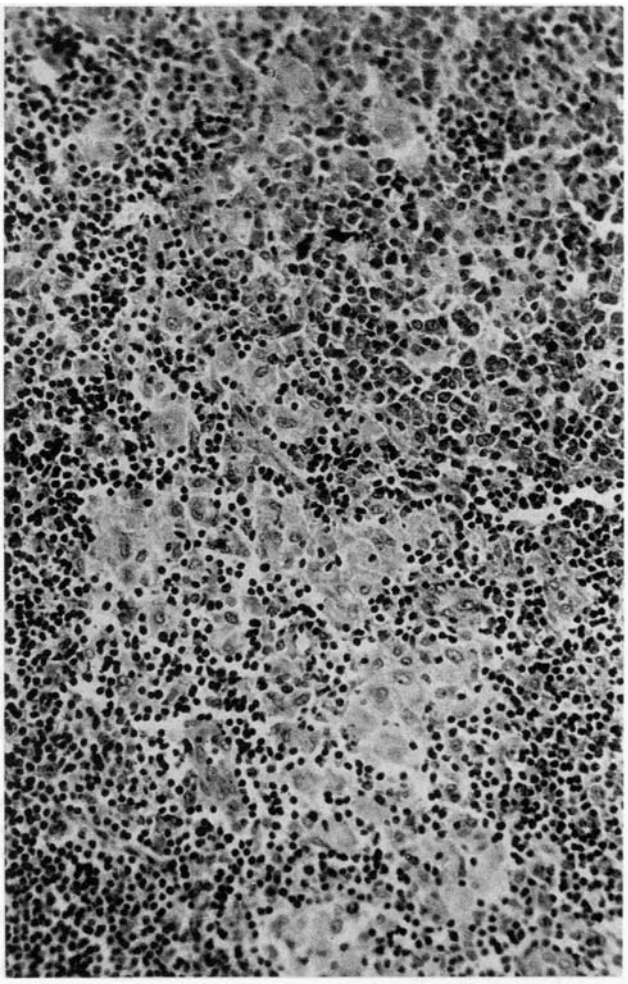

FIG. 2
Epithelioid clusters in interfollicular areas (H & E; × 200).

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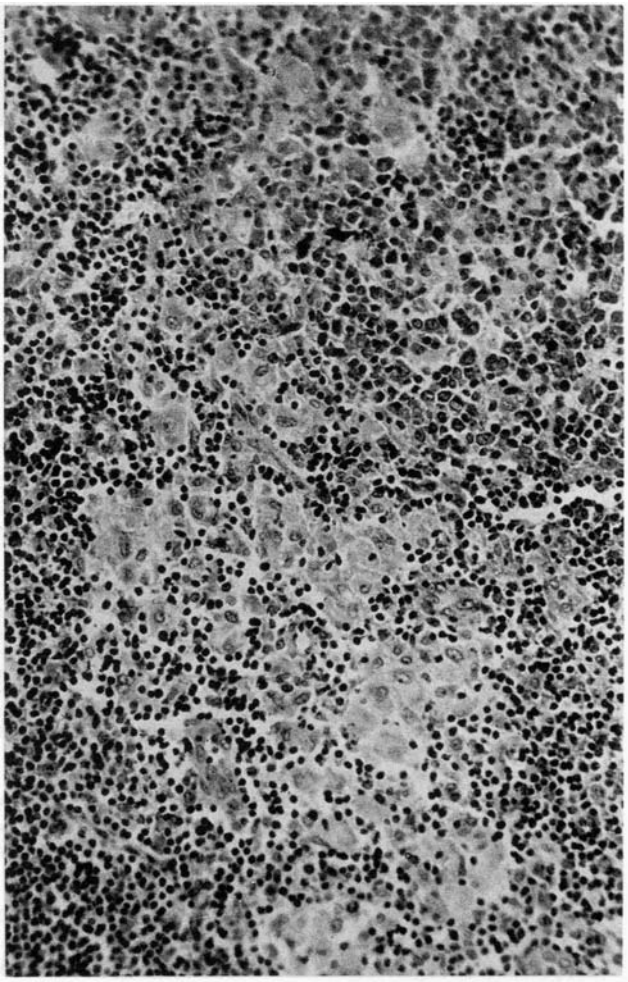

FIG. 3
Perisinusoidal cells (H & E; × 200).

within both germinal centres and interfollicular areas in all of the cases (Figure 2). Perisinusoidal cells with abundant clear cytoplasm and round to indented vesicular nuclei (Figure 3), mostly located within distended subcapsular or medullary sinuses, were present in 95 per cent of cases.

Among the 80 patients in whom serological tests were requested, 69 revealed positive results. Results are summarized in Table II. Amongst 30 patients with a positive Toxo-IHA test, five had titres of between 1:64 to 1:128 and 25 had titres of 1:512 or higher. The ELISA test gave positive results in 39 out of 43 patients (90.7 per cent). The IgG ELISA test was positive in 28, whereas the IgM ELISA test was positive in 11 patients. ELISA values ranged from 0.640 to 0.952 for IgG and 0.508 to 0.663 for IgM.

In 11 patients, although the histological criteria were consistent with the diagnosis of toxoplasmic lymphadenitis, the serological tests yielded negative results (IHA in seven, ELISA in four cases).

Amongst 34 patients with nonspecific reactive hyperplasia, 11 (32.35 per cent) had positive IHA titres of 1/64 and positive IgG-ELISA values ranged from 0.463 to 0.472. The IgM-ELISA was negative in all of them.

Amongst the 3091 patients that represented the regional population, the frequency of latent *Toxoplasma* infection was found to be 36 per cent.

Discussion

In our Department of Pathology all reactive lymph nodes are examined for *Toxoplasma* if there is suspicion of toxoplasmic lymphadenitis from the histological appearance in H & E sections. Analysis of our case population reveals that the majority of our patients are women (57 per cent) and 70 per cent are less than 30 years of age. Cervical lymph nodes are most commonly involved followed by axillary lymph nodes. These features are in line with previous studies (Dorfman and Remington, 1973; Rafaty, 1977; McCabe *et al.*, 1987).

It is apparent, in retrospect, that serological investigations indicated that 80–97 per cent of patients with this type of lymphadenitis had *Toxoplasma*-positive serology, in contrast to 36–57 per cent of *Toxoplasma*-positive serological tests amongst the regional population (Dorfman and Remington, 1973; Welch *et al.*, 1980; McCabe *et al.*, 1987).

Twenty-five of our patients with histologically suggestive toxoplasmic lymphadenitis had raised toxo-IHA titres of 1:512 or higher. These are accepted values for toxoplasmosis, since fewer than one per cent of the normal population fall in this

TABLE II
SEROLOGICAL TEST RESULTS IN TOXOPLASMIC ADENITIS AND CONTROL GROUPS

Patient group	Serological test	Titres	No. of cases	%
Suggestive of toxoplasmic lymphadenitis (80 cases)	IHA (+) (n: 30/37)	1:64–1:128	5	13.51
		>1:512	25	67.56
		Total	30	81.08
	ELISA (+) (n: 39/43)			
	IgM (+)	0.508–0.663	11	25.58
	IgG (+)	0.640–0.952	28	65.11
		Total	39	90.69
Control group (34 cases)	IHA (+)	1:64	11	32.35
	ELISA IgG (+)	0.463–0.472	3	8.82
	ELISA IgM (+)		0	00.00
		Total	14	41.17

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range (Lunde, 1973; Remington and Desmonts, 1973). The remaining five patients had toxo-IHA titres of 1:64 to 1:128 which could not differentiate recent exposure from an early asymptomatic infection, since up to 30 per cent of the normal population may fall in this range (McCabe *et al.*, 1987).

Occurrence of toxoplasmosis-like histological changes in the lymph nodes are found in many different diseases. The epithelioid cell aggregates are not pathognomonic of toxoplasmosis. They can be seen in granulomatous diseases such as tuberculosis and sarcoidosis. However, the usual absence of sinus B lymphocytosis in affected nodes in these diseases may be helpful in distinguishing between early stages of these diseases and toxoplasmosis, in which this type of sinus reaction is always present. Leishmanial lymphadenitis differs from toxoplasmic lymphadenitis by the readily discernible presence of the *Leishmania* in the cytoplasm of the epithelioid cells. Changes such as reactive centres with stainable body macrophages similar to that seen in the lymph nodes in some cases of persistent generalized human immunodeficiency virus (HIV) lymphadenopathy are mentioned. Also clusters and sheets of monocytoid B-cells are often present. However the combination of all findings (particularly the presence of plasmacytosis, polykaryocytes, mantle zone loss and monocytoid B-cells, follicular hyperplasia) should, within the right clinical setting, suggest the possibility of HIV infection. It is rarely accompanied by evidence of active infection with toxoplasmosis (Symmers, 1992).

Therefore, diagnosis of toxoplasmic lymphadenitis should be established by a combination of the histological criteria mentioned, together with positive antibody titres. In recent years ELISA kits have become commercially available for the detection of *Toxoplasma*-specific IgM and IgG antibodies. The demonstration of IgM antibodies can be a useful and specific indicator of recently acquired toxoplasmosis (Naot and Remington, 1980; Wielaard *et al.*, 1983; Johnson *et al.*, 1987). Of the 112 patients, 71.8 per cent presenting with histologically suggestive toxoplasmic lymphadenitis had *Toxoplasma*-IgM specific antibodies, whereas 28 per cent of them had only IgG-specific antibodies.

Both of the serological assays used in this study correlated similarly with the histological features that are suggestive of toxoplasmic lymphadenitis. Eighty-one per cent for IHA, 90.6 per cent for ELISA. In 13.7 per cent of patients although the lymph node histology was compatible with toxoplasmic lymphadenitis the diagnosis was not backed-up by serology. IHA was employed in 64 per cent of these cases, therefore, it is possible that an early infection was overlooked in those patients.

In Turkey, the incidence of positive *Toxoplasma* antibodies in the normal population ranges from 42.7 to 49.2 per cent (Ozcan, 1981). In our prospective study among 34 patients with nonspecific reactive hyperplasia, 32 per cent had positive serology. However, none of the histological criteria were found in these 11 patients. The frequency of 32 per cent represents the same rate of positivity as the regional hospital population.

Conclusion

The diagnosis of toxoplasmic lymphadenitis is made by a combination of the histological features together with findings of serologic tests. Since lymph node biopsy usually precedes serological testing, awareness of the above mentioned histopathological criteria should enable the pathologist to diagnose toxoplasmic lymphadenitis.

References

Dorfman, R. F., Remington, J. S. (1973) Value of lymph node biopsy in the diagnosis of acute acquired toxoplasmosis. *New England Journal of Medicine* **289:** 878–881.

Elliot, D. L., Tolle, S. W., Goldberg, L., Miller, J. B. (1985). Pet-associated illness. *New England Journal of Medicine* **313:** 985–995.

Frenkal, J. K. (1985) Symposium on parasitic infections: Toxoplasmosis. *Pediatric Clinics of North America* **32:** 917–932.

Gray, G. F. Jr., Kimball, A. C., Kean, B. H. (1975) The posterior cervical lymph node in toxoplasmosis. *American Journal of Pathology* **28:** 42–49.

Johnson, A. M., Gu, Q. M., Roberts, H. (1987) Antibody patterns in the serological diagnosis of acute lymphadenopathic toxoplasmosis. *Australia, New Zealand Journal of Medicine* **17:** 430–434.

Knobber, D., Schetzle, W. (1987) Lymphadenitis toxoplasmatica. *Laryngo-Rhino-Otologie (Stuttgart)* **66:** 70–72.

Lunde, M. N. (1973) Laboratory methods in the diagnosis of toxoplasmosis. *Health and Laboratory Science* **10:** 319–328.

McCabe, R. E., Brooks, R. G., Dorfman, R. F., Remington, J. S. (1987) Clinical spectrum in 107 cases of toxoplasmic lymphadenitis. *Pathology Review of Infectious Disease* **9:** 754–774.

Naot, Y., Remington, J. S. (1980) An enzyme-linked immunoabsorbent assay for detection of IgM antibodies to *Toxoplasma gondii*: use for diagnosis of acute acquired toxoplasmosis. *Journal of Infectious Diseases* **142:** 457–766.

Ozcan, K. (1981) Detection of latent toxoplasmosis in healthy individuals by using indirect hemaglutination (IHA). *Bulletin of Microbiology* **15:** 121–129.

Pringer-Kuchinga, A., Martin, I., Thalhammer, O. (1958) Uber die vorzuglich cervico-nuchale lymphadenitis mit kleinherdiger epthelioidzell. *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizina* **131:** 522–535.

Rafaty, F. M. (1977) Cervical adenopathy secondary to toxoplasmosis. *Archives of Otolaryngology* **103:** 547–549.

Remington, J. S., Desmonts, G. (1973) Congenital toxoplasmosis: variability in the IgM fluorescent antibody response and some pitfalls in the diagnosis. *Journal of Pediatrics* **83:** 27–30.

Sadauddin, A., Agha, F., Anwar, F., Ghafoor, A. (1991) Seroepidemiology of *Toxoplasma gondii* infection in young school children in Islamabad. *Journal of Pakistan Medical Association* **41:** 131–134.

Sauerbrei, A., Wutzler, P., Pfister, W., Kaiser, U., Schreiber, D., Rudiger, K. D. (1990) Microbiological and morphological findings in reactive lymphadenopathy. *Zentralblatt fuer Allgemeine Pathologie und Pathologische Anatomie* **136:** 419–425.

Saxen, E., Saxen, L., Gronroos, P. (1958) Glandular toxoplasmosis a report on 23 histologically diagnosed cases. *Acta Pathologica Scandinavica* **44:** 319–328.

Seidal, J. S. (1985) Protozoal infections. *Pediatric Clinics of North America* **32:** 1064–1067.

Stansfeld, A. G. (1961) The histologic diagnosis of toxoplasmic lymphadenitis. *Journal of Clinical Pathology* **14:** 565–573.

Symmers, W. St. C. (1992) Lymphadenitis caused by infection

and infestation. In *Thymus, Lymph Nodes, Spleen and Lymphatics, Systemic Pathology*, 3rd Edition, (Henry, K., Symmers, W. St. C., eds.). Churchill Livingstone, Edinburgh, pp 438–446.

Welch, C., Masur, H., Jones, T. C., Remington, J. S. (1980) Serological diagnosis of acute lymphadenopathic toxoplasmosis. *Journal of Infectious Diseases* **142:** 256–264.

Wielaard, F., van Grvijthvijsen, H., Dvermeyer, W., Jess, A. W. L., Skinner, L., Williams, H., van Elven, E. H. (1983) Diagnosis of acute toxoplasmosis by an enzyme immunoassay for specific immunoglobulin M antibodies. *Journal of Clinical Microbiology* **17:** 981–987.

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