


Case Report

## Toxoplasma cyst detection in *Piringer-Kuchinka* lymphadenitis. Report of two cases and literature review

 Luca Ventura<sup>1,2\*</sup>, Magda Zanelli<sup>3\*</sup>, Maurizio Zizzo<sup>4,5</sup>, Francesca Sanguedolce<sup>6</sup>, Giovanni Martino<sup>7</sup>, Carolina Castro Ruiz<sup>4,5</sup>, Valerio Annessi<sup>4</sup>, Stefano Ascani<sup>8</sup>

<sup>1</sup> Division of Pathology, San Salvatore Hospital, L'Aquila, Italy; <sup>2</sup> Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy; <sup>3</sup> Pathology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy; <sup>4</sup> Surgical Oncology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy; <sup>5</sup> Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy; <sup>6</sup> Pathology Unit, Azienda Ospedaliero-Universitaria - Ospedali Riuniti di Foggia, Foggia, Italy; <sup>7</sup> Hematology Unit, CREO, Azienda Ospedaliera di Perugia, University of Perugia, Italy; <sup>8</sup> Pathology Unit, Azienda Ospedaliera Santa Maria di Terni, University of Perugia, Terni, Italy;

\* These Authors contributed equally to this work

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### Correspondence

Maurizio Zizzo  
Surgical Oncology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Arcispedale Santa Maria Nuova di Reggio Emilia, viale Risorgimento 80, 42123 Reggio Emilia, Italy  
Tel.: +39 0522 296372  
Fax: +39 0522 295779  
E-mail: zizzomaurizio@gmail.com

### Conflict of interest

The Authors declare no conflict of interest.

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### Summary

The diagnosis of acute toxoplasmic lymphadenitis is traditionally based on the combination of lymph node excisional biopsy with specific tests. The classic triad (marked follicular hyperplasia, small irregular clusters of epithelioid histiocytes in germinal centers, and sinusoidal distension by monocytoid B lymphocytes) is considered diagnostic of the so-called *Piringer-Kuchinka* lymphadenitis. *Toxoplasma gondii* organisms have been exceptionally disclosed in such histopathological setting, establishing the diagnosis of toxoplasmic lymphadenitis. Two cases of *Piringer-Kuchinka* lymphadenitis with toxoplasma cyst demonstration are reported, along with a complete review of the literature.

**Key words:** follicular hyperplasia, toxoplasmic lymphadenitis, toxoplasma cyst, bradyzoites, *Toxoplasma gondii*

### Introduction

The diagnosis of acute toxoplasmic lymphadenitis has been traditionally based on the combination of lymph node excisional biopsy with specific serologic tests. A well-known histopathological triad (marked follicular hyperplasia, small irregular clusters of epithelioid histiocytes encroaching on germinal centers, and sinusoidal distension by monocytoid B lymphocytes) has been considered to be diagnostic of the so-called *Piringer-Kuchinka* lymphadenitis <sup>1</sup>. Exceptionally, organisms have been disclosed in such nodes during histopathologic examination, with no more than 15 reported cases <sup>2-11</sup>. Two cases of *Piringer-Kuchinka* lymphadenitis with toxoplasma cyst demonstration are presented here, along with a complete review of the literature.

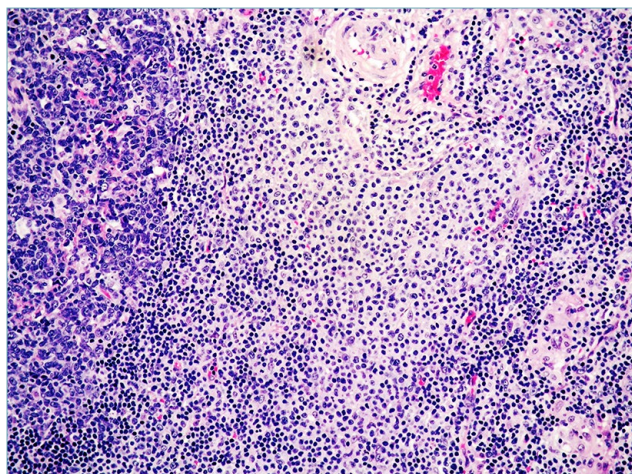
### Case 1

A 30-year-old immune-competent woman presented with 1-month history of neck swelling, fatigue and night sweats. Clinical examination and ul-

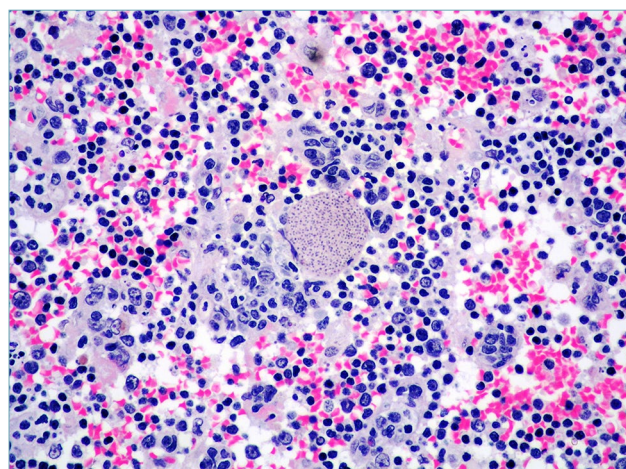
trasound scan revealed multiple not painful, enlarged lymph nodes, 2 cm in maximum diameter, in the neck, axillae and groins. Blood count was within normal limits. C-reactive protein (PCR) was mildly elevated (1 mg/dl). Serology for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) was negative for acute infection. The excised cervical node, measuring 2.2 cm x 2 cm x 1.5 cm, had a hard, white cut surface with a faintly nodular appearance. Histology displayed prominent follicular hyperplasia, small clusters of epithelioid histiocytes sometimes invading germinal centers and aggregates of monocytoïd B cells (Fig. 1). Only rare, characteristic bradyzoites-filled cysts (Fig. 2), positive for anti-toxoplasma antibody (Fig. 3), were found in the histological sections. Toxoplasma lymphadenitis diagnosis was subsequently confirmed by serology. The patient underwent clinical follow-up; no therapy was administered. A spontaneous resolution of lymphadenopathy and symptoms occurred after several weeks.

## Case 2

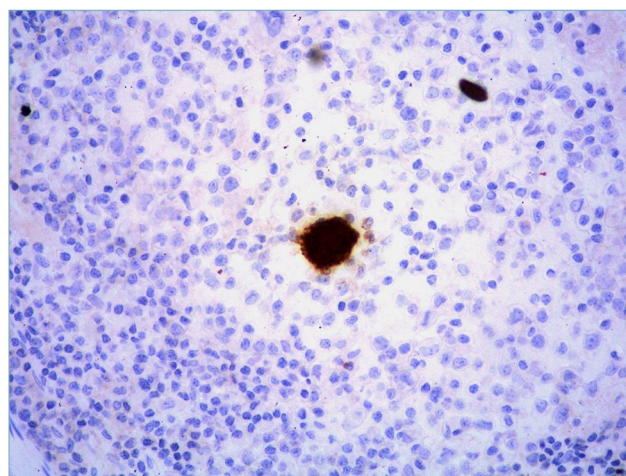
A 32-year-old immuno-competent male presented with recently enlarged right cervical lymph nodes, without significant past clinical history. A node measuring 3 cm in largest diameter was excised to be submitted to histopathologic examination. In addition to routine H&E slides, additional sections were serially stained with Ziehl-Neelsen, PAS, Grocott, and immunostained for CD20, CD10, and bcl-2. The presence of the classic triad allowed us to suspect a toxoplasmic lymphadenitis (Fig. 4). The sections stained with PAS, Grocott, and



**Figure 1.** Medium power view of lymph node showing a reactive germinal center (left), sheets of monocytoïd cells (middle) and small clusters of histiocytes (right) (HE 200x).



**Figure 2.** High power view disclosing a bradyzoites-filled cyst (HE 400x).

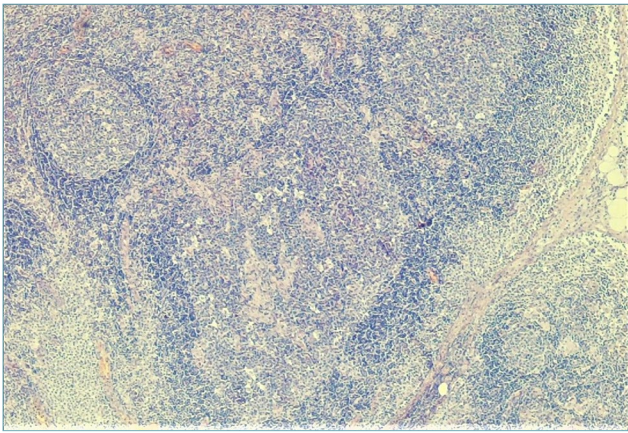


**Figure 3.** Anti-toxoplasma antibody positivity (immunostain).

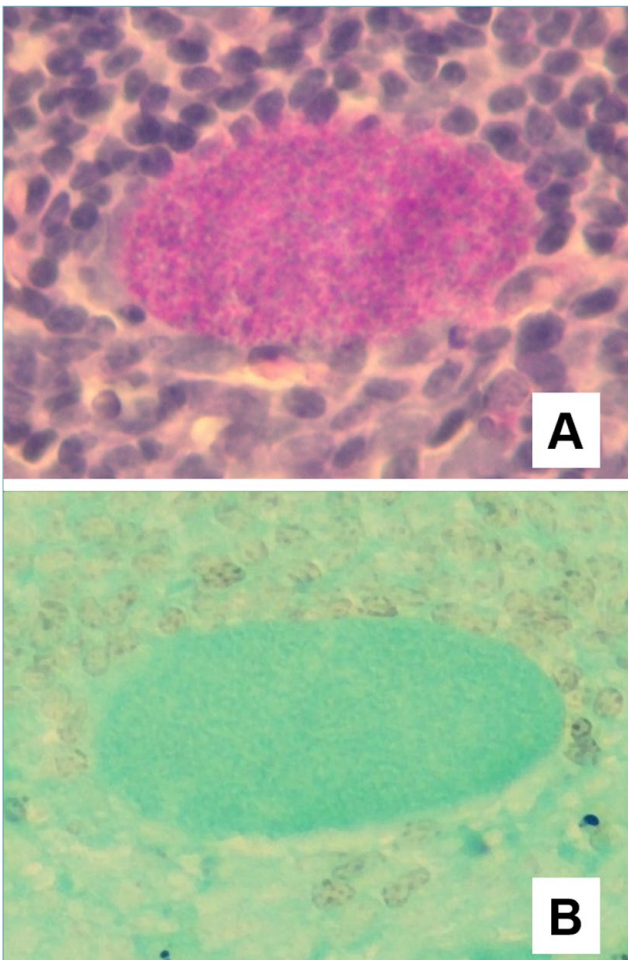
the immunostains displayed a single toxoplasma cyst located at the margin of a hyperplastic germinal center (Figs. 4, 5). The cyst, containing several bradyzoites, was stained pale red by PAS and resulted negative after other stains. The diagnosis was confirmed by serological tests performed one month after surgery. Microparticle Enzyme ImmunoAssay for *Toxoplasma gondii* showed IgG at a level of 1418.6 IU/ml (normal < 3.0 IU/ml) and IgM at a level of 0.860 IU/ml (normal < 0.5 IU/ml).

## Discussion

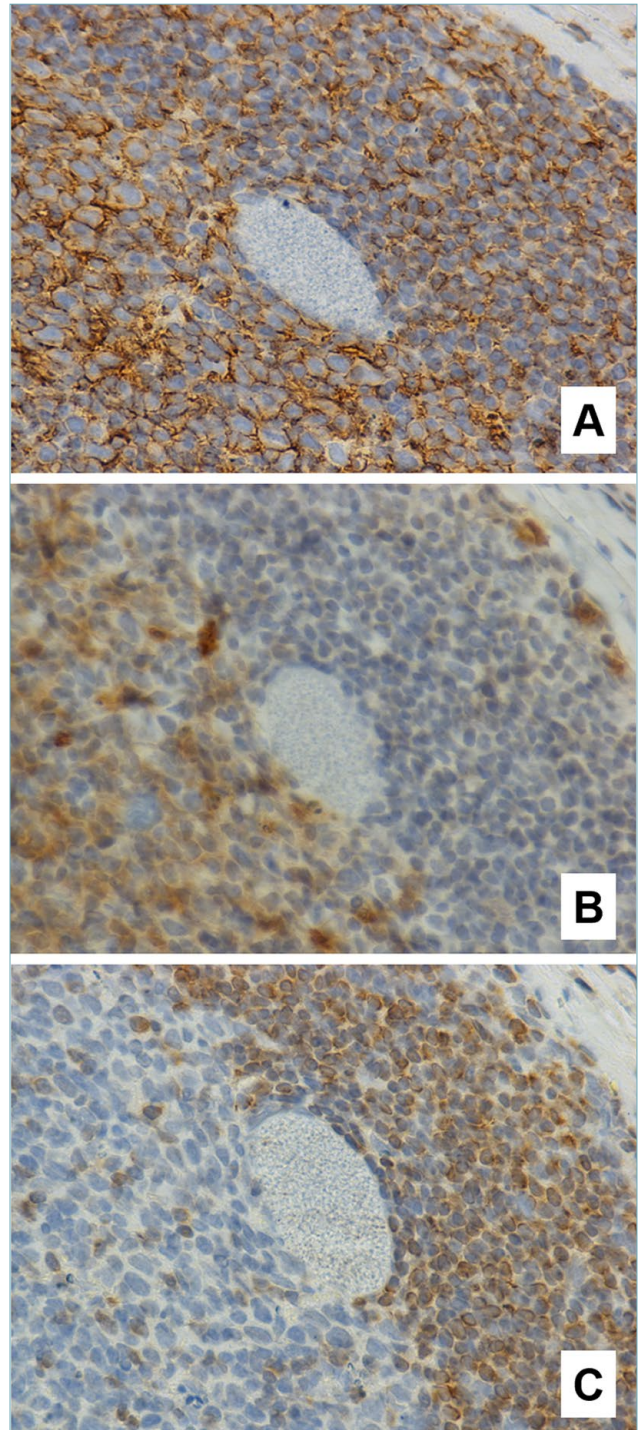
Toxoplasmosis is a common zoonosis caused by *Toxoplasma gondii*<sup>12</sup>. The common sources of human



**Figure 4.** Lymph node showing reactive germinal centers with small clusters of histiocytes and sinusoidal distension by monocytonoid cells (HE 100x).



**Figure 5.** *Toxoplasma* cyst located at the margin of a hyperplastic germinal center, stained with (A) PAS, and (B) Grocott (400x).



**Figure 6.** Immunostains for (A) CD20, (B) CD10, and (C) bcl-2 (200x).

infections are ingestion of undercooked meat containing cysts, cat stools containing oocysts and mother to fetus transplacental transfer<sup>12</sup>. *Toxoplasma gondii* infection is a serious disease in immunocompromised

patients, often acutely disseminating to many organs, especially central nervous system, myocardium and lungs, and resulting in patient death<sup>13</sup>. Infection, especially during early pregnancy, can cause fetal loss or malformations<sup>12</sup>. In immunocompetent individuals, the infection often results in solitary cervical lymph node enlargement, although other lymph nodes of axilla and groin can be involved<sup>14</sup>. Patients can be either asymptomatic or present with nonspecific symptoms such as sore throat, low-grade fever and fatigue<sup>4</sup>. The persistence of lymph node enlargement even for months and the presence of systemic symptoms may lead to the clinical suspect of lymphoma<sup>14</sup>. The histological triad consisting of florid reactive follicular hyperplasia, small clusters of histiocytes and sinusoidal distension by monocytoid B cells is considered suggestive, although not diagnostic of toxoplasma lymphadenitis<sup>15,16</sup>. The differential diagnosis includes Leishmaniasis, cytomegalovirus infection, mononucleosis and early stages of cat-scratch disease, all of which may show histological features resembling toxoplasma lymphadenitis<sup>14,15</sup>. Serology is needed to confirm the diagnosis. Despite being a common infection, it is exceedingly rare to find toxoplasma cysts in histological specimens.

Two forms of *Toxoplasma gondii* may exist in human organs. The trophozoite is the invasive form, which is responsible for manifestations of acute infection; the tissue form (bradyzoites or toxoplasma cyst) is responsible for the persistence of latent infection in multiple organs<sup>8,9</sup>. The tissue forms may persist for years after infection. Their presence may thus be unrelated to the active disease, but in patients with *Piringer-Kuchinka* lymphadenitis they represent sufficient evidence to establish the diagnosis.

Only few reports describe the presence of toxoplasma cysts in histological sections<sup>2-11</sup> (Tab. I). At the Armed Forces Institute of Pathology (AFIP), they were found in less than 1/100 cases of toxoplasmic lymphadenitis<sup>2</sup>. In the other reported cases, M:F ratio is 1:1, whereas the age of the patients is 15-62 years (average: 31.2; median: 38.5). The anatomical site of the excised lymph node was almost always cervical<sup>2-5,7-11</sup> with 1 para-aortic<sup>6</sup> and 1 inguinal node<sup>2</sup>. In the AFIP cases, as well as in the one reported by Gray et al., the age of the patients and the anatomical site of the nodes are not specified<sup>2,5</sup>. It is worth noting that in one of the single case reports the abstract claims the disclosure of a toxoplasma cyst, but no convincing evidence of it can be found in the full text and figures<sup>11</sup>. As in the present cases, the usual location of the cyst within the node was the margin of the germinal center<sup>2,4-9</sup>. In one case from the AFIP series the cyst was located within the follicle<sup>2</sup>. In the first report by Stan-

**Table I.** Features of reported cases.

Reference	Year	Sex	Age	Site	Location
Stanton et al.	1953	F	26	cervical	peripheral sinus (multiple)
Stansfeld	1961	F	30	cervical	follicle margin
Gray et al.	1972	NA	NA	cervical	follicle margin
Frenkel	1976	NA	NA	1 inguinal	follicle
		NA	NA	5 cervical	follicle margin
Faruqui et al.	1976	M	62	para-aortic	follicle margin
Aisner et al.	1983	M	15	cervical	paracortical
Cohen et al.	1984	F	22	preauricular	follicle margin
Ito et al.	1988	M	15	cervical	paracortical/venules
Suh et al.	2002	F	40	cervical	NA
Oh et al.	2004	M	40	cervical	NA
Our case 1	2020	F	30	cervical	follicle margin
Our case 2	2020	M	32	cervical	follicle margin

NA: not assessed

ton and Pinkerton, two cysts laying in the peripheral sinus were identified<sup>3</sup>. Another case harbored two cysts in perifollicular area as well as in the lumina of small venules adjacent to germinal centers. This led the authors to hypothesize that ingested toxoplasms might have reached the cervical nodes via blood vessels<sup>9</sup>. Finally, in two reports the location of the cyst was not specified<sup>10,11</sup>. In all reported patients, the diagnosis was usually made by the chance discovery of the cyst during histopathological examination. The examination of multiple sections gave opposite results, with none other definite organisms found<sup>4</sup> or the demonstration of an additional cyst<sup>3</sup>.

The difficulty in identifying toxoplasma cysts might be due to the very small size (2-6 µm) of bradyzoites, easily missed on histological evaluation, in the absence of aggregates. Unlike in immunocompetent individuals, it is much easier to identify large numbers of parasites in tissues of immunocompromized patients. When the classical triad of *Piringer-Kuchinka* lymphadenitis is noticed, the examination of slides obtained at multiple levels may be of help in highlighting the potentially underestimated finding of a toxoplasma cyst. However, at light microscopy, toxoplasma cysts can still resemble protozoa such as *Leishmania donovani* or *Trypanosoma cruzi*. The chance discovery of cysts in lymph node sections, as in our cases, helps pathologists to suggest toxoplasmosis and the additional use of immunohistochemistry may be an aid to confirm the diagnosis<sup>17</sup>.

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