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Clinical report

A cluster of probable primary toxoplasmic lymphadenitis in a Thai family: case reports and a review of the literature

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Background: Primary toxoplasmosis is frequently asymptomatic in immunocompetent adults. To our knowledge, a cluster of primary toxoplasmosis in Thailand has not been previously reported.
Objectives: To report a cluster of primary toxoplasmosis in a Thai family.
Methods: Physical examination, complete blood count, liver function tests, blood chemistry, chest radiography, and lymph node histopathology.
Results: A previously healthy 39-year-old man presented with painless bilateral cervical lymphadenopathy for one month. Simultaneously, his 6-year-old son had painless cervical lymphadenopathy. Lymph node histopathology of the man showed the classic triad of characteristics of toxoplasmic lymphadenitis. Both patients were doing well when last seen two months after symptomatic and supportive treatment.
Conclusions: Patients with toxoplasmic lymphadenitis can survive without specific antiparasitic treatment. Normal hosts may have a benign clinical presentation.

Keywords: Immunocompetent hosts, primary toxoplasmosis, toxoplasma, toxoplasmic lymphadenitis, toxoplasmosis

Toxoplasmosis is a parasitic infestation caused by the obligate intracellular protozoan, *Toxoplasma gondii*. Infection in humans occurs by the consumption of undercooked meat that has tissue bradyzoite-containing cysts, by the ingestion of food or water contaminated with sporozoite-containing oocysts, by transplacental transmission from a mother with gestational primary toxoplasmosis, and, less frequently, by contaminated or infected transplanted organs [1, 2]. There are 2 forms of clinical manifestation in this disease. The first form, primary infection, is usually observed in immunocompetent children and young adults, pregnant women, and neonates. The second form, reactivation of chronic asymptomatic infection, commonly occurs in immunocompromised patients including those with acquired immunodeficiency syndrome (AIDS), organ transplantation, and malignancy [1]. Central nervous system toxoplasmosis is the most common manifestation of this form especially in AIDS patients. In primary toxoplasmosis, only a minority of patients are symptomatic [1-4]. To date, there have been a few reported cases of symptomatic primary toxoplasmosis in nonpregnant, nontransplanted, and noncongenitally infected patients. The most common manifestation in immunocompetent hosts is asymptomatic lymphadenopathy, which usually resolves within a few months without treatment. The most common site of lymphadenopathy are cervical lymph nodes, followed by occipital, retroauricular, axillary, supraclavicular, submaxillary, inguinal, and submental lymph nodes [2]. However, any or all lymph node groups can be involved. The other infrequently associated symptoms include malaise, fever, generalized myalgia, arthralgia, anorexia, splenomegaly, and hepatomegaly [2]. The other infrequent presentations in primary toxoplasmosis include myocarditis, polymyositis, pneumonitis, hepatitis, and encephalitis. Another common

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presentation is ocular manifestation (toxoplasmic chorioretinitis), which present in congenital infections [1].

The seroprevalence of antibodies to *Toxoplasma* varies among different geographic areas and individuals [1-5]. The incidence of antibodies increases with increasing age. The differences between countries and areas are probably because of several factors including cultural habits and environmental exposures. The seroprevalence rates among women of childbearing age in western and central Europe including France, Austria, Switzerland, Belgium, and Germany range from 37% to 58% [5]. The seroprevalence is much higher in Latin America and western Africa. It is lower in Southeast and East Asia, and Scandinavia. In Thailand, the seroprevalence of *Toxoplasma* antibodies was studied in immunocompetent individuals including cat owners, pregnant women, and blood donors [6, 7]. Antibodies to *Toxoplasma* were present in only 6.4% of cat owners in Bangkok [6]. IgG *Toxoplasma* antibodies were found in only 5.3% of non-HIV-infected pregnant Thai women [7].

To our knowledge, a cluster of primary toxoplasmosis in Thailand has not yet been reported. Here we report a cluster of primary toxoplasmosis in a Thai family.

Case report

A previously healthy 39-year-old man presented with painless bilateral cervical lymphadenopathy that had persistent for at least 1 month. He had noted abnormal masses upon palpating his neck. He denied fever, arthralgia, myalgia, or weight loss. His 6-year-old only son also had painless bilateral cervical lymphadenopathy at the same time. The patient had at that time been a worker in a rubber plantation in the Thap Put district of Phang Nga province, South Thailand. He owned pigs, ducks, and several cats.

Physical examination found a body temperature of 37.2°C, a pulse rate of 80/min, a respiratory rate of 16/min, and a blood pressure of 120/80 mm Hg. There was multiple, painless, rubbery, bilateral anterior and posterior cervical enlarged lymph nodes of approximately 1 cm. There was no hepatosplenomegaly.

A complete blood count showed a hematocrit of 40%, 7,450 white blood cells/mm^3 (53% neutrophils, 42% lymphocytes, and 5% monocytes), and 291,000 platelets/mm^3. Liver function tests found 0.7 mg total bilirubin/dL, 71 U alkaline phosphatase/L (normal range 20-140 U/L), 20 U aspartate transaminase/L (normal range 8-40 U/L), 22 IU alanine transaminase/L (normal range 10-40 U/L), and 4.3 g albumin/dL. Anti-HIV antibody and HIV antigen were negative (HIV Ag/Ab Combo, Abbott, Wiesbaden, Germany). Other blood chemistries were normal.

Chest radiography was normal. Lymph node biopsy was performed, and histopathology showed the classic triad of characteristics of toxoplasmic lymphadenitis, which comprise florid follicular hyperplasia with multifocal monocytoid aggregates and one cluster of epithelioid cells. Neither cysts nor trophozoites of *T. gondii* were demonstrated by hematoxylin and eosin or G□m□ri methenamine silver stains. A diagnosis of toxoplasmic lymphadenitis was made, and then the patient's serum samples were tested for *Toxoplasma* IgG and IgM antibodies by microparticle enzyme immunoassay (MEIA) (Abbott) and were found negative for the antibodies. In addition, a polymerase chain reaction (PCR) test for *T. gondii* was conducted on lymph node and serum specimens, and showed negative results. Both patient and his son were doing well with a complete resolution of all cervical lymphadenopathy when last seen two months after symptomatic and supportive treatment. Unfortunately, a second serum sample was not available because the patient denied further blood tests.

The father provided documented informed consent for diagnostic evaluations of himself and his son and was informed of the results, and consented to the publication of his case and that of his son. Anonymity of both patients is preserved and the conditions of care and procedures were in agreement with the current Declaration of Helsinki.

Discussion

Toxoplasmic lymphadenitis is infrequently reported in non-HIV-infected patients. To our knowledge, simultaneous primary toxoplasmic lymphadenitis in two family members in Thailand has not hitherto been reported. Our patients presented with a typical course of painless cervical lymphadenopathy with a presumptive histopathological diagnosis even though the differential diagnosis of isolated cervical lymphadenopathy includes many etiologies such as infections, malignancy, and immune disorders [8], there is a very high specificity of the triad of characteristics of toxoplasmic lymphadenitis based on histopathology alone. The diagnostic histopathological triad of

toxoplasmic lymphadenitis comprises reactive follicular hyperplasia, multifocal monocytoid aggregates, and clusters of epithelioid cells. Eapen et al. reported this classic triad of histopathological features yielded a very high specificity of 96.6%, but had a very low sensitivity of only 44.4% [9]. In addition, Eapen et al. had devised a composite criteria comprising (1) the presence of microgranulomas, (2) the lower than grade 2 macrogranuloma, (3) the absence of giant cells, and (4) the follicular hyperplasia, which can be used to diagnose toxoplasmic lymphadenitis with a high degree of sensitivity (100%) and specificity (96.6%). Therefore, our patients were diagnosed toxoplasmic lymphadenitis using this composite criterion.

Trophozoites of *T. gondii* are identified in tissue histopathology in <1% of patients with toxoplasmosis [4, 9]. In our patient, the lymph node histopathology also revealed no organisms.

In our patient, PCR for *T. gondii* in lymph nodes and serum specimens was negative. Variable sensitivity of PCR tests is reported after previous studies depending on the types of specimens, methods, the gene targets, and the detection system used [10-12]. In a study of primary toxoplasmic lymphadenitis in immunocompetent patients, the positivity (sensitivity) of PCR in serum specimens was 35% [11]. However, there was high specificity (100%) and high positive predictive value (100%) in the diagnosis of toxoplasmic lymphadenitis.

In our patient, both anti-*Toxoplasma* IgG and IgM by MEIA were negative in the first serum sample. IgG antibodies can be detected by several serological tests including the Sabin–Feldman dye method, enzyme linked immunosorbent assay (ELISA), indirect fluorescent antibody, IgG avidity, and agglutination and differential agglutination tests. IgG antibodies usually appear within a few weeks after primary infection and persist for life [1-4]. The Sabin–Feldman dye test is considered the reference serological test because it is very sensitive and specific. Unfortunately, it is not available in Thailand because of the need to grow live organisms. The IgG ELISA is acceptable as an alternative serological test with relatively high sensitivity and specificity. IgM antibodies usually appear early and persist for years after primary infection. The IgM ELISA is widely used in clinical practice, but some commercial test kits have a low specificity [13, 14].

We assume that the patient's son also had primary toxoplasmic lymphadenitis based on a simultaneous compatible self-limited benign clinical course of asymptomatic cervical lymphadenopathy even though a confirmation by histopathology, serology, and PCR test were not available. Several previous reports described outbreaks of primary toxoplasmosis in a community or a family setting, caused by the consumption of raw meat or the ingestion of water contaminated with oocysts [15, 16].

Our patients made a complete recovery within 6 weeks of symptomatic therapy. Specific anti- parasitic therapy for primary toxoplasmic lymphadenitis in immunocompetent individuals is rarely indicated because of the self-limited and benign course of this disease.

There have been only two reports of primary toxoplasmosis in Thailand (**Table 1**) [17, 18]. The first report described three adult patients who presented with prolonged fever, hepatitis, and mesenteric lymphadenopathy [17]. They died after hospitalization and ineffective treatment with pyrimethamine/ sulfadiazine or cotrimoxazole. The second report described a 28-year-old woman who presented with prolonged fever, lymphadenopathy, cutaneous lesions, and eventually developed myocarditis, and meningoencephalitis [18]. None of these four patients had a history of consumption of raw meat. They did keep pigs and ducks, and cared for several cats. In Thailand, studies have shown the presence of *Toxoplasma* antibody in several domestic animals including cats, dogs, pigs, and cows [19, 20]. Our reported two patients survived without specific anti-parasitic treatment. Both were normal hosts with a benign clinical presentation. To our knowledge, this is the first published report of a cluster of primary toxoplasmosis in Thailand.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Table 1. A summary of 6 primary toxoplasmosis in nonpregnant, nontransplanted, and noncongenitally infected patients in Thailand

Patient/ year	Sex, age (years)	Province	Animal exposure	Clinical manifestations	Presence of cyst or tachyzoite in pathology	Treatment	Outcome
1/1976 [17]	M, 51	Chachoengsao	NA	20 days of fever, hepatitis, mesenteric lymphadenopathy	Yes	Pyrimethamine + sulfadiazine	Died 40 days after hospitalization
2/1976 [17]	F, 25	Bangkok	NA	3 weeks of fever, erythema nodosum, hepatitis, myocarditis mesenteric lymphadenopathy	Yes	Pyrimethamine + sulfadiazine	Died from *E. coli* septicemia 68 days after hospitalization
3/1976 [17]	M, 25	Samut Sakhon	NA	5 months of fever, hepatitis, pneumonia, supraclavicular, mesenteric lymphadenopathy	Yes	Anti-tuberculous drugs, Cotrimoxazole	Died 60 days after hospitalization
4/1985 [18]	F, 28	Chiang Mai	NA	Prolonged fever, lymphadenopathy, arthralgia, skin lesions, myocarditis, meningoencephalitis, pleuritis	Yes	NA	NA
5/2010*	M, 39	Phang Nga	Cat, pig, duck	1 month of cervical lymphadenopathy without fever	No	No	Complete recovery within 6 weeks of illness
6/2010*	M, 6	Phang Nga	Cat, pig, duck	1 month of cervical lymphadenopathy without fever	No	No	Complete recovery within 6 weeks of illness

*Our cluster

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