Unilateral Axillary Lymphadenopathy due to Toxoplasmosis: A Ubiquitous Infectious Disease Important for Differential Diagnosis of Solid Malignancies

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Abstract
A 30-year-old woman was pointed out for her right axillary lymphadenopathy in a medical checkup. Ultrasonography showed two swollen lymph nodes and the presence of lymph node hilum with a convex shape in the larger lymph node. Under the tentative diagnosis of lymphadenitis, the patient was initially treated with antibiotic therapy, leading to no improvement in her lymphadenopathy for 1 month. Positron emission tomography after antibiotic therapy showed a maximum standardized uptake value of 7.0 in the swollen lymph nodes without any other avidities. Neither mammography nor ultrasonography showed any abnormalities in the breasts. The serum IL-2R level was within the normal range. Despite the lack of malignant cells in the aspiration biopsy cytology specimen, the patient received lymph node excisional biopsy to avoid undertreatment. A postoperative pathological study showed a swollen lymph node with preserved lymph node structure, follicular hyperplasia, and lymphoid hyperplasia. The irregularly dilated germinal center had microglanulomas, tingible body macrophages, enlarged aggregation of monocytoid B cells with neutrophil interminglement, and no giant cells, leading to the diagnosis of toxoplasmosis. A detailed interview after the lymph node biopsy revealed that she did not have any cats but had chickens and had her right forearm a little injured by the roof edge of a chicken coop 5 weeks before the medical checkup. Postoperative serologic testing to further confirm the toxoplasma infection showed elevated IgG and IgM antibody levels.
Oncologists and infectious disease specialists should note this type of transmission of *Toxoplasma gondii* and unilateral lymphadenopathy as an important clinical manifestation of toxoplasmosis.

**Introduction**

The axilla is not an organ in itself and does not have its own epithelium, naturally never developing so-called primary axillary cancer. The axilla, however, contains many lymph nodes and develops various inflammatory diseases and primary or metastatic lymph node lesions [1]. Axillary lymph nodes receive lymphatic drainage from the arm, thoracic wall, and breast [2]. Breast cancer including occult breast carcinoma [3–5] most typically explains this lymphatic flow. In addition, malignant lymphoma and various infectious diseases sometimes develop in the axilla. Malignant lymphoma can occur in the unilateral axillary lymph nodes without any extra-axillary lesions. Infectious diseases, however, confined to unilateral axillary lymph nodes are extremely rare, except for cat scratch disease.

Toxoplasmosis is caused by *Toxoplasma gondii*, i.e., a ubiquitous protozoan parasite, infection [6]. Only a limited number of patients infected with *Toxoplasma gondii* develop mild symptoms such as fever and chills, lasting only for a very short term, i.e., 2 or 3 days. Vast majority of patients, therefore, do not even notice their toxoplasma infection unless some kind of unpleasant symptoms annoy the patients. A seroepidemiologic survey revealed that the rate of *Toxoplasma gondii* infection differed among geographic areas and ranged from approximately 10% to nearly 80% [7]. Felines are the only animals in which *Toxoplasma gondii* can complete its reproductive cycle [6]. Infection with *Toxoplasma gondii* occurs when *Toxoplasma gondii* oocysts invade orally or through a wound. Toxoplasma protozoan oocysts are found in cat feces and contaminated raw meat/water. We herein report a unilateral axillary lymphadenopathy presumably due to extremely rare transmission form, i.e., through minor injury on the forearm, of *Toxoplasma gondii*.

**Case Report**

A 30-year-old woman was pointed out for her right axillary lymphadenopathy in a medical checkup. On the next day, the woman was referred to our hospital for a detailed examination of the lymphadenopathy. Ultrasonography (US) showed two swollen lymph nodes, oval and round lymph nodes with or without lymph node hilum, of 27 mm and 14 mm in size, respectively (Fig. 1). Under the tentative diagnosis of axillary lymphadenitis, the patient was initially treated with antibiotic therapy for 1 week. No lymph node shrinkage in 1 month made the patient consult us further. US showed still swollen two axillary lymph nodes with blood flow into the enlarged lymph node cortices but no significant findings in the right breast. Mammography showed no abnormalities in the breasts either. To explore some clues to the diagnosis, aspiration biopsy cytology was done to the larger lymph node but showed no malignant cells. Blood test showed white blood cells of 4,800/μL, C-reactive protein of 0.031 mg/dL, and sIL-2R of 215 U/mL (normal range; 122–496 U/mL). Positron emission tomography showed a maximum standardized uptake value of 7.0 in the swollen lymph nodes without any other avidities (Fig. 2). To avoid
undertreatment and based on the patient’s strong request, diagnostic lymph node excisional biopsy was done to the patient. Frozen section of the biopsied node did not provide any definitive diagnoses during the operation. A postoperative pathological study showed a swollen lymph node with preserved lymph node structure, follicular hyperplasia, and

Fig. 1. US of the axilla. a A round lymph node showed very low internal echoes (asterisk) and slightly enhanced posterior echoes (arrow). b A larger lymph node had eccentric cortical hypertrophy and distinct lymph node hilum in a convex fashion (arrow).

Fig. 2. PET showed strong avidities in the axillary lymph nodes (arrow) with maximum standardized uptake value of 7.0. PET, positron emission tomography.
lymphoid hyperplasia. Irregularly dilated germinal center had microgranulomas, tingible body macrophages, enlarged aggregation of monocytoid B cells with neutrophil interminglement, and no giant cells, leading to the diagnosis of toxoplasmosis (Fig. 3). In response to a postoperative detailed interview, she replied that she did not have any cats but had chickens in the yard. In addition, the patient had hurt her forearm a little with the roof edge of the chicken coop but did not receive any treatment for the minor injury 5 weeks before the medical checkup. In addition, the patient had not eaten any undercooked meat and had never drunk any water other than tap water before the event. Serologic testing to further confirm the toxoplasma infection after lymph node biopsy showed IgG antibody level of 64.9 IU/L (normal range; 0–1.6 IU/L) and IgM antibody level of 2.03 Index (normal range; 0–0.5 Index). The patient recovered uneventfully with good wound healing and did not receive any further treatments.

**Discussion**

Oral ingestion of *Toxoplasma gondii* oocytes excreted by the cats causes no clinically significant symptoms in the vast majority of infected patients or, if any, most often causes minor symptoms, e.g., fever, chills, and sweats, with bilateral cervical lymphadenopathy [6–8]. In this case, only right axillary lymph nodes were affected with toxoplasmosis. Taken the lymphatic flow to the axilla into consideration [1, 2], *Toxoplasma gondii* oocytes should be infected through the minor injury on the forearm. The patient did not have any cats but had many chickens in the yard. On asking in detail about the chicken coop, the patient replied...
that she had seen some cats wandering around it many times. It is well known that a single cat may shed more than 100 million oocysts and oocysts can survive longer in warm and moist weather [6]. It was in such a climate, i.e., rainy season in Japan, when she had her forearm injured with the roof edge of the chicken coop. There are no evidence that Toxoplasma gondii oocytes were attached to the roof of the chicken coop and caused lymphadenopathy through the wound on the forearm. However, it should be reasonable to judge that Toxoplasma gondii invaded through the minor wound on the forearm due to the localized infection of the ipsilateral axillary lymph nodes.

Malignant lymphoma, especially diffuse large B cell lymphoma (DLBCL), can occur both in the breast and/or axilla. DLBCL generally present with very low internal echoes on US, implying extremely aggressive growing nature of DLBCL [9, 10]. This nature also implies the expanding growth pattern of DLBCL. Even when affected with DLBCL, lymph node hilum can sometimes be present but, if present, generally shows a concave shape due to the rapid growing nature of DLBCL, proliferating mainly in the cortex of the affected lymph nodes and generally showing an expanding pattern. In this case, one of the two swollen lymph nodes showed an enlarged lymph node with marked cortical hypertrophy and large convex shape hilum. These findings should be useful to make a differential diagnosis between some kinds of lymph node infection and DLBCL.

Enlarged lymph nodes with toxoplasmosis are generally smaller than 3 cm in size, being in good agreement with the findings in this case. Ultrasound findings also showed no caseous necrosis in the lymph nodes, leading to the omission of tuberculin skin test for differential diagnosis. In addition, mammography and US cannot exclude occult breast carcinoma. Even magnetic resonance imaging with some kind of contrast agent cannot detect occult breast carcinoma in 20–30% [3–5] of such patients. The age of 30 years, however, could highly exclude the possibility of occult breast carcinoma.

Frozen section could not provide us intraoperative definitive diagnosis in this case. It is reported that the presence of microgranulomas, absence of giant cells, and follicular hyperplasia with prominent germinal centers plays an important role in the diagnosis of toxoplasmosis [11]. In this case, pathological findings were well matched to these findings. Oncologists and infectious disease specialists should note these typical pathological findings in order not to surgically overtreat the patient based on frozen section findings.

Vast majority of patients infected with toxoplasmosis live well without any symptoms. Some patients, however, present with similar findings often observed in malignant diseases. Physicians, therefore, should well recognize that toxoplasmosis is a very common infectious disease worldwide and should always pay much attention to this disease in differential diagnosis of solid malignancies.

In conclusion, we experienced an extremely rare case of toxoplasmosis presumably transmitted through the minor injury on the forearm by the contact with the roof edge of the chicken coop. Preoperative measurement, if had been done, of IgM and IgG level should have led us to avoid unnecessary lymph node biopsy. In addition, the presence of convex shape hilum in the lymph node might be a useful clue to the diagnosis of Toxoplasma gondii infection. Physicians should note that toxoplasma infection, one of the most popular infectious diseases, can be an important differential disease for malignant tumors.

**Statement of Ethics**

The study was approved by the Kishiwada Tokushukai Hospital Ethics Committee (IRB #Case 20-03). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ryoki Doami contributed to the design of the report. Shoji Oura drafted the manuscript. Shinichiro Makimoto revised the manuscript. All the authors have read and approved the final version of the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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