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Case Report

Necrotizing Lymphadenitis: Possible Acute Toxoplasmic Infection

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Summary. A rapid rise in serum hemagglutination antibody (HA) titers for toxoplasma was detected about 2 months after the onset of cervical lymphadenopathy in two patients with necrotizing lymphadenitis. These lymph nodes proliferation of histiocytes with nuclear debris, phagocytized macrophages and necrotic areas, and the association suggested that necrotizing lymphadenitis might be caused by acute toxoplasmic infection.

Key words: Necrotizing lymphadenitis – Toxoplasma.

Introduction

In 1972, Kikuchi described an unusual lymphadenititis, which mainly affected the cervical nodes of young adults and showed histologically localized proliferations of histiocytes and reticulum cells associated with abundant nuclear debris. The same lymph nodal changes were also independently reported by Fujimoto et al. as cervical subacute necrotizing lymphadenitis in 1972. Subsequently about 150 cases of this lesion have been reported as necrotizing histiocytic lymphadenitis (Shimamine et al., 1974), necrotizing lymphadenitis (Wakasa et al., 1975), phagocytic necrotizing lymphadenitis (Kikuchi and Uryu, 1976) and pseudolymphomatous hyperplasia in lymph nodes (Michaelek, 1977). These authors recognized that the lesion might be a new entity of unknown etiology, because of the characteristic clinicopathological features. According to these reports, the lymphadenopathy occures mainly young adults, is more frequent in woman, and most commonly involves the neck, less often the axillary nodes and rarely appears as a generalized lymphadenopathy. The nodes are seldom painful but are often tender and commonly 1.0 to 1.5 cm in diameter. They remain discrete, never break down, and gradually return to a normal size but may take 2 or 3 months to do so. Sometimes the patients have a remittent fever and a normal or decreased white blood cell count with some atypical lymphocytes.

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Histologically the affected lymph node shows focal cortical or paracortical proliferation of histiocytes, reticulum cells or transformed lymphocytes, associated with numerous phagocytes containing nuclear debris and large or small central necrotic areas. No pronounced sinus histiocytosis, enlarged lymph follicles or neutrophilic infiltrates are present. Although the lesion is thought to be reactive, induced by some toxin, virus or bacteria, no causative agents have been identified.

Recently we found elevation of hemagglutination antibody (HA) titers for toxoplasma and a few small positive areas of fluorescent antibody staining for toxoplasma in the affected nodes in 2 patients with this disease. Subsequently these 2 cases of necrotizing lymphadenitis were thought to be acute toxoplasmic infection.

Reports of Cases

Case 1. 26-year-old male.

The patient was in good health until 6 days prior to the admission on September 22, 1976 to Fukuoka Central National Hospital, when he began to complain of high fever (39° C) mild diarrhoea and malaise. Several tender lymph nodes, about 1.0 cm in diameter, were palpable in both sides of the neck on admission. His general condition improved but abdominal pain, diarrhoea and fever of 39° C with painful left cervical lymphadenopathy reappeared at the end of October 1976. A nodal biopsy from the neck was performed on November 9. The specimen was a lymph node, measuring $1.0 \times 0.5 \times 0.5$ cm. The cut surface was grayish-white. Histologically large foci

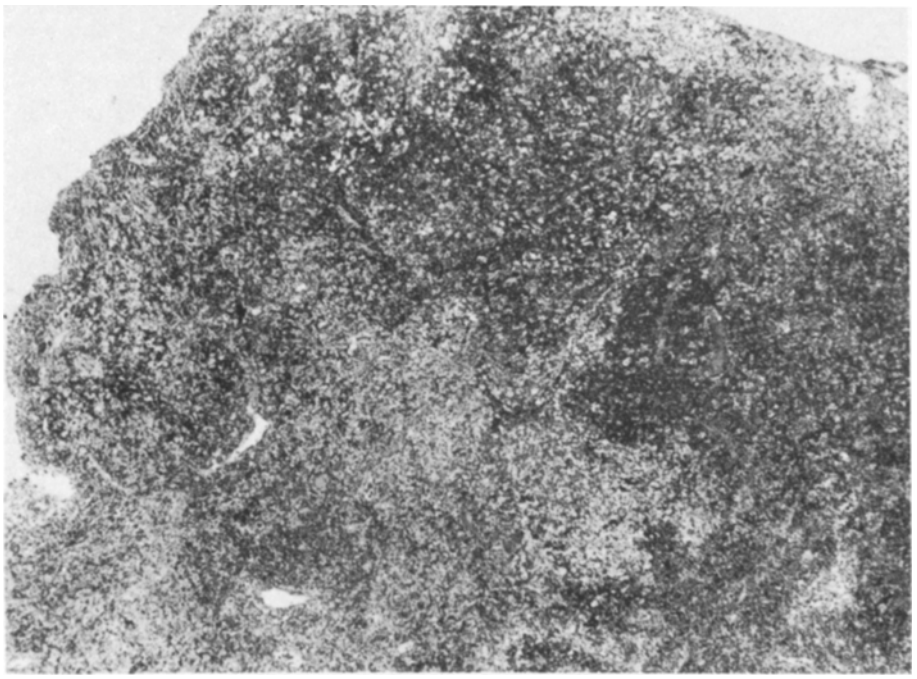

Fig. 1. Cervical lymph node of Case 1. Large foci of proliferated histiocytes and scattered swollen reticulum cells and histiocytes. Hematoxylin-eosin. ×44

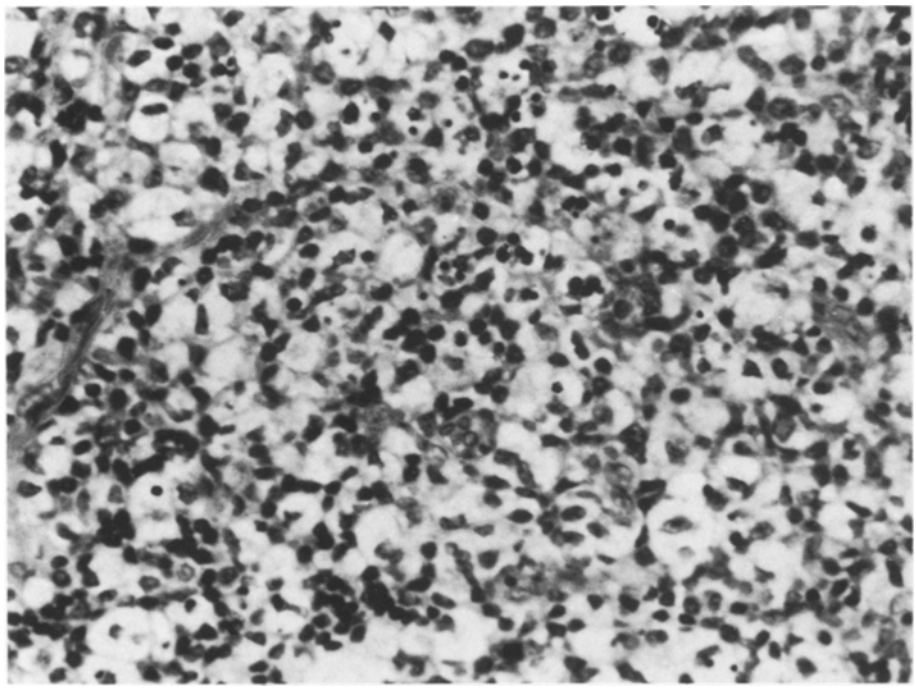

Fig. 2. Same lymph node as Figure 1. Proliferation of histiocytes and nuclear debris in some phagocytes. Hematoxylin-eosin. ×800

of proliferated histiocytes were found in the cortex with some phagocytized nuclear debris and tiny necrotic areas, together with focal collections of swollen reticulum cells and foamy histiocytes (Figs. 1 and 2). No sinus histiocytosis, enlargement of lymph follicles, neutrophil infiltrates or perinodal vein thrombosis were noted. After the biopsy a transient rash on the chest appeared for 3 days.

He was completely well 6 months after onset of the disease. Initially the HA tests were positive with a titer of 1:512 on 3 occasions (Titers of 1:512 and greater are positive). Seven weeks later the HA rose above 1:8192. Four months later the titer had returned to the initital value. Heterophile agglutinin tests were negative. The main laboratory data are shown in Table 1.

Case 2. 19-year-old female.

The patient was in her usual state of good health until the sudden onset of painful lymphadenopathy on the right side of the neck, with the appearance of erythematous macules on her thighs on December 8, 1976. She was admitted to Hamanomachi Hospital with general malaise, high fever (39° C) and extension of erythema on December 14. Antibiotics did not affect the high fever. On January 5, 1977, a lymph node biopsy was performed. The lymph node was $1.2 \times 0.5 \times 0.5$cm in size. Focal yellowish areas were seen on cut surface. Histologically some large necrotic foci were found in the cortex surrounded by many histiocytes and phagocytes with nuclear debris. (Figs. 3 and 4). No sinus histiocytosis, neutrophil infiltrates or reactive enlargement of lymph follicles were detected. Pericapsular fibrosis and chronic inflammatory infiltrates were evident, but no venous thrombosis was found.

Her clinical condition rapidly improved after the biopsy. She was clinically completely well and free from detectable disease 5 months after onset of the disease. The HA titer was initially 1:32, a month later 1:512, and by six months later the titer had fallen to 1:128. Paul-Bunnel test was negative. Attempts to grow anaerobic, mycobacteria and pyogenic cocci and viruses (Incubation with Hela cells, Vero cells, kidney cells of African green monkey and human synovial cells) from the biopsied node were unsuccessful. The main laboratory findings are tabulated in Table 1.

Table 1. Toxoplasma HA tests and some other laboratory findings in both patients

	Case 1	Case 2
HA test for toxoplasma[a]	24– 9–1976 × 512 6–10–1976 × 512 1–11–1976 × 512 10–11–1976 × 8192 17–11–1976 × 8192 >
29–11–1976 × 8192 >
17– 1–1977 × 2048
31– 1–1977 × 2048
28– 2–1977 × 2048
14– 3–1977 × 2048
28– 3–1977 × 512	4–1–1977 × 32 17–1–1977 × 128 24–1–1977 × 512 4–2–1977 × 512 30–3–1977 × 128
WBC count	24– 9–1976 4700 30–10–1976 5900 4–11–1976 4800(2)[b] 15–11–1976 5500(1) 29–11–1976 5300	21–22–1976 9300(1) 27–12–1976 3700(1) 6– 1–1977 3700(9) 27– 1–1977 4300
Paul-Bunnel test	6–10–1976 (–) 18–11–1976 (–)	22–12–1976 (–) 4– 1–1977 (–)
Weil-Felix reaction	1–10–1976 (–)	22–12–1976 (–) 4– 1–1976 (–)
Widal reaction	1–10–1976 (–)	22–12–1976 (–)
Mumps test	17–10–1976 (–)	
Rubella test	6–10–1976 (–)	
Adenovirus test	17–10–1976 (–)	
Cultivation of biopsed lymph node		Anaerobic b. (–) Mycobacteria (–) Pyogenic c. (–)
Co-cultivation for virus of biopsied lymph node		Hela cells (–) Vero cells (–) Kidney cells of African green monkey (–) Human synovial cell (–)

[a] Titers of 1:512 and greater are positive, Toxotest, Eiken Co. Japan
[b] % of atypical lymphocytes

Discussion

Serum HA titers for toxoplasma have previously been measured in 5 patients with necrotizing lymphadenitis (Wakasa et al., 1975; Takagi et al., 1976). No elevation of the titers was found in any case.

In the present study the first patient showed a persistent rise in HA titer during the first month after onset of illness and the titer rose suddenly to exceed 1:8192 later. This high value was maintained for 3 weeks and returned to 1:512 after 6 months. In the second patient the titer was initially 1:32 and rose to 1:512 within 7 weeks of the onset of the disease. This positive value was maintained for about 2 weeks and then fell to 1:128 after 2 months. Both

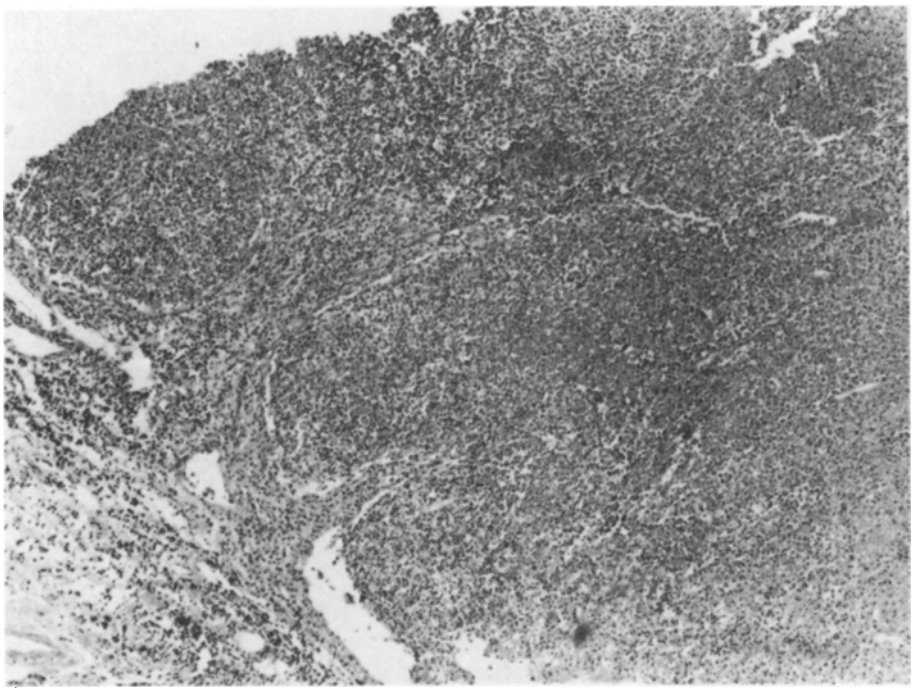

Fig. 3. Cervical lymph node of Case 2. Loss of the normal architecture and massive necrosis in the cortex. Hematoxylin-eosin. ×44

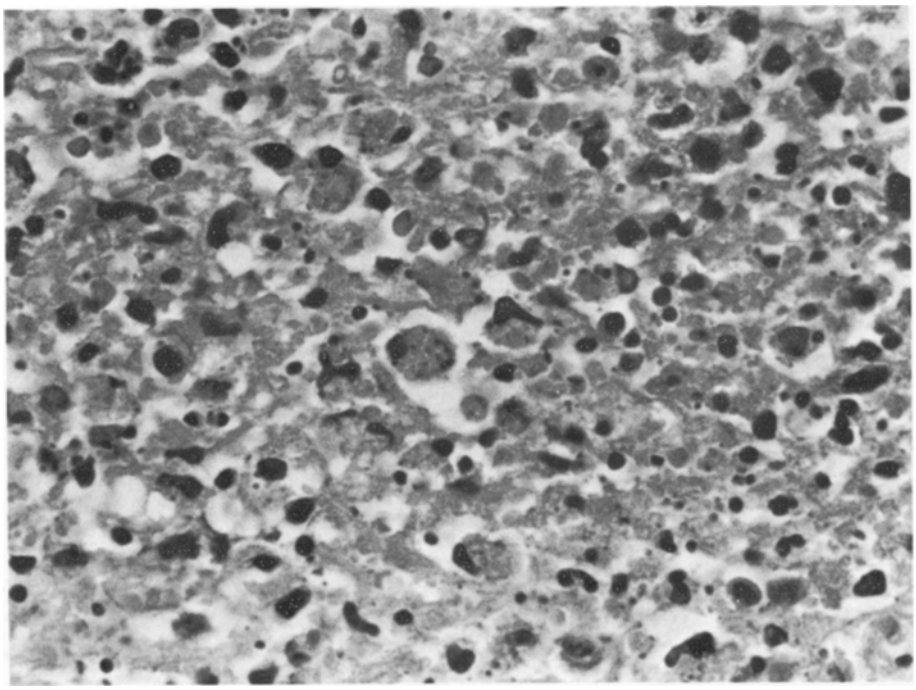

Fig. 4. Same node as Figure 3. Acute necrosis with abundant phagocytes with nuclear debris. Hematoxylin-eosin. ×800

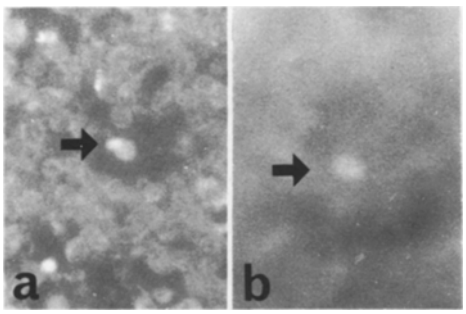

Fig. 5. Toxoplasma-like body (arrow) in affected area. **a.** Case 1, ×1200, **b.** Case 2, ×2000. Fluorescent antibody stain for toxoplasma

patients showed a rise in HA titer after 2 months from the onset of the disease, maintenance of these levels for 2 to 3 weeks, and a subsequent fall. This fluctuation of HA titers suggested that acute toxoplasmic infection might be responsible for the lymphadenitis. It has been reported that antibody titers rise rapidly in the first 6 to 8 weeks after infection, are maintained for few more weeks and then fall steadily (Beverley, 1973). The negative titers reported by Wakasa et al. (1974) and Takagi et al. (1976) might be a consequence of premature measurement. It has been suggested that acute toxoplasmic lymphadenitis (Piringer's lymphadenitis) occurs mainly in young adult females, as cervical lymphadenopathy and that the disease has a high spontaneous recovery rate (Frenkel, 1971). Histologically the characteristic changes are small clusters of epitheloid histiocytes in the cortex and lymph follicles, severe compact proliferation of large histiocytes in sinuses and reactive hyperplasia of lymph follicles with germinal centers (Lennert, 1964; Dorfman and Remington, 1973). In the 2 cases presented the age, site of enlarged lymph nodes and good prognosis were consistent with those of previously reported cases of acquired acute toxoplasmic lymphadenitis, but the histological findings were dissimilar. Lennert (1961) described a patient with massive necrosis who had a high titer in the Sabin-Feldman test. He suspected that these histological changes might be responsible for toxoplasmic infection, but no further explanation was made. Histological findings in our two cases, especially in case 2, seemed to resemble those of his case. The difference between previously reported cases of acute toxoplasmic lymphadenitis and our 2 cases could be due to an earlier and more severe reactive change in our cases, related to the fluctuating pattern of HA titers. The cause of the necrotic change was uncertain. Davis and Stansfield (1972) reported extensive necrosis of superficial nodes following thrombosis of veins, but in our cases no venous thrombosis was found in the nodes of either patient.

Examination of fluorescent antibody using labelled antibody for toxoplasma (Nisseiken Co. Japan) was tried with formalin-fixed and paraffin-embedded specimens in both cases. Some small oval bodies with positive reaction were detected in the affected areas (Fig. 5). Tsunematsu et al. (1964) described these non-characteristic positive bodies in one case of acute toxoplasmic lymphdenitis and supposed that they might be degenerative changes in the parasite after exposure to antibodies. Due to the presence of latent infection and equivocal clinical symptoms in toxoplasmosis, the positive findings in HA tests and pres-

ence of toxoplasma-like bodies in the node does not always provide enough data in support of the diagnosis, but the alteration in pattern of HA titers in both patients is strongly suggestive of acute toxoplasmic infection.

In Japan the incidence of patients with toxoplasmic infection, as judged by antibody tests, is nearly the same as that in Europe and the United States (Oniki, 1967). However, acute toxoplasmic lymphdenitis is extremely rare (Shimamine et al., 1974). If necrotizing lymphadenitis is caused by acute toxoplasmic infection, the discrepancy between rates is partly explained. To help resolve the problem, serial examination of HA titers for toxoplasma, innoculation of biopsied lymph node material into mice and examination of toxoplasma in fresh lymph node by fluorescent techniques in further cases of necrotizing lymphadenitis should be carried out.

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