Review Article

Granulomatous Lymphadenitis

Shigeyuki Asano

In this review, representative types of granulomatous lymphadenitis (GLA) are described. GLA can be classified as noninfectious GLA and infectious GLA. Noninfectious GLA includes sarcoidosis and sarcoid-like reaction. The cause of sarcoidosis remains unknown, but it has good prognosis. Sarcoid-like reaction, which is considered to be a biological defense mechanism, is observed in regional lymph nodes with many underlying diseases. Infectious GLA can be classified as suppurative lymphadenitis (LA) and nonsuppurative LA. Suppurative LA generally shows follicular hyperplasia and sinus histiocytosis in the early phase. In tularemia and cat scratch disease, monocytoid B lymphocytes (MBLs) with T cells and macrophages contribute to the formation of granuloma. However, none of the epithelioid cell granulomas of Yersinia LA contains MBLs like in cat scratch disease. In addition, almost all have a central abscess in granulomas induced by Gram-negative bacteria. In terms of the lymph nodes, tularemia and cat scratch disease are apt to affect the axillary and cervical regions while Yersinia LA affects the mesenteric lymph node. Nonsuppurative LA includes tuberculosis and BCG-histiocytosis. These are induced by delayed allergic reaction of *M. tuberculosis*. Tuberculosis LA mainly appears in the cervical lymph node. Organisms are histologically detected by Ziehl-Neelsen staining in the necrotic area. Toxoplasmosis is also a nonsuppurative protozoan infection (*Toxoplasma gondii*). In toxoplasma LA, MBLs can also be seen, but round and organized, well-formed granulomas are not found in this disease. Furthermore, necrosis is not induced and there are no accompanying neutrophils, eosinophils and fibrosis. GLA described above is associated with characteristic histological findings. An accurate pathological diagnosis using the above findings can lead to precise treatment. 〔*J Clin Exp Hematopathol 52(1) : 1-16, 2012*〕

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INTRODUCTION

Granulomatous lymphadenitis can be classified into noninfectious and infectious types[1] (Table 1). Noninfectious granulomatous lymphadenitis includes berylliosis, Hodgkin's lymphoma, non-Hodgkin's lymphoma, lymph node draining neoplasms (sarcoid-like reaction), lymph node draining Crohn's disease and sarcoidosis. These rarely have abscesses and necrosis in the center of granulomas.

Infectious granulomatous lymphadenitis can be classified into suppurative lymphadenitis and nonsuppurative lymphadenitis. The former is exemplified by tularemia, cat scratch disease, Yersinia lymphadenitis and lymphogranuloma venereum. These almost all have central abscesses and necrosis in granulomas induced by Gram-negative bacteria and chlamydia. In terms of the lymph nodes, tularemia and cat scratch disease are apt to affect the axillary and cervical regions, Yersinia lymphadenitis affects mesenteric lymph node and lymphogranuloma venereum affects inguinal lymph nodes.

Table 1. Granulomatous lymphadenitis

1. Noninfectious granulomatous disorders
1) Sarcoidosis lymphadenitis
2) Sarcoid-like lymphadenitis
3) Berylliosis
2. Infectious granulomatous disorders
A. Suppurative
1) Tularemia lymphadenitis
2) Cat scratch lymphadenitis
3) Yersinia lymphadenitis
4) Lymphogranuloma venereum
5) Fungal infection
B. Non-suppurative
1) Tuberculous lymphadenitis
2) Atypical mycobacterial infection
3) BCG-lymphadenitis
4) Toxoplasma lymphadenitis (Piringer-Kuchinka lymphadenopathy)
5) Lepra
6) Syphilis
7) Brucellosis
8) Fungal infection (Cryptococcus, Histoplasma, Coccidioidomycosis, Pneumocystis)

The latter, that is, nonsuppurative lymphadenitis, includes tuberculosis and Bacillus Calmette-Guérin (BCG)-lymphadenitis. These have nonsuppurative hypersensitivity-type granulomas induced by mycobacterium. Tuberculous lymphadenitis mainly appears in the cervical lymph node. Predominant histiocytes with smaller numbers of T cells, dendritic cells and peripheral B cells are recruited for granuloma formation. Organisms are histologically detected by Ziehl-Neelsen staining in the necrotic area. Toxoplasmosis is also a nonsuppurative protozoan infection (*Toxoplasma gondii*).

Here we clinicopathologically describe eight representative types of granulomatous lymphadenitis, namely, sarcoidosis, sarcoid-like reaction, tularemia, cat scratch disease, Yersinia lymphadenitis, tuberculosis, BCG-lymphadenitis and toxoplasmosis.

SARCOIDOSIS

Sarcoidosis means "meaty chunk-like lesions" in Latin. The cause of the disease remains unknown, but it is non-hereditary with a good clinical course. The disease involves multiple organs, such as pulmonary hilar lymph nodes, lungs, eyes and skin.[2] The nodes show variously sized non-caseous epithelioid granulomas. Blindness, difficulty breathing and heart failure, which are complications of sarcoidosis, may interfere with daily life. In Japan, anaerobic bacteria such as *Propionibacterium acne* (*P. acne*) and *P. granulosum* are considered among the causative agents of sarcoidosis because genes of these bacteria have been detected in the lungs and lymph nodes in such cases. On the other hand, in Europe, associations between sarcoidosis and *Mycobacterium tuberculosis* (*M. tuberculosis*), virus and autoimmune disease have been reported.[3-6]

Epidemiology

Sarcoidosis is found worldwide, affecting people of all races and ages. Seasonal clustering occurs during winter and early spring.[7] Sarcoidosis occurs twice as frequently in women as in men, but rarely in children.[8,9] Adults between 20 and 40 years of age are usually affected. In Japan, there are no seasonal and regional biases, but those of both sexes in their twenties are most often affected, with very few symptoms. Recently, cases in women after their forties (fifties and sixties, in particular) have also been seen. In addition, the global annual incidence is approximately eight cases per 100,000 peoples, but 3.1 cases in Japan. Susceptible organs are the lungs and hilar lymph nodes (80%), eyes (50%), skin (20%) and other lymph nodes, namely, cervical, axilla and inguinal lymph nodes.

History

In terms of the history of sarcoidosis, Hutchinson (1877) was the first to describe such macroscopic findings of the skin and Boeck (1897) histologically examined macular rash of the skin in this disease. In Japan, around 1950, sarcoidosis was recognized as pulmonary hilar lymphadenopathy.

Clinical Findings

Sarcoidosis involves multiple organs, most commonly the lungs, skin and eyes, and the symptoms depend on the affected organs. Ocular involvement presents blurred vision, photophobia and floaters, dermatologic involvement presents nodules and plaque, while respiratory lesions are associated with cough and breathing discomfort. Cardiac involvement is more common and causes arrhythmia.

Sudden death occurs in 5% to 10% of patients with sarcoidosis.[10] Lymphadenopathy is frequently presented, most commonly in pulmonary hilar lymph nodes (93.5%). Cervical (12.2%), axillary (5.2%) and inguinal (3.3%) lymph nodes are also affected.

The useful factors for diagnosis of sarcoidosis are as follows : bilateral hilar lymphadenopathy for X-p (Fig. 1a) and computed tomography, increased angiotensin-converting enzyme, hypercalcemia, negative on tuberculin test, bronchio-alveolar liquid (BAL) cytology and increased $CD4^+/CD8^+$ ratio, and positive on the Kveim test.

The granulomas of sarcoidosis can usually be distinguished from tuberculosis, fungal infection, silicosis, berylliosis and Hodgkin's lymphoma by their characteristic sharp demarcation, lack of central necrosis and special staining, such as acid-fast and silver impregnation staining.[6]

Histopathology of Lymph Nodes

In the early phase, follicular hyperplasia and sinus histiocytosis appear like nonspecific lymphadenitis. Subsequently, small epithelioid cell nodules appear in the cortex after a decrease of histiocytes.

In the peak phase, well-demarcated granulomas composed of epithelioid cells with scattered multinucleated giant cells are observed throughout the lymph node. Granulomas may occasionally coalesce (Fig. 1b, 1c).

In the late phase, increased collagen fibers result in fibrosis and hyalinization.[6] This type of granulomatous disease has no neutrophils, and small foci of central fibrinoid and coagulation necrosis are uncommon. CD4/CD8 ratio, usually over 3.5, is increased, which indicates a state of cell-mediated hyperreactivity in sarcoidosis. Furthermore, T lymphocytes, dendritic cells and macrophages are important components for granuloma formation.[11] There are various inclusion bodies such as asteroids (Fig. 1d), Schaumann or
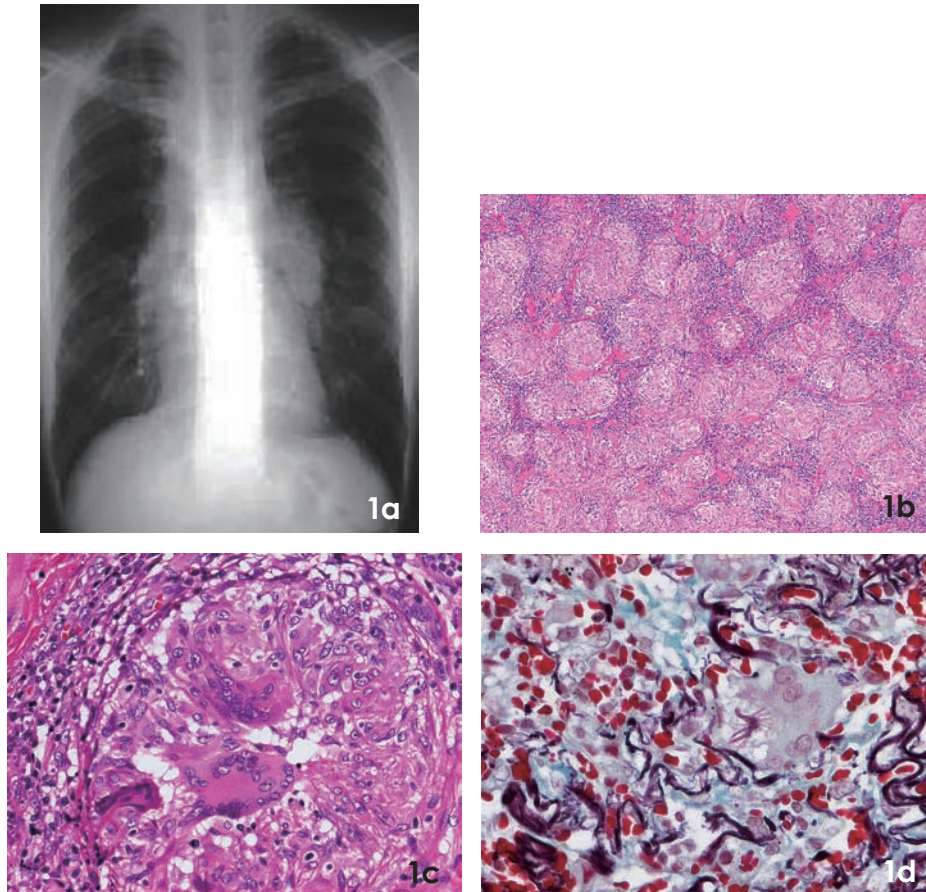
Fig. 1. Sarcoidosis lymphadenitis. (*1a*) Chest X-p shows bilateral hilar lymph node swelling. (*1b*) Lymph node is occupied by numerous granulomas that have not coalesced with each other. There are many plasma cells around each granuloma. (*1c*) Granuloma is composed of epithelioid cells and multinucleated giant cells. (*1d*) Asteroid body is observed in the cytoplasm of multinucleated giant cell.

Hamazaki-Wesenberg bodies.[7,12]

SARCOID-LIKE REACTION (SARCOID-LIKE GRANULOMA)

Epithelioid granuloma resembling sarcoidosis is occasionally observed in regional lymph nodes with an underlying disease, but it is not indicative of systemic sarcoidosis. This is called a sarcoid-like reaction.[13] There are many underlying diseases as follows : carcinoma, toxoplasmosis, fungal infection, tuberculosis, atypical mycobacterial disease, pneumoconiosis, immunocompromised status (Crohn's disease, primary biliary cirrhosis and Sjögren's syndrome), extrinsic allergic inflammatory alveolitis (farmer's lung) and anticancer chemotherapy, as well as associations with chemicals (beryllium, zirconium, silicon, starch granules and pine pollen).[14] Carcinomas of uterus, breast, lung and stomach are associated with this type of reaction.[13,15-17] It is also known that ad-

vanced cancer accompanied by sarcoid-like reaction has good prognosis.[18,19]

This reaction is considered to be a long-term biological defense mechanism of persistently stimulated lymph nodes against metabolites and breakdown products of malignant tumors.[20,21]

History

Wolbach (1911)[22] and Brincker (1986)[13] reported that 4.4% of cancers, 7.3% of non-Hodgkin's lymphomas and 13.8% of Hodgkin's lymphoma are accompanied by sarcoid-like reaction. More recently, these reactions have been observed in the lymph nodes in various diseases.

Clinical Findings

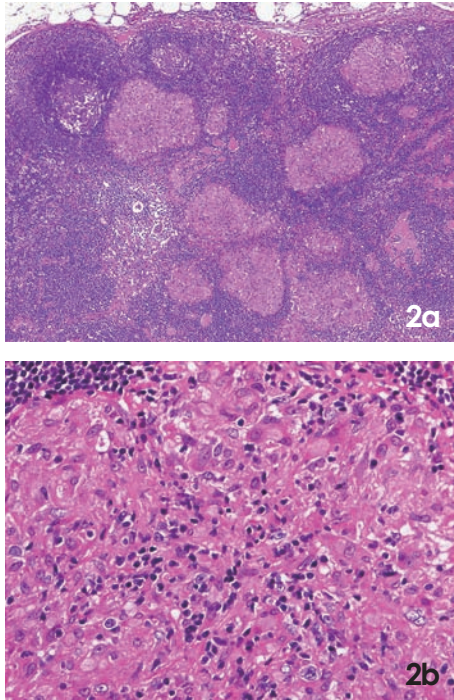Symptoms often depend on the underlying disease and

Fig. 2. Sarcoid-like lymphadenitis. (gastric carcinoma) (*2a*) Irregularly shaped epithelioid granulomas are observed in regional lymph nodes accompanied by sinus and follicular hyperplasia. (*2b*) Lymphocytes are intermingled with epithelioid cells in granuloma.

there are no specific clinical symptoms. In chest X-ray, there are no signs of hilar lymphadenopathy. Results of tuberculin skin and Kveim test are also negative.

Histopathology of Lymph Nodes

Scattered small epithelioid granulomas, composed of sparsely arranged epithelioid cells, are accompanied by lymphocyte infiltration among granuloma cells. In addition, the border of granulomas is often obscure (Fig. 2a, 2b). T lymphocytes, dendritic cells and macrophages are important components for granuloma formation. A CD4/CD8 ratio of 0.8 to 2.25 is observed in confluent-type rather than solitary-type granuloma.[23] The clinical course and laboratory data are useful for differential diagnosis between sarcoidosis and sarcoid-like reaction.

TULAREMIA (OHARA'S DISEASE)

Tularemia is a zoonosis caused by the Gram-negative coccobacillus *Francisella tularensis* (*F. tularensis*), which is the etiologic agent of this acute infectious disease.

This disease is generally spread among wild animals such as rodent (hare, mouse), bird and dog, and it is lethal to animals. There are several modes of infection to humans, such as direct contact, eating of raw meat of an infected animal, bite by infective arthropods, ingestion of contaminated water or food and inhalation of infective aerosols.

F. tularensis invades not only via mucous membranes but also via skin, and bacteria grow at the site of invasion. Then, *F. tularensis* moves to the lymph node via lymphatic drainage and induces infection during its stay there. There is no transmission from person to person.

The genus *Francisella* consists of two species, *F. tularensis* and *F. philomiragia*.[24] *F. philomiragia* is a bacterium causing opportunistic infections, which may cause diseases in accident victims and immunocompromised patients, for example. *F. tularensis* is currently divided into three subspecies, namely, subspecies (subsp.) *tularensis*, subsp. *holarctica* and subsp. *mediasiatica*. Among these, only subsp. *tularensis* (type A) in North America shows high virulence, while subsp. *holarctica* (type B) is distributed in Eurasia from Europe to Japan and shows attenuated virulence.[25-27] The third subspecies, *mediasiatica*, has only been isolated in Central Asia and has virulence similar to that of subsp. *holarctica*.

Epidemiology

Subsp. *holarctica* is widely distributed throughout the Northern Hemisphere around a latitude of 30 degrees north, including in Japan. Tularemia is likely to occur during the hunting season (November to January) and during the season when bloodsucking insects such as ticks are particularly active (April to June).[27,28] In Japan, parts of the Kanto region and the whole of the Tohoku region (east and north of Japan) are particularly affected by tularemia.[29] In Japan, there were 1,372 reported cases from 1924, when records began, until 1994. Since then, there have been reports of one case in Chiba Prefecture in 1999, and one case each in Fukushima Prefecture and Chiba Prefecture in 2008. The number of case reports of this disease has decreased year by year.

History

Soken Honma, a physician in Mito, Ibaraki Prefecture, Japan, described tularemia as "hare meat poisoning" (1837)[30] in the oldest report of the disease. In California, USA, McCoy (1911)[31] reported a plague-like disease affecting squirrels. Francis[30,32] confirmed its transmissibility to humans. *Francisella tularensis* was named after Francis and the town in which the bacterium was isolated: Tulare, California, USA (1921).[31] In Japan, Hachiro Ohara established the Ohara Institute in Fukushima, Japan, for the active study of tularemia (1925).[30] Japanese armed forces (1932-1945) and the U.S. Army (1950-1960) undertook studies to develop tularemia bacteria for use as a biological weapon.[3,5,9]

After the bioterrorism attacks with anthrax in 2001, the

Centers for Disease Control (CDC) classified tularemia into the group of most dangerous pathogens, Category A, along with smallpox and anthrax.[33] Thereafter, cases of tularemia have been reported worldwide,[25,34] but it has become an exceedingly rare disease in Japan. Although the incidence of this disease has decreased, its details must be reviewed because of its potential for use in acts of bioterrorism[25,32,35] and its danger as an infectious disease transmitted by animals.[24,30,32]

Clinical Findings

The incubation period is 1-21 days, usually 3-5 days, and the onset is sudden, with high fever (38-40℃), chillness, headache, generalized pain (especially back pain), sore throat, and cough and chest pain. Sweating chills, exhaustion and weight loss are observed without treatment. After diffuse spread of *F. tularensis* throughout the body, pneumonia, sepsis and meningitis occur. In addition, plague-like symptoms are seen in ingestion cases. However, these are rare and there have been no lethal cases in Japan.

Tularemia is clinically divided into two types, surgical tularemia and internal medicine tularemia, depending on the initial entry route of bacteria. The former group is referred to as *glandular*, *ulceroglandular*, *oculoglandular*, *oropharyngeal* and *tonsillar* types, and the latter as *typhoid* and *latent* types. *Glandular* and *ulceroglandular* types are the most common.

In recent years, it has become relatively easy to determine the strain and subspecies of *F. tularemia* using advanced molecular biological methods,[26,27,36] although there are other useful examinations such as culture, serum agglutination and skin tests.[25,31,32]

The first choice for treatment is the antibiotics streptomycin and gentamicin, but chloramphenicol and macrolides can be useful.

Histopathology of Lymph Nodes

1) Skin lesion

In terms of skin lesions, the fingers are most often invaded. The dermis is slightly edematous and capillaries are distended, and lymphocytes are infiltrated into the dermis. Several abscesses are formed where *F. tularentersis* antigen and genome are detected. Several monocytoid B lymphocytes (MBLs) are observed adjacent to abscesses. Dermal ulcers are seen until the second week after infection, and thereafter granuloma appears in the dermis (Fig. 3a). *F. tularensis* antigen is detected in the central necrotic area of granuloma (Fig. 3b). The antigen is decreased after formation of granuloma. *F. tularensis* antigen is detected from the second day to the 14th day in skin.

2) Lymph node lesion[32]

The right axillary and right elbow lymph nodes are mostly affected. The cut surface shows yellow pus-like appearance (Fig. 3c). Lymphadenopathy is histologically divided into three forms, namely, *abscess*, *abscess-granuloma* and *granuloma*.

In the early phase, until the second week after infection, many lymph follicles appear and histiocytic cells gather in subcapsular sinus. Abscess with central necrosis and mononuclear cells is formed (*Abscess form*) (Fig. 3d, *inset*). In this phase, several MBLs are detected adjacent to the abscess and primitive granulomatous lesion, the same as in skin lesions.

From the second week to the sixth week after infection, several small epithelioid granulomas with central necrosis appear at the cortex and the paracortex. These lesions fuse with each other and form irregular large lesions with central abscess (*Abscess-granulomatous form*) (Fig. 3e). Several multinucleated giant cells also appear in the peripheral epithelioid cell layer. CD4+ cells are more abundant than CD8+ cells throughout the lesion in this phase. CD4+ cells with B cells may contribute to the formation of granuloma.

After the sixth week from infection, necrosis is homogenized and progresses to caseous necrosis in the center of the granulomatous lesion (*Granulomatous form*) (Fig. 3f).

Lymph node lesion is formed one week later than skin lesion. *F. tularensis* antigen is detected from the seventh day to the 92nd day in lymph node.

F. tularensis penetrates the finger skin immediately after contact with infected hares. Subsequently, the primary lesion gradually transfers from skin to regional lymph nodes. The regional lymph node lesions induced by the skin lesion are designated as dermatopathic lymphadenopathy.

CAT SCRATCH DISEASE (FEVER)

Cat scratch disease (CSD) is an infectious disease mainly caused by Gram-negative *Bartonella henselae* (*B. henselae*) and/or *B. quintana*.

The primary lesion at the site of a scratch or bite, usually by a wild male kitten, is often not visible, and the disease is dominated by regional suppurative lymphadenitis. The lymph nodes are usually affected in axillary, inguinal and cervical regions and swell up to three cm in size. The disease usually affects children and youths under 18 years old, with an equal male/female ratio. CSD is likely to occur from fall to winter, which coincides with cat-flea breeding season. In Japan, it has been reported that 9 to 15% of cats have antibodies for *B. henselae*. This bacterium is barely pathogenic for cats.[37]

A flea sucks blood from an infected cat, and bacteria transmitted with the blood are subsequently excreted in the feces of the flea. Thereafter, bacteria attached to a tooth or
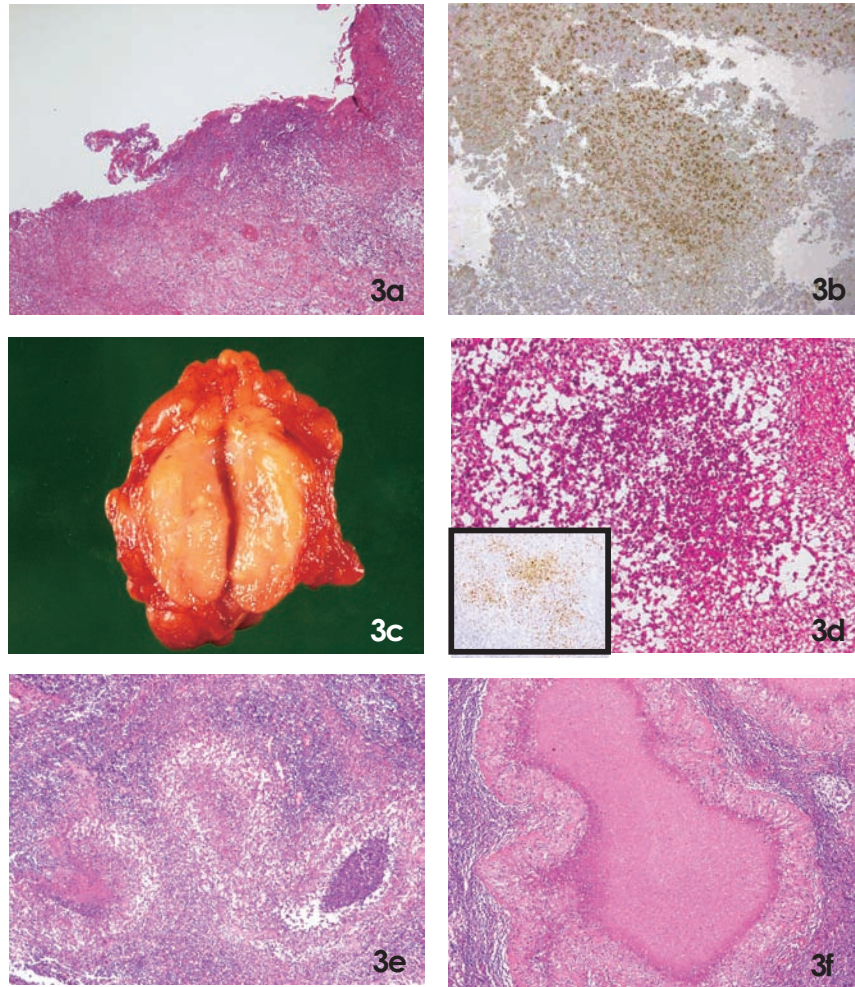
Fig. 3. Tularemia lymphadenitis. (*3a*) Variously sized granulomas at the ulcer base of finger skin (14 days after infection). (*3b*) Immunostaining of skin lesion. *F. tularensis* antigens are detected mainly in abscess and necrotic area (14 days after infection) (anti-*F. tularensis* antibody). (*3c*) Markedly swollen axillary lymph node on a cut section. (*3d*) Abscess form (12 days after infection). Abscess and necrosis lesion without epithelioid granuloma in lymph node. **Inset** : *F. tularensis* antigens are detected mainly in abscess and necrotic area. (*3e*) Abscess granulomatous form. Central abscess and necrosis lesions are surrounded by thickened epithelioid cells. These granulomas are apt to fuse with each other (27 days after infection). (*3f*) Granulomatous form. Large granuloma with central homogenized necrosis and with radiative pattern of epithelioid cells (81 days after infection).

nail of the cat invade the human skin via the scratch or bite wound. The annual incidence of CSD has been estimated at 9.3 cases per 100,000 people per year in the United States, although there are no national statistics for Japan.[38]

History

Parinaud first described only a small subset of CSD ; subsequently, Greer and Keefer published the first report on CSD in the American literature, in which they described a broad spectrum of CSD manifestations.[39] Patients with CSD have a high titer of seropositivity for *Rochalimaea henselae*, as in AIDS patients, but low titer for *Afipia felis*.[40] After genotypic evaluation, the nomenclature, *R. henselae*, was replaced by *B. henselae*, which was identified as the causative bacterium.[41]

Clinical Findings

Erythema (20 to 50%), papules, blisters (vesicular) and abscess are observed at the injury site within three to ten days

of cat scratch. The upper extremities are mostly affected, followed by the cervical and facial regions. After one to three weeks, regional lymphadenopathy with continued pain, usually in the cervical (33%), axillary (27%) and inguinal regions (18%), appears. Most patients visit a doctor complaining of systemic signs such as fever, malaise, headache and lymph node swelling.[39-42] Other rare complications such as Parinaud syndrome (periauricular lymphadenopathy and conjunctivitis), encephalitis, endocarditis, hepatitis and thrombocytopenic purpura have been reported.

Kaposi's sarcoma-like granuloma (epithelioid angiomatosis) arising on the skin is reported in immunocompromised patients (AIDS).[40]

The diagnosis of CSD is made on the basis of the following features and procedures[42] : 1) history of contact with a cat (on rare occasions, a dog), 2) checking of injury site, 3) regional lymph node swelling, 4) characteristic histology of lymph node and 5) skin test for CSD.

In recent years, immunohistochemical staining and polymerase chain reaction (PCR) have been recommended for diagnosis of CSD instead of skin test.[43-46]

Histopathology of Lymph Nodes[47]

1) Early phase (non-specific reaction)

Hyperplasia and enlargement of follicles appear in the early phase of CSD.[46,48] The afferent lymphatic vessels, subcapsular sinus and paracortical area are initially filled with immunoblasts, histiocytic cells, macrophage-phagocytized apoptotic bodies, neutrophils and plasma cells (Fig. 4a, 4b).

2) Intermittent phase (microabscess formation)

Microabscess with central necrosis and without epithelioid granuloma and cluster of neutrophils appears first under the subcapsular sinus, and then the lesion gradually spreads from the cortex to the medulla. MBL cluster (Fig. 4c) is observed adjacent to microabscess. Then, the foci of the central necrotic lesion composed of neutrophil aggregation and fibrinoid material progress to suppuration over time.[49] Thereafter, macrophages surrounding the abscess form epithelioid cell granuloma with rare multinucleated giant cells of Langhans type (stellate microabscess). In this phase, Warthin-Starry silver stain-positive bacteria, which are small and curved Gram-negative bacilli, are seen more frequently until 15 days
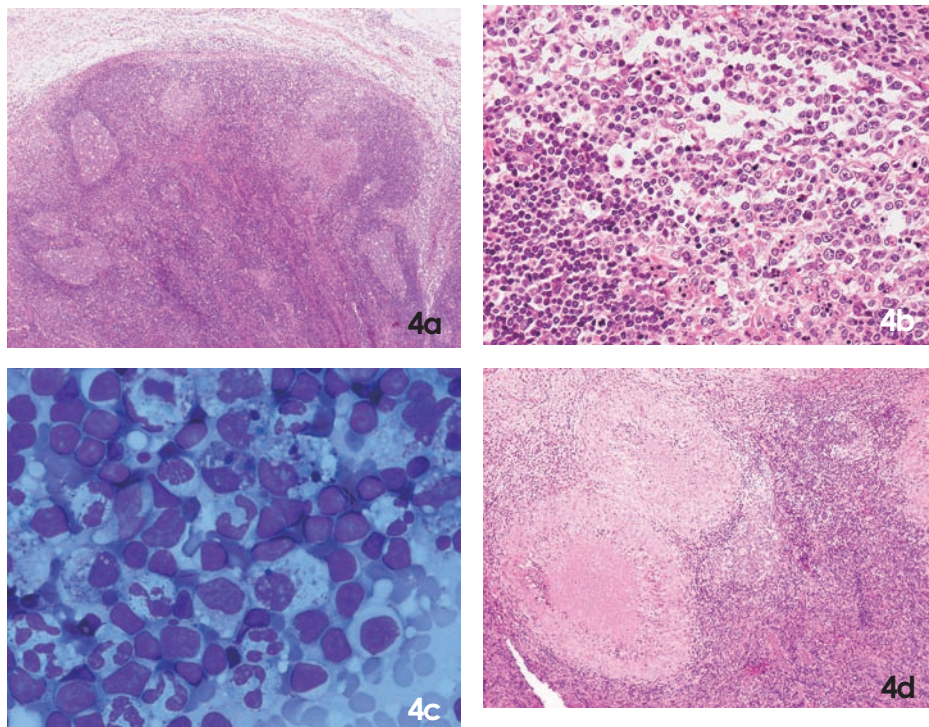

Fig. 4. Cat scratch lymphadenitis. (*4a*) Follicular hyperplasia and sinus mononucleosis, such as of immunoblasts, histiocytes and macrophages in the early phase. (*4b*) Sinus mononucleosis in distended subcapsular sinus. (*4c*) Imprint feature in the early phase. Many histiocytes, macrophages and monocytoid B lymphocytes are observed (Giemsa staining). (*4d*) Large epithelioid cell granuloma with central abscess and necrosis.

after onset or in the very early lesions.[43,50,51]

Immunohistochemical staining with antibodies to *B. henselae* in formalin-fixed paraffin-embedded tissue sections can specifically identify the bacillus of CSD.[44,52] In addition, rapid assay for the detection of *B. henselae* in formalin-fixed paraffin-embedded lymph nodes and aspirated pus from lymph nodes is available by PCR.[43,45,46]

3) Late phase (granulomatous abscess)

In the late phase, coalescence of stellate microabscesses leads to formation of an irregularly shaped large abscess (geographic abscess) (Fig. 4d). Furthermore, the capsule of lymph node often shows fibrosis or marked inflammation. The detection rate of bacteria becomes lower than that in the previous phase.

YERSINIA LYMPHADENITIS (MESENTERIC LYMPHADENITIS)

Bacteria of the genus *Yersinia* are not detected in normal human gut flora, but *Yersinia enterocolitica* (*Y. ent.*) and *Yersinia pseudotuberculosis* (*Y. pseud.*), which are Gram-negative small bacilli, are important human pathogens.

The disease Yersinia lymphadenitis is characterized by acute febrile gastroenteritis, with symptoms that mimic appendicitis, and occurs predominantly in infants, children and youths. The route of infection is orally, involving infected meat, drinking water or other food.[53]

Yersinia bacteria arrive at the mesenteric lymph nodes via lymphatic vessels of the intestine after ingestion of infected material, and form the characteristic lesion. The lymph node enlarges due to an inflammatory process, resulting in abdominal pain.

In this disease, there are no specific findings except for swelling of mesenteric lymph nodes, even though acute appendicitis or terminal ileitis can be shown.

History

This group of bacteria was described under different names, such as *Bacterium enterocoliticum*,[54] *Pasteurella X*[55] and *germe X*,[56] from 1939 to the early 1960s. The first *Y. ent.* infections in humans were described in 1949[57] as infections with *Pasteurella pseudotuberculosis*. Since then, there have been many reports on *Y. ent.* infection in Western Europe and the United States.[58-60]

Clinical Findings

The incubation period is 24 to 48 hours after the onset of ingestion. The most common symptoms of *Y. ent.* infection are diarrhea (80%), lower right quadrant pain (50%), nausea,

vomiting and fever (38~39℃) with flu-like symptoms, which are somewhat correlated with patient age. Thereafter, diarrhea is likely to develop in infants, but terminal ileitis, appendicitis and mesenteric lymphadenitis occur in children and youths.[58,59] Given the abdominal findings described above, these cases are often diagnosed as appendicitis, mesenteric lymphadenitis and terminal ileitis. Other symptoms such as arthritis, erythema nodosum, sepsis, Reiter's syndrome, meningitis and cutaneous lesions appear in older patients.[58,59] On the other hand, *Y. pseud.* infection is seen in infants and has symptoms similar to those of *Y. ent.* infection. The patients are younger than those with appendicitis. The diagnosis is made by culture of stool, blood, vomit, resected appendix and lymph node. Furthermore, diagnosis also requires serum antibody titer. Therapy is usually not necessary, but tetracycline is useful, and amikacin, chloramphenicol and gentacin are also effective.[61]

Histopathology of Lymph Nodes

1) Lymph nodes

Yersinia lymphadenitis is caused by the bacteria *Y. ent.* and *Y. pseud.*[53] In this disease, lymph nodes of the ileocecal region are often enlarged up to 1.5 cm in size. They do not coalesce with each other and show an elastic-soft appearance without distinctive necrosis on cut sections.[62]

In the early phase of lymphadenopathy by *Y. ent.*, lymphocytes, immunoblasts and plasma cells are packed within dilated sinuses. In addition, hyperplastic follicles are often observed in cortex and paracortex with increases in the cells described above. These findings coincide with nonspecific reactions.

In progression and later phases, thickened edematous capsule occasionally contains lymphocytes, immunoblasts and plasma cells. In addition, the same kinds of cells are observed in extended sinuses (Fig. 5a, 5b). Later, many epithelioid cell granulomas (EPGs) emerge in the germinal centers and they are predominantly nonsuppurative (Fig. 5c, 5d).[63] Some EPGs show suppuration of the centers of granulomas (central microabscesses) (Fig. 5e). These lesions eventually enlarge to form round microabscesses, but no giant cells. EPGs are composed of histiocytes with or without epithelioid cell features along with scattered small T lymphocytes and plasmacytoid monocytes.[64] EPGs of this type of lymphadenitis do not contain MBLs like in cat scratch disease and lymphogranuloma venereum.[65] Gram-negative acid-fast diplobacilli may be identified in the lesions.[53,58,59,62,66]

On the other hand, lymphadenopathy induced by *Y. pseud.* is quite similar to that of *Y. ent.* infection in the initial phase.[53] In the progression phase, *Y. pseud.*-infected lymph nodes show massive neutrophil infiltration, and later, there are scattered microabscess lesions with central pus formation sur-
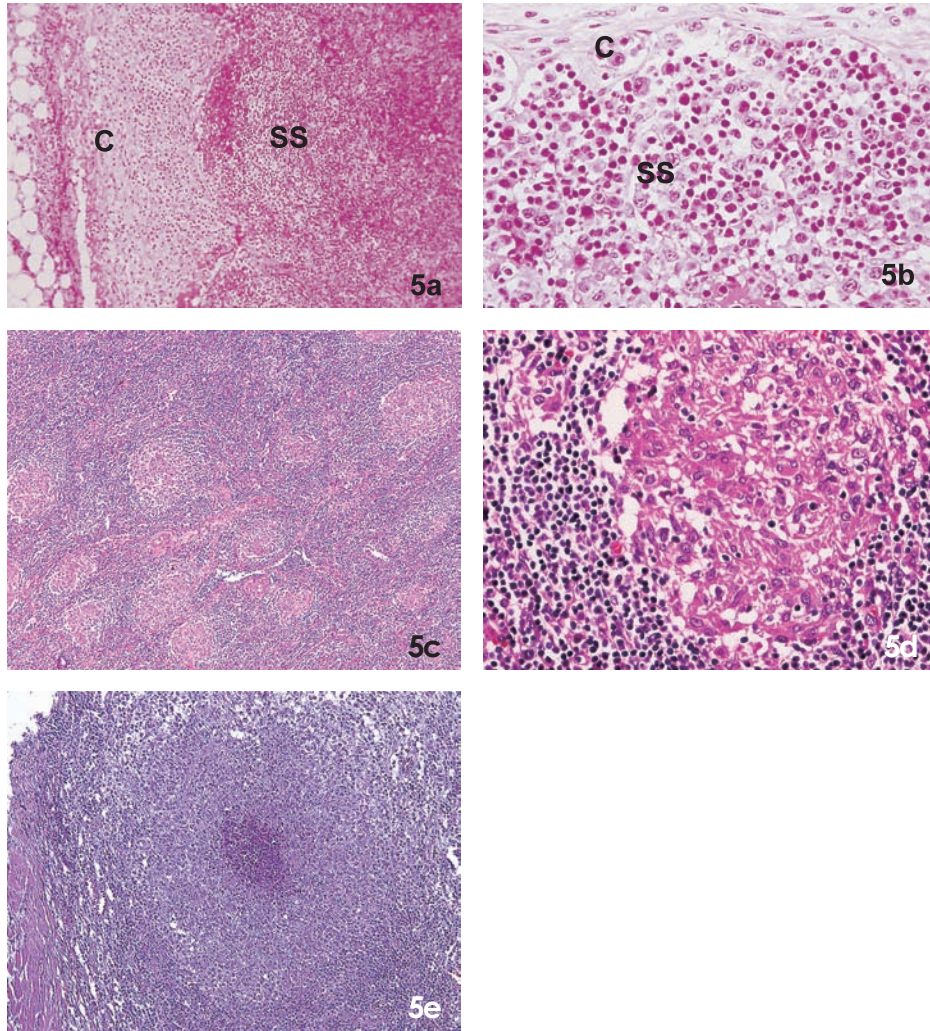
Fig. 5. Yersinia lymphadenitis. (*5a & 5b*) Edematous thickening capsule (*C*) and markedly dilated subcapsular sinuses (*SS*) contain innumerable lymphocytes, immunoblasts and plasma cells. (*5c*) Many epithelioid cell granulomas appear in the germinal centers and are predominantly nonsuppurative. (*5d*) Enlargement of granuloma with nonsuppurative lesion. (*5e*) Granuloma with microabscess formation.

rounded by plump histiocytes (suppurative granulomas) identical to those seen in cat scratch disease,[53,58,66,67] a feature that is rare with *Y. ent*.

2) Appendix and terminal ileum

In this disease, the wall of the appendix is thickened and the mucosa is edematous. Appendical lesions contain transmural, mixed inflammatory infiltrates with numerous lymphoid follicles and EPGs. EPGs are predominantly nonsuppurative. In addition, they are usually surrounded by small T lymphocytes and plasmacytoid monocytes. EPGs do not contain MBLs like regional lymph nodes.[64] However, some cases show mild hemorrhage and catarrh, although re-

gional lymph nodes show typical EPGs.

TUBERCULOUS LYMPHADENITIS

Tuberculosis is a chronic airborne infectious disease induced by *M. tuberculosis*. In Japan recently, tuberculosis has been ranked as only the 20th most common cause of mortality, so it has been relatively ignored. However, cases are still conspicuous and outbreaks are occasionally reported. The major problem for tuberculosis is the severity of illness in association with the global spread of AIDS. Tuberculosis has become remarkable as a reemerging infectious disease not only in developing countries but worldwide.[68,69]

Epidemiology

According to global statistics, two billion people are affected by tuberculosis globally. At present, there are eight million new patients and three million deaths every year, and almost all patients reside in the developing countries.[70,71] Meanwhile, in Japan, the rate of mortality from tuberculosis among the elderly has been gradually decreasing. The reduction of mortality slowed down in the 1980s, and it then began to increase again. Given these circumstances, in 1999, an emergency declaration to thwart the spread of tuberculosis was issued.[70,72]

Clinical Findings

In the case of highly virulent *M. tuberculosis* or individuals with weakened resistance against tuberculosis during primary infection, lymphadenitis occurs at pulmonary hilar and cervical lymph nodes. Tuberculous meningitis and military tuberculosis occur by lymphogenous spread of *M. tuberculosis*. In the case of longstanding multifocal adhesive lymphadenitis, lymph node biopsy, tuberculin reaction and PCR[73] are recommended for diagnosis of tuberculous lymphadenitis.[74,75]

Histopathology of Lymph Nodes

M. tuberculosis grows within alveolar macrophages and consequently forms a well-established primary lesion in the lungs. It mostly occurs subjacent to the pleura of the upper lobe. Some bacteria arrive at the bronchopulmonary lymph node via lymphatic vessels and form lymphadenopathy, classical Ghon complex.

The primary infection begins with inhalation of *M. tuberculosis* and ends with T cell-mediated immune response that induces hypersensitivity against the organism. The inhaled organism is phagocytized by alveolar macrophages and transported by these cells to hilar lymph nodes. After a few weeks, T cell-mediated immunity develops in two ways. One is formation of epithelioid cell granuloma by CD4+ cells and the other is formation of caseating granuloma by CD8+ cells.[75] Thereafter, epithelioid granulomas are encapsulated and progress to central caseous necrosis, eventually resulting in healing.

This lymphadenitis is induced by *M. tuberculosis* and can be seen as a part of the primary complex or secondary (organ) tuberculosis. About 90% of tuberculous lymphadenitis mainly appears in the cervical lymph node and others are in the mediastinal node. Sometimes it is difficult to distinguish among tuberculous lymphadenitis, malignant lymphoma and metastatic tumors.
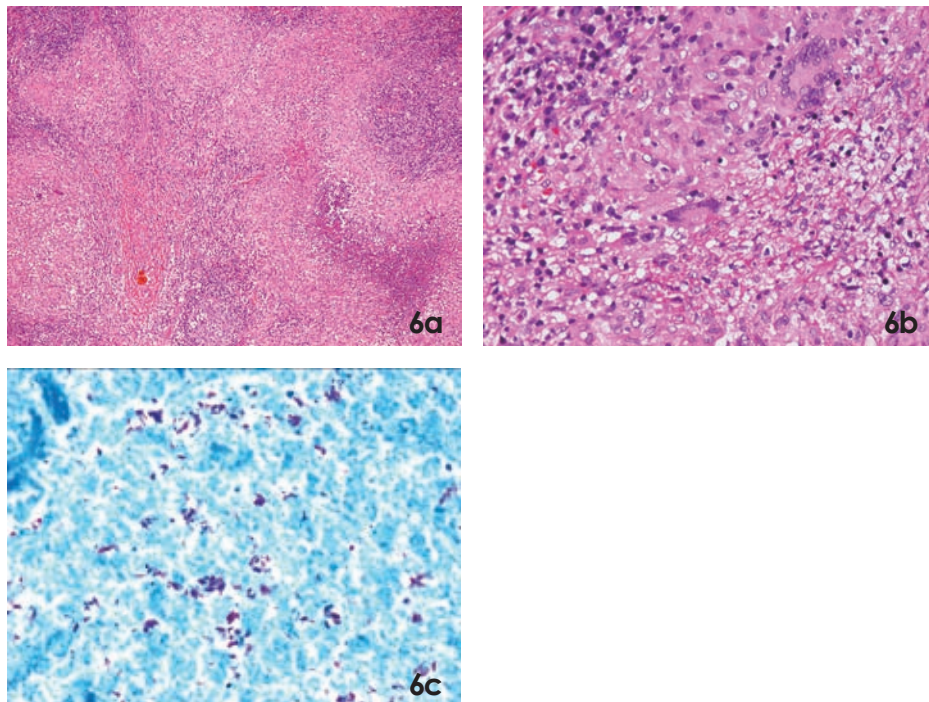
Fig. 6. Tuberculous lymphadenitis. (*6a*) Many granulomas fuse, resulting in large irregular nodules with central coagulation necrosis. (*6b*) Langhans giant cells in epithelioid granuloma. (*6c*) Ziehl-Neelsen staining shows rod-shaped *M. tuberculosis*.

In the early phase of tuberculous lymphadenitis, the lymph node shows elastic hard tumor like nonspecific lymphadenitis. Inflammatory cells gradually infiltrate and periadenitis appears over time.

After the formation of abscesses in the lymph node, they enlarge and gradually change to caseous necrosis and soften. The histology of tuberculous lymphadenitis is characterized by central caseous necrosis surrounded by epithelioid cell layer and sporadic Langhans giant cells (Fig. 6a, 6b). In addition, in the outermost layer can be seen lymphocytes and fibroblasts, but no plasma cells are observed. This node is called tuberculous nodule, type IV allergic reactions against *M. tuberculosis*. Tuberculous lymphadenitis is distinguished from sarcoidosis lymphadenitis by the presence of central caseous necrosis.

In this phase, Ziehl-Neelsen staining occasionally shows short rod-shaped bacteria (*M. tuberculosis*) in the coagulation necrosis (Fig. 6c). Organisms are now most easily detected by PCR. Finally, healing occurs with calcification.[76]

BCG-LYMPHADENITIS (BCG-HISTIOCYTOSIS)

Immunization of BCG (Bacillus Calmette-Guérin) vaccine, as an immunostimulant, is very useful for preventing the dissemination of *Mycobacterium tuberculosis* from the primary complex. BCG is conventionally re-injected for tuberculin-test-negative patients, but according to the revision of the Tuberculosis Prevention Law, from 2005, infants under 6 months should be immunized only once without tuberculin test. BCG is a version of *Mycobacterium bovis* with attenuated virulence, and is the weakest strain globally. After vaccination of BCG, the bacillus moves to regional lymph node and arrives at systemic organs within several hours. Although tuberculous lesions in systemic organs such as regional lymph node, liver and spleen can appear, there may be spontaneous healing without specific lesions.[77,78] Redness and suppuration at the inoculation site within ten days of vaccination may indicate tuberculosis infection. About three months later, the lesion heals with desquamation, crusting and scar.

Clinical Findings

The side effects of BCG-vaccination can include localized ulcer, abscess formation and regional lymph node enlargement. In terms of the lymph nodes, they are usually affected in axillary and cervical regions and swell up to two to three cm in size. Side effects are observed more frequently in cases of intradermal vaccination than percutaneous one.[79]

The incidence of side effects is 0.73 to 2.2% in vaccinated children. Younger children are more susceptible to infection, and lymphadenopathy occurs from one week to 9 months after vaccination.[80,81] BCG lymphadenopathy of over 3 cm must be surgically resected, but follow up is necessary for those smaller than 3 cm.

In children with congenital immune deficiencies[82] and in patients with HIV infection and AIDS, suppurative lymphadenitis and tuberculosis sometimes develop.[80]

Histopathology of Lymph Nodes[83]

BCG-lymphadenopathy is usually smaller than tuberculous lymphadenopathy. Follicular hyperplasia and sinus histiocytes are observed as in nonspecific lymphadenitis in the early phase. Later, micronodules of epithelioid granulomas without necrosis and epithelioid cell granuloma with central coagulation necrosis are observed (Fig. 7a, 7b). Langhans giant cells rarely appear.

TOXOPLASMA LYMPHADENITIS (PIRINGER-KUCHINKA LYMPHADENITIS)

Toxoplasmosis is a common zoonosis caused by *Toxoplasma gondii* ; it is found worldwide, and is prevalent in warm and humid climates, but infrequent in cold and dry areas.[84]
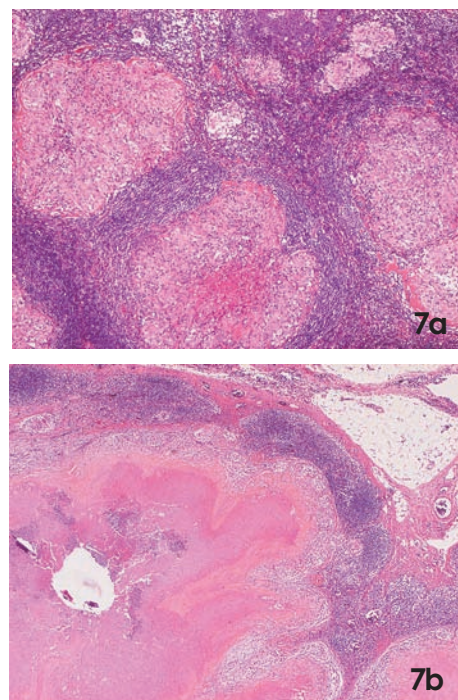

Fig. 7. BCG-lymphadenitis. (*7a*) Epithelioid cell granulomas with central coagulation necrosis are observed. (*7b*) Old granuloma with central liquefaction necrosis.

Epidemiology

In the United States, toxoplasmosis is the most common parasitic infection and over 60 million people are infected. Fifty percent of Americans have antibodies, but most exhibit asymptomatic infection. In Western Europe, there are occasional infections through the ingestion of *bradyzoit*, a type of trophozyte of *Toxoplasma gondii*, from contaminated undercooked or close-to-raw meat.[85] In France, the prevalence of antibodies is 85%.[86] Similarly, the antibody titers are high in Germany, the Netherlands and Brazil, but the prevalence in Japanese adults is around 20~30%.

Clinical Findings

Toxoplasma parasitizes a wide range of warm-blooded animals that include humans and rodents as intermediate hosts, and cats as the definitive host.[83]

The symptoms of toxoplasmosis resemble acute infectious mononucleosis with slight fever in the general population. There are three predominant sources of infection in humans, namely, ingestion of undercooked meat containing cysts, oo- cysts in cat stool and transplacental transfer from mother to fetus. *Toxoplasma gondii* mainly exists in humans in two forms, namely, *tachyzoites* within macrophages in the circulation and *bradyzoites* within intracellular cysts. Oocysts are found only in cat stool. If humans ingest oocysts or cysts, symptoms appear after 5 to 20 days, and 10 days to several weeks, respectively, although almost all patients are asymptomatic.

In immune-deficient patients, such as those with leukemia, lymphoma, acquired immunodeficiency syndrome (AIDS) and undergoing immunosuppressive therapy, as well as in fetuses, *Toxoplasma gondii* infection becomes acutely disseminated and results in death from myocarditis, pneumonitis, chorioretinitis and encephalitis.[87] The damage to the fetus is serious when transmission occurs in early pregnancy.

Histopathology of Lymph Nodes

Toxoplasmic lymphadenitis is diagnosed histologically and confirmed by serologic assays.[88-90] In immunologically normal adults, localized posterior cervical lymphadenopathy with fever is a common symptom.[91]
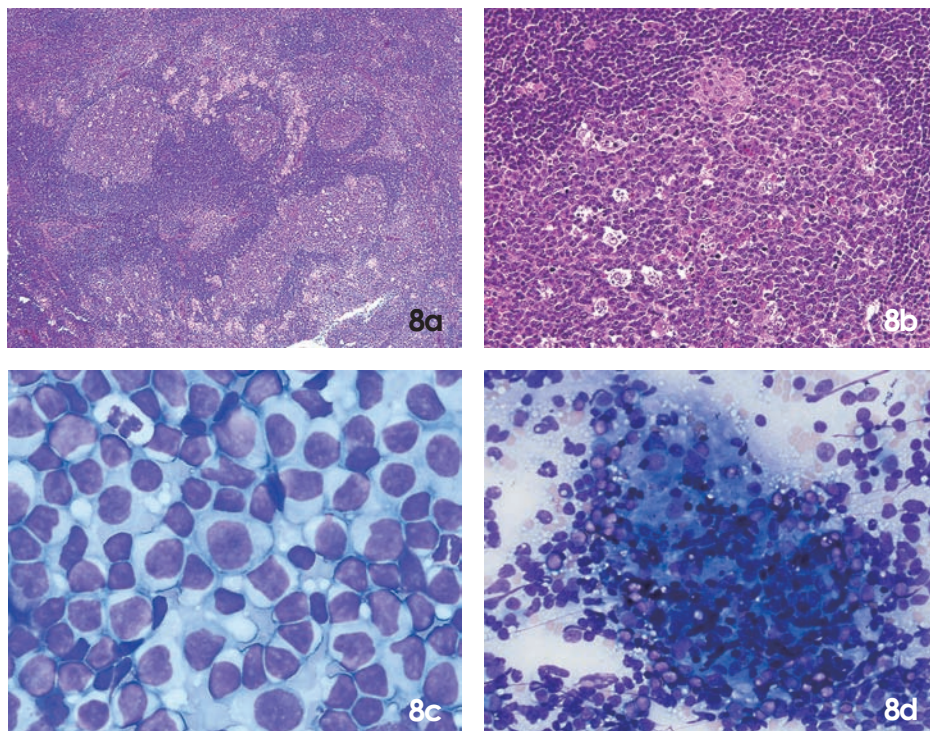

Fig. 8. Toxoplasma lymphadenitis (Piringer-Kuchinka lymphadenopathy). (*8a*) The characteristic features such as reactive follicular hyperplasia, cluster of epithelioid cells and patches of monocytoid B lymphocyte (MBL) proliferation are seen in lymph node. (*8b*) Enlarged follicles with reactive germinal centers include increased centroblasts, mitosis and macrophages containing tingible bodies. (*8c*) Imprint smear shows MBLs with clear cytoplasm and darkly stained nuclei are observed (Giemsa staining). (*8d*) Mononuclear cells, macrophages and elongated epithelioid cells are observed by imprint smear (Giemsa staining).

The characteristic main three histological findings of lymph node are florid reactive follicular hyperplasia, cluster of epithelioid cells and patches of MBL proliferation (Fig. 8a-8c). The follicles are enlarged by the intensely reactive germinal centers, including increased number of centroblasts, mitosis and macrophages containing tingible bodies (Fig. 8b). MBLs with clear cytoplasm and darkly stained nuclei (Fig. 8c) are observed in distended sinuses and adjacent to blood vessels. MBLs can also be seen in cat scratch disease[51] and human immunodeficiency virus (HIV) infection,[92] although they are more common in toxoplasmic lymphadenitis. There are ill-defined aggregations of epithelioid cells scattered throughout the cortex, paracortex and occasionally within germinal centers. They do not form round, organized, well-formed granulomas (Fig. 8a, 8d). They also do not induce necrosis and are not accompanied by neutrophils, eosinophils and fibrosis.

Toxoplasmic lymphadenitis can be diagnosed using reliable serologic testing and the three main histological findings with immunohistochemistry rather than PCR.[93,94]

CONCLUSION

Histopathologically, infectious granulomatous lymphadenitis generally shows follicular hyperplasia and sinus histiocytosis in the early phase. In tularemia and cat scratch disease, numerous neutrophils, MBLs, histiocytic cells, T cells and dendritic cells gradually appear around granulomas. MBLs are found adjacent to granulomatous foci. It may be considered that MBLs recruit neutrophils and promote necrosis, and MBLs with T cells and macrophages contribute to the formation of granuloma. However, none of the EPGs of *Y. ent*. lymphadenitis contains MBLs like in cat scratch disease and lymphogranuloma venereum. Furthermore, *Y. ent*. lymphadenitis EPGs differ from other types of suppurative lymphadenitis and the EPGs emerge in the germinal centers and are predominantly nonsuppurative.

Granuloma without suppuration of tuberculosis and BCG-lymphadenitis are induced by delayed allergic reaction of *M. tuberculosis*. These types of lymphadenitis and sarcoidosis involve B-cell-negative hypersensitivity. In toxoplasma lymphadenitis, MBLs can also be seen and ill-defined aggregations of epithelioid cells are scattered throughout the lymph node. However, they do not form round, organized, well-formed granulomas. Furthermore, they do not induce necrosis and are not accompanied by neutrophils, eosinophils and fibrosis.

Organisms are easily detectable by some staining, immunohistochemical and molecular biological methods such as PCR. Accurate pathological diagnosis by using the above procedures can lead to precise treatment.

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