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Atypical large plasma cells in lymph node granulomas in cat-scratch disease

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Summary. A histological variant of plasma cells found in the granulomas of cat-scratch disease (CSD) lymphadenitis is reported. Though the lesion shows the typical features of suppurative granulomatous lymphadenitis, many atypical giant cells which have abundant basophilic cytoplasm and bizarre nuclei with occasional multinucleated forms are noted among epithelioid histiocytes. The diagnosis of CSD lymphadenitis was confirmed by comparing clinical, histopathological, and histochemical (Warthin-Starry silver impregnation stain) studies on lymph node sections from five cases with features typical of the disease. Histochemical (methyl green-pyronine stain) and immunohistochemical examination provided several lines of evidence indicating that the atypical giant cells in our case were plasmacytic and confirmed that its proliferation was reactive, not neoplastic. Multinucleated giant cells were also occasionally present in the other five cases, but they had histological and immunohistochemical features of Langhans' type giant cells. We stress the importance of distinguishing such atypical large plasma cells from neoplastic cells.

Key words: Cat-scratch disease lymphadenitis – Warthin-Starry silver impregnation stain – Immunohistochemistry – Atypical multinucleated plasma cells

Introduction

Cat-scratch disease (CSD) is an infectious disorder characterized by subacute regional lymph node swelling which occurs a few days to several weeks after cutaneous inoculation. Histologically, the characteristic feature of the nodal lesion of CSD is the suppurative granulomatous lymphadenitis composed of microabscesses surrounded by epithelioid histiocytes. Multinucleated giant cells of Langhans' type are occasionally seen. The nodal lesion of CSD may be indistinguishable from that of lymphogranuloma venereum, and clinical features are important in the differential diagnosis (Ioachim 1982; Stansfeld 1985). In 1983, Wear et al. showed by Warthin-Starry silver impregnation (WS) stain that gram-negative bacilli are present in the lymph nodes of many CSD patients. This finding appears to be helpful in distinguishing CSD lymphadenitis from other necrotizing or suppurative granulomatous lesions. Based on the study which succeeded in the isolation, cultivation, and fulfillment of Koch's postulates (English et al. 1988), these bacilli have been regarded as the causative agent of CSD.

Recently we encountered a patient with axillary lymph node swelling in which histopathological examination showed numerous atypical giant cells with occasional multinucleated forms in otherwise typical CSD lymphadenitis. In order further to characterize this lesion, comparative histochemical and immunohistochemical studies with five other cases of CSD lymphadenitis were performed. The results indicated that the lesion of the above case was one of CSD lymphadenitis and that the atypical giant cells possessed several features of plasma cells. Since there were no such cells in the other five cases, we report this histological variant of plasma cells in CSD lymphadenitis.

Materials and methods

Lymph node specimens from six patients were examined. The patient in which lymph node sections showed atypical giant cells is listed as case 1. The other five cases (cases 2–6) were collected from our files. The diagnosis of the lesion was based on clinical features (patient's age, history of contact with cats, presence of scratch wound, and site of lymph node enlarged), negative laboratory studies for other causes of lymph node swelling, and characteristic histopathology of lymph nodes. Cases showing inguinal lymphadenopathy without scratch wound or history of contact with cats were not included in the present study.

Formalin-fixed, paraffin-embedded sections were stained with haematoxylin and eosin, periodic acid-Schiff (PAS), methyl green-pyronine (MGP), WS (Luna 1968), Giemsa, silver reticulin, toluidine blue, Grocott's Gomori methenamine silver, and Ziehl-Neelsen stains.

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Immunohistochemical examination was performed on paraffin sections by the avidin-biotin-peroxidase complex (ABC) method (Hsu et al. 1981). The primary antibodies used were: rabbit antibodies to each heavy and light chain of immunoglobulin (Ig) (Dakopatts, Copenhagen, Denmark), J-chain of Ig (Nordic Immunological Laboratories, Tilburg, The Netherlands), lysozyme (Behringwerke, Marburg, FRG), non-specific cross-reacting antigen, α_1-antitrypsin, α_1-antichymotrypsin, S-100 protein, factor VIII-related antigen, and albumin (Dakopatts). A mouse monoclonal antibody to CD15 (Leu M1, Becton-Dickinson, Calif.) was also used. Biotinylated secondary antibodies and ABC were purchased from Vector Laboratories (Burlingame, Calif.). After immunoperoxidase staining, the slides were counterstained with methyl green, and examined with a light microscope.

Results

The main clinical features of the six patients are summarized in Table 1. A history of scratches by cats was apparent in case 2 and case 6. In case 1, some linear wounds were found on the left forearm. In case 4, the patient's family kept a cat. There was no information of contacts with cats in the other two cases. Five patients were treated with antibiotics before lymph node biopsy.

All cases showed suppurative granulomatous lymphadenitis characterized by microabscesses surrounded by palisaded epithelioid histiocytes. Giant cells of Langhans' type were occasionally seen among the histiocytes. In all cases, the residual lymphoid tissue between the granulomas showed reactive follicular hyperplasia with accumulation of mature plasma cells in the interfollicular areas. In case 1, numerous atypical giant cells were noted in and around the epithelioid histiocytes, while typical Langhans' type giant cells were rarely seen (Fig. 1a). These atypical cells varied in size and had abundant basophilic cytoplasm. Many of them had a conspicuous paler region adjacent to the nuclei. The nuclei showed irregularities such as multilobation, hyperconvolution, and multinucleation with abundant heterochromatin (Fig. 1b). The nucleoli were inconspicuous. These cells were not seen in the residual lymphoid tissue.

In all cases, at least a few pleomorphic bacilli were demonstrated by WS stain (Fig. 2). Other stains for micro-organisms gave negative results. On PAS stain, atypical giant cells in case 1 showed perinuclear punctate staining, while Langhans' type giant cells in cases 2–6 showed diffuse weak cytoplasmic staining. The atypical giant cells were strongly pyroninophilic with perinuclear

Table 1. Clinical features of patients

Case	Age/sex	Lymph node biopsied	History of cat-scratch	Treatment before biopsy
1[a]	11/F	Axillary (l)	Wound (+)	Antibiotics
2	34/F	Inguinal (r)	Contact (+)	Antibiotics
3	22/M	Antecubital (r)	Unknown	Unknown
4	7/M	Axillary (l)	Contact (+)	Antibiotics
5	30/F	Cervical (r)	Unknown	Antibiotics
6	17/F	Inguinal (r)	Wound (+)	Antibiotics

[a] A case with atypical giant cells

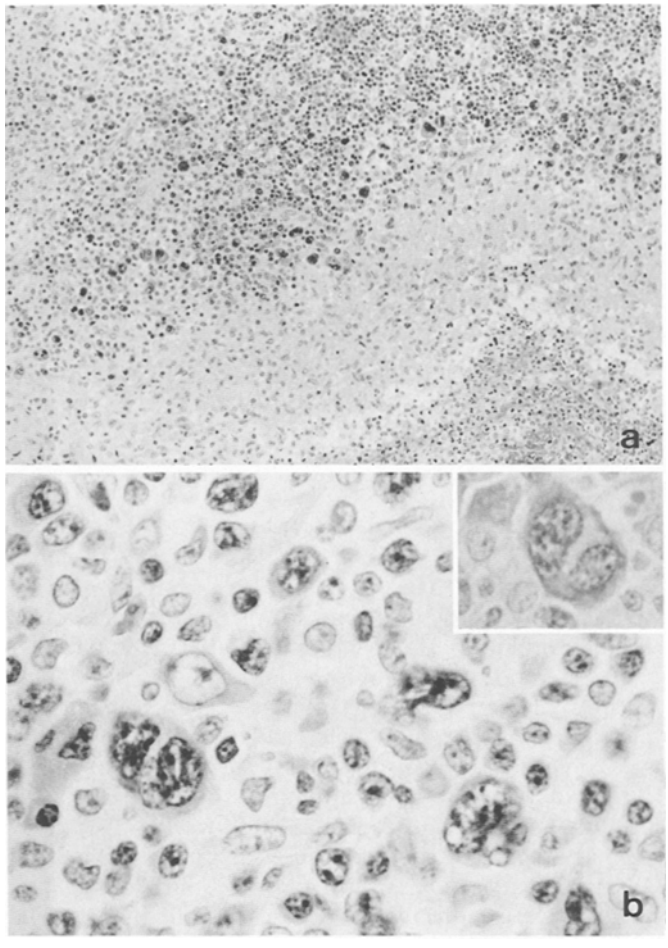

Fig. 1a, b. Histopathological features of an axillary lymph node of case 1. **a** Numerous atypical giant cells are noted in and around palisaded epithelioid histiocytes around the abscess. Haematoxylin and eosin, ×116. **b** At the higher magnification, the giant cells possess lobulated or convoluted nuclei and abundant basophilic cytoplasm. Haematoxylin and eosin, ×704. *Inset:* These cells show cytoplasmic pyroninophilia with clear perinuclear sparing. Methyl green-pyronine, ×704

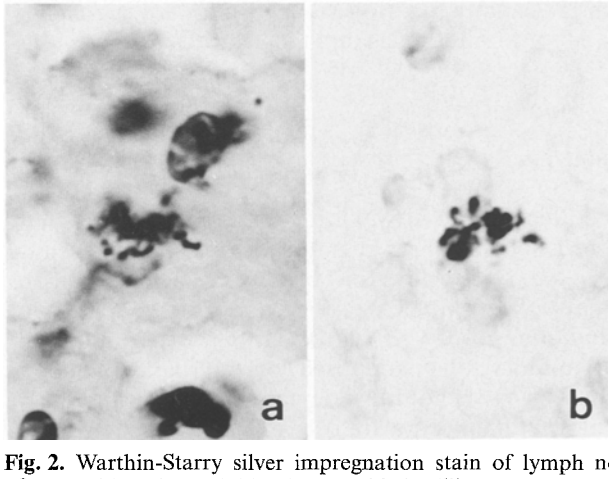

Fig. 2. Warthin-Starry silver impregnation stain of lymph nodes of case 1 (**a**) and case 3 (**b**). Pleomorphic bacilli are present around the histiocytes. ×2000

sparing on MGP stain (Fig. 1b, inset), but Langhans' type giant cells were not stained with pyronine.

The immunohistochemical profiles of the atypical giant cells in case 1 and Langhans' type giant cells in case 2–6 are shown in Table 2. Atypical giant cells showed positive cytoplasmic stainings for κ, λ, γ, and J-chains of Ig molecules (Fig. 3). Although almost all of the atypical cells were stained for γ-chain, some of them were not stained when κ, λ, and J-chains were examined. These cells resisted staining with antibodies against lysozyme, Leu M1 (CD15), non-specific cross-reacting antigen, α_1-antitrypsin, α_1-antichymotrypsin, S-100 protein, factor VIII-related antigen, and albumin. Langhans' type giant cells were positively stained for lysozyme, α_1-antitrypsin, and α_1-antichymotrypsin, but they resisted staining with antibodies against other antigens. Epithelioid histiocytes in all cases showed a similar immunohistochemical profile to that of Langhans' type giant cells.

Table 2. Immunohistochemical profiles of atypical and Langhans' type giant cells

Antigens	Atypical giant cells in case 1	Langhans' type giant cells in cases 2–6
Ig* molecules		
κ, λ	+[a]	−
γ	+	−
μ, α	−	−
J	+[a]	−
Lysozyme	−	+
Leu M1 (CD15)	−	−
NCA*	−	−
α_1-Antitrypsin	−	+
α_1-Antichymotrypsin	−	+
S-100 protein	−	−
fVIII-Ag	−	−
Albumin	−	−

Ig, Immunoglobulin; NCA, non-specific cross-reacting antigen; fVIII-Ag, factor VIII-related antigen

[a] Some atypical cells were not stained

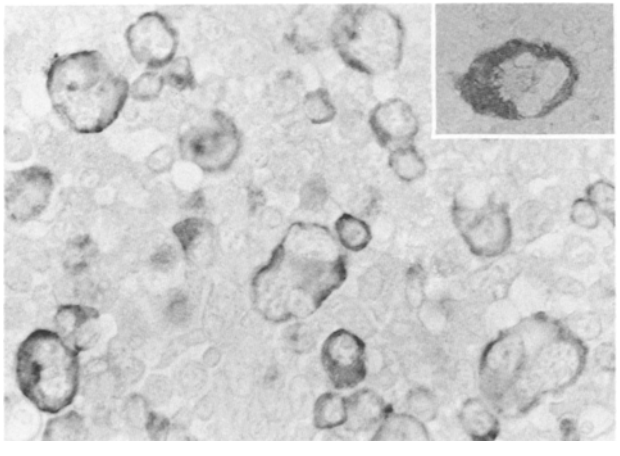

Fig. 3. Some of the giant cells are positive for κ light chain. Anti-λ antibody showed similar pattern of staining. *Inset:* An atypical giant cell containing J-chain. Immunoperoxidase stain with methyl green counterstain, ×600

Discussion

In case 1, CSD lymphadenitis was initially suspected, but the numerous atypical giant cells suggested a possible neoplastic process. The present study was, thus, performed to characterize the nodal lesion and to clarify the origin of the atypical cells in this patient.

A comparison with the other five cases of CSD lymphadenitis in the file showed no such atypical cells, although there were granulomatous lesions with reactive follicular hyperplasia similar to those of case 1. WS stain revealed pleomorphic bacilli in case 1 as well as in other cases examined. Since the first report of Wear et al. (1983) demonstrating the presence of gram-negative bacilli in the lymph nodes of many patients with CSD, there have been a number of reports confirming this finding (Margileth et al. 1984; Gerber et al. 1985; Kitchell et al. 1985; Wear et al. 1985; Cotter et al. 1986; Millar-Catchpole et al. 1986), and WS stain appears to be one of the important methods for the diagnosis of CSD at present.

Since the atypical giant cells may have represented a possible variant of Langhans' type giant cells or a neoplastic process, histochemical and immunohistochemical features were also compared (Table 2), and it was found that the atypical giant cells were stained positively for Ig molecules, whereas typical Langhans' type giant cells possessed lysozyme, α_1-antitrypsin, and α_1-antichymotrypsin. It is well known that several types of giant cells such as Reed-Sternberg cells of Hodgkin's disease and megakaryocytes show positive staining for cytoplasmic Ig because of passive diffusion of plasma proteins during tissue processing (Isaacson 1979; Isaacson and Wright 1979). Thus it is necessary to examine albumin, a representative component of plasma protein, and J-chain of Ig for accurate interpretation. Positively stained Ig molecules in the cytoplasm can not be characterized as endogenous in origin when the cells are positive for albumin and negative for J-chain. The Ig molecules in the present atypical plasma cells, however, were considered to be synthesized by the cells because of the presence of J-chain and absence of albumin. These finding together with the absence of other antigens examined led us to conclude that the atypical giant cells in case 1 are IgG-producing plasma cells. The patterns of histochemical staining of these cells with PAS and MGP support the above conclusion. Furthermore, their reactive, but not neoplastic, nature was confirmed by their polyclonal staining for κ and λ light chains.

Since WS stain revealed several bacilli and the atypical giant cells were found to be reactive plasma cells, the nodal lesion in case 1 was characterized as CSD lymphadenitis. The significance of these atypical plasma cells is unknown. Although their presence in and around granulomas, but not in the residual lymphoid tissue, suggests that they may be closely related to the causative bacilli, we could not find any bacilli in these cells.

The accumulation of plasma cells may be noted in

CSD lymphadenitis, but they are usually mature with no nuclear atypia and are found mainly in the interfollicular areas of the residual lymphoid tissues (Stansfeld 1985). To our knowledge, appearance of atypical plasma cells in and around granulomas has never been described in CSD lymphadenitis. It has been known that abnormal large or multinucleated plasma cells are occasionally seen in rheumatoid arthritis lymphadenopathy (Cruickshank 1958) and in patients treated by cytotoxic drugs for haematological neoplasms. However, review of lymph nodes specimens, including three cases of rheumatoid arthritis lymphadenopathy, in our surgical pathology file failed to find such cells. We stress the importance of distinguishing large plasma cells with marked nuclear atypia like those in our case from a possible variant of Langhans' giant cells or neoplastic cells such as Reed-Sternberg cells. Immunohistochemistry is useful, but the result should be interpreted carefully. We suggest that these atypical plasma cells could be defined as "cytological variant of plasma cells", and further examination should be made on similar cases to study the pathogenesis of these cells.

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