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Case report

A case of histiocytic necrotizing lymphadenitis with bone marrow and skin involvement

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Summary. We report a case of histiocytic necrotizing lymphadenitis (HNL) with bone marrow extension in a 29-year-old male in which many large mononuclear cells infiltrated the bone marrow and mimicked malignant lymphoma. A lymph node biopsy confirmed the diagnosis of HNL. Immunohistologically, the infiltrating cells in the bone marrow were positive for lysozyme, LeuM1, Kp-1 and T-cell markers. The cells did not show haemophagocytosis. A skin biopsy from an accompanying facial skin rash revealed a proliferation of large cells similar to those observed in affected foci of the lymph node in subcutaneous tissue. The infiltrating cells were mainly lysozyme and Kp-1-positive histiocytes, some with phagocytosis of nuclear debris but none characteristic of haemophagocytosis. Transformed T-cells were also infiltrating.

Key words: Histiocytic necrotizing lymphadenitis – Kikuchi's disease – Bone marrow infiltration – Skin infiltration

Introduction

Histiocytic necrotizing lymphadenitis (HNL), which has a broad morphological spectrum, is readily mistaken for malignant lymphoma (Kikuchi 1972). However, as recently, in both Japan (Fujimori et al. 1981; Fujimoto et al. 1972; Kikuchi et al. 1986, 1990) and in Europe and the United States (Ali and Horton 1985; Chamulak et al. 1990; Chan and Saw 1983; Turner et al. 1983, Pileli et al. 1982), many cases have been reported, its differential diagnosis is becoming relatively easy. Patients with cutaneous involvement have been observed and the histological diagnosis based on the cutaneous lesion alone is occasionally difficult to differentiate from cutaneous lymphoma (Kuo 1990). We report a patient with involvement of the bone marrow and skin, which we suspected initially to be a infiltration by malignant lymphoma.

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Case report

The patient was a 29-year-old male, with the main complaints of fever, skin rashes, and neck lymph node swelling. Familial and past history revealed nothing remarkable.

From the end of September 1989, the patient noticed a swelling of a lymph node in his neck, and fever over 38° C. At a clinic, malignant lymphoma was suspected after a bone marrow biopsy. After being transferred to the university hospital, he underwent further careful examination and treatment. Skin and lymph node biopsies were performed. Skin biopsy of the facial erythema showed infiltration by atypical lymphocytes, histiocytes, and inflammatory cells suggestive of malignant lymphoma. However, the lymph node biopsy was diagnosed as HNL and the re-examined bone marrow was considered to show an infiltration of histiocytes and transformed lymphocytes related histologically to HNL. Immediately after steroid treatment, the fever disappeared and the swollen lymph node and skin rashes gradually diminished. The patient was discharged after a 3-week hospitalization with no clinical symptoms.

Specimens from the bone marrow, skin and lymph node were fixed in formalin or B-5 solution, embedded in paraffin, and used for routine histopathological study and immunohistochemical study using the alkaline phosphatase-conjugated avidin-biotin complex method (Nanba et al. 1987). The anti-human monoclonal antibodies employed are tabulated in Table 1.

Table 1. Specificities of monoclonal antibodies

Antibody	Antigen recognized/ distribution	Source
LeuM1	CD15, monocytes, myeloid cells	Dakopatts Copenhagen, Denmark
Kp-1	Macrophage myeloid cell, plasmacytoid T-cell	Dakopatts
Lysozyme	Macrophage, granulocytes	Dakopatts
UCHL-1	CD45RO, memory T-cells	Dakopatts
L-26	Pan B-cells	Dakopatts

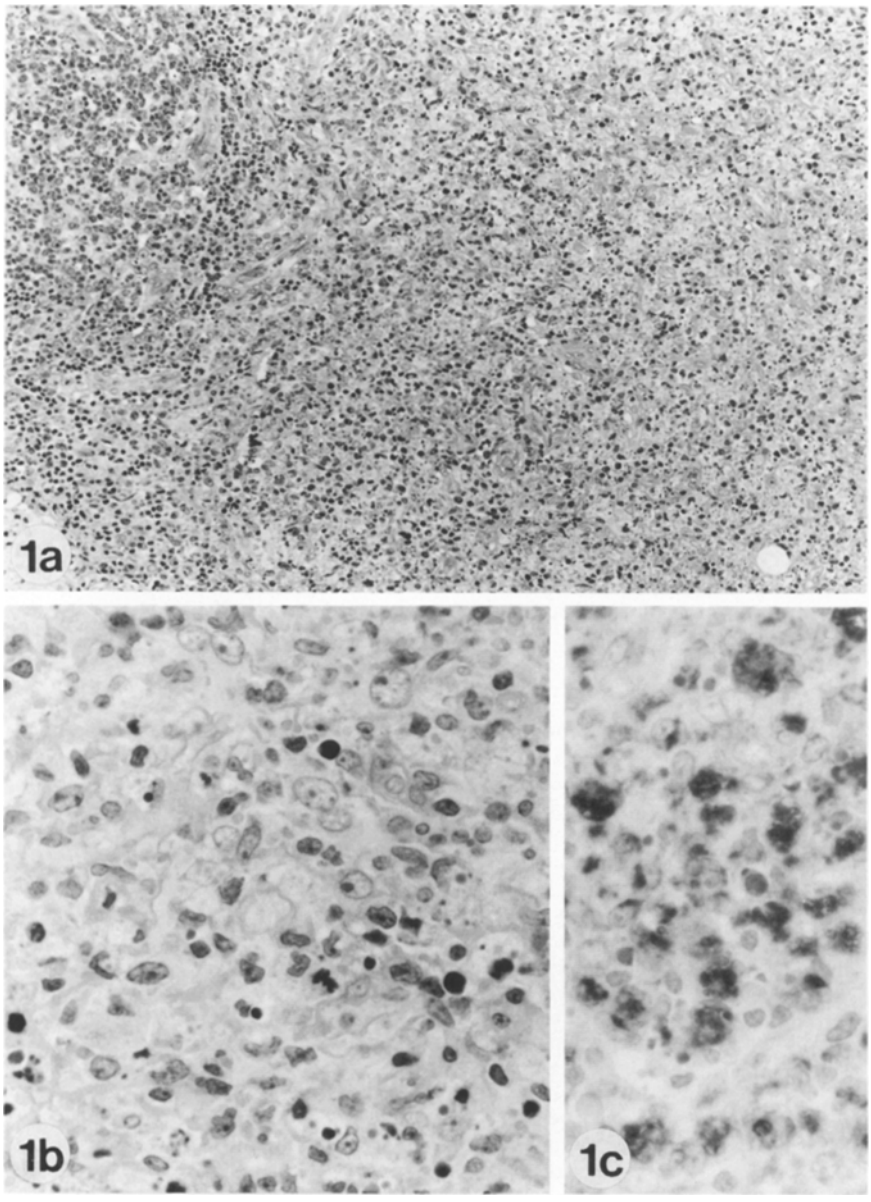

Fig. 1. a Low magnification of lymph node, in which affected area is pale and well circumscribed in the enlarged paracortex. Neck lymph node, ×105. **b** High magnification of **a** shows numerous transformed lymphocytes, immunoblasts, histiocytes and a proliferation of nuclear debris. ×640. **c** Many lysozyme-positive cells were detected in the affected area. Lysozyme-positive cells showed pale or abundant cytoplasm and mild irregularly shaped nuclei. Lysozyme, ×640

Table 2. Analysis of bone marrow findings

	(%)		(%)		(%)
Pro. Er. bl.	0.5	Neutrophils Pro.	6.0	Mo. Pro.	0.5
Macro. P.	0.5	Mye.	18.0	Mono.	7.0
Normo. B.	0.5	Meta.	15.0	Lympho.	9.0
P.	10.5	Stab.	20.5	Plasma	0.5
O.	5.0	Eosinophils Stab.	0.5	Atypical cells	0.5
		Seg.	1.0		

Pathological findings

Laboratory data from initial clinical visits showed a white blood cell count of 3000/mm^3 with 61% neutrophils, 35% lymphocytes and 3% atypical lymphocytes. Serum lactate dehydrogenase was 1307 units/l, and glutamic oxaloacetic transaminase was 50 units/l. Analysis of the bone marrow smear is revealed in Table 2. Increased monocytes and a few abnormal cells were detected.

Laboratory examination on admission to the university hospital revealed a white blood cell count of 2300/mm^3 with 53% neutrophils, 30% lymphocytes, 12% monocytes and 4% atypical lymphocytes. The haematocrit was 37.8%, and haemoglobin was 11.8 g/dl. Serum lactate dehydrogenase was 1550 units/l, glutamic oxaloacetic transaminase was 83 units/l, and glutamic purubic transaminase was 88 units/l. Serum titres of viruses and protozoa were EB.VCA IgG 1 in 320, EV.VCA IgM 1 in 10, EBNA 1 in 80, toxoplasma IgG 1 in 320, and toxoplasma IgM 1 in 10.

The histopathology of the lymph node in the neck showed focal changes. The affected area was characteristically pale at low magnification (Fig. 1a), and showed a proliferation of transformed lymphocytes including immunoblasts, histiocytes with or without phagocytosis, necrobiotic cells and numerous nuclear debris. No histiocytes with haemophagocytosis, plasma cells or granulocytes were present (Fig. 1b). Immunohistologically, the proliferating cells were composed mainly of lysozyme (Fig. 1c) and Kp-1-positive histiocytes, and UCHL-1-positive T-cells. L-26-positive B-cells were few in number.

The sections of the facial skin showed compact large cell infiltrates around the small vessels in the dermis (Fig. 2a). The infiltrat-

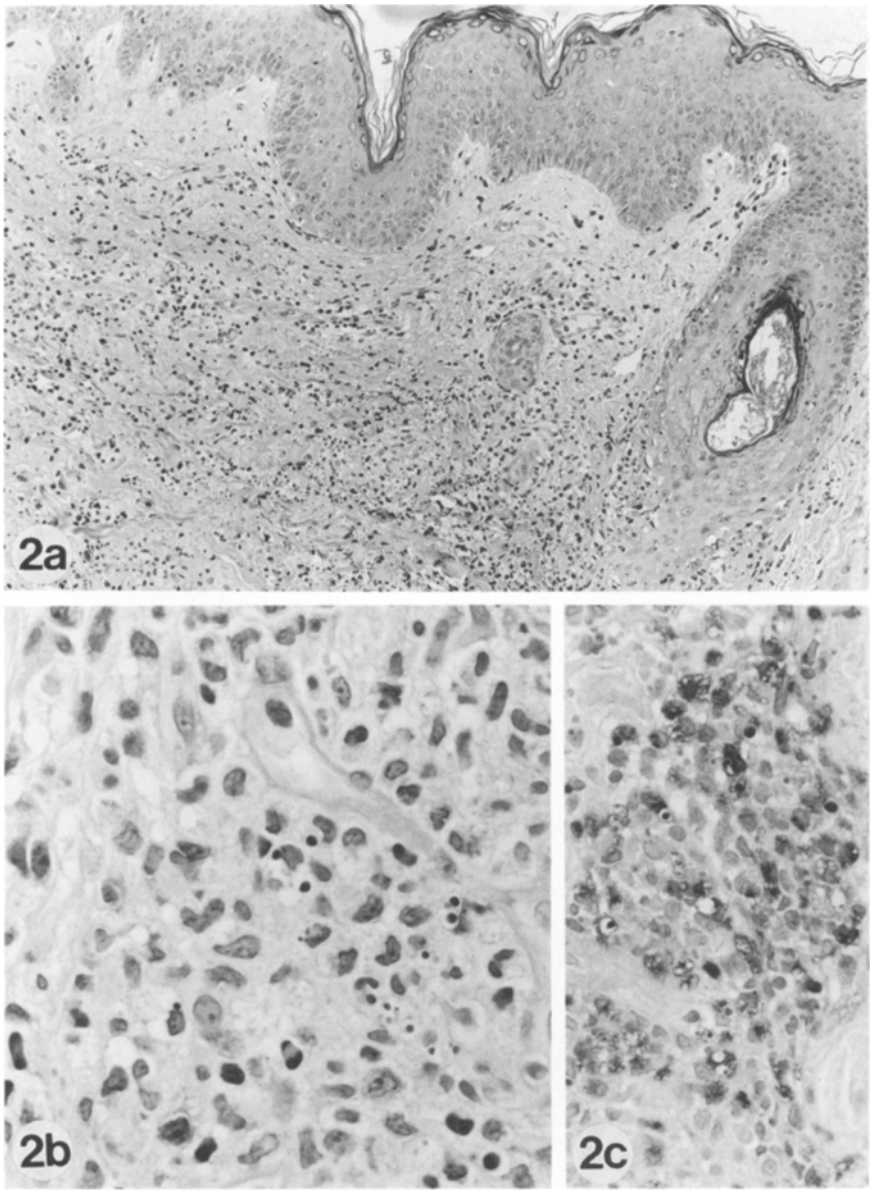

Fig. 2. **a** Low magnification of a skin biopsy specimen shows patchy cellular infiltrates in the dermis. Skin, ×105. **b** High magnification of **a** showing many mononuclear cells with irregularly shaped nuclei. Some contain phagocytic materials within their cytoplasm. These findings resembled mixed cleaved cell lymphoma. ×640. **c** These infiltrated cells with irregularly shaped nuclei are positive for lysozyme. Lysozyme, ×640

ing cells were composed of large cells with indented, oval or cleaved nuclei, fine chromatin, indistinct nucleoli and some necrotic cells. Mild exocytosis was noted in the histiocytes with some nuclear debris and small lymphocytes (Fig. 2b). The cleaved cells were positive for Kp-1 and lysozyme (Fig. 2c) and oval nuclear cells were positive for UCHL-1. Small lymphocytes were positive for UCHL-1. Few L-26-positive cells were detected. We noted that some histiocytes contained nuclear debris in the cytoplasm, but haemophagocytosis was not observed.

The cytological analysis of the sternal bone marrow smear is shown in Table 2. The cellularity was within the normal range with a mild increase of monocytes. A few atypical lymphoid cells with oval or indented nuclei, prominent nucleoli and slightly basophilic cytoplasm were present. Some macrophages with vacuolated cytoplasm were also noted.

The bone marrow biopsy showed normoplastic characteristics with moderate increase of the myeloid series in every maturation stage and a diffuse infiltration of atypical cells with oval or irregular nuclei and abundant cytoplasm and lymphoid cells (Fig. 3a). Immunohistologically, most of these atypical cells were positive for lysozyme, Kp-1, markers for histiocytes (Fig. 3d) and negative for UCHL-1 and NASDA. Lymphoid cells were positive for UCHL-1 T-cell marker. In the smear, histiocytes with phagocytosis (Fig. 3b) and medium-sized lymphoid cells with mild irregularly shaped nuclei (Fig. 3c) were detected in small numbers. Haemophagocytosis was not observed.

Discussion

HNL was first reported in 1972 as a lymphadenitis with focal proliferation of reticular cells accompanied by extensive nuclear debris and numerous phagocytes (Kikuchi 1972). The disease has characteristic clinical findings with localized lymphadenopathy in the neck, leukopenia, fever, occasional skin rashes, and natural healing within a few months (Kikuchi et al. 1990). It primarily affects adolescent females between 15 and 35 years of age. From these clinical manifestations, a viral aetiology is strongly suspected. Epstein-Barr virus (Takada et al. 1980),

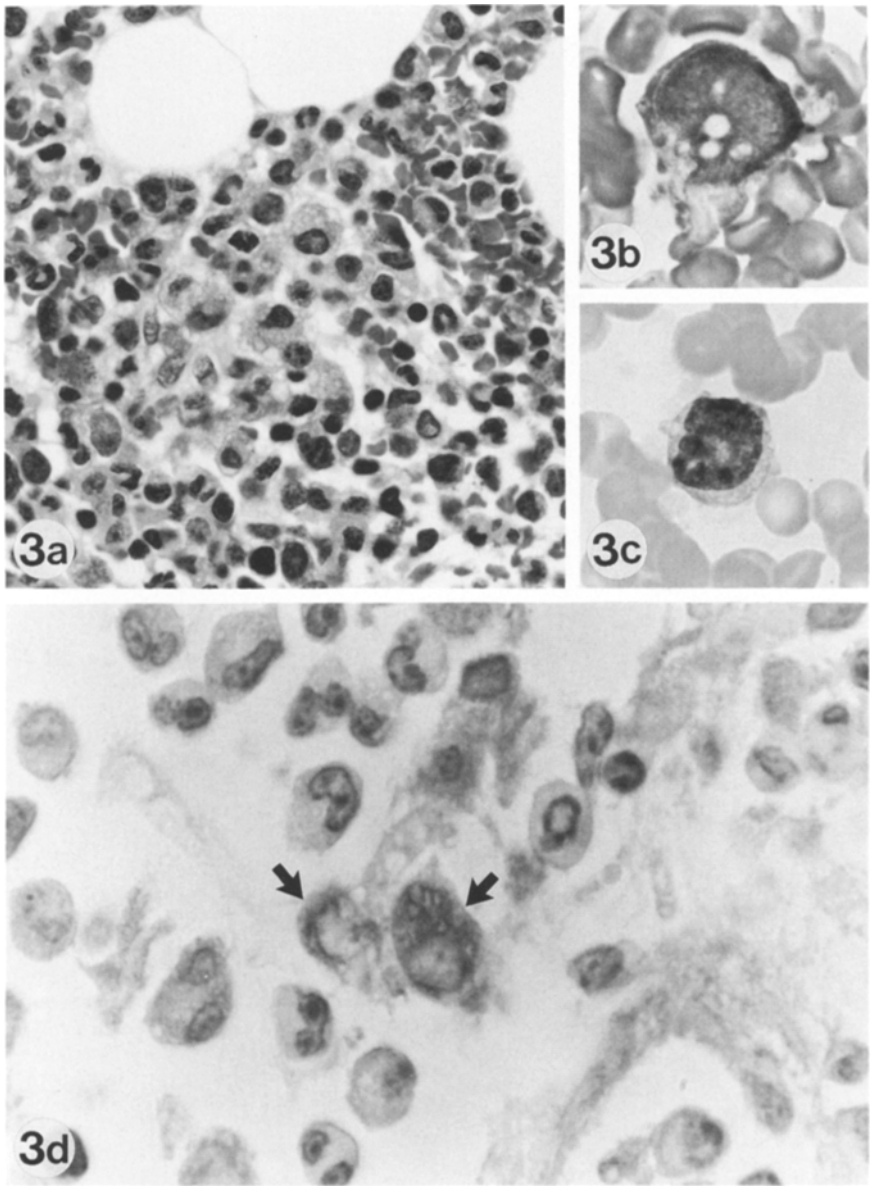

Fig. 3. **a** Some large mononuclear cells with abundant cytoplasm and oval or cleaved nuclei are infiltrated in the bone marrow. Bone marrow, ×640. **b** A histiocyte with mild irregularly shaped nuclei in bone marrow smear. Giemsa, ×1600. **c** An atypical lymphoid cell in bone marrow smear. Giemsa, ×1600. **d** Lysozyme-positive cells show diffuse cytoplasmic reaction. These positive cells have abundant cytoplasm and oval nuclei. Lysozyme, ×1600

HHV-6 (Eizuru et al. 1989) and other viruses have been suspected, but no identification of a causative virus has been achieved. Our patient demonstrated increase of EBNA and EV.VCA IgG but EV.VCA IgM was not elevated in serum. In about 30% of the cases, infiltration to the skin has been recognized (Kikuchi et al. 1990) and histologically only a minor lymphocytic infiltration in the subcutaneous tissue was characteristic. In some cases, infiltration of transformed lymphocytes and histiocytes with mild irregularly shaped nuclei were difficult to differentiate from the cutaneous invasion of malignant lymphoma. It is important to realize that cutaneous involvement of Kikuchi's disease can be misdiagnosed as malignant lymphoma.

Kuo (1990) reported one case of HNL diagnosed as a diffuse, large cell type malignant lymphoma by skin biopsy. According to his report, the cells with mildly cleaved or round nuclei infiltrated into the perivascular region of subcutaneous tissue and adipose tissue. Immunohistological staining revealed a majority of infiltrated cells positive for lysozyme and Kp-1 without showing haemophagocytosis.

Extranodal involvement other than in the skin has been reported in only one case with infiltration into the myocardium (Chan et al. 1989). Some reports indicate that the bone marrow of HNL is normal (Miyazaki et al. 1985; Ohkawa et al. 1980) or hypoplastic (Haruyama et al. 1979; Oka et al. 1983). One describes the proliferation of large histiocytes with haemophagocytosis in hypoplastic marrow (Inaba et al. 1988). According to the report of EB virus-associated haemophagocytic syndrome (Risdall et al. 1979), most of the histiocytes infiltrated in the skin and bone marrow showed haemophagocytosis; hepatosplenomegaly was found clinically. In our patient an increase of EBNA was noted, and histiocytes, which infiltrated into the skin and bone marrow,

showed phagocytosis of nuclear debris, but no haemophagocytosis was found.

Kuo (1990) described a patient with HNL accompanied by involvement of extranodal sites where the progress of clinical signs was more severe than in patients without extranodal sites. In our patient, hospital discharge was about 3 weeks after the initiation of treatment with no recurrence observed thereafter. The histological features in the extranodal HNL lesion were very difficult to differentiate from some cases of malignant lymphoma. It may be useful in diagnosis to bear in mind that, as in the present case, there are some cases with infiltration into the bone marrow.

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