 

# Cytophagic histiocytic panniculitis/panniculitis-like T-cell lymphoma (CHP/PLTL) in a two-years-old boy

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**Cytophagic histiocytic panniculitis/panniculitis-like T-cell lymphoma (CHP/PLTL) in a two years-old Japanese boy was reported. Recurrent peculiar subcutaneous nodules appeared dominntly in his lower extremities. Laboratory examination indicated cytopenia, anemia and a small number of atypical lymphocytes in the peripheral blood, stimulated histiocytes in the bone marrow, and abnormal liver function tests. The subcutaneous nodules were examined two times and showed multifocal and diffuse growth of muramidase-positive histiocytes and infiltration of a small number of atypical TIA1-positive CD8 T-cells. The infiltrating T-cells became more numerous and showed more irregular-shaped nuclei in the second biopsy than in the first biopsy. Rare Ki-67 antigen (MIB-1)-positive proliferating cells were seen in the T-cells. Epstein-Barr virus (EBV) infection was not shown in the EBER-1 in-situ hybridization. Polymerase chain reaction analysis indicated clonal T-cells and developing rearrangement in TCR$\beta$ chain gene. In spite of rare proliferating cells in the T-cells and no complication of hemophagocytic syndrome and high-grade T-cell lymphoma, these recurrent peculiar subcutaneous nodules were diagnosed as those of an early phase of CHP/PLTL under the consideration of its pathogenesis.**

**Key words: Cytophagic histiocytic panniculitis (CHP), Subcutaneous T-cell lymphoma, Panniculitis-like T-cell lymphoma (PLTL), Immunohistochemistry, CD8, TIA1, Polymerase chain reaction (PCR), T-cell receptor $\beta$ chain gene**

## Introduction

Recently cytophagic histiocytic panniculitis (CHP) (Winkelmann & Bowie, 1980: Crotty & Winkelmann, 1981: Alegre & Winkelmann, 1989: White & Winkelmann, 1989: Perniciaro et al, 1994) is thought to be neoplastic disease of CD8 T-cells (Hytiroglou et al, 1992) and is categorized as CHP/panniculitis-like T-cell lymphoma (PLTL) (Jaffe et al, 1997) because its fatal cases complicate hemophagocytic syndrome (HPS) (Gonzalez et al, 1991). But there were reports (White & Winkelmann, 1989) of CHP with benign clinical course free from HPS. In children there were several reports of benign and fatal cases of CHP (Yanagawa et al, 1990: Garcia-Consuegra, 1991: Chan et al, 1994: Inatomi et al, 1995: Sandlund et al, 1997).

Polymerase chain reaction (PCR) analysis of immunoglobulin heavy chain (IgH) gene and T-cell receptor $\beta$ or $\gamma$ chain (TCR$\beta/\gamma$) gene has been introduced to surgical pathology of malignant lymphoma (McCarthy et al, 1990, 1991, 1992). Then, it is possible to examine clonality in lymphocytes even in a small piece of surgical material such as skin biopsy.

We experienced repeated multifocal panniculitis-like skin lesions in a two-years-old boy. By means of immunohistochemistry and the above-mentioned PCR analysis, TIA1-positive clonal CD8 T-cells and many muramidase-positive histiocytes were indicated in the subcutaneous tissue. We diagnosed these lesions as an early phase of CHP/PLTL. Here,

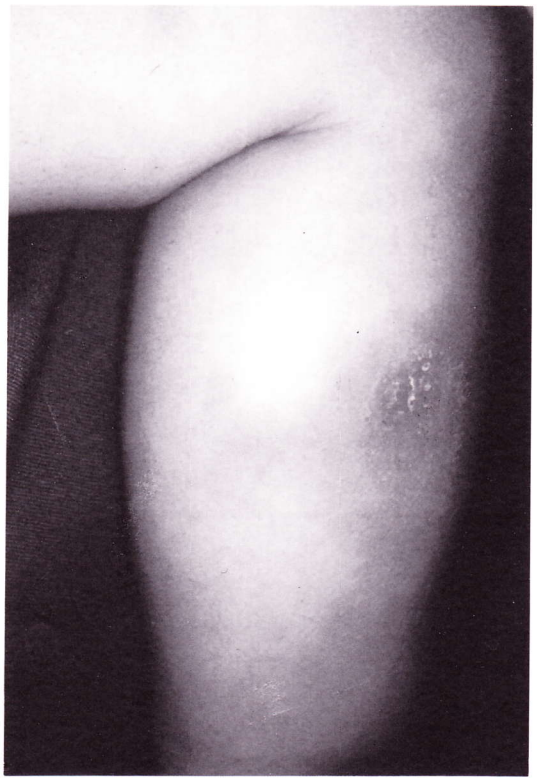


**FIGURE 1**, Multiple subcutaneous nodules in his right lower leg at the second biopsy. Healing skin eruption is also seen.

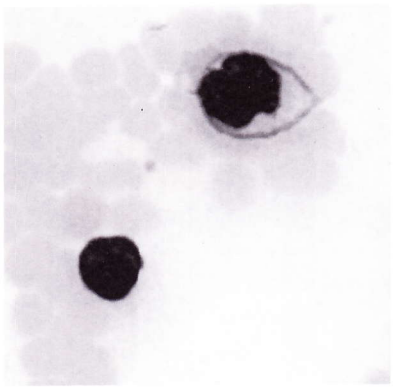


**FIGURE 2**, An atypical lymphocyte in peripheral blood.

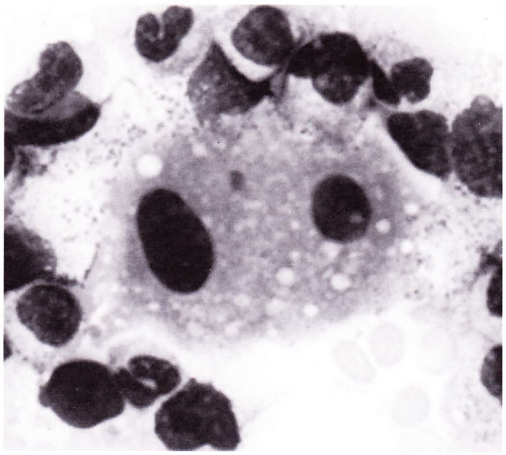


**FIGURE 3**, A cytophagic histiocyte in bone marrow aspiration

this case is reported with discussion about problems in the diagnosis of CHP/PLTL and its pathogenesis.

## Case

The patient was a two-years-old Japanese boy. His grandmother suffered from unknown fever. But further informations about her were not gotten.

In February 1997, multiple subcutaneous nodules appeared in his bilateral legs. By the steroid therapy the subcutaneous nodules regressed in two months. In May 1997, the subcutaneous nodules appeared again around mouth, on back and in bilateral legs. His body temperature was 37.0℃. One of the subcutaneous nodules in the right thigh was examined in a hospital in June 1997 (the first biopsy). Multifocal and diffuse growth of histiocytes and infiltration of a small number of atypical lymphocytes were noticed in the subcutaneous adipose tissue. The subcutaneous nodules disappeared in one month without any therapy.

He was checked up in Departments of Dermatology and of Pediatrics, University Hospital, Kagoshima in July 1997. He was 84.2 cm and weighed 11.3 kilograms. His consciousness was clear but mild mental retardation was recognized. Small cervical lymph nodes were palpated. Ill-defined subcutaneous nodules (2 cm in diameter in maximum) were noticed in the right lower leg (Fig. 1).

At his admission, his peripheral blood showed decreased number of white blood cells (WBC), mild anemia and appearance of a small number of atypical lymphocytes (Fig. 2). Laboratory findings were as follows; WBC: 2,800/$mm^3$ (decreased), (Stab:21%, Seg:27%, Ly:48%, atypical Ly:3%, Mo:1%), RBC: 4,070,000/$mm^3$, Hb: 7.7 g/dl (decreased), Ht : 26.6% (decreased), Platelet: 210,000/$mm^3$, PT: 90%, PT-INR: 1.06, APTT: 45.8 sec., Fibrinogen: 313mg/dl, HPT: 85%, HPT-INR: 1.08, TT: 69%, myelogram (NCC:$8.6x10^4$/$mm^3$, Meg: 12.5/$mm^3$, blasts: 4.2%, stimulated cytophagic histiocytes (+, Fig. 3), hemophagocytic cells (-)), CRP: 0.8mg/dl, GOT: 98 U/l (elevated), GPT: 31U/l, LDH: 1,208U/l (elevated), ALP: 186U/l, CHE: 171U/l, T-Bil: 0.2mg/dl, $\gamma$-GTP: 13U/l, AMY: 44U/l, CK: 60U/l, BUN: 13.7mg/dl, CRE: 0.4mg/dl, UA: 5.9mg/dl, Na: 135mEq/l. K: 4.9mEq/l, Cl: 107mEq/l, Ca: 8.4mg/dl (decreased), P: 3mg/dl, Fe: 11$\mu$g/dl (decreased), TP: 6.1g/dl (decreased), Alb: 4.5g/dl, A/G:1.75, (Alb: 63.7%, $\alpha_1$glo: 3.8% (increased), $\alpha_2$ glo: 14.2% (increased), $\beta$ glo:10.3%, $\gamma$ glo: 8% (decreased)), T-CHO: 99 (decreased), ferritin: 365ng/ml (elevated), C3: 143mg/dl, C4: 38mg/dl, ssDNA: <10U/ml, dsDNA: <10IU/ml, ANA: <20x, Vit. $B_{12}$: 558PG/ML, fetal Hb: 0.8%, serum $\beta$-2 microglobulin (BMG): 2.2mg/l (increased), urinary BMG:20,051$\mu$g/l (increased), EBV-VC-G: <10x, EBV-VC-M: <10x, EBV-EBNA: <10x.

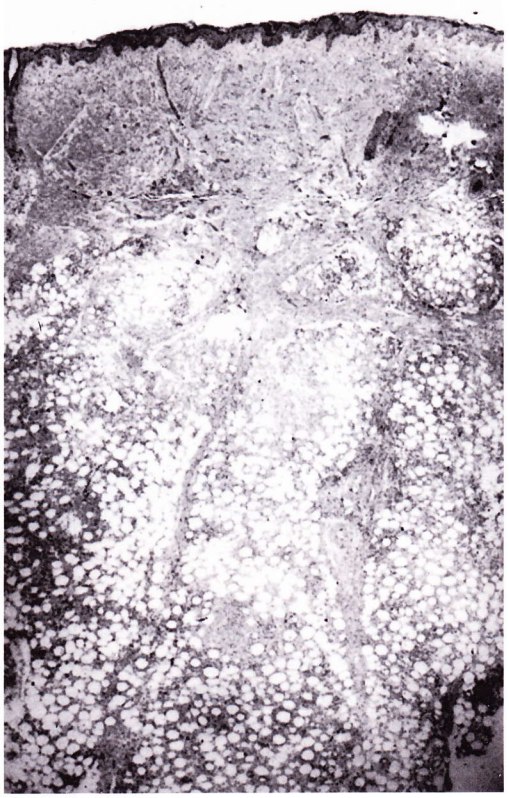
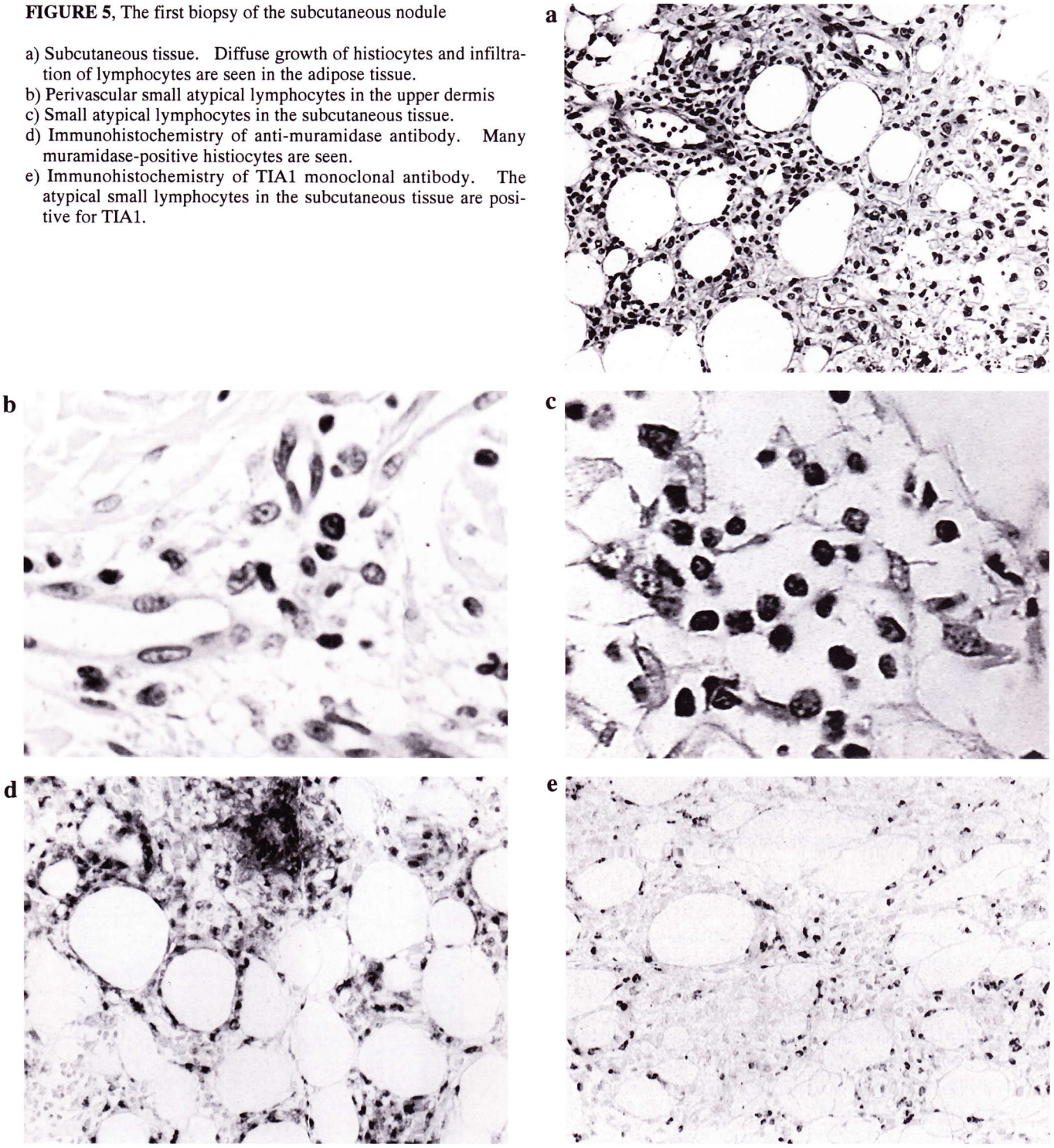


**FIGURE 4**, The first biopsy of the subcutaneous nodule in right lower leg.

**FIGURE 5**, The first biopsy of the subcutaneous nodule

a) Subcutaneous tissue. Diffuse growth of histiocytes and infiltration of lymphocytes are seen in the adipose tissue.
b) Perivascular small atypical lymphocytes in the upper dermis
c) Small atypical lymphocytes in the subcutaneous tissue.
d) Immunohistochemistry of anti-muramidase antibody. Many muramidase-positive histiocytes are seen.
e) Immunohistochemistry of TIA1 monoclonal antibody. The atypical small lymphocytes in the subcutaneous tissue are positive for TIA1.




In one month of his admission, peripheral blood WBC decreased to 2,000/mm$^3$ and returned gradually to the normal range. RBC decreased to 3,560,000/mm$^3$ and returned gradually to the normal range. CRP decreased gradually. GOT returned to the normal range. LDH raised to 1,584 U/l, decreased gradually but was above the normal range. Calcium decreased to 7.6 mg/dl and returned to the normal range. One of the subcutaneous nodules in his left thigh was examined (the second biopsy). As the abnormal laboratory findings returned to the normal range, the subcutaneous nodules disappeared.

After his admission, the subcutaneous nodules appeared and disappeared in time twice.

He is followed up.

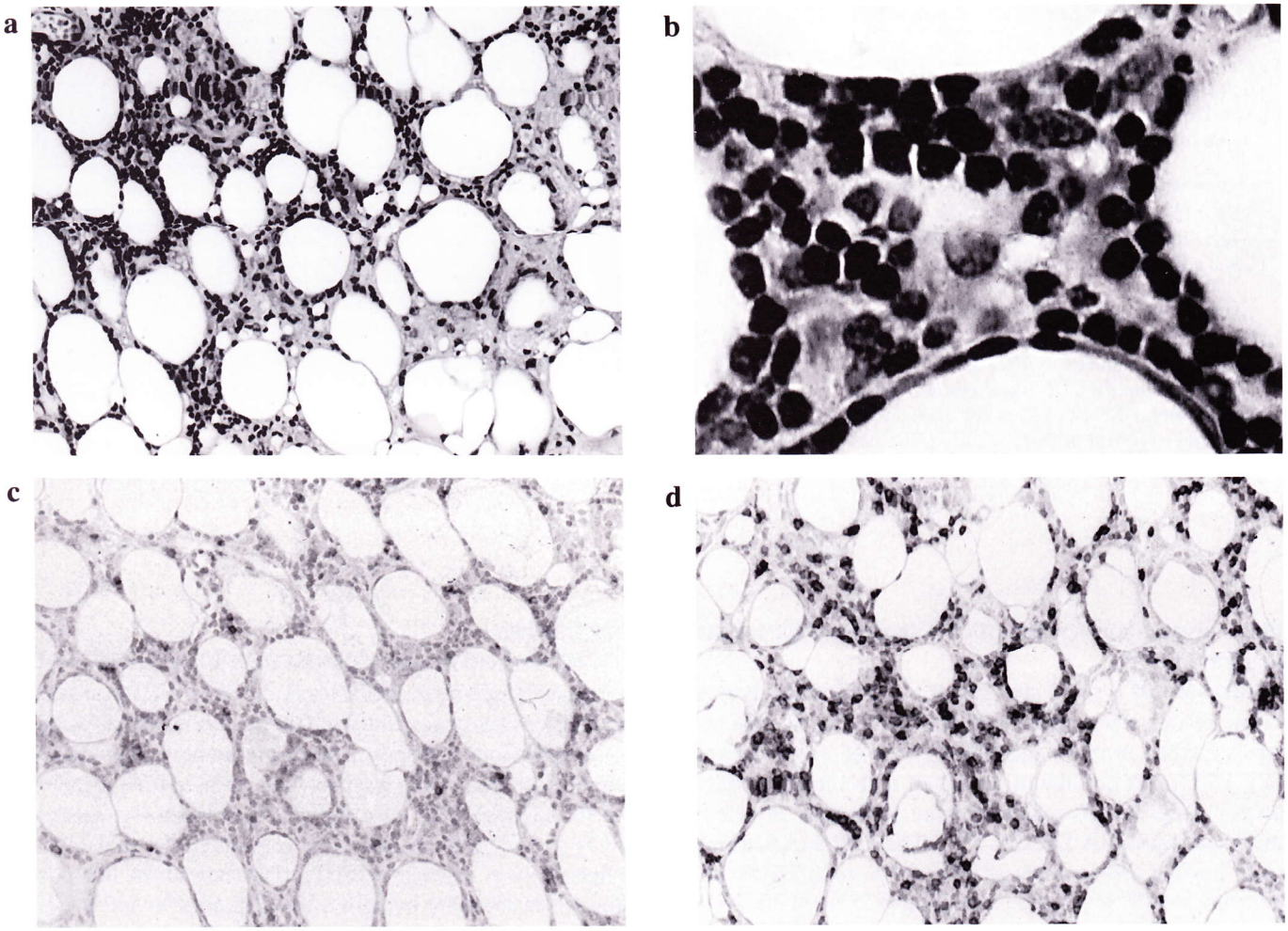


**FIGURE 6**, The second biopsy of the subcutaneous nodule
a) Infiltration of the lymphocytes in the subcutaneous tissue.
b) High-power-view of the infiltrating lymphocytes. The atypical lymphocytes have irregular-shaped nuclei.
c) Immunohistochemistry of CD4. Only a few CD4 T-cells are seen.
d) Immunohistochemistry of CD8. Most of the infiltrating lymphocytes are CD8 T-cells.

## Pathology

The first biopsy of the subcutaneous nodule (Fig. 4) showed multifocal and diffuse growth of many histiocytes and infiltration of a small number of lymphocytes in the subcutaneous adipose tissue (Fig. 5a). In the upper dermis a few small atypical lymphocytes were seen around blood vessels (Fig. 5b). The lymphocytes in the subcutaneous adipose tissue were small but had indented thick nuclear membrane (Fig. 5c). The histiocytes were positive for KP-1 and muramidase (Fig. 5d) and were negative for S100 protein. In parts the histiocytes aggregated around blood vessels. S100 protein-positive cells were rare in the subcutaneous lesion. The small lymphocytes in the subcutaneous tissue were CD3+ CD4- CD8- TIA1+ (Fig. Fig. 5b) OPD4+ T-cells.

The second biopsy of the subcutaneous nodules showed increase of the infiltrating small lymphocytes in parts in the subcutaneous tissue (Fig. 6a). Some of the small lymphocytes had more irregular-shaped nuclei (Fig. 6b) than those in the first biopsy. The small lymphocytes were CD3+ CD4- (Fig. 6c) CD8+ (Fig. 6d) TIA1+ OPD4+ T-cells. Among the lymphocytes a few cytophagic histiocytes were seen. In other areas of the subcutaneous tissue, diffuse growth of muramidase-positive histiocytes with few lymphocytes was seen.

In the both first and second biopsies, Ki-67 antigen (MIB-1)-positive proliferating cells were rare in the infiltrating lymphocytes.

### EBER-1 in-situ-hybridization

By means of the in-situ hybridization employing DAKO PNA-EBER-1 probe and its detection system, it was examined whether these panniculitis-like lesions were related to Epstein-Barr virus (EBV) infection or not.

No signals of EBER-1 were seen in nuclei of the lymphocytes and the histiocytes in the subcutaneous tissue of the first and second biopsies, whereas obvious signals were recognized in lymphocytes in gastric mucosa of a control case with EBV infection.

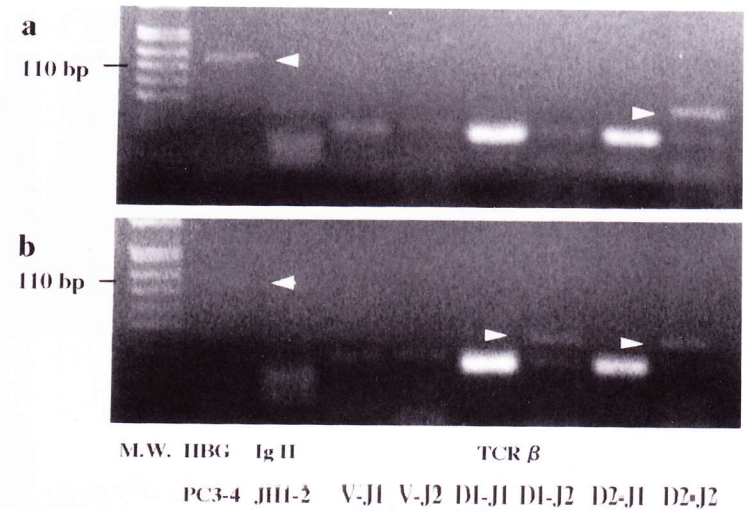
**FIGURE 7**, Electrophoresis of PCR products

a) The DNA extracted from the subcutaneous tissue of the first biopsy
b) The DNA extracted from the subcutaneous tissue of the second biopsy

M.W.: Molecular weight size marker 9
HBG: Human $\beta$ globin gene
IgH: Immunoglobulin heavy chain gene
TCR$\beta$: T-cell recptor $\beta$ chain gene

A faint but clear band of HBG is seen at 110bp in a) and b), suggesting an enough amount of the templete DNA for PCR.

Bands of amplified DNA are seen at 50bp in a pair of primers D2-J2 of PCR for TCR$\beta$ in a) and b) and in a pair of primers D1-J2 of PCR for TCR$\beta$ in b).




**Polymerase chain reaction (PCR) analysis of the infiltrating lymphocytes**

Because of a small number of the infiltrating lymphocytes, subcutaneous tissue with the infiltrating lymphocytes was collected from 10 paraffin-sections of 3$\mu$m thickness into a 1.5 ml microtube by means of a needle under microscope. From the subcutaneous tissue, DNA was extracted by means of TAKARA DEXPAT™. The PCR was performed as following; pre-denature at 94℃ for 5 min., 30 cycles of denature at 94℃ for 30 sec., annealing at 55℃ for 30 sec. and extension at 72℃ for 30 sec., and extension at 72℃ for 5 min.

In order to see whether an amount of the extracted DNA was enough to be examined by PCR of IgH gene and of TCR $\beta$ gene, human $\beta$-globin gene was amplified by the PCR employing a primer sets of PC03 and 04.

As shown in Fig. 7, no amplification of DNA was noted in the PCR of a primer set of JH1 and JH2 for IgH gene. In the PCR for TCR$\beta$ gene, a band of amplified DNA was noted at 50bp length in the primer set of D2-J2 in the DNA extracted from the subcutaneous tissue of the both first (Fig. 7a) and second biopsies (Fig. 7b) , and in the primer set of D1-J2 in the DNA extracted from the subcutaneous tissue of the second biopsy (Fig. 7b).

Because the PCR system detecting TCR$\beta$ gene rearrangement indicates a band of amplified DNA in the combination of PCR of the primers; V-J2, D1-J2 and D2-J2, in T-cell malignant lymphomas (McCarthy et al, 1991), these findings of the PCR analysis indicated that the infiltrating lymphocytes in the subcutaneous tissue of the both first and second biopsies were clonal T-cells, although rearrangement of TCR$\beta$ gene was developed more in the second biopsy.

Therefore, the peculiar panniculitis-like lesions in the first and second biopsies were diagnosed as those in an early phase of CHP/PLTL.

## Discussion

CHP has been thought to be one entity of cutaneous T-cell malignant lymphomas (Gonzalez et al, 1991). CHP is usually misdiagnosed as panniculitis, but the occurrence of histological progression that shows more pronounced ctyological atypia in the infiltrating lymphocytes can help for a pathologist to diagnose CHP as malignant lymphoma (Jaffe et al, 1997). It has been reported several times that overt lymphoma was not seen in CHP. But, nowadays, it is possible to see clonality even in a small number of infiltrating lymphocytes by means of PCR, as shown in this study. The PCR examination detecting a clonality in the infiltrating lymphocytes is necessary for the diagnosis of CHP/PLTL. And, because the clonal CD8 T-cells in CHP do not show enough atypia to be diagnosed as overt lymphoma except entities of low grade T-cell lymphomas such as T-cell chronic lymphocytic leukemia, the authors thought that CHP/PLTL would be categorized further into two subtypes; the early phase of CHP/PLTL in which clonal CD8 T-cells can not be diagnosed as overt lymphoma, and the late phase of CHP/PLTL in which overt lymphoma (large cell or anaplastic large cell T-cell lymphoma) is recognized. Then, this case must be categorized in the early phase of CHP/PLTL.

On the other hand, it must be discussed whether subcutaneous lymphomas are CHP/PLTL or not. It is well known that subcutaneous involvement is seen in many entities of T-cell lymphomas (Avinoach, 1994: Takeshita et al, 1994: Marzano et al, 1997) and in angioimmunoproliferative lesion that often associates B-cell lymphoma (Takeshita et al, 1995). Therefore, malignant lymphoma involving subcutaneous tissue should be tried at first to be categorized in entities other than CHP/PLTL.

Interferon gamma and granuocyte-monocyte colony stimulating factor produced by the lymphoma cells (Burg et al. 1991) induce hemophagocytic syndrome (HPS) that precipitates a fulminant downhill clinical course of CHP/PLTL

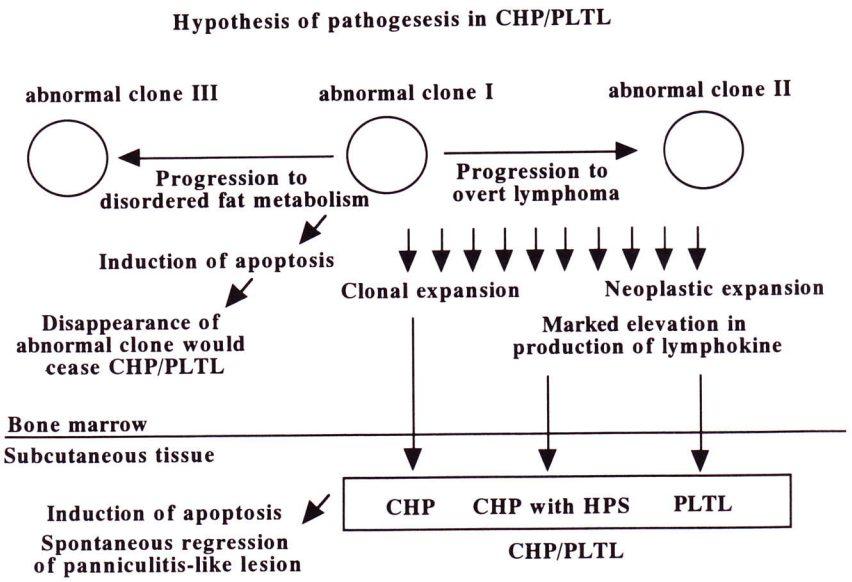



**FIGURE 8**, Hypothesis of pathogenesis of cytophagis histiocytic panniculitis/panniculitis-like T-cell lymphoma (CHP/PLTL)

Postulating an abnormal CD8 clone or its stem cell in bone marrow, pathogenesis of CHP/PLTL might be understood as following. Oncogenic progression in the abnormal clone associates recurrent clonal expansion to supply the clonal CD8 T-cells infiltrating into the subcutaneous tissue. The clonal CD8 T-cells produce an enough amount of lymphokines to evoke hemophagocytic syndrome (HPS). The oncogenic progression reachs after overt lymphoma. On the contrary, the oncogenic progression induces apoptosis in the clonal CD8 T-cells to end in spontaneous regression of the subcutaneous panniculitis-like lesion. The apoptosis in the stem cell may cease CHP/PLTL. Disordered fat metabolism may be induced by the other aspect of the oncogenic progression.

(Jaffe et al, 1997). But HPS is induced in several condition such as EBV infection (Smith et al, 1991: Harada et al, 1994). It is unknown whether a subcutaneous CD8 T-cell lymphoma with HPS is CHP/PLTL or not. The authors believed that only the subcutaneous CD8 T-cell lymphoma with features of the early phase of CHP/PLTL in parts can be regarded as CHP/PLTL. And the features of the early phase of CHP/PLTL would be multifocal and diffuse growth of muramidase-positive histiocytes with or without infiltration of small atypical lymphocytes, from which the extracted DNA must show clonal characters in the PCR analysis.

It is unusual in the diagnosis of high-grade lymphomas that there are rare Ki-67 antigen (MIB-1)-positive proliferating cells in the infiltrating lymphoma cells. In this case the rare proliferating cells must be understood as a feature of low-grade lymphoma and, in other hand, might be explained by the on-going apoptotic nature of lymphoma cells in CHP/PLTL (Kumar S et a, 1997). And it must be discussed where the infiltrating clonal CD8 T-cells came from. The cytophagic histiocytes in the bone marrow in Fig. 3 (Ichikawa et al, 1989: Galende et al, 1994) suggested that the bone marrow is also involved by CHP/PLTL. The infiltrating clonal CD8 T-cells may originate from an abnormal clone in the bone marrow. The abnormal clone can be postulated in CHP/PLTL, because CHP-like panniculitis was reported in graft-versus-host reaction after the bone marrow transplantation (Galende et al, 1994). Because there were no reports about abnormality in thymus in CHP/PLTL, the clonal CD8 T-cells may develope through extrathymic pathway. Recurrent expansion of the abnormal clone in the bone marrow would supply the clonal CD8 T-cells that infiltrate into the subcutaneous tissue. The atypical lymphocytes in the peripheral blood (Fig. 2) and around the blood vessels in the upper dermis (Fig. 5b) stand for this hypothesis (Fig. 8). The more atypical nuclei (Fig. 6b) and more developed rearrangement of TCR$\beta$ (Fig. 7) in the CD8 T-cells in the second biopsy than in the first biosy must reach after overt lymphoma (Jaffe et al, 1997). Oncogenic progression in the abnormal clone in CHP/PLTL might cease the development of CHP/PLTL by the induction of apoptosis (Kumar S et a, 1997) in the abnormal clone. This contrary end-result of the oncogenic progression may explain the benign clinical course in some cases of CHP/PLTL (White & Winkelmann, 1989). The oncogenic progression in the abnormal clone possibly induce disordered fat metabolism in some cases of CHP/PLTL (Yanagawa et al, 1990: Inatomi et al 1995).

Further investigations about abnormal lymphocytes in the peripheral blood and the precursor or stem cells in the bone marrow in CHP/PLTL are expected to elucidate the pathogenesis.

## Acknowlegement

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