Cytophagic Histiocytic Panniculitis and Subcutaneous Panniculitis-like T-Cell Lymphoma
Report of 7 Cases

Angelo V. Marzano, MD; Emilio Berti, MD; Marco Paulli, MD; Ruggero Caputo, MD

Background: Cytophagic histiocytic panniculitis (CHP) is a rare subtype of panniculitis that usually follows a fatal course, with a terminal hemophagocytic syndrome. Recent reports on a subset of peripheral T-cell lymphoma named subcutaneous panniculitis-like T-cell lymphoma (SPTL) raised the question about the relationship between these entities.

Observations: We describe 7 patients in the study: 1 with fatal CHP, 4 with SPTL, and 2 with long-term CHP. The 5 patients with fatal CHP and SPTL died of complications of hemophagocytic syndrome, with a disease duration ranging from 8 to 74 months. The other 2 patients were still alive 6 and 41 years after disease onset. Immunohistochemical results proved that 2 of the SPTL cases were type α/β and expressed the cytotoxic/suppressor antigen CD8, while the other 2 were type γ/δ and were positive for the natural killer–associated antigen CD56. In these 4 cases, molecular biology studies by polymerase chain reaction detected T-cell receptor γ gene rearrangement, indicating a clonal process. In contrast, in the 2 patients who had long-term CHP, the polymerase chain reaction results failed to disclose clonality. In the subject with fatal CHP, genotypic analysis was not performed.

Conclusion: Our observations suggest that CHP and SPTL may span a clinicopathologic spectrum in which there is a natural disease progression from CHP to SPTL.

Arch Dermatol. 2000;136:889-896

RESULTS

CLINICAL FEATURES

The clinical findings in these 7 patients are summarized in Table 2 and Table 3 (see also Figure 1). The patients included 5 females and 2 males with a median age of 37 years (range, 10-56 years). The duration of disease ranged from 6 months to 38 years. The range of follow-up was 2 months to 3 years. Four patients (patients 4-7) diagnosed as having SPTL died of the disease 8 to 74 months following its onset. Patient 1 was diagnosed as having CHP and experienced a rapidly progressive clinical course (8 months). In contrast, the other 2 patients with CHP were still alive 6 and 41 years after the onset of the disease.

HISTOPATHOLOGIC FINDINGS

In 4 patients (patients 4-7), histopathologic findings of skin biopsy specimens disclosed a dense and diffuse infiltrate of atypical small to medium lymphocytes in the dermis and subcutis consistent with SPTL. This report describes the clinical presentation and course, and the pathologic, immunohistochemical, and molecular genetic findings of 7 patients, 5 of whom had fatal CHP or SPTL, while the other 2 had a long-term form of CHP. We suggest that CHP and SPTL exist in a continuum and that the former may precede the latter.
PATIENTS, MATERIALS, AND METHODS

PATIENTS

The study included 7 patients with CHP or SPTL registered in the files of the Institute of Dermatological Sciences of the University of Milan and IRCCS, Milan, Italy. Staging procedures included routine blood cell counts and chemistry analyses, cervicothoracoabdominal computed tomography, and bone marrow biopsy and aspirates. Autopsy was performed in one of these cases (patient 1). Clinical parameters evaluated were age, sex, type of skin lesions at presentation, systemic symptoms and signs, duration of disease, treatment, outcome, and follow-up.

HISTOPATHOLOGY

Skin biopsy specimens obtained from each patient both at onset and whenever possible during the progression of the disease were all reviewed. The skin specimens were fixed in 10% buffered formalin, embedded in paraffin, and sectioned into 3-µm sections that were stained with hematoxylin-eosin.

IMMUNOHISTOCHEMISTRY

Immunohistochemical stains were performed in all cases on paraffin-embedded skin sections and on frozen material by using the panel of antibodies indicated in Table 1. A standard alkaline phosphatase anti–alkaline phosphatase technique (Dakopatts, Glostrup, Denmark) was carried out according to a previously described method.

MOLECULAR BIOLOGY

T-cell receptor (TCR) gene rearrangement was evaluated in 6 of the 7 cases by a polymerase chain reaction assay coupled with nonnaturating polyacrylamide gel electrophoresis (PAGE) according to a method previously described. The amplification of the TCRγ chain locus V-J functional region was performed by using the oligonucleotide-specific primers for J coupled with V2a, V9, and V10. Fifteen microliters of the amplified material then was run overnight on 12% nonnaturating PAGE in Tris, boric acid, EDTA (TBE) buffer at 70 V. Finally, heteroduplex patterns were revealed by ethidium bromide staining. The presence of a nongermline band, compared with previously identified positive and negative controls, was indicative of rearrangement of the TCRγ chain.

EPSTEIN-BARR VIRUS EBER1 IN SITU HYBRIDIZATION

In all 7 cases, in situ hybridization studies for the detection of Epstein-Barr virus (EBV) RNA were performed using a 30-base pair oligonucleotide probe complementary to a portion of the EBER1 gene, a region of the EBV genome that is actively transcribed (up to 10⁷ copies per cell) in latently infected cells. The methods for these studies have been reported previously.

Table 1. Antibody Reagents Used for Immunohistochemical Studies for CHP and SPTL

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Antibody (Source)</th>
<th>Antigen Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD1a</td>
<td>Leu-6 (BD)</td>
<td>Cortical thymocytes and Langerhans cells</td>
</tr>
<tr>
<td>CD2</td>
<td>Leu-5 (BD)</td>
<td>Pan T lymphocytes</td>
</tr>
<tr>
<td>CD3</td>
<td>Leu-4 (BD)</td>
<td>Pan T lymphocytes</td>
</tr>
<tr>
<td>CD4</td>
<td>Leu-3a (BD)</td>
<td>Memory/helper T lymphocytes</td>
</tr>
<tr>
<td>CD5</td>
<td>Leu-1 (BD)</td>
<td>Pan T lymphocytes, B lymphocyte subset</td>
</tr>
<tr>
<td>CD7</td>
<td>Leu-9 (BD)</td>
<td>T lymphocytes</td>
</tr>
<tr>
<td>CD8</td>
<td>Leu-2a (BD)</td>
<td>Suppressor/cytotoxic T lymphocytes</td>
</tr>
<tr>
<td>CD19</td>
<td>B4 (CD)</td>
<td>Pan B lymphocytes</td>
</tr>
<tr>
<td>CD22</td>
<td>T015 (Dako)</td>
<td>Pan B lymphocytes</td>
</tr>
<tr>
<td>CD25</td>
<td>IL-2R (Dako)</td>
<td>Activated lymphocytes</td>
</tr>
<tr>
<td>CD30</td>
<td>Ber-H2 (Dako)</td>
<td>Activated lymphocytes and Reed-Sternberg cells</td>
</tr>
<tr>
<td>CD45R0</td>
<td>UCHL-1 (Dako)</td>
<td>Memory/helper T lymphocytes</td>
</tr>
<tr>
<td>CD56</td>
<td>123C3 (Monosan)</td>
<td>Natural killer and natural killer–like T cells</td>
</tr>
<tr>
<td>CD68</td>
<td>KP-1, Y182 (Dako)</td>
<td>Myeloid and macrophage cells</td>
</tr>
<tr>
<td>TIA-1</td>
<td>2G9 (CD)</td>
<td>Natural killer and cytotoxic T cells</td>
</tr>
<tr>
<td>TCRd</td>
<td>pF1 (T-Cell Sciences)</td>
<td>α/β T cells</td>
</tr>
<tr>
<td>TCRβ</td>
<td>TCRβ1 (T-Cell Sciences)</td>
<td>γδ T cells</td>
</tr>
</tbody>
</table>

*CHP indicates cytophagic histiocytic panniculitis; SPTL, subcutaneous panniculitis-like T-cell lymphoma.
†BD indicates Becton Dickinson, Mountain View, Calif; CO, Coulter Immunology, Hialeah, Fla; and Dako, Dakopatts, Glostrup, Denmark. Monosan is located in Uden, the Netherlands; T-Cell Sciences in Needham, Mass.

peripheral T-cell lymphoma involving subcutaneous tissue (Figure 2, A and B, and Table 3). Hemophagocytosis, particularly leukophagocytosis, was evident. In the other 3 cases, histologic findings suggested CHP (Figure 2, C). Histopathologic features of other organ sites are also summarized in Table 3 (Figure 2, D).

IMMUNOHISTOCHEMISTRY

Results from immunohistochemical studies are in Table 4. In all 4 cases (patients 4-7) in which the histopathologic findings were suggestive of lymphoma, the atypical lymphocytes showed a CD2+, CD3+, and CD45RO+ T-cell phenotype with clear evidence of T-cell antigen loss (CD5− and/or CD7−). All cases expressed TCRs: 2 cases (patients 6 and 7) proved to be α/β (BF1+) SPTL positive for the cytotoxic/suppressor CD8 antigen (Figure 3, A), while the other 2 (patients 4 and 5) were γδ (TCRδ−1+) SPTL expressing the natural killer (NK)—associated antigen CD56. Interestingly, in all the above cases, most of the neoplastic lymphocytes were strongly labeled with monoclonal antibodies directed against T-cell restricted intracellular antigen 1 (TIA-1), a cytotoxic cell marker that often forms a ring around fat vacuoles in the subcutaneous tissue (Figure 3, B). In addition, in case 4, we found intense staining for CD68 (KP1) in abundant histiocytes, some of which were large and cytophagic (Figure 3, C).

In case 1, a strong expression of CD68 by the benign histiocytes, several of which were cytophagic, admixed with numerous CD3+ and CD8+ T lymphocytes,
which were moderately positive for TIA-1, in the subcutaneous infiltrate was demonstrated. In case 2, in addition to CD68+ histiocytes, numerous CD4+ and CD8+ T lymphocytes slightly expressing TIA-1 were seen. 

In case 3, the cellular infiltrate in the subcutis was mainly composed of CD68+ histiocytes with several CD4+ and scattered CD8+ T lymphocytes negative for TIA-1.

**MOLECULAR BIOLOGY**

Results from genotypic analysis are shown in Table 3 and Figure 4.

**EBV EBER1 IN SITU HYBRIDIZATION**

In all 7 cases, results did not show any positive hybridization signals to EBER1 in the skin biopsy tissue sections.
In their report on CHP, Crotty and Winkelmann described 5 patients with multiple inflammatory subcutaneous nodules who experienced a terminal hemorrhagic diathesis after a clinical course of 6 months to 10 years. Clinical manifestations of systemic involvement consisted of fever, hepatosplenomegaly, mucosal ulcers, and...
serosal effusions. Pancytopenia, liver failure, and intra-
vascular coagulation were present in all their patients. The
histologic picture was characterized by a mixed lobular
and segmental histiocytic cytophagic panniculitis. Eryth-
rophagocytosis and cytophagocytosis by benign-ap-
pearing histiocytes were observed in internal organs, par-
ticularly the lymph nodes, spleen, liver, and bone marrow.

Single reports of patients with CHP who have not
experienced a fatal outcome 5, 16, and 28 years after the
onset of the disease have been subsequently pub-
lished.25,26 This nonfatal form of CHP differed in that sys-
 temic signs and symptoms were lacking, and cytopha-
gia was not evident in extracutaneous organs.

With the widespread use of immunocytochemistry
to characterize cellular infiltrates, the existence of ma-
lignant T-cell proliferations mimicking inflammatory pan-
niculitis has been recognized.2-20

Gonzales et al2 first described T-cell lymphoma in-
volving subcutaneous tissue as a rare, distinct subset of
peripheral T-cell lymphoma (PTL) characterized by a pro-
pensity to be associated with a hemophagocytic syn-
drome and by an aggressive clinical course. This entity
was categorized as a subtype of PTL by the International
Lymphoma Study Group in 1994 under the term subcu-
taneous panniculitis-like T-cell lymphoma (SPTL).27

Thus, both the precise nature of SPTL and the over-
all complex relationship between CHP and SPTL re-
main to be clarified.

Peters and Winkelmann28 suggested that CHP might
be a preneoplastic syndrome or a reactive process to a
neoplastic disease. In fact, it is well known that eryth-
rophagocytic syndromes occur uncommonly in a mul-
titude of disorders, including infectious and neoplastic
conditions.16

According to Wang et al,13 CHP is probably a low-
grade T-cell lymphoma ab initio that with time might
progress to the more aggressive SPTL.

We reported the clinical presentation, course,
laboratory, histopathologic, immunocytochemical, and
molecular genetic findings of 7 patients (5 female and
2 male) with CHP or SPTL to further characterize these
entities.

Five patients (patients 1 and 4-7) died of compli-
cations of hemophagocytosis between 8 and 74 months
following the onset of the disease. Four of these cases were
characterized by the occurrence of panniculitis-like sub-
cutaneous nodules initially difficult to classify as lym-
phoma with benign-appearing skin biopsy specimens.

Figure 2. A, Histopathologic findings from biopsy skin specimen of case 6 showing a cellular infiltrate entirely involving the subcutaneous tissue
(hematoxylin-eosin, original magnification ×12.5). B, Case 7: Dense infiltrate mainly composed of small to medium atypical lymphocytes, sometimes showing an
angiocentric distribution and forming rings around the adipose tissue lobules (hematoxylin-eosin, original magnification ×400). C, Case 2: Inflammatory
lymphohistiocytic infiltrate in the subcutis with tissue necrosis and karyorrhexis. Several cytophagic histiocytes are visible (hematoxylin-eosin, original
magnification ×400). D, Case 1: Bone marrow biopsy specimen with prominent erythrophagia indicated by large histiocytes of multiple erythrocytes
(hematoxylin-eosin, original magnification ×400).
mmented by TCRγ gene rearrangement studies. In the other case (patient 1), immunohistological results were interpreted as classic CHP without proven lymphoma, but genotypic analysis could not be performed because adequate biopsy material was not available.

Cytophagia, particularly erythrophagia, was observed in bone marrow specimens of the patients cited above, but no bone marrow involvement by lymphoma was demonstrated in any of these cases. These findings are in agreement with the literature, extracutaneous involvement by SPTL having only rarely been described.9,16 In addition, autopsy studies2,16,29 of patients who died of CHP or SPTL have rarely been published. Autopsy examination performed in case 1 of our series revealed the presence of hemophagocytic histiocytosis without evidence of lymphoma in multiple organ sites, as previously reported.20 In the 4 cases in which histopathologic findings were consistent with subcutaneous lymphoma, immunohistostudies showed a CD2+, CD3+, CD45RO+ T-cell phenotype of the neoplastic lymphocytes, with evidence of T-cell antigen loss (CD5− and/or CD7−). Two of these cases (patients 6 and 7) proved to be α/β T-cell lymphomas expressing the T-suppressor/cytotoxic cell antigen CD8, which is usually related to aggressive clinical behavior.30,31 The other 2 cases (patients 4 and 5) were γ/δ T-cell lymphomas and expressed the antigen CD56. The CD56 antigen marks the cutaneous NK and NK-like T-cell lymphomas, recently described as a rare subset of aggressive cutaneous lymphomas.32 Interestingly, in all cases the atypical lymphocytes were strongly labeled with the monoclonal antibody directed against TIA-1/GMP-17 (a granule membrane protein of the cytotoxic lymphocytes).33 Expression of this monoclonal antibody has recently been described in several lymphomas regarded as being derived from lymphocytes with cytotoxic potential and thus characterized by aggressive clinical behavior.34 In this regard, this immunohistohostory and the others mentioned above could help explain the rapidly fatal course of SPTL. In the other 2 cases (patients 2 and 3), characterized by histopathologic aspects of CHP and absence of clonality, the patients experienced a chronic course and were still alive 6 and 41 years after the disease onset, respectively. These patients lacked all of the clinical features typical of the fatal form of CHP and also presented without pancytopenia. However, such a long duration does not permit the certain conclusion that this is a nonfatal disease, since anaplastic transformation could occur with time, as previously described.24,35 This possibility may also be supported by the observation that both these cases and 2 of those classified as SPTL (patients 6 and 7) initially presented with a spectrum of systemic symptoms, including fever, polyarthritis, and pericarditis, that mimicked an autoimmune disorder. Thus, a lupus-like clinical presentation seems to represent an initial disease stage marking an immunological dysfunction that could be one of the factors promoting the progression to lymphoma.

Perniciaro et al8 suggested that 2 distinct clinical presentations of SPTL exist. The first is characterized by a protracted CHP-like phase and the other type by a rapidly progressive clinical course. Various factors, most notably genetic or viral, may be involved in triggering the progression from panniculitis to malignant lymphoma. Emphasis has been placed on gene rearrangement studies to establish malignancy and to differentiate between CHP and SPTL, but this should not be done. In fact, clonal T-cell proliferations are seen in a multitude of benign conditions and are not predictive of outcome.36

Latent EBV infection has been detected in SPTL12,35,37 but neither in nonfatal33 nor in fatal27 CHP by EBV RNA (EBER1) in situ hybridization studies. Other investigators have also reported negative results for EBV at multiple organ sites from a patient with fatal CHP.37 In this regard, Craig et al37 recently suggested that CHP and SPTL may not be identical.

Table 4. Immunohistochemical Studies of 7 Cases of CHP and SPTL

<table>
<thead>
<tr>
<th>Antigen</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4a</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD8</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>CD19</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD22</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD25</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD30</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD45RO</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD45RO</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD68</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>TIA-1</td>
<td>+/−</td>
<td>+/−</td>
<td>−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
</tr>
<tr>
<td>TCRβ</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TCRα-1</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

CHP indicates cytophagic histiocytic panniculitis; SPTL, subcutaneous panniculitis-like T-cell lymphoma; minus sign, no reaction; plus sign(s), increasing reaction; and +/-, variable reaction.
Figure 3. Immunohistochemical studies showing reactivity for CD8 (A), T-cell restricted intracellular antigen 1 (TIA-1) (B), and CD68 (C) (original magnification × 400).
We also performed EBV RNA (EBER1) in situ hybridization on skin biopsy specimens from all patients in this series and obtained negative results both for CHP and for SPTL.

In summary, our observations suggest that it does not seem appropriate to differentiate SPTL and CHP and that, on the contrary, there is a natural disease progression from CHP to SPTL.

Accepted for publication December 20, 1999.

Corresponding author: Angelo V. Marzano, MD, Istituto di Scienze Dermatologiche, University of Milan and IRCCS Ospedale Maggiore, Via Pace, 9, 20122 Milan, Italy.

REFERENCES


