Cutaneous Lymphoid Hyperplasia Presenting as a Solitary Facial Nodule

Clinical, Histopathological, Immunophenotypical, and Molecular Studies

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**Objective:** To elucidate the clinicopathological, immunophenotypical, and molecular characteristics of cutaneous lymphoid hyperplasia presenting as a solitary facial nodule.

**Design:** Retrospective study.

**Setting:** University dermatology department.

**Patients:** Three patients with a solitary facial nodule were studied clinically, histologically, immunophenotypically, and molecularly for T-cell receptor and immunoglobulin heavy chain gene rearrangements.

**Main Outcome Measures:** Histological, immunophenotypical, and molecular characteristics in relation to the clinical outcome.

**Results:** Histologically, dense diffuse lymphocytic infiltrates were present throughout the dermis, occasionally extending into the subcutaneous fat and the epidermis and hair follicles. Small lymphocytes predominated, but in 2 cases there were also medium to large atypical lymphocytes, with some blastlike lymphocytes. The lymphocytic population was mixed with more CD3+ T cells than CD20+ B cells, without germinal centers. There were more CD4+ than CD8+ cells, and some of the T cells stained for the memory T-cell marker CD45RO. Numerous CD68+ histiocytes were scattered or formed small aggregates, and in 1 case small granulomas and many scattered S100 protein–positive and CD1a+ dendritic cells were present. In addition, several polytypic plasma cells, eosinophils, and extravasated erythrocytes were found. Immunostaining for CD10, CD21, CD30, CD56, and BCL6 was negative. The Ki-67 proliferation index was relatively low (5%-10%). Results of the T-cell receptor gene rearrangement studies were positive in 2 cases, 1 of which also harbored clonal B cells. Serologic test results for *Borrelia burgdorferi*, *Borrelia afzelii*, and *Borrelia garinii* were negative in all 3 cases. Two lesions regressed spontaneously after an incisional biopsy, and none of the cases showed recurrence or extracutaneous spread during a follow-up period of 5.0 to 5.5 years.

**Conclusions:** Cutaneous lymphoid hyperplasia that presents as a solitary facial nodule may share clinical, cyto logical, immunophenotypical, and molecular features with other benign reactive lymphocytic infiltrates and cutaneous lymphomas, and therefore a careful clinical and therapeutic approach is warranted.

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**METHODS**

Three patients, 2 females and 1 male aged 12 to 54 years with a solitary nodule on the face diagnosed as CLH, were included in the study. The biopsy specimens that were obtained from the facial nodule of each patient were fixed in 4% buffered formalin and processed according to the routine methods. The histological sections were stained with hematoxylin–eosin, Ziehl-Neelsen, and periodic acid–Schiff stains.
and viewed with light and polarizing microscopes. Immunophenotyping was performed on routinely fixed, paraffin-embedded tissue sections with a panel of antibodies to CD3, CD21, CD68, BCL6, S100 protein, and Ki-67 (Dako Corporation, Glostrup, Denmark); CD56, CD4, CD30, CD45RO, and CD20 (Zymed Laboratories, San Francisco, Calif); CD8 (Diagnostic BioSystems, Pleasanton, Calif); CD10 (Novocastra Laboratories, Newcastle upon Tyne, England); CD1a (Biocare Medical, Walnut Creek, Calif); and κ and λ light chains (BioGenex, San Ramon, Calif) with an automatic Ventana machine (Ventana Medical Systems, Tucson, Ariz). Appropriate positive and negative controls were included. The staining results were assessed semiquantitatively.

Immunoglobulin heavy chain (IgH) and T-cell receptor (TCR) γ gene rearrangements were studied on DNA extracted from fresh skin biopsy specimens using the polymerase chain reaction (PCR) technique, as previously described.8 Borrelia serologic testing was recently performed in all 3 patients using an enzyme-linked immunosorbent assay technique for the detection of IgG and IgM antibodies and a Western blot technique. Both methods detect antibodies to Borrelia burgdorferi, Borrelia afzelii, and Borrelia garinii. The medical records of each patient were reviewed, and each person was contacted. All 3 patients were followed up for 5.0 to 5.5 years after the initial examination.

## RESULTS

### PATIENTS

The clinical characteristics of the study patients are presented in the Table. Three patients were included in the study: 2 females aged 54 years each (patients 1 and 2) and 1 male aged 12 years (patient 3). All 3 patients presented with a solitary erythematous nodule that had appeared rapidly on the face (Figure 1). In 2 patients (patients 1 and 3) the lesions were itchy. None of them recalled an external insult. Patient 1 recalled an itchy brown macule on the nose present for 3 years before the appearance of the nodule on the same spot, and patient 3 was on a field trip 3 months before the appearance of the nodule on his cheek (Figure 1) but did not recall any insect bite. Past illnesses and medications did not seem to be related to the appearance of the lesions, and continued use of the medications was not associated with the appearance of new lesions. A complete physical examination was performed in all 3 patients, and 2 of them (patients 2 and 3) underwent routine laboratory tests and imaging procedures, which did not provide evidence of extracutaneous involvement (Table 1). The serologic test results for Borrelia were negative and ruled out present

### Table. Results of the Clinical and Molecular Study

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Medical History and Medications</th>
<th>Duration of Lesion, mo</th>
<th>Type of Lesion/Site</th>
<th>Workup for Extracutaneous Involvement</th>
<th>Immunoglobulin Gene Rearrangements</th>
<th>Therapy</th>
<th>Follow-up, y</th>
<th>Present Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/54</td>
<td>Hypertension, enalapril maleate (3 y)</td>
<td>2</td>
<td>Dome-shaped nodule/nose</td>
<td>NA</td>
<td>−</td>
<td>Spontaneous regression after incisional biopsy</td>
<td>5.5</td>
<td>NED</td>
</tr>
<tr>
<td>2/F/54</td>
<td>Hypertension, bisoprolol fumarate (1 y), hysterectomy (myoma uteri), basal cell carcinoma in chest</td>
<td>1</td>
<td>Dome-shaped nodule/anterior temple</td>
<td>Blood cell count and routine chemical analysis, CT of the neck, chest, abdomen, and pelvis</td>
<td>−</td>
<td>+</td>
<td>Excision and local irradiation</td>
<td>5.5</td>
</tr>
<tr>
<td>3/M/12</td>
<td>NA</td>
<td>3</td>
<td>Dome-shaped nodule/cheek</td>
<td>Blood cell count and routine chemical analysis, chest x-ray examinations, and abdominal ultrasound</td>
<td>−</td>
<td>+</td>
<td>Spontaneous regression after incisional biopsy</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; IgH, immunoglobulin heavy chain; NA, not applicable; NED, no evidence of disease; TCR, T-cell receptor; +, positive result; −, negative result.

First specimen.

Second specimen.

Figure 1. An erythematous dome-shaped nodule on the cheek (patient 3).
and past infections. In 2 patients (patients 1 and 3) the nodules regressed spontaneously after incisional biopsy specimens were obtained from the centers of the lesions. In the other patient (patient 2) a full surgical excision was performed, which was followed by local irradiation. During a 5.0- to 5.5-year follow-up, no evidence of recurring disease was found in all 3 patients (Table 1).

HISTOLOGICAL ANALYSIS

A dense diffuse infiltrate throughout the dermis, which was the common feature in all 3 patients (Figure 2), extended deep into the subcutaneous fat in 1 case (patient 2). The infiltrates were predominantly composed of lymphocytes separated by a grenz zone from the overlying epidermis (Figure 2). On higher magnification, however, some exocytosis of lymphocytes into the epidermis and pilosebaceous units was evident, with marked epidermotropism of single lymphocytes and marked folliculotropism with the formation of Pautrier-like collections observed in the lesions of patients 3 and 1, respectively (Figure 3). The dense dermal lymphocytic infiltrates were intermingled with numerous histiocytes with abundant pale-staining cytoplasm, singly and in small aggregates (Figure 4). Some plasma cells, eosinophils, and extravasated erythrocytes were also found. The eosinophils were usually few except for the subcutaneous fat in patient 2, which contained small epithelioid-cell granulomas and a larger number of eosinophils within the dense lymphocytic infiltrate. Lymphocytes with medium to large, moderately irregular nuclei, with some large blastlike cells, were also present in the dermal infiltrates of patients 2 and 3 (Figure 5 and Figure 6). Polaroscopic microscopy and Ziehl-Neelsen and periodic acid–Schiff stains failed to detect foreign bodies, atypical mycobacteria, and fungi, respectively, in all 3 cases.

IMMUNOHISTOCHEMICAL ANALYSIS

Most lymphocytes, including the epidermotropic and folliculotropic ones, stained for the pan–T-cell marker CD3 (Figure 7A), and a minority of the lymphocytes (20%-40%) stained for the pan–B-cell marker CD20 (Figure 7B). The CD20+ lymphocytes were scattered or in small aggregates without germinal centers. Results of the stains for CD21, which highlight follicular dendritic cells, and CD10 and BCL6, which stain germinal center cells, were both negative. The medium lymphocytes stained for CD3 or CD20, but the large lymphocytes stained more frequently for CD20 than for CD3. Some of the CD3+ T cells stained for the memory T-cell marker CD45RO, and more CD4+ helper T cells were found than CD8+ cytotoxic and suppressor T cells. Results of the stains for CD56 and CD30 were both negative. Immunostaining for κ and λ light chains demonstrated polytypic plasma cells. A total of 3% to 10% of the cells in the dermal infiltrates stained for the proliferation marker Ki-67. Most of the histiocytes stained for the histiocytic marker CD68 (Figure 7C). The immunostaining for S100 protein and CD1a highlighted many scattered dendritic cells (Figure 7D).
MOLECULAR STUDIES

The results of the molecular studies are presented in the Table. The results of the IgH and TCR gene rearrangement studies were negative in patient 1, and a T-cell clone was demonstrated in patient 3. A T-cell clone was also found in the freshly obtained biopsy specimen of patient 2, but an additional PCR study on the deparaffinized biopsy specimen, which was performed in another laboratory (L. Cerroni, Graz, Austria, written communication, November 17, 2000), demonstrated both B-cell and T-cell clones (Table).

COMMENT

A typical case of CLH exhibits a patch to confluent dense lymphoid infiltrate throughout the dermis that spares the epidermis and is separated from it by a narrow grenz zone. Immunophenotyping studies have shown that most cases of CLH consist of a mixture of reactive polytypic B cells, T cells, macrophages, and dendritic cells. Occasionally, B cells are rare or absent, and the infiltrate is predominantly composed of T cells. When germinal centers are present, they simulate nodal lymphoid hyperplasia and lack (14; 18) translocation or bcl-2 expression by the germinal center cells. Cutaneous lymphoid hyperplasia may be idio- pathic or may arise in response to a wide variety of foreign antigens, including arthropod bites, stings, and infestations, tattoos, vaccinations, trauma, injection of foreign substances, pierced ear jewelry, and drugs. Some cases have been attributed to infection with B burgdorferi. These associations suggest that CLH may begin as a reactive response to newly encountered antigens.

Our 3 idiopathic cases demonstrated a mixed infiltrate of predominantly T cells but also a substantial number of B cells. There were more CD4+ helper cells than CD8+ suppressor and cytotoxic T cells, and only some of the CD3+ T cells were memory cells. In 2 cases medium to large atypical lymphocytes were also found, some of which had a blastlike appearance. The atypical lymphoid cells stained for pan– T-cell or B-cell markers, although the larger cells stained more frequently for the B-cell marker. Both of these cases demonstrated clonal TCR gene rearrangements, one of which demonstrated IgH clonal gene rearrangements in an additional sample obtained from the same lesion. All 3 cases were characterized by the presence of numerous histiocytes singly and in small aggregates and in 1 case also as small subcutaneous granulomas. Many dendritic cells were demonstrated by positive staining for S100 protein and CD1a. Some polytypic plasma cells, eosinophils, and extravasated erythrocytes were also part of the infiltrate in all 3 cases. The heterogeneity of these infiltrates favors a reactive rather than a neoplastic process, supported by the fact that in 2 cases the lesions regressed spontaneously after an incisional biopsy and none recurred or demonstrated extracutaneous involvement during a follow-up of at least 5 years. However, the presence of medium to large atypical lymphocytes and the finding of dominant lymphocytic clones in 2 cases is considered more congruent with cutaneous lymphoma.
Van der Putte et al described 3 cases of solitary non-
epidermotropic T-cell pseudolymphomas of the skin with a
tendency for self-regression. These lesions were domi-
nated by numerous large lymphocytes with hyperchro-
matic cerebriform nuclei along with a mixture of mod-
erate numbers of histiocytes, macrophages, and plasma
cells and a few eosinophils. Rijlaarsdam et al noted self-
regression of pseudo–T-cell lymphomas when the
causative drug was removed and in the idiopathic cases
after topical or intralesional steroid therapy or sponta-
neously. These authors divided cutaneous pseudo–T-
cell lymphomas histologically into a bandlike pattern and
nodular pattern. The nodular pattern is characterized by
a mixed cellular infiltrate with scattered T-blast cells and
lymphocytes with medium or large cerebriform nuclei
and admixture of many small reactive lymphocytes. Medium blastlike cells may also be scattered
within the infiltrates. A background of numerous histi-
ocytic giant cells. A strong histiocytic component was more
commonly found in nodular pseudo–T-cell lymphoma
and rarely in pleomorphic T-cell lymphomas. Promi-
nent granulomatous reaction (exceeding 25% of the der-
mal infiltrate) was found in only 1.8% of all cases with
cutaneous B-cell or T-cell lymphoma registered in the files
of the Department of Dermatology of the University of
Graz. Most of the cases were mycosis fungoides, but there
were a few cases of cutaneous panniculitis-like T-cell
lymphoma and small or medium pleomorphic T-cell lymphoma
and single cases of follicle center cell lymphoma,
large B-cell lymphoma, and secondary cutaneous peripheral
T-cell lymphoma. Bakels et al believe that a
considerable admixture of reactive CD8+ T cells (15%
to 60%), B cells (up to 20%), and macrophages are more
characteristic of pseudo–T-cell lymphoma, whereas
Griesser et al were not able to discriminate clinically and
immunohistochemically cutaneous T-cell–rich re-
active lesions from malignant lymphoproliferation.
Recently, a locally aggressive CLH characterized by the pres-
ence of necrotizing granulomas and arising within the
influenza inoculation site has been described.

The presence of a strong histiocytic component, as seen
in our 3 cases, and its tendency for self-regression favor
the diagnosis of a pseudolymphoma, although a granu-
logomatous reaction may rarely be found in cutaneous
lymphoma, and some forms of cutaneous lymphomas, such as
CD30+ anaplastic large-cell lymphoma and lympho-
amatoid papulosis, often regress spontaneously. The
presence of a clone of lymphocytes is generally considered
supportive of cutaneous lymphoma. Bakels et al did not
detect any clonal population of lymphocytes in
11 cases of pseudo–T-cell lymphoma, whereas it was found in most cases of mycosis fungoides and pleomor-
phic cutaneous T-cell lymphoma. Recently, however,
several studies that used the sensitive PCR technique
detected clonal T-cell populations in pseudolymphomas,
in various inflammatory disorders such as psoriasis, lichen planus, and pityriasis lichenoides, and in potential
precursor lesions of cutaneous T-cell lymphoma such as
clonal dermatitis. Because of the high sensitivities of
the present PCR techniques to detect gene rearrangements,
the significance of the small clones of lymphocytes de-
tected (as little as 1% of all infiltrating cells) is currently
unclear and cannot be used as a single and independent
diagnostic criterion to diagnose malignant T-cell
lymphoma.

Nihal et al demonstrated clonal CLH in 61% of their
44 cases with CLH, most of them with the mixed B-cell
and T-cell type and with an idiopathic origin. There were
almost equal numbers of TCR-positive and IgH-positive
cases and few cases with both TCR-positive and IgH-
positive clones. Two cases (2%) (1 of which was a T-cell
CLH) progressed to overt cutaneous B-cell lymphoma. Although the high prevalence of dominant clones in this
series may have resulted from the sensitivity of the PCR
technique and from patient selection, the clonal over-
growth found occasionally in CLH may link it to lymph-
oma.

Our cases share some clinical and histological fea-
tures with a subset of CLH termed pseudolymphomatous
folliculitis. Pseudolymphomatous folliculitis usually pre-
seas as a solitary nodule on the face with a tendency to
self-regress after an incisional biopsy. Histopathologi-
cally, a dense lymphocytic infiltrate is present in the der-
mis and subcutaneous fat, often intermingled with many
atypical lymphocytes. Characteristically, the walls of
follicles are enlarged and irregularly deformed, with their
epithelium blurred by lymphocytic infiltrates. Immu-
nohistochemically, B cells or T cells may predominate,
and all lesions show increased numbers of perifollicular
cellular–associated dendritic cells, often in aggregates that
express S100 protein and CD1a. The results of TCR γ-
chain and IgH gene rearrangement studies are negative
in all cases. One of our cases (patient 1) demonstrated
marked folliculotropism of small lymphocytes, negative
TCR and IgH gene rearrangement study results, and sponta-
neous regression after an incisional biopsy, but the re-
mainder 2 cases (1 of which also regressed spontane-
ously) demonstrated dominant lymphocytic clones.

In summary, CLH that appears on the face as a soli-
tary facial nodule forms a spectrum in which the differen-
tiation between pseudolymphoma and lymphoma may be
difficult. The presence of a polymorphous infiltrate of
T and B cells, plasma cells, eosinophils, and many his-
tiocytes and dendritic cells; the lack of atypical lympho-
cytes and dominant lymphocytic clones; and spontane-
ous regression after an incisional biopsy support the
diagnosis of pseudolymphoma. On the other hand, the
presence of atypical lymphoid cells and T-cell and/or B-
cell clones hampers the distinction from cutaneous
lymphoma and calls for a careful clinical and therapeu-
tic approach.

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Analysis and interpretation of data: Bergman, Khamaysi, Sahar, and Ben-Arieh. Drafting of the manuscript: Bergman, Khamaysi, Sahar, and Ben-Arieh.

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