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 polyclonal 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 garii 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, cytological, immunophenotypical, and molecular features with both benign reactive lymphocytic infiltrates and cutaneous lymphomas, and therefore a careful clinical and therapeutic approach is warranted.

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CUTANEOUS PSEUDOLYMPHOMA refers to a heterogeneous group of benign reactive T- or B-cell lymphoproliferative processes of diverse causes that simulate cutaneous lymphomas clinically and/or histologically.1 The term cutaneous lymphoid hyperplasia (CLH) has been used to describe the benign end of the spectrum of lymphoproliferative disorders, with cutaneous lymphoma at its malignant extreme.2 Most CLH consists histologically of a mixture of B and T cells along with macrophages and dendritic cells, and only a few types of CLH are composed almost entirely of T cells.2,3 An intermediate condition termed clonal CLH has recently been proposed as a transitional state capable of evantuating into overt lymphoma because a few clonal lesions have been shown to do so.2 Cutaneous lymphoid hyperplasia can involve any area of the skin but is most common on the face.4 In most cases the origin of CLH (or pseudolymphoma) cannot be identified.3,8 The present study was performed to further elucidate the clinical, histological, immunohistochemical, and molecular characteristics of CLH that appears as a solitary facial nodule.

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.7,8 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>Excision and local irradiation</td>
<td>5.5</td>
<td>NED</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>Spontaneous regression after incisional biopsy</td>
<td>5.0</td>
<td>NED</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 epitheloid-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). Polarscopic 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 5% 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).
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).

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 t(14; 18) translocation or bcl-2 expression by the germinal center cells. Cutaneous lymphoid hyperplasia may be idopathic 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\textsuperscript{13} described 3 cases of solitary non-epidermotropic T-cell pseudolymphomas of the skin with a tendency for self-regression. These lesions were dominated by numerous large lymphocytes with hyperchromatic cerebriform nuclei along with a mixture of moderate numbers of histiocytes, macrophages, and plasma cells and a few eosinophils.\textsuperscript{13} Rijlaarsdam et al\textsuperscript{12} 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 spontaneously. 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 with admixture of many small reactive lymphocytes.\textsuperscript{12,13} Medium blastlike cells may also be scattered within the infiltrates.\textsuperscript{13} A background of numerous histiocytes is often found within the infiltrate, as seen in the paracortical areas of reactive lymph nodes. The histiocytes are often closely apposed and may form histiocytic giant cells. A strong histiocytic component was more commonly found in nodular pseudo–T-cell lymphoma and rarely in pleomorphic T-cell lymphomas.\textsuperscript{14,15} Prominent granulomatous reaction (exceeding 25% of the dermal infiltrate) was found in only 1.8% of all cases with a considerable admixture of reactive CD8\textsuperscript{+} T cells (15% to 60%), B cells (up to 20%), and macrophages are more characteristic of pseudo–T-cell lymphoma, whereas Griesser et al\textsuperscript{18} were not able to discriminate clinically and immunohistochemically cutaneous T-cell–rich reactive lesions from malignant lymphoproliferation. Recently, a locally aggressive CLH characterized by the presence of necrotizing granulomas and arising within an influenza inoculation site has been described.\textsuperscript{19}

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 granulomatous reaction may rarely be found in cutaneous lymphoma,\textsuperscript{16} and some forms of cutaneous lymphomas, such as CD30\textsuperscript{+} anaplastic large-cell lymphoma and lymphomatoid papulosis, often regress spontaneously.\textsuperscript{20} The presence of a clone of lymphocytes is generally considered supportive of cutaneous lymphoma.\textsuperscript{17,21,22} Bakels et al\textsuperscript{17} 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 pleomorphic 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.\textsuperscript{21} Because of the high sensitivity of the present PCR techniques to detect gene rearrangements, the significance of the small clones of lymphocytes detected (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.\textsuperscript{21}

Nihal et al\textsuperscript{2} 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.\textsuperscript{3} 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 overgrowth found occasionally in CLH may link it to lymphoma.

Our cases share some clinical and histological features with a subset of CLH termed pseudolymphomatous folliculitis.\textsuperscript{23} Pseudolymphomatous folliculitis usually presents as a solitary nodule on the face with a tendency to self-regress after an incisional biopsy. Histopathologically, a dense lymphocytic infiltrate is present in the dermis and subcutaneous fat, often intermingled with many atypical lymphocytes. Characteristically, the walls of hair follicles are enlarged and irregularly deformed, with their epithelium blurred by lymphocytic infiltrates.\textsuperscript{23} Immunohistochemically, B cells or T cells may predominate, and all lesions show increased numbers of perifollicular T-cell–associated dendritic cells, often in aggregates that express S100 protein and CD1a.\textsuperscript{23} The results of TCR \(\gamma\)-chain and IgH gene rearrangement studies are negative in all cases.\textsuperscript{23} One of our cases (patient 1) demonstrated marked folliculotropism of small lymphocytes, negative TCR and IgH gene rearrangement study results, and spontaneous regression after an incisional biopsy, but the remaining 2 cases (1 of which also regressed spontaneously) demonstrated dominant lymphocytic clones.

In summary, CLH that appears on the face as a solitary facial nodule forms a spectrum in which the differentiation between pseudolymphoma and lymphoma may be difficult. The presence of a polymorphous infiltrate of T and B cells, plasma cells, eosinophils, and many histiocytes and dendritic cells; the lack of atypical lymphocytes and dominant lymphocytic clones; and spontaneous 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 therapeutic approach.

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