Granulomatous Slack Skin: Clonal Rearrangement of the T-Cell Receptor β Gene Is Evidence for the Lymphoproliferative Nature of a Cutaneous Elastolytic Disorder

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Granulomatous slack skin (GSS) is characterized by the slow evolution of bulky, erythematous skin folds that have a granulomatous histology, and show destruction of dermal elastic tissue. Several cases have been putatively associated with Hodgkin's disease, and histologic similarities to mycosis fungoides have also been noted. We examined tissue from 3 cases of GSS to determine whether the condition was inflammatory or lymphoproliferative in nature.

We found an abnormal, monomorphous T-helper cell immunophenotype, and in all 3 cases, clonal rearrangement of the T-cell receptor β gene. We conclude that GSS is an indolent cutaneous T-cell lymphoma associated with granulomatous inflammation that mediates elastolysis, producing a distinctive clinical appearance. J Invest Dermatol 89: 183-186, 1987

MATERIALS AND METHODS

Skin biopsies were obtained from 3 patients (A, B, and C) with clinically (Fig 1) and histologically (Fig 2) characteristic GSS (Table I). Tissue from Patient B was a kind gift of Drs. C. R. White and H. Platter, and details of this case are reported elsewhere [4]. Tissue from all 3 cases was examined following both routine histopathologic processing and plastic embedding using a technique that preserves cell surface antigens [6]. Avidin-biotin immunoperoxidase was used to determine the immunophenotype in plastic sections (Patients A, B, and C) and in frozen sections (Patients A and C). Electron microscopy was performed on material from Patients A and C.

Deoxyribonucleic acid (DNA) was extracted from lesional tissue of all 3 cases, and from a mononuclear cell fraction of peripheral blood of Patient A, and from unrelated placenta and thymus. Ten to 30 μg of DNA from each specimen was digested with the restriction enzymes EcoRI, BamHI, or HindIII, electrophoresed on a 0.8% agarose gel, transferred to nitrocellulose membranes, hybridized to a radiolabeled complementary DNA probe to the T-cell receptor β-chain gene, and analyzed by autoradiography [7].

RESULTS

Skin biopsies from all 3 patients showed a lymphohistiocytic infiltrate with numerous giant cells permeating the dermis and subcutis (Fig 2). Many of the giant cells showed numerous lymphocytes within their cytoplasm. Lymphocytic epidermotropism was present in some biopsies from all 3 patients. The majority of lymphoid cells in the infiltrate were moderately convoluted but not strikingly atypical, a finding confirmed by electron microscopy, which also confirmed lymphphagocytosis.

An elastic-van Gieson stain showed near absence of elastic tissue.
fibers in lesional skin in each case. Rare fragments of elastic fibers were observed within histiocytic giant cells. Biopsies of nonlesional skin from Patients A and C showed an entirely normal pattern of elastic fibers.

Immunophenotypic studies in all 3 cases demonstrated that the lymphoid infiltrate was composed almost entirely of T cells, in that 90% or more bound the Leu-4 antibody (Table II). Two cases were examined in greater detail; in both of these, nearly all of the T cells exhibited the helper cell (Leu-3a⁺) phenotype, but most cells lacked the Leu-8 and Leu-9 determinants. The giant cells in the infiltrate were apparently derived from mononuclear phagocytes, in that they showed membranous staining for the marker Leu-M5 and diffuse cytoplasmic positivity for the enzyme α-naphthyl acetate esterase, but lacked T- or B-lymphocytic determinants.

Clonal rearrangement of the T-cell receptor β gene was present in all 3 cases (Fig 3). Anomalous gene fragments were detected in lesional skin, but not in peripheral blood, from Patient A following digestion with the EcoRI. Gene rearrangements were not seen in lesional skin following digestion with HindIII, and results with BamHI were equivocal. Tissue from Patient B showed rearranged bands following EcoRI and HindIII digestion, with equivocal results following digestion with BamHI. Lesional skin

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Onset (years)</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F</td>
<td>14</td>
<td>Ten-year duration of progressive laxity of skin in axillae, flanks, groins, and hand</td>
</tr>
<tr>
<td>B</td>
<td>M</td>
<td>46</td>
<td>Progressively enlarging skin folds on flanks [4], since lost to follow-up</td>
</tr>
<tr>
<td>C</td>
<td>M</td>
<td>42</td>
<td>Enlarging, bulky plaques on arm and buttocks with sagging; progression despite attempted excision of arm lesion</td>
</tr>
</tbody>
</table>

Figure 1. Erythematous, pendulous skin folds in flexural areas characterize the clinical presentation of granulomatous slack skin (Patient A).

Figure 2. A, Patient A: A diffuse infiltrate containing numerous small lymphoid cells and multinucleate histiocytic giant cells is present in the dermis. B, Patient C: The epidermis is permeated by relatively small, convoluted lymphocytes with only slight spongiosis. C, Patient C: Only a few elastic fibers (arrow) remain within an infiltrated area (elastic-van Gieson stain). D, Patient C: The vast majority of the mononuclear infiltrate expresses the pan-T-cell antigen Leu-4, which is absent from the giant cells (arrow) (glycol methacrylate section, avidin-biotin peroxidase).
Table II. Immunophenotypic Features of the Lymphoid Infiltrate in Granulomatous Slack Skina

<table>
<thead>
<tr>
<th>Antiserab</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu-4 (pan-T-cell)</td>
<td>90%</td>
<td>90%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Leu-2 (suppressor T cell)</td>
<td>35%</td>
<td>ND</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Leu-3 (helper T cell)</td>
<td>90%</td>
<td>ND</td>
<td>&lt;95%</td>
</tr>
<tr>
<td>Leu-8 (majority T cell)</td>
<td>&lt;5%</td>
<td>ND</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Leu-9 (majority T cell)</td>
<td>&lt;30%</td>
<td>ND</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Leu-M1 (myelomonocytic cells, activated T cells, T-cell lymphoma, some carcinoma, Hodgkin's cells)</td>
<td>30–50%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Pan-B (B cells)</td>
<td>0%</td>
<td>0%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Ki-1 (Reed-Sternberg cells)</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

a Immunophenotypic data were derived from avidin-biotin-immunoperoxidase stained plastic sections of all 3 cases, and cryostat sections from Patient A and C.

b All antisera were purchased from Becton-Dickinson (Sunnyvale, California), with the exception of Pan-B and Ki-1 (Dako, Santa Barbara, California).

ND = not done.

from Patient C showed equivocal results with EcoRI, and rearranged bands following digestion with both HindIII and BamHI. The aberrant fragments that we detected, seen as nongermline bands on the Southern blot, imply clonal rearrangement of the T-cell receptor β gene in all 3 cases.

**DISCUSSION**

Granulomatous slack skin is a rare condition that produces loose, hanging masses of skin that show a granulomatous histology. It has been suggested that the disease is lymphoproliferative, autoimmune, or inflammatory in nature. We sought to determine whether GSS showed either an abnormal immunophenotype or clonality, features that are characteristic of lymphoproliferative disorders.

Our immunohistochemical studies showed that the lymphoid population in GSS is composed almost entirely of T cells, and may show an abnormal phenotype. In all 3 cases the lymphoid population expressed the pan-T-cell antigen Leu-4 and the 2 cases in which frozen section immunohistochemistry was performed showed both expression of Leu-3, the helper cell antigen, and decreased expression of the T-cell antigens Leu-8 and Leu-9. Leu-8 and Leu-9 are antigens expressed by the majority of normal peripheral blood T-cells. Decreased numbers of Leu-8-positive lymphocytes are frequently present in specimens of MF, but this finding may also be present in benign, inflammatory dermatoses [8,9]. A dominant Leu-3+ β-phenotype is not altogether unexpected in some benign dermatoses, as the Leu-3+ β-subset is thought to augment B-cell development into secretory plasma cells. Somewhat more specific to MF is diminished expression of Leu-9, which in one study [8] was only decreased to below 33% of the infiltrate in 1 of 29 specimens from a group of diverse patients with inflammatory dermatoses.

Genotypic studies using a probe to the T-cell receptor β chain and the Southern blot technique showed rearranged bands, indicating a major clonal population of lymphoid cells in each case. These bands are produced by the uniform rearrangement of T-cell receptor genes in a clone of lymphocytes, which uniformly alters the distance between the sites at which restriction enzymes cut. Clonality is a characteristic feature of T-cell lymphoma, [7,10–14], but is not always indicative of malignant behavior. Clonally rearranged T-cell receptor genes have been shown in some cases of angioimmunoblastic lymphadenopathy [15], lymphomatoid papulosis [16], and T-lymphocytosis [7], all conditions that, although regarded as lymphoproliferative in nature, lack one or more clinical or histologic features classically seen in malignant lymphoma. The finding of clonality in a T-cell infiltrate is presumed to be specific for lymphoproliferative disease by most investigators at this time [7,10–14]. Although a larger number of cases from a wider variety of nonneoplastic diseases needs to be studied to confirm that assumption, to date, nonlymphoproliferative disorders have not been identified as harboring clones of T cells that are numerous enough (2–5% of the infiltrate) to be detectable by the Southern blot method. Aside from our finding of clonal T-cell β receptor gene rearrangements, the inexorable progression of lesions in GSS, its monomorphic, uniform, immunophenotypically abnormal lymphoid population, the presence of epidermotropism, and resistance to anti-inflammatory therapy, all lead us to conclude that GSS is a slowly progressive lymphoma.

The destruction of elastic tissue in GSS, which results in the characteristic laxity of affected skin, appears to be mediated by a granulomatous infiltrate that includes histiocytic giant cells. Elastic fibers were of normal appearance in nonlesional skin, but were absent from the heavily infiltrated lesions, with only scant fibers remaining, some within giant cells.

Granulomatous slack skin has many features in common with MF. Both diseases are initially characterized by an epidermotropic infiltrate of convoluted lymphocytes, and detectable disease can remain limited to the skin for decades. Both diseases are characterized by clonal T-lymphocyte populations. Granulomatous slack skin, like MF, may exhibit a Leu-3+, 4+, 8+, 9+ immunophenotype. Granulomatous slack skin, however, does not appear to be merely MF associated with local elastic tissue destruction. Although only a few cases of GSS are reported to date, a clinical presentation different from that of MF appears to be characteristic. Patients with GSS are younger at onset, as a group, than patients with MF, show a marked tendency toward the development of flexural lesions, develop bulky lesions without strikingly atypical lymphoid cells, as are present in tumor stage lesions of MF, and do not have typical lesions of MF at other sites.

A few patients with MF have shown granulomatous inflammation associated with the lymphomatous infiltrate, a process that has been termed granulomatous MF. One patient with such lesions [17,18] survived for decades after developing tumor stage disease, suggesting that the granulomas may play a role in limiting the proliferation of neoplastic cells. Published photomicrographs...
of this case [17,18] and another case [19] of granulomatous MF show histiocytic giant cells with intracytoplasmic lymphocytes, as in our cases of GSS. If indeed the presence of granulomas is a limiting factor in the expansion of the T-cell clone in either disease, the mechanism may be phagocytosis and destruction of T cells by histiocytic giant cells. The occurrence of this mechanism in GSS is supported by our electron microscopic finding of lymphocyte fragments within giant cell cytoplasm.

Whether GSS is truly associated with Hodgkin’s disease, as the reported course of several patients would suggest, is less clear. Our cases of GSS clearly demonstrate a T-cell population in the skin lesions, both by immunophenotypic and genotypic studies. In only one case did the T-cell population express the Leu-M1 antigen, which is present on Hodgkin’s cells, myelomonocytic cells, activated nonneoplastic T-cells, and on the cells of some T-cell lymphomas [20]. The Hodgkin’s disease-associated antigen Ki-1 was not present on lymphoid cells in any of our cases.

Transformation of T-cell neoplasms to Hodgkin’s disease has been postulated [21], and might occur in GSS. Alternatively, specimens from GSS patients thought to represent Hodgkin’s disease could represent the evolution of the neoplastic T-cell population to a histologically more pleomorphic form as it involves lymph nodes. Pleomorphic T-cell neoplasms may be difficult to distinguish microscopically from Hodgkin’s disease, and neither immunophenotypic nor genotypic studies have been performed on such specimens from patients with GSS to date.

Our studies demonstrate that GSS is characterized by a clonal T-cell population that has an abnormal helper-cell phenotype. Based on these findings, we propose that GSS is an indolent T-cell lymphoma. The elastolysis that produces slack skin is apparently mediated by a granulomatous infiltrate that may also play a role in limiting the expansion of the T-cell population.

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REFERENCES


