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Rapid Communication

Clonal Rearrangements of Immunoglobulin Genes and Progression to B Cell Lymphoma in Cutaneous Lymphoid Hyperplasia

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Cutaneous lymphoid hyperplasia (CLH) is a disorder characterized by the development of one or more skin lesions containing dense lymphoid infiltrates that exhibit the histopathologic features of a benign, reactive process. Nevertheless, some cases have been associated with the subsequent development of clinically overt lymphomas. This suggests that monoclonal populations may exist in some cases of CLH and that these cases may represent a subset more likely to evolve into lymphoma. To determine if such a subset of CLH can be distinguished, Southern blot analysis of DNA was used to study the immunogenotypic features of lesions from 14 patients with clinical, histopathologic, and immunopathologic findings characteristic of CLH. Five cases exhibited detectable clonal rearrangements of immunoglobulin genes. Furthermore, one of these five cases evolved into overt diffuse large cell lymphoma of B cell lineage during a 2-year follow-up of recurrent disease at the original cutaneous site. The immunoglobulin gene rearrangements of this lymphoma were identical to those of the prior CLH lesion. There was no evidence of detectable t(14;18) chromosomal translocations or clonal rearrangements of the β gene of the T cell receptor in any case. It was concluded that CLH can be divided into two subsets based on the presence or absence of a clonal B cell population, and that overt lymphoma can arise from the former subset and contain the same B cell clone identified in the pre-existent CLH lesion. (Am J Pathol 1989, 135: 13–19)

Cutaneous lymphoid hyperplasia (CLH) is a disorder characterized by papules, nodules, or plaques in a solitary, regional, or disseminated distribution.[1-7] Light microscopical examination reveals a dense lymphoid infiltrate involving the dermis, usually separated from the overlying normal epidermis by a narrow uninvolved region known as the Grenz zone. The infiltrate may contain reactive lymphoid follicles but lacks morphologic evidence of lymphoma. Immunohistologic examination reveals a mixture of polytypic B cells, T cells of various subsets, macrophages, and dendritic cells.[3,8-11] Immunophenotypic features indicative of lymphoma, such as monotypic B cells, immunoglobulin-negative B cells, or anomalous patterns of T cell antigen expression,[12,13] are not present. Immunogenotypic analysis of β and γ T cell receptor genes has not revealed evidence of clonal T cells in two cases each of CLH or Jessner's lymphocytic infiltrate, another type of chronic, cutaneous lymphoid lesion.[14]

Patients with CLH are typically in good general health. There is no peripheral lymphadenopathy, hepatosplenomegaly, or peripheral blood abnormality. Nevertheless, patients with CLH may occasionally develop overt cutaneous lymphoma in the same cutaneous site.[1,2] Furthermore, studies of cutaneous B cell lymphomas reported that some patients had a prior diagnosis of CLH involving the same cutaneous site.[15,16] These findings suggested the possibility that some patients with CLH may harbor

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Table 1. *Cutaneous Lymphoid Hyperplasia: Clinical Features*

Patient	Sex	Age at biopsy*	Prior duration	Clinical course
1	F	73	<1 year	Nodules involving chest; topical steroid therapy; A^{+} (1.5 years)†
2	F	44	9 years	Nodules involving lower legs; intralesional steroid therapy; A^{++} (3 years)
3	M	32	2 years	Papules and plaques involving face, chest, back; topical steroid therapy; A^{+} (1.2 years)
4	M	38	2 years	Papules involving wrist, chest, buttock; no therapy; no follow-up
5	M	64	1 year	Nodules involving thigh, lower legs; excision of thigh lesion; A^{++} (1 year)
6	M	67	2 years	Plaques involving back; no therapy; A^{O} (2 years)
7	M	53	<1 year	Nodule involving cheek; excision therapy; A^{O} (4.5 years)
8	M	68	2 years	Nodules involving scalp; radiation therapy; A^{O} (3.3 years)
9	M	27	1 year	Papules involving upper arm; topical steroid therapy; A^{O} (3 years)
10	F	56	<1 year	Papules involving back, neck, forehead; no therapy; A^{O} (2 years)
11	F	65	5 years	Nodules involving scalp; topical steroid therapy; no follow-up
12	M	55	1 year	Nodule involving forehead; no therapy; no follow-up
13	F	NA	NA	Nodule involving ankle; no therapy; A^{O} (5 years)
14	M	50	9 years	Papules and nodules involving temple; intralesional and topical steroid therapy; developed large cell lymphoma at same site 2 years later (11 years after onset); surgical excision/ radiation therapy; A^{O} (2 years)

* Refers to age at time of biopsy for immunophenotypic/immunogenotypic analysis. Several patients also had prior lesional biopsies interpreted as CLH based on routine histopathologic examination.

† Refers to years since the time of biopsy for immunophenotypic/immunogenotypic analysis.

A^{++}, alive with progressive disease; A^{+}, alive with persistent disease; A^{O}, alive without disease.

occult clonal B cell populations that might eventually expand to form clinically overt lymphomas. To explore this hypothesis, we studied a series of well-documented CLH lesions for immunogenotypic evidence of B cell clonality. We determined that a subset of CLH lesions contain clonal B cells and also that such lesions may progress to B cell lymphoma containing the same clone that is present in the original CLH lesion.

Materials and Methods

Skin-biopsy specimens were obtained from 14 patients who satisfied the clinical, histopathologic, and immunohistologic criteria for CLH detailed below. The patients and specimens chosen for study were selected solely on the basis of there being frozen tissue available for study.

Clinical Criteria

None of the patients had a history of lymphoproliferative disorder proceding the development of their skin lesions. The clinical features of these patients are summarized in Table 1, and Patient 14 is described separately below as a case report. Of the other patients, none had fever, malaise, night sweats, weight loss, peripheral lymphadenopathy, or hepatosplenomegaly associated with their skin lesions. Complete blood counts (obtained in Patients 1, 2, 5, 6, 8, and 9), chest x-rays (obtained in Patients 1, 2, 5, 6, and 8), and abdominal–pelvic CT scans (obtained in Patients 1 and 5) revealed no evidence of internal involvement by lymphoma/leukemia.

Histopathologic Criteria

Hematoxylin and eosin-stained paraffin sections of lesional skin-biopsy specimens in each case showed patchy or diffuse dense lymphoid infiltrates within the dermis, with or without discernable lymphoid follicles. The overlying epidermis was uninvolved and was typically separated from the infiltrate by a thin zone of superficial dermis (the Grenz zone). Histologic features indicative of cutaneous lymphoma[1–7,13,15,16] were absent except in the second biopsy from Patient 14, which showed diffuse large cell lymphoma.

Immunohistologic Criteria

Frozen sections of a representative skin-biopsy specimen from Patients 1 through 13 and two specimens from Patient 14 were analyzed immunophenotypically. A three-stage tissue-staining technique was used involving monoclonal antibodies, biotin, and avidin.[17] Although the antibody panel varied from case to case, each was studied with a core panel including antibodies directed against immunoglobulin chains (mu, kappa, and lambda), pan B cell antigens, pan T cell antigens, cytotoxic/suppressor T

cell antigen (CD8), and helper T cell antigen (CD4). Most cases were also stained with antibodies reactive with dendritic reticulum cells, macrophages, and Langerhans cells. With the exception of the second specimen from Patient 14, all specimens contained a mixture of polytypic B cells, T cells, macrophages, and dendritic cells typical of CLH.[3,8–11] None of these CLH specimens exhibited the immunohistologic features indicative of B cell or T cell lymphoma.[12,13]

Immunogenotypic Analysis

The residua of the frozen tissue blocks used for immunohistologic analysis were processed for immunogenotypic analysis.[13,14,18] Digests of total-tissue DNA prepared with Bam HI or EcoRI restriction enzymes were analyzed according to the Southern blot hybridization procedure using ^{32}P-radiolabeled DNA hybridization probes for immunoglobulin genes (J_H, C_K, and C_λ), t(14;18) chromosomal translocations (PFL-1, PFL-2, and PFL-3), and the T cell receptor β gene ($J_{\beta 1}$ and $J_{\beta 2}$). The J_H probe consisted of a 6.5-kb Bam HI/EcoRI DNA fragment that contains the entire immunoglobulin heavy chain J region in addition to several kilobases of flanking DNA.[18] The C_K probe contained a 2.5-kb EcoRI DNA fragment spanning the entire kappa light chain constant region.[18] The combined C_λ probe consisted of a 3.5-kb EcoRI/Hind III DNA fragment and a 2.5-kb EcoRI/Hind III DNA fragment that detected all six nonallelic lambda light chain constant region genes.[18] The major breakpoint cluster probe PFL-3 was a DNA fragment from the t(14;18) chromosomal translocation breakpoint and lay adjacent to PFL-1.[19] The minor cluster probe PFL-2 was a chromosome 18-specific subclone (fragment A).[20] It detects most t(14;18) translocations that lie outside the major breakpoint region.[21] Probes for the beta T cell receptor gene consisted of a 550 base-pair Xbal fragment of DNA that detects rearrangements of the $J_{\beta 1}$ region and a 4.3-kb EcoRI fragment of DNA that detects rearrangements in the $J_{\beta 2}$ region.[14]

Case Report

Patient 14, a 54-year-old man, presented in 1977 with a 2.5 cm pruritic, erythematous, annular plaque involving the left preauricular skin. The lesion had been present for 2 years. The remainder of the physical examination was unremarkable except for a soft 1.0-cm left supraclavicular lymph node that regressed spontaneously shortly thereafter. The patient's medical history included only mild hypertension treated with hydrochlorothiazide. Light microscopical examination of a representative lesional skin biopsy revealed CLH (Figures 1 and 2). Chest roentgenogram, bone marrow aspiration and biopsy, erythrocyte sedimentation rate, general blood chemistry panel, urinalysis, and VDRL were all normal or negative. A complete blood count with differential cell count was also normal except for a mild lymphocytosis that resolved within a few weeks. The skin lesion was treated with several intralesional corticosteroid injections over a 9-year period. After each treatment, the lesion resolved clinically, only to recur within 1 or 2 months in the same site as papules, nodules, and plaques. Lesional biopsies were repeated in 1977, 1983, and 1984, showing features diagnostic of CLH. Immunophenotypic analysis of the 1984 biopsy also showed findings characteristic of CLH with T cells, polytypic B cells, and occasional reactive B cell follicles.

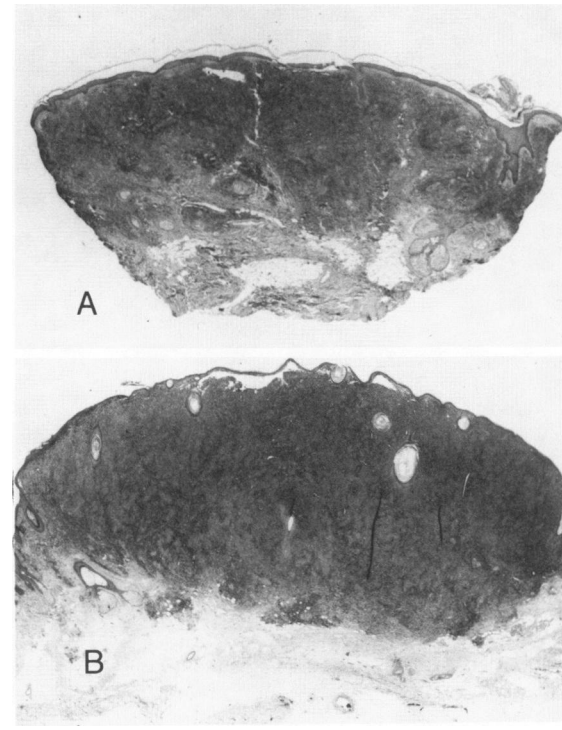

Figure 1. *Patient 14: Cutaneous lymphoid hyperplasia and cutaneous lymphoma.* **A:** *Low-power view of a punch biopsy of the cutaneous lymphoid hyperplasia lesion shows a diffuse dermal infiltrate with separation from the overlying normal epidermis by an uninvolved superficial dermal Grenz zone. The infiltrate is top-heavy and does not extend deeper than the reticular dermis (H&E, ×50).* **B:** *Low-power view of an excisional biopsy of the cutaneous lymphoma lesion shows a much more massive, diffuse dermal infiltrate with focal impingement upon the overlying epidermis. The infiltrate is not top-heavy and it extends through the reticular dermis to the subcutis (H&E, ×25).*

Because the recurrent skin lesions gradually increased in size, another biopsy was peformed in 1986 that showed diffuse large cell lymphoma (Figures 1 and 2). The lesion was surgically excised and the prior biopsy diagnosis was confirmed. Immunophenotypic studies of both these specimens revealed from 33% to 50% abnor-

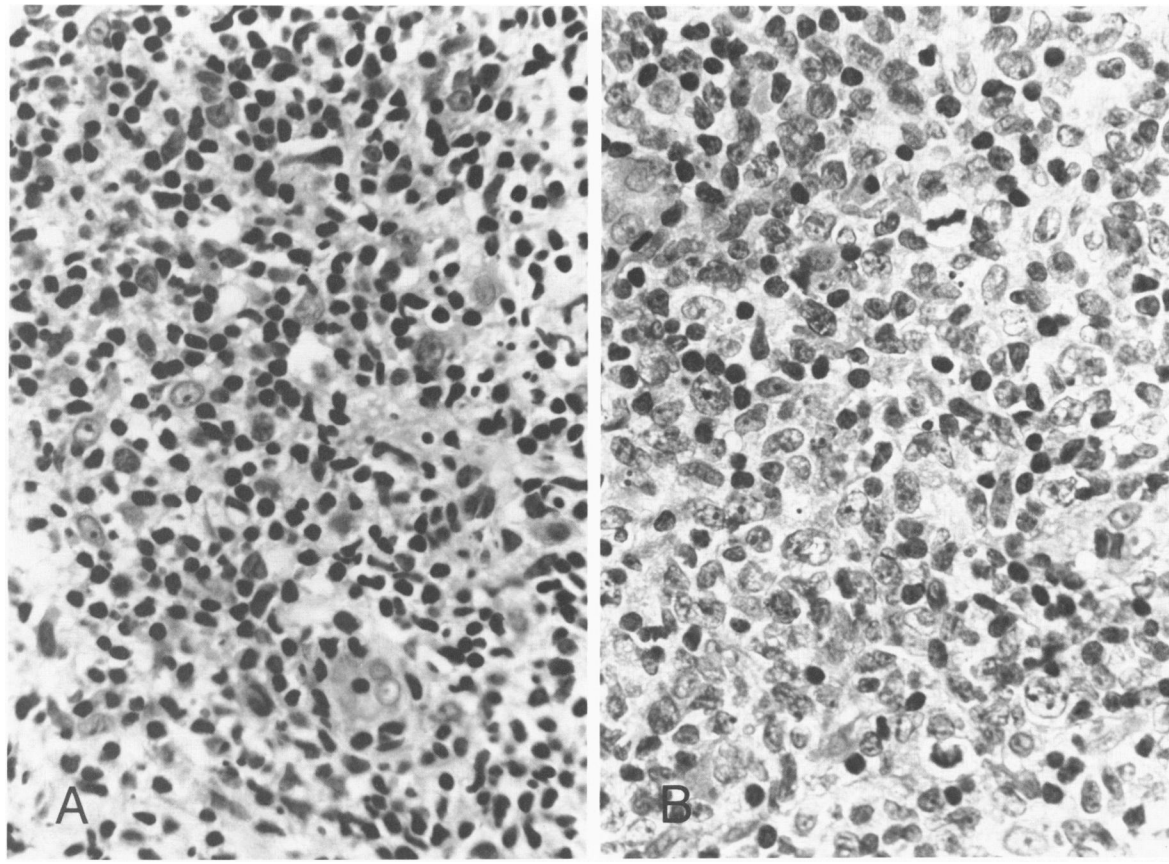

Figure 2. *Patient 14: Cutaneous lymphoid hyperplasia and cutaneous lymphoma.* **A:** *High-power view of the same cutaneous lymphoid hyperplasia specimen shown in Figure 1A shows that most cells are small mature lymphocytes with scattered medium and large lymphoid cells admixed. Immunophenotyping was consistent with lymphoid hyperplasia (H&E, ×500).* **B:** *High-power view of the same cutaneous lymphoma specimen shown in Figure 1B shows that most cells are relatively monomorphous large lymphoid cells with only scattered small mature lymphocytes admixed. Immunophenotyping was consistent with Ig^- B cell lymphoma (H&E, ×500).*

mal cells that expressed multiple B cell antigens but lacked immunoglobulin heavy chains (μ, δ, γ, and α) and light chains (κ and λ). A small percentage of polytypic (mixed κ^+ and λ^+) B cells were also present, as well as occasional reactive B cell follicles. The remainder of the infiltrate was composed predominantly of T cells that were normal immunophenotypically. The patient underwent a lymphoma staging work-up that included a complete physical examination, CT scans of the chest, abdomen, and pelvis, lymphangiogram, chest roentgenogram, bone marrow biopsy, and hemogram with differential count; all were negative or normal. The patient was classified as Stage I-e-A diffuse large cell lymphoma of Ig^-B cell lineage. The left preauricular surgical excision site was treated with orthovoltage radiation to a total dose of 4000 rad. There has been no clinical evidence of recurrence during a follow-up period of 2 years.

Results

Southern blot analysis of lesional DNA was performed for each of the 14 CLH patients using DNA probes for immunoglobulin heavy chain genes (J_H), immunoglobulin light chain genes (C_κ and C_λ), t(14;18) chromosomal translocations (PFL-1, PFL-2, and PFL-3), and the T cell receptor β gene ($J_{\beta 1}$ and $J_{\beta 2}$). The results are summarized in Table 2.

DNA hybridization studies using the J_H probe demonstrated that five patients (7, 8, 10, 11, and 14) had either one or two rearranged, nongerm-line bands detectable in analyses with the Bam HI restriction enzyme. It is interesting to note that, although the 14 patients were evenly divided into those with and without head and neck involvement, the five patients with clonal B cells all had head or head and neck lesions. Representative immunogenotypic findings are shown in Figure 3. Patient 11 also had one rearranged band found in an analysis using the J_H probe and EcoRI restriction enzyme. In studies using the C_κ probe, Patients 10 and 14 had one or two rearranged bands detectable in analyses with Bam HI enzyme. Patients 10 and 11 had one or two rearranged bands detectable in analyses using the C_λ probe and EcoRI enzyme. The rearranged bands detected with J_H and C_κ probes in DNA analyses of Patient 14's initial CLH lesion were

identical to those found 2 years later in a large cell lymphoma lesion obtained from the same cutaneous site (Figure 3).

None of the 14 patients had detectable t(14;18) chromosomal translocations in lesional DNA in analyses using probes for either the major (PFL-1 and PFL-3) or minor (PFL-2) breakpoint clusters in analyses with Bam HI enzyme (PFL-1 and PFL-2) or EcoRI enzyme (PFL-2 and PFL-3). Similarly, no detectable clonal rearrangements of the T cell receptor β gene were found in analyses using a combined $J_{\beta 1}/J_{\beta 2}$ probe and Bam HI or EcoRI enzymes.

Discussion

The current DNA hybridization studies indicate that CLH, defined by well-established clinicopathologic and immunophenotypic criteria,[1-11] is divisible into two subsets based on the presence or absence of detectable clonal B cells. These clonal populations presumably are only a small percentage of the total lymphoid infiltrate because immunophenotypic analysis revealed no evidence of abnormal B cells in any of the CLH lesions in this series.[12,13] This interpretation is also consistent with the relatively faint intensity of rearranged bands seen in the Southern blot autoradiograms.

The immunogenotypic findings in lesions from Patients 7, 8, and 10 conformed to the accepted hierarchy of immunoglobulin gene rearrangements during B cell differentiation: heavy chain followed first by kappa chain and then by lambda chain.[23] Deletion of rearranged kappa gene alleles probably accounted for the lack of detectable clonal C_κ bands in analyses of the lesion from Patient 11. The absence of clonal beta T cell receptor gene rearrangements in these lesions suggests that clonal T cell populations are not a part of this disease, and that none of the clonal B cell populations detected contained beta T cell receptor rearrangements seen in occasional cases of leukemias and lymphomas.[24,25]

Results similar to our own have been reported in a study of ocular lymphoid infiltrates in which three of five cases with polytypic B cells by immunophenotypic analysis contained clonal B cells by immunogenotypic analysis.[22] Also, clonal immunoglobulin gene rearrangements have been described in the benign lymphoepithelial lesions characteristic of Sjogren's disease.[26] The absence of detectable clonal T cells in the current CLH cases also parallels the results of immunogenotypic studies of ocular lymphoid infiltrates in which there was no evidence of clonal T cells regardless of whether clonal B cells were detected.[22,23] Together these findings suggest that occult clonal B cell, but not T cell, populations may be a relatively common finding among extranodal lymphoid hyperplasias containing B cells that are polytypic by immunophenotypic criteria.

Table 2. *Summary of Southern Blot Results for Those Cases of CLH that Showed Clonal Immunoglobulin Gene Rearrangements*

	Immunoglobulin Genes*			
	Heavy Chain		Light Chain	
Patient*	J_H BamHI	J_H EcoRI	C_K BamHI	C_λ EcoRI
7	R (1)	G	G	G
8	R (1)	G	G	G
10	R (1)	G	R (2)	R (1)
11	R (2)	R (1)	G	R (2)
14a	R (2)	G	R (1)	G
14b	R (2)	G	R (1)	G

* Patients 1 through 6, 9, 12, and 13 showed only germline configurations of immunoglobulin genes. None of the 14 patients showed detectable clonal rearrangements of the T cell receptor β gene using a combined $J_{\beta 1}/J_{\beta 2}$ probe, or t(14; 18) chromosomal translocations using probes PFL-1, PFL-2, or PFL-3.

R, rearranged band; G, germ line; numbers in parentheses, numbers of rearranged bands.

The PFL-1, PFL-2, and PFL-3 probes used in this study detect t(14;18) chromosomal translocations in approximately 95% of follicular lymphomas.[19-21] The inability to detect such translocations in the current CLH lesions suggests that any overt lymphomas developing in these patients would probably be of the nonfollicular variety. This, in fact, occurred in Patient 14 whose second biopsy contained a diffuse large lymphoma of B cell lineage. J_H and C_κ clonal gene rearrangements were detected in Southern blots; however, the lack of immunoglobulin heavy and light chain staining of the tumor cells in immunohistologic analyses suggests that their immunoglobulin chains were not expressed at all or that they were expressed at an undetectably low level.

At present it is unknown if "clonal CLH" is an intermediate step between CLH and overt cutaneous B cell lymphoma, or if it can arise *de novo* as do these other entities.[1-11,13,15,27-29] Whichever is the case, the clinical course of Patient 14 indicates that once clonal CLH becomes established, it has the potential to progress to lymphoma. Furthermore, the identity between the clonal B cells in this patient's initial CLH lesion and his subsequent lymphoma lesion suggests a direct link between clonal CLH and lymphoma in this case. That is, the clinicopathologically recognizable lymphoma arose from proliferation of the same B cell clone that was present, albeit histopathologically and immunophenotypically unapparent, in the preceding clonal CLH lesion. A direct link was also supported by the immunophenotypic findings that showed that the lymphomatous lesion still contained the vestiges of typical CLH manifested as a minor population of polytypic B cells, reactive B cell follicles, and T cells admixed with the Ig^- B-lineage tumor cells.

In this context, it is important to recognize that, among the so-called benign monoclonal gammopathies, there is a slow, steady progression to various B cell lymphoproliferative disorders at the rate of approximately 2% per

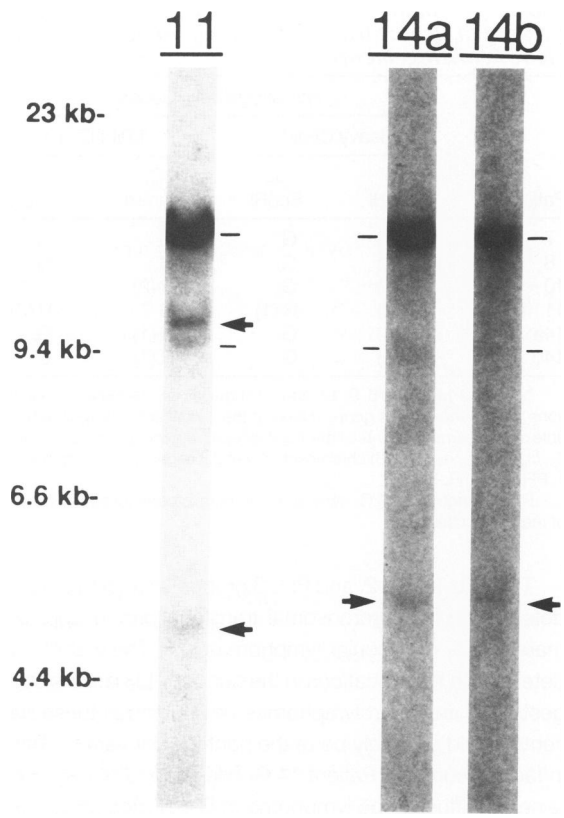

Figure 3. *Southern blot analysis of representative cases. Results are shown from cases 11, and 14, (specimen a, diagnosed as lymphoid hyperplasia and specimen b, diagnosed as diffuse large cell lymphoma). In each example, DNA was digested with Bam HI restriction enzyme and hybridized with a probe for the joining region of the immunoglobulin heavy chain gene. The relative position of DNA fragment size markers is shown at the left. Unrearranged germline bands are indicated by dashes and bands indicating clonal rearrangements by arrows.*

year.[30] Similarly, clinically benign clonal cutaneous T cell disorders such as lymphomatoid papulosis,[31] pityriasis lichenoides,[14] pagetoid reticulosis,[32] granulomatous slack skin,[33] and regressing atypical histiocytosis[34] are all associated with eventual cutaneous T cell lymphomas in a variable percentage of cases.

In a way analogous to CLH, lymphoid infiltrates involving the ocular adnexae can be divided into monoclonal and polyclonal subsets based on the results of immunophenotypic or immunogenotypic analysis of lesional B cells.[16,22,35,36] Patients with ocular lymphoid infiltrates often have an indolent clinical course regardless of whether their lesions are monoclonal or polyclonal by immunophenotypic criteria,[22,35] and when recognizable lymphomas arise in such lesions they are typically low-grade B cell tumors such as small lymphocytic lymphomas.[16,22,35,36] In contrast, B cell lymphomas presenting with cutaneous involvement are often diffuse large-cell lymphomas,[27-29] such as the one diagnosed in Patient 14. These tumors are either intermediate- or high-grade lesions in the working formulation,[37] often also involve extracutaneous sites,[27-29] and can be fatal despite therapy.[27-29] Therefore, the identification of clonality within lymphoid infiltrates may prove to have greater significance for cutaneous lesions than for ocular lesions.

It is tempting to speculate that the presence or absence of B cell clonality within CLH lesions defines subsets of CLH patients at correspondingly high or low risk for the subsequent development of overt cutaneous B cell lymphoma. The clinical course of Patient 14 is consistent with this hypothesis but does not prove it, especially as Patient 10, who also harbored a clonal B cell population, exhibited clinical resolution of his lesions without therapy. Alternatively, it is possible that the presence of any CLH lesion may prove to be the manifestation of an underlying lymphoproliferative diathesis, which itself places the individual at increased risk for the development of lymphoma independent of the clonality of the original CLH lesion. Thorough clinicopathologic, immunophenotypic, and immunogenotypic characterization of CLH lesions in conjunction with long-term follow-up is required to resolve this issue. In the interim, the knowledge that patients with clonal CLH may develop overt cutaneous B cell lymphomas should prompt physicians to monitor them carefully.

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