Differentiation between actinic reticuloid and cutaneous T cell lymphoma by T cell receptor γ gene rearrangement analysis and immunophenotyping

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Abstract

Aims—Differentiation between actinic reticuloid and cutaneous T cell lymphoma can be extremely difficult. Demonstration of clonal T cell receptor (TCR) gene rearrangements has been suggested as a potential diagnostic criterion, but the results obtained thus far have been conflicting. This study investigated whether TCR γ gene rearrangement analysis, using polymerase chain reaction (PCR) in combination with denaturing gradient gel electrophoresis (DGGE) and immunohistochemistry, can serve as a diagnostic criterion.

Methods—PCR/DGGE was performed on skin, peripheral blood mononuclear cells, and/or lymph nodes of seven patients with actinic reticuloid, 11 patients with Sézary syndrome, and 15 patients with a benign form of erythroderma. The results of PCR/DGGE and Southern blot analysis of TCR β gene rearrangements were compared. In addition, CD4:CD8 ratios in skin and peripheral blood samples were investigated.

Results—Clonal T cell populations were detected in 19 of 21 samples obtained from patients with Sézary syndrome but were not detected in any of the 12 samples from patients with actinic reticuloid. Clonal T cells were detected in the peripheral blood of only one of 15 patients with a benign form of erythroderma. PCR/DGGE and Southern blot analysis gave concordant results in 28 of 29 samples. Immunophenotypic analysis demonstrated increased proportions of CD8⁺ T cells in skin (seven of seven cases) and peripheral blood (four of seven cases) of patients with actinic reticuloid.

Conclusion—The results of this study demonstrate that gene rearrangement analysis, in combination with immunohistochemistry, may be an important adjunct in differentiating between actinic reticuloid and cutaneous T cell lymphoma. In patients suspected of having actinic reticuloid, application of both techniques is recommended.

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Actinic reticuloid is a severe, chronic photosensitivity disorder, first described by Ive.¹ The clinical picture is characterised by an eczematous, pruritic eruption, predominantly present on light exposed areas of skin. Frequently, lesions spread to covered areas, leading to erythroderma. This erythrodermic variant of actinic reticuloid can resemble Sézary syndrome, a type of cutaneous T cell lymphoma. Apart from erythroderma, pruritus, lymphadenopathy, and the presence of atypical lymphocytes in the peripheral blood, patients with the erythrodermic form of actinic reticuloid and patients with Sézary syndrome may also have alopecia, palmoplantar hyperkeratosis, or onychodystrophy.^{2,3}

Histologically, actinic reticuloid is characterised by the presence of extensive dermal infiltrates of medium sized lymphoid cells with cerebriform or convoluted nuclei. These cells show epidermotropism and sometimes even form Pautrier-like microabscesses.^{1,3} These cellular and histological features are also characteristic for mycosis fungoides, the most common variant of cutaneous T cell lymphoma, and Sézary syndrome.

Because of the clinical and histological similarities, it can be difficult to distinguish actinic reticuloid from mycosis fungoides and Sézary syndrome. Previous studies suggested that immunophenotyping and morphometric analysis (nuclear contour indexing) of atypical lymphocytes might provide additional criteria to differentiate between actinic reticuloid and cutaneous T cell lymphoma.^{4,5} It is not known whether demonstration of clonal T cell populations in skin or peripheral blood can also serve as a useful differential diagnostic criterion. Clonal T cell receptor (TCR) gene rearrangements have been found in almost 100% of patients with unequivocal cutaneous T cell lymphomas,⁶⁻¹¹ but studies for the presence of clonal T cells in patients with actinic reticuloid have been few and the results have been conflicting.^{8,12,13}

Therefore, we investigated the presence of clonal T cell populations in skin, lymph node and/or peripheral blood samples of patients with actinic reticuloid, Sézary syndrome, or a benign form of erythroderma, by means of polymerase chain reaction (PCR) amplification of the TCR γ gene in combination with denaturing gradient gel electrophoresis (DGGE). In addition, immunophenotypic analysis was performed on skin and peripheral blood samples to assess the proportions of CD4⁺ and CD8⁺ T cells.

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Table 1 Cumulative data from 33 patients with actinic reticuloid, Sézary's syndrome, or benign forms of erythroderma

Patient/ sex/age*	Tissue	Leucocytes† (×10 ⁹ /l)	Lymphocytes† (%)	CD4/CD8 %† (ratio)	PCR/DGGE		
					V γ I	V γ II	TCR β SBA
<i>Actinic reticuloid</i>							
1/M/49	Skin	15	33	13/40 (0.3)	P	P	ND
	Lymph node				P	P	ND
2/M/69	Skin	4	20	31/67 (0.5)	P	P	ND
3/M/75	Skin	14	36	28/31 (0.9)	P	P	ND
	Skin				P	P	ND
	PBMC				P	P	P
4/M/81	Skin	10	20	46/28 (1.6)	P	P	ND
5/M/67	Skin	11, 2	20	50/32 (1.5)	P	P	ND
	Skin				P	P	ND
	PBMC				P	P	ND
6/M/67	Skin	7.7	20	47/44 (1.0)	P	P	ND
7/M/56	Skin	11	10	36/24 (1.5)	P	P	ND
<i>Sézary syndrome</i>							
8/M/36	PBMC	18.0	75	85/1 (85)	C	P	C
9/F/82	PBMC	8.4	29	82/6 (13.6)	C	P	C
10/M/58	PBMC (1981)	16.8	76	92/5 (18.4)	C	P	C
	PBMC (1984)	ND	ND	ND	C	P	C
11/F/67	PBMC	28	83	95/3 (31.6)	C	P	C
12/M/63	PBMC	8.2	30	70/7 (10)	C	P	C
	Skin				P	P	ND
13/F/64	PBMC	12.8	47	92/1 (92)	C	P	C
14/M/71	PBMC (1981)	8.5	61	93/3 (31)	C	P	P
	PBMC (1985)	6.6	30	ND	C	P	C
	Skin				C	P	ND
	Skin				C	P	ND
	Lymph node				C	P	ND
15/M/50	PBMC	75	80	85/2 (42.5)	C	P	C
16/M/76	PBMC (1983)	9.7	20	32/37 (0.9)	P	P	P
	PBMC (1984)	5.3	18	ND	C	P	C
	Skin				C	P	ND
17/F/64	PBMC	17.2	48	80/2 (40)	C	P	C
18/F/60	PBMC	23.1	58	96/4 (23)	C	P	ND
	Skin				C	P	ND
	Skin				C	P	ND
<i>Benign erythroderma</i>							
19	PBMC	8, 4	23	33/8	C	P	C
20–33	PBMC	5.6–10.9	12–56	(1.45–11)	P	P	P

*Age at time of diagnosis; †data presented refer to peripheral blood.

PCR/DGGE, Polymerase chain reaction/denaturing gradient gel electrophoresis; TCR β SBA, T cell receptor β gene rearrangement analysis by Southern blotting; PBMC, peripheral blood mononuclear cells; P, polyclonal T cell population; C, clonal T cell population; ND, not done.

Methods

PATIENTS AND TISSUES

Thirty three patients were studied: seven with actinic reticuloid, 11 with Sézary syndrome, and 15 patients with a benign form of erythroderma. All seven patients with actinic reticuloid had: (1) a chronic photosensitivity reaction confirmed by phototests and/or photopatch tests⁴; (2) characteristic skin lesions including erythroderma (five patients) or extensive lesions on both light exposed and non-light exposed skin areas (two patients); and (3) histological features suggesting a cutaneous T cell lymphoma. Histological examination revealed perivascular to band-like infiltrates in the upper dermis containing a high proportion of atypical lymphocytes with medium sized, cerebriform nuclei, similar to those observed in mycosis fungoides and Sézary syndrome. In some samples, epidermotropism and Pautrier-like microabscesses were seen. During a follow up period of three to 11 years (median, seven years), none of the patients with actinic reticuloid developed a malignant lymphoproliferative disease, illustrating the benign character of this disorder. Altogether, nine skin biopsies, two peripheral blood samples, and one lymph node with the histological picture of dermatopathic lymphadenopathy were examined.

All 11 patients with Sézary syndrome had a pruritic erythroderma, lymphadenopathy, and atypical lymphoid cells (Sézary cells) in the peripheral blood. Criteria for peripheral blood involvement were: (1) the presence of more than 15% circulating Sézary cells, as defined by morphometric criteria¹⁴; and (2) an expanded CD4⁺ T cell population resulting in a highly elevated CD4:CD8 ratio (> 10)¹⁴ (see table 1). Ten Sézary syndrome patients died of their disease two to nine years (median, four years) after diagnosis and one patient is still alive with active disease 22 months after diagnosis. Fourteen peripheral blood samples from 11 patients, six skin biopsies from four patients, and one lymph node were examined.

In the 15 patients with a benign form of erythroderma, only peripheral blood samples were tested. None of these peripheral blood samples met the morphometric and immunophenotypic criteria for Sézary syndrome, as described above.¹⁴ This group comprised 11 patients with an erythroderma on the basis of chronic dermatitis, three patients with erythrodermic psoriasis, and one patient with a generalised drug eruption. None of these 15 patients developed evidence of Sézary syndrome or other types of a cutaneous lymphoma during follow up of seven to 15 years (median, 12 years).

Figure 1 A representative dilution experiment demonstrating the sensitivity of polymerase chain reaction/denaturing gradient gel electrophoresis (PCR/DGGE) analysis. Graded numbers of HSB-2, a monoclonal T cell line, which is rearranged for the V_{γ_9} (V_{γ} II family) gene segment, were mixed with peripheral blood mononuclear cells of a healthy donor, providing a polyclonal background. DNA was isolated and PCR was performed with the V_{γ_9} and $J_{\gamma_{1,2}}$ primer set. Numbers given are the percentages of HSB-2 cells, and the arrow indicates the rearranged band of the HSB-2 cell line in a diffuse background smear resulting from polyclonal rearrangements in the peripheral blood mononuclear cells.

GENE REARRANGEMENT ANALYSIS

PCR mediated DGGE was used to analyse TCR γ gene rearrangements as described previously.¹⁵ Briefly, DNA was extracted from representative samples of skin, lymph node, and/or peripheral blood mononuclear cells by

column isolation (Qiagen; GmbH, Hilden, Germany). Tissue sections (5 μ m) were cut before and after the sections used for DNA extraction, to check whether the biopsy specimens contained sufficient and characteristic lymphoid infiltrate. Approximately 0.5–1 μ g genomic DNA was used to perform PCR amplification of the TCR γ V–J gene segments. A consensus primer recognising $V_{\gamma_{1-8}}$ (V_{γ} I family) gene segments, a primer specific for the V_{γ_9} (V_{γ} II family) gene segment, and a consensus primer recognising J_{γ_1} and J_{γ_2} gene segments were used.^{16,17} The amplification products were fractionated by DGGE, a technique based on separation of double stranded DNA fragments according to their nucleotide sequence rather than size.¹⁸ If a significant proportion of PCR products have identical nucleotide sequence and size, a clear band can be seen in a polyclonal background smear after staining with ethidium bromide and illuminating with ultraviolet light.

In several dilution experiments, we tested the $V_{\gamma_{1-8}}$ primer on the cutaneous T cell lymphoma derived T cell line, HUT-78, which has rearranged one allele for the V_{γ_5} gene; in addition, we tested the V_{γ_9} primer on the HSB-2 cell line, which contains a V_{γ_9} gene rearrangement. For both primers we were able to detect DNA from $\geq 1\%$ clonal T cells diluted into polyclonal peripheral blood mononuclear cells of a healthy donor (fig 1).¹⁵

The results of PCR/DGGE on 13 samples of 10 patients with Sézary syndrome and 15 patients with a benign form of erythroderma from the present study, and another 63 samples obtained from patients with cutaneous T cell lymphoma or a benign dermatosis, were compared with the results of Southern blot analysis, which in our hands has a sensitivity of 1–2.5%.^{19–21} Concordant results were found in 89 of 91 samples. Clonality was detected by PCR/DGGE but not by Southern blot analysis in only two samples.²⁰ This suggests that PCR/DGGE is useful for demonstrating clonality in cases where insufficient DNA is available to perform Southern blot analysis.

IMMUNOPHENOTYPING

To determine the CD4:CD8 ratio in peripheral blood, the mononuclear cell fraction obtained by Ficoll-Isopaque density centrifugation was incubated with anti-CD4 (fluorescein isothiocyanate labelled) and anti-CD8 (phycoerythrin labelled) monoclonal antibodies (Becton Dickinson, Mountain View, California, USA), and cells were quantified using flow cytometry. Immunophenotyping using monoclonal antibodies against CD3, CD4, and CD8 was performed on frozen sections from the same (or concurrent) biopsies used for genotypic analysis.²²

Results

The results of gene rearrangement analysis obtained by PCR/DGGE of the TCR γ gene, Southern blot analysis of the TCR β gene, and immunophenotyping are summarised in table 1. No clonal bands were detected in any of the 12 samples obtained from the patients with actinic

Figure 2 Representative polymerase chain reaction/denaturing gradient gel electrophoresis (PCR/DGGE) analysis for T cell receptor γ gene rearrangements of DNA obtained from patients described in this study. Lanes 1–6 show discrete bands in a polyclonal background smear indicating clonal T cell populations in the peripheral blood of five patients with Sézary syndrome. Lanes 3 and 4 contain amplification products of the first and second blood samples, respectively, from the same patient (case 10), obtained with a three year interval. Lanes 7–15 show diffuse smears representing polyclonal T cell populations in skin (lanes 7–13) and peripheral blood (lanes 14 and 15) of seven patients with actinic reticuloid. In lane 15, a faint band can be seen that does not represent a band resulting from a clonal T cell population, but represents a well known artefact.¹⁶ These faint bands can often be seen in different test samples and always migrate to the same position in the gel and, therefore, do not interfere with the interpretation of the results.

reticuloid. In these samples, the denaturing gradient gels only showed diffuse smears representing polyclonal reactive lymphocytes (fig 2).

All 11 patients with Sézary syndrome showed a clonal T cell population in the peripheral blood (fig 2). In addition, clonality was detected in five of the six skin samples and in the lymph node. In the group of patients with a benign form of erythroderma, a clonal T cell population was found, both by PCR/DGGE and Southern blot analysis, in the peripheral blood of one of 15 patients. Altogether, comparison of PCR/DGGE and Southern blot analysis showed concordant results in 28 of 29 samples (table 1). In only one patient (with Sézary syndrome; case 14), was clonality detected by PCR/DGGE but not by Southern blot analysis.

All clonal rearrangements found by PCR/DGGE were rearranged for the TCR V γ I family and none were rearranged for the TCR V γ II family. In four patients showing clonality in different samples, identical bands were observed. Lanes 3 and 4 in fig 2 show amplification products of two different blood samples from one patient (case 10) obtained with a three year interval.

Immunophenotyping of skin lesions from patients with actinic reticuloid demonstrated a predominance of CD8⁺ T cells in five of seven biopsies, whereas the two remaining cases revealed equal numbers of CD4⁺ and CD8⁺ cells. In contrast, skin biopsies from all patients

with Sézary syndrome showed a predominance of CD4⁺ T cells. Immunophenotyping of peripheral blood lymphocytes in patients with actinic reticuloid demonstrated decreased or even inverted CD4:CD8 ratios in four of seven cases (table 1). In contrast, an increase in the proportion of CD4⁺ T cells resulting in greatly increased CD4:CD8 ratios was observed in 10 of 11 peripheral blood samples from patients with Sézary syndrome.

Discussion

Because of the clinical and histological similarities between actinic reticuloid and cutaneous T cell lymphoma, in particular, the presence of atypical T cells with cerebriform nuclei in the skin and peripheral blood, differentiating between these two diseases can be extremely difficult.^{3 4 23} Moreover, the development of malignant (non-cutaneous) lymphoma in the course of actinic reticuloid has been reported.^{24–26} Whereas cutaneous T cell lymphoma is characterised by a clonal proliferation of CD3⁺, CD4⁺, CD4RO⁺, CD8[–] helper T cells, actinic reticuloid and other photosensitivity reactions often demonstrate increased CD8⁺ populations, both in the skin and peripheral blood.⁴ Consequently, the presence of a predominant CD8⁺ T cell population in skin infiltrates or demonstration of an increased proportion of CD8⁺ T cells and a reversed CD4:CD8 ratio in the peripheral blood have been considered as useful additional criteria favouring a diagnosis of actinic reticuloid rather than cutaneous T cell lymphoma. However, some patients with actinic reticuloid may demonstrate predominant CD4⁺ T cell skin infiltrates,^{3–5} and three of seven actinic reticuloid patients in the present study showed normal CD4:CD8 ratios in the peripheral blood. These observations indicate that immunophenotypic criteria cannot be relied on in all cases.

Recent studies demonstrated that morphometric analysis (nuclear contour indexing) of circulating atypical T cells may also contribute to the differentiation between actinic reticuloid and Sézary syndrome.⁵

In the present study we investigated whether demonstration of clonal TCR rearrangements can be used as an additional criterion to differentiate between actinic reticuloid and cutaneous T cell lymphoma. Because only small skin samples, which contained insufficient DNA to perform Southern blot analysis, were available from most patients with actinic reticuloid, the PCR/DGGE technique was used. Dilution experiments performed with both primer sets demonstrated that, in our hands, this technique can detect ~1% clonal T cells in peripheral blood mononuclear cells of a healthy donor.¹⁵ Using this technique, no clonal T cell populations could be detected in 12 skin, lymph node, and peripheral blood samples from seven patients with actinic reticuloid. In contrast, using PCR/DGGE, clonal TCR gene rearrangements were found in 19 of 21 samples from patients with Sézary syndrome.

Previous studies in cutaneous infiltrates of patients with actinic reticuloid showed

conflicting results. Altogether, clonal T cell populations were detected in two of 10 patients.^{8 12 13} However, follow up data of these two patients were not presented.

The failure to detect clonal T cells in our patients with actinic reticuloid could be caused by: (1) low numbers of clonal T cells, below the level of detection; or (2) the presence of clonal T cells that are not detected with either the $V_{\gamma 1-8}$ or the $V_{\gamma 9}$ primer because their TCR γ gene rearrangements use the $V_{\gamma 10}$ or $V_{\gamma 11}$ gene segments. However, rearrangements using these variable gene segments are very rare and T cell populations expressing a $V_{\gamma 10}$ or $V_{\gamma 11}$ chain at the cell surface have never been reported.²⁷ Therefore, the presence of clonal TCR γ gene rearrangements using $V_{\gamma 10}$ and $V_{\gamma 11}$ gene segments in these cases of actinic reticuloid is considered to be most unlikely.

In conclusion, our study demonstrates that gene rearrangement analysis can be considered as an important adjunct in differentiating between actinic reticuloid and cutaneous T cell lymphoma. In patients suspected of having actinic reticuloid, both gene rearrangement analysis and immunophenotyping should be performed.

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