T-Cell Clonality in Pityriasis Lichenoides et Varioliformis Acuta

A Heteroduplex Analysis of 20 Cases

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Background: Cutaneous lesions of pityriasis lichenoides et varioliformis acuta (PLEVA), a T cell–mediated cutaneous inflammatory condition, are clinically similar to lymphomatoid papulosis (LyP), leading some authors to hypothesize that they are part of the same spectrum of lymphoproliferative disorders, although reports of the development of cutaneous lymphoma in patients with PLEVA are not as frequent as they are for patients with LyP. Furthermore, unlike in cases of LyP, no systematic search for a dominant T-cell clone has been carried out in cases of PLEVA, whereas clones have been detected in a few cases of PLEVA using mainly Southern blot analysis.

Objective: To investigate T-cell clonality in a series of archival PLEVA lesions.

Tissues: Archival paraffin-embedded biopsy specimens from 20 clinically and pathologically typical cases of PLEVA were selected.

Main Outcome Measure: Identification of a dominant T-cell clone by polymerase chain reaction and heteroduplex analysis targeted on the TCRγ gene. Peripheral blood mononuclear cells (PBMCs) and Jurkat cells were used as negative and positive controls. Serial dilutions of Jurkat T-cell lymphoma DNA in PBMC DNA were used to assess the sensitivity of the method.

Results: Analysis of 13 (65%) of 20 PLEVA biopsy specimens revealed the presence of a dominant T-cell clone. Positive and negative controls confirmed the specificity of the procedure. The sensitivity was determined to be between 1% and 5% of the total T-cell infiltrate.

Conclusions: This study provides further evidence for the presence of a dominant T-cell clone in skin lesions of some patients with PLEVA and supports the hypothesis that PLEVA is part of the spectrum of clonal–T-cell cutaneous lymphoproliferative disorders.

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PITYRIASIS lichenoides et varioliformis acuta (PLEVA) is an acute or subacute inflammatory erythematous disease first described by Mucha and Haberman in 1916.² Considered a rare condition, its epidemiological pattern has not been studied in large surveys, and its actual incidence is largely unknown. Pityriasis lichenoides et varioliformis acuta affects predominantly young people with inflammatory and usually diffuse erythematous papules of rapid onset with crusted or necrotic central areas that sometimes evolve into small pox–like scars. The usual outcome is a spontaneous disappearance of the lesions within weeks or months after one or several flares, although in some patients it may evolve toward the chronic form of the disease.³ The histological pattern is dominated by occasional keratinocyte necrosis, extravasation of erythrocytes, basal vacuolization, lymphocyte infiltration of the epidermis, and a dermal-perivascular and lichenoid-lymphohistiocytic infiltrate. Some atypical large mononuclear cells may be present in the dermal infiltrate.³ The lymphocytes are mainly of the CD8⁺ suppressor/cytotoxic subset, but CD4⁺ helper T cells are usually present. The few atypical large cells are usually CD30⁻.⁴⁻⁶ None of these cells display atypical immunological features such as the lack of CD5 or CD7 expression.

Controversy exists as to whether PLEVA is an inflammatory reaction to various, possibly infectious, triggering agents; an immune complex–mediated hypersensitivity vaculitis⁵; or a genuine lymphoproliferative process that is part of the cutaneous T-cell lymphoproliferative spectrum, possibly related to lymphomatoid papulosis (LyP).⁶⁻¹¹ In this latter case, a vigorous host immune reaction might prevent PLEVA from evolving into

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<p>MATERIALS AND METHODS</p>

PATIENTS AND TISSUES

Paraffin-embedded cutaneous biopsy specimens from 20 patients with PLEVA were selected from the University Hospital of Montpellier, France; there were 12 men and 8 women and their ages ranged from 6 to 42 years (mean ± SD, 26 ± 3 years). The cutaneous eruptions lasted for an average of 4.2 weeks before the biopsy was performed. In all cases, a diagnosis of PLEVA was made on the basis of the following features: (1) an eruption of inflammatory papules with a central crust and an occasional necrotic pattern leaving atrophic scars; (2) exocytosis, extravasation of erythrocytes, necrosis of scattered keratinocytes, basal layer vacuolization, and a dermal lymphohistocytic infiltrate with a lichenoid and/or perivascular distribution without a significant presence of large lymphoid cells; and (3) predominance of CD2⁺CD3⁺CD8⁺ lymphocytes in the dermal infiltrate. A dominant T-cell clone in the lesions, which seems to favor the hypothesis of a lymphoproliferative disorder, but the number of studied cases is too small to draw a definite conclusion. Therefore, we studied T-cell clonality in cutaneous lesions of 20 clinically and histologically typical cases of PLEVA from a university hospital using sensitive polymerase chain reaction (PCR) amplification followed by heteroduplex analysis of the TCRγ gene, a reliable and sensitive method to detect the presence of a dominant T-cell clone in a mixed cutaneous infiltrate. A dominant clone was found in 13 of 20 cases, which supports the hypoth-
Peripheral blood mononuclear cells and all cases of lichen planus displayed a polyclonal pattern with the 4 sets of primers. This was the expected result because lichen planus is a known polyclonal disease. Conversely, the DNA from Jurkat cells, a T-cell lymphoma line, showed a distinct band of the predicted size (300 base pairs [bp]) and had practically no background smear in the analysis of PCR products with the V\text{\textsubscript{Y1}}-J\text{\textsubscript{Y}} primers, whereas no band was present in the analysis of PCR products from the other sets of primers. These results were also expected because all the cells contained the same TCR\text{\textsubscript{Y}} gene rearrangement. The sensitivity assessment showed that a band was detectable up to a range of dilution between 1% and 5% Jurkat lymphoma cells in polyclonal DNA, which means that a T-cell clone can be detected by this method when it represents at least 5% of the T cells from which DNA has been extracted (Figure 1). The mycosis fungoides case displayed the expected monoclonal band as well.

Of the 20 PLEVA cases examined, 13 (65%) displayed a homoduplex pattern with a clear band of the expected size but of variable intensity (Figure 2), which is consistent with the presence of a dominant T-cell clone within the dermal lymphoid infiltrate. In all cases, this result was obtained when using the PCR products from the V\text{\textsubscript{Y1}}-J\text{\textsubscript{Y}} amplification, whereas only a polyclonal pattern was obtained when using the 3 other sets of primers. In all cases, these results were confirmed by a second round of PCR-heteroduplex analysis.

In this study, we searched for the presence of a dominant T-cell clone within the dermal lymphoid infiltrate in 20 cases of PLEVA using PCR-heteroduplex analysis to detect rearrangements of the TCR\text{\textsubscript{Y}} gene. We found that skin lesions from 13 (65%) of 20 cases disclosed a pattern consistent with the presence of a dominant clone, whereas negative and positive controls showed the expected results. Cases of LyP were excluded by strict pathologic and immunophenotypic criteria. The possibility of contamination by a single clonal sample was excluded by direct sequencing of the monoclonal bands, which displayed a unique sequence in each case (data not shown). It is possible that the actual percentage of PLEVA cases with a dominant T-cell clone is even higher, since the sensitivity of the heteroduplex method was only about 5% in this study, which is similar to the data in the literature.20

There are several possible interpretations for our findings. One is that PLEVA is a cutaneous lymphoproliferative disorder with a theoretical malignant potential. This hypothesis is supported by the rare development of malignant lymphomas in patients with PLEVA.12-15 Another possibility is that PLEVA is closely related to LyP, which clearly has a malignant potential and was a clonal T-cell disorder in most cases.21 This hypothesis is supported by the similar clinical presentations and the possible occurrence of both PLEVA and LyP in the same patient.10,11 However, in most patients PLEVA and LyP seem to have different histopathologic and immunophenotypic features, with PLEVA lacking the frequent CD30\textsuperscript{+} large atypical cells characteristic of LyP21,22 and having a predominant CD8\textsuperscript{+} infiltrate at the dermoepidermal junction that is generally lacking in LyP.2 Still another explanation for our findings is that the dominant T-cell clone in PLEVA represents a clonal immunologic response to an unknown antigen or infectious agent.2,5,22,25

We favor the hypothesis that PLEVA is part of the clonal T-cell cutaneous lymphoproliferative spectrum, such as small plaques parapsoriasis,26 as previously suggested.6 The rare occurrence of lymphoma during the course of PLEVA and, in most cases, a spontaneous regression after several months, suggests that a vigorous host immune reaction controls and eventually eliminates the T-cell clone. Additional genetic alterations, which remain to be defined, may be required for the infrequent progression of PLEVA into malignant lymphoma. As an example, we have demonstrated that the progression of

**Primers for the TCR\textsubscript{Y}-Targeted Polymerase Chain Reaction**

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence</th>
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<tbody>
<tr>
<td>V\text{\textsubscript{Y1}}</td>
<td>5’-TACATCCACTGTATTCAAGCA-3’</td>
</tr>
<tr>
<td>V\text{\textsubscript{Y}9}</td>
<td>5’-TACATGGTTCTGGTCGTCC-3’</td>
</tr>
<tr>
<td>V\text{\textsubscript{Y}10}</td>
<td>5’-GCAGGATGGTTAACAGCAAG-GC-3’</td>
</tr>
<tr>
<td>V\text{\textsubscript{Y}10}/11</td>
<td>5’-TACATCTGTTACCGGAGAACAAA-3’</td>
</tr>
<tr>
<td>J\text{\textsubscript{Y}1/2}</td>
<td>5’-CCGGTGGACTACCGTGGAAATGTGATTCC-3’</td>
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**Figure 1.** Heteroduplex analysis of successive dilutions of Jurkat lymphoma cell DNA in peripheral blood mononuclear cell DNA (molecular weight [mw] ladder [arrow, 300 base pairs]; lane 1, peripheral blood mononuclear cells; lane 2, Jurkat cells; lane 3, mycosis fungoides; lanes 4-15, increasing ratio of Jurkat cell DNA in peripheral blood mononuclear cell DNA [1:2, 1:3, 1:4, 1:5, 1:10, 1:20, 1:33, 1:50, 1:100, 1:200, 1:500, and 1:1000]). Disappearance of the monoclonal pattern occurred between 1:50 and 1:100.

**Figure 2.** Heteroduplex analysis of polymerase chain reaction products of pityriasis lichenoides et varioformis acuta cases (molecular weight [mw] ladder [arrow, 300 base pairs]; lane 1, mycosis fungoides; lanes 1-7 and 8, pityriasis lichenoides et varioformis acuta cases; lane 7, Jurkat cells. There was a monoclonal pattern for samples corresponding to lanes 2-4, 6, and 8.)
the T-cell clone in LyP is associated with the loss of growth regulation by transforming growth factor β because of mutations within the transforming growth factor β receptor complex.27,28

In this study, 10 of 13 PLEVA patients with a dominant T-cell clone experienced a usual clinical course with spontaneous disappearance of skin lesions after several months, whereas 3 cases evolved toward a more chronic form but without any evidence of a lymphoid malignancy after a follow-up of at least 2½ years. In conclusion, our study gives further support to the hypothesis that PLEVA may be in some, if not most cases, a clonal T-cell cutaneous lymphoproliferative disorder.

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