Myositis Fungoides Exhibits a Th1-Type Cell-Mediated Cytokine Profile Whereas Sezary Syndrome Expresses a Th2-Type Profile

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We determined T-cell cytokine profiles in the epidermis, dermis, and blood of cutaneous T-cell lymphoma to differentiate whether unique cytokine profiles were associated with mycosis fungoides (MF) versus Sezary syndrome. Punch biopsy specimens from plaque stage MF (n = 7) were compared to Sezary skin (n = 3) after undergoing rapid heat-saline separation of epidermis from dermis. Normal adult skin (n = 11), neonatal foreskin (n = 4), untreated psoriatic plaques (n = 6), and normal donor peripheral blood leukocytes (n = 3) were studied as controls. Total RNA was extracted from all skin specimens, as well as peripheral blood leukocytes from MF (n = 3) and Sezary patients (n = 7), and was converted to cDNA by reverse transcriptase. Polymerase chain reaction amplification of cDNAs using interleukin 2 (IL-2), IL-4, IL-5, IL-10, and interferon γ—specific primers was used to differentiate Th1-type responses (IL-2+ and interferon γ+) from Th2-type responses (IL-4+, IL-5+, and IL-10+). β-actin specific primers were included as a positive control for mRNA integrity. All MF specimens contained mRNAs for IL-2 and interferon γ limited to epidermis but no IL-4, IL-5, or IL-10. In contrast, Sezary skin and blood showed a cytokine mRNA pattern dominated by IL-4, IL-5, and IL-10. MF blood showed a pattern similar to normal peripheral blood T cells with mixed detection of all T-helper cell cytokine mRNAs. All psoriasis samples contained mRNAs for IL-2 and interferon γ in both epidermis and dermis with no IL-4 or IL-10 in either compartment. These findings demonstrate that the cutaneous lesions of MF are characterized by an epidermal Th1-type cytokine profile, whereas both the blood and skin of patients with Sezary syndrome is characterized by a Th2-type profile. This work suggests that differences in cytokine production may be related to the pathophysiology and clinical presentation in cutaneous T-cell lymphoma. Key words: cutaneous T-cell lymphoma/cytokines/psoriasis/interleukins/gamma interferon/PCR. J Invest Dermatol 103:29–33, 1994

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ure T-helper cells have been divided into two distinct functional subsets (Th1 and Th2) [1]. The difference between these two types of cloned T-helper cells is primarily defined by the profiles of cytokines synthesized. Th1 clones synthesize interleukin 2 (IL-2), interferon γ (IFNγ), and lymphotoxin, which results in augmented cell-mediated immunity, T-cell proliferation, and macrophage activation. These cytokines are not expressed in Th2 clones, which preferentially synthesize IL-4, IL-5, and IL-10 and augment humoral responses, while suppressing cell-mediated immunity [2]. Patterns of cytokine mRNA expression can be used to separate T-cell subclass differences, and increasing evidence supports that many of the functions of T-helper cells are predicted by the cytokines they synthesize. Separation of human T-helper cell clones into analogous subsets is now established [3], and human skin diseases can be differentiated based on their characteristic cytokine profiles [2,3].

Lesions of tuberculoid leprosy and psoriasis are characterized by a Th1 cytokine profile and these diseases are characterized by intact cell mediated immunity. Conversely, lepromatous leprosy and atopic dermatitis bear a Th2 profile and are characterized by altered cell mediated immunity [2–4]. We have used the reverse transcriptase-polymerase chain reaction (RT-PCR) technique to determine the cytokine mRNA expression profiles in cutaneous T-cell lymphoma (CTCL) in comparison to psoriasis and normal skin. In CTCL we wanted to determine if distinctive cytokine profiles were present in mycosis fungoides (MF) versus Sezary syndrome and, if so, how would they compare with the recently characterized patterns in infectious skin disease (i.e., Hansen's disease) and reactive cutaneous diseases (i.e., psoriasis and atopic dermatitis). Differences in cytokine response profiles may be related to prognosis, as patients with CTCL are known to lose cell mediated immunity as their disease progresses. Not unlike Hansen's disease, CTCL is clinically characterized by limited cutaneous disease that is well tolerated and features intact cell-mediated immunity, whereas disseminated forms of the disease (e.g., extensive tumor stage MF and Sezary syndrome) are frequently fatal and lack adequate cell mediated immunity. We extend the previous report of Th1 cytokine pattern in psoriasis [3] and report that MF patients are characterized by a distinct epidermal Th1-type phenotype, whereas Sezary syndrome
patients express a Th2-type cytokine profile in both blood and skin compartments.

**MATERIALS AND METHODS**

**Patient Specimens** Skin punch biopsy samples (4 to 6 mm) were obtained from adult patients with histologically confirmed plaque-stage MF (n = 7), and erythematous skin of patients with untreated Sezary syndrome (n = 3). All skin biopsies from CTCL patients were of classic histopathology with a moderately dense infiltrate of hyperchromatic lymphocytes in the dermis. Healthy volunteers (n = 11), and normal donor blood samples (n = 3). All procedures were under approval of the Henry Ford Hospital and the University of Michigan Medical Center, Institutional Review Boards.

**Heat-Split Skin** Skin biopsies were immersed in 0.15 M NaCl, preheated to 60°C, for 5–7 min in a water bath, and then transferred to 0.15 M NaCl on ice. Epidermis was then peeled off dermis with sterile forceps and separated epidermal sheets and dermal fragments were placed in guanidinium isothiocyanate buffer (5.5 M guanidinium isothiocyanate containing 25 mM Na-sodium citrate, pH 7.0, with 0.5% sarcosine and 0.1 M 2-mercaptoethanol) for RNA extraction. This technique has been previously reported to cause a separation in the lamina lucida and routinely provides viable RNA for PCR studies [5].

**RNA Extraction** Total RNA was isolated from skin biopsies anduffy coat preparations of peripheral blood by the cesium trifluoroacetate method. Six specimens, including peripheral blood from (each) deoxynucleoside triphosphate. The reaction mixture was incubated at 37°C for 60 min, heated at 95°C for 5 min, and then chilled on ice to inactivate the enzyme [6].

**PCR Amplification** Two- to five-microliter aliquots from the cDNA reaction products were PCR amplified in 100 μl reaction as follows: 10 μl of 10 X PCR reaction buffer, 1 mM from each of the deoxynucleotide triphosphates, 20 μM from each primer, and 2.5 units of Taq polymerase enzyme (Perkin-Elmer Cetus, Norwalk, CT) and overlaid with mineral oil to prevent evaporation. The reaction was initiated by heating at 95°C for 1 min, annealing/extension for 2 min at 55°C (IFNγ, IL-2, and IL-5) or 60°C (IL-4, IL-10, β-actin). This was repeated for 35 cycles using the PCR (Perkin-Elmer Cetus). After the final cycle, the temperature was maintained at 72°C for 7 min to allow completion of synthesis of amplified products [6,7]. PCR products were visualized with 2% agarose gel electrophoresis stained with ethidium bromide. All results were confirmed by Southern blotting of these gels. The gel was transferred onto nylon membranes by capillary blotting, and then hybridized with 32P end-labeled “nested” probes designed to recognize intervening sequences between each respective set of primers (1,2, see below).

**PCR Primers** Cytokine-specific primers used for all specimens in this study were identical to those reported elsewhere [3]. These primers were chosen to span introns that helped ensure amplification of only cDNA and not genomic DNA. Nucleotide sequences for the upstream and downstream primers used were as follows:

<table>
<thead>
<tr>
<th>IL-2</th>
<th>5'-CTCCACCCTCTGTCTTCTCCT-3' and 5'-TTTCTCTTGACGCTTTCAG-3'</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-5</td>
<td>5'-ATGAGGTGTCTTCTGCATTTG-3' and 5'-TCCACTCTCTATATTCCACGCTTTCTAC-3'</td>
</tr>
<tr>
<td>IL-10</td>
<td>5'-ATGCATCAAGCTGAAAGACGACAGCCAA-3' and 5'-CTCCTCTCAGGGGCTGAC-3'</td>
</tr>
<tr>
<td>IFNγ</td>
<td>5'-AGTATTACCTGCTTCTTCA-3' and 5'-ACCGGAAATTAGCTGACGGT-3'</td>
</tr>
<tr>
<td>β-actin</td>
<td>5'-GTGGGGGCCCGCCCAGCAGCA-3' and 5'-CTCCTTATGCTACGACGATTC-3'</td>
</tr>
</tbody>
</table>

**Nested Probes for Southern Blot of PCR Products**

IL-2 probe: 5'-AGCTAAATTTACGAGACTCTTCGAG-3' IL-4 probe: 5'-CTCCTCTGTGCTGACTGCCTGTCT-3' IL-5 probe: 5'-GCCAATAGGAGATCTGAGGTCTTCTCGT-3' IL-10 probe: 5'-ATTTGGCTCTGCAATTTTTCTGT-3' IL-20 probe: 5'-CAGGGTCAGAATCTTATATAAGCTCCAAAGAAAGGCATCCTACAAAGCAAGTGGAGAGATCTGAGGTCTTCTCGT-3' IL-4 probe: 5'-AGTATTACCTGCTTCTTCA-3' and 5'-ACCGGAAATTAGCTGACGGT-3' IL-5 probe: 5'-AGTATTACCTGCTTCTTCA-3' and 5'-ACCGGAAATTAGCTGACGGT-3' IL-10 probe: 5'-AGTATTACCTGCTTCTTCA-3' and 5'-ACCGGAAATTAGCTGACGGT-3' IL-20 probe: 5'-AGTATTACCTGCTTCTTCA-3' and 5'-ACCGGAAATTAGCTGACGGT-3'

**Controls and Standardization** cDNA amplification products were distinguished from genomic DNA by size on agarose gel electrophoresis. β-actin, which is constitutively expressed by all cell types, was used to ensure that viable total cellular mRNA was recovered from each specimen. As a negative control, the reverse transcriptase reaction mixture from each specimen was amplified without reverse transcriptase from the reaction mixture from each specimen to distinguish between amplification of contaminating genomic DNA from mRNA in each sample.

**RESULTS**

The results of the cytokine mRNA analyses of MF and Sezary skin lesions, and peripheral blood T cells in these CTCL patients, as compared to normal skin, neonatal foreskin, lesional psoriatic skin, and normal T cells are summarized in Table 1. cDNA specimens from epidermis, dermis, and buffy coat cells were separately PCR amplified with IL-2, IL-4, IL-5, IL-10, and IFNγ primers. PCR products were examined by agarose gel electrophoresis, stained with ethidium bromide, and confirmed by Southern blot analysis. The results were compared to the β-actin signal to allow comparisons between samples (Fig 1).

All MF specimens contained mRNA transcripts for IL-2 and IFNγ limited to epidermis, with no detectable IL-4, IL-5, or IL-10 in either skin compartment (Fig 2). The skin from Sezary patients showed a Th2-type cytokine profile with mainly IL-2, IL-4, and IL-10 mRNAs present in three of three epidermal skin specimens (no detectable T-helper cell cytokines were found in Sezary dermis as in MF dermis). One of three Sezary skin samples revealed detectable IFNγ mRNA in the epidermis by Southern blot analysis (all three were negative on ethidium bromide gels, results not shown).

All seven Sezary blood T cells contained readily detectable mRNAs for IL-4 and IL-10 but no IL-2 or IFNγ mRNAs (Fig 2). IL-5 was detected in two of five specimens of Sezary blood T cells studied. The absence of IL-4, IL-5, and IL-10 mRNAs in MF skin as well as the absence of IL-2 and IFNγ mRNAs in Sezary blood and skin samples was confirmed by Southern blot. Peripheral blood T cells from MF patients gave a mixed pattern of H-helper cell cytokine expression with mRNAs.

All normal adult skin specimens contained detectable mRNA for IL-10 in the epidermis. Four of 11 also had IFNγ in both epidermis and dermis, but no IL-2, IL-4, or IL-5 in either compartment (Fig 3A) by ethidium bromide staining. The variability of IFNγ expression in normal adult skin was confirmed by Southern blot of PCR products from separated epidermis versus dermis. Of the specimens with negative results for IFNγ mRNA in normal adult skin on ethidium bromide stained gels, five of seven epidermal specimens had detectable IFNγ by Southern blot (Fig 3B).

All psoriasis specimens contained detectable IFNγ mRNA, but no IL-2 and IFNγ in both epidermis and dermis but no IL-4 or IL-10 in either compartment (Fig 4), confirming a previous report using intact skin samples [5]. Neonatal foreskin epidermis and dermis contained mRNAs for...
IL-10 and IFNγ (four of four samples), IL-2 (three of four epidermis, two of four dermis), and IL-4 (three of four dermis only), suggesting a mixed cytokine pattern, consistent with nonspecific inflammation (see Table I). IL-5 was not studied in psoriasis or foreskin samples. Normal donor leukocytes were found to express detectable mRNAs for IL-2, IL-4, IL-10, and IFNγ in all samples and IL-5 in three of eight samples (results not shown).

**DISCUSSION**

We report that cutaneous lesions of MF are characterized by a distinct epidermal Th1-type cytokine phenotype, whereas the leukemic variant of CTCL, Sezary syndrome, expresses a Th2-type phenotype in both blood and skin. This study highlights that both malignant and reactive T-cell-mediated skin diseases are characterized by unique cytokine mRNA profiles as data is also presented that confirms that psoriasis also expresses a Th1-type profile [2]. These results qualitatively demonstrate that cutaneous lesions of plaque-stage MF are shown to be characterized by IL-2 and IFNγ mRNAs, and the predominant source of these cytokines appears to be epidermal. Sezary syndrome is also reported to have cutaneous cytokine transcription restricted to the epidermis with only IL-4, IL-5, and IL-10 regularly detected. The dermis of all CTCL specimens studied was devoid of these cytokine mRNAs despite consistent yields of RNA as evidenced by positive dermal β-actin signals (see Fig 1) indicative of ongoing transcriptional activity. The restriction of specific cytokine-response profiles to the epidermis in CTCL is consistent with our recent observations that proliferative (Ki-67+), clonal T-cell populations in MF are also restricted to the epidermis [8–10]. Thus it appears that the epidermis of MF and Sezary syndrome are both characterized by clonal, proliferative T cells yet are associated with completely different cytokine profiles.

The blood of MF patients showed no unique cytokine pattern as compared to normal blood, in agreement with the lack of detection of malignant clones by Southern blot in the blood of most MF

**Table I. Cytokine mRNA Profiles in Skin and Blood of Cutaneous T-Cell Lymphoma Patients as Compared to Psoriasis and Controls**

<table>
<thead>
<tr>
<th>Cytokine mRNA</th>
<th>MF (n = 7)</th>
<th>MF (n = 5)</th>
<th>SZ (n = 3)</th>
<th>SZ (n = 7)</th>
<th>NS (n = 11)</th>
<th>FK (n = 4)</th>
<th>PS (n = 6)</th>
</tr>
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<tbody>
<tr>
<td>IL-2</td>
<td>+</td>
<td>–</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>±</td>
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<tr>
<td>IL-4</td>
<td>–</td>
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<tr>
<td>IL-5</td>
<td>–</td>
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<tr>
<td>IFNγ</td>
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<td>β-actin</td>
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<td>–</td>
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<td>–</td>
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</table>

* NS, normal skin; FK, foreskin; PS, psoriasis; MF, mycosis fungoides lesional skin; SZ, Sezary syndrome.

* E, epidermis; D, dermis; B, peripheral blood T cells; ±, mRNA detected in all samples; +, mRNA detected in some but not all samples (all results confirmed by Southern analysis using 3P-labeled nested probes).

**Figure 1.** RT-PCR analysis of β actin from representative specimens of each tissue studied. PCR analysis of total RNA isolated from the epidermis (E) and dermis (D) from one representative skin biopsy each of mycosis fungoides (MF), psoriasis (PS), neonatal foreskin (FK), and normal skin (NS). RNA samples were PCR amplified using primers specific for β-actin. PCR products were electrophoretically separated on 2% agarose gel and visualized by ethidium bromide staining.

**Figure 2.** RT-PCR analysis of T-helper cytokine mRNAs in mycosis fungoides and Sezary syndrome. A) PCR analysis of total RNA isolated from the epidermis (E) and dermis (D) of a skin biopsy from a patient with untreated patch-stage mycosis fungoides (M). B) PCR analysis of total RNA isolated from peripheral blood leukocytes from a patient with Sezary syndrome (SZ). In both experiments, RNA samples were PCR amplified using primers specific to IL-2, IL-4, IL-10, and IFNγ. PCR products were electrophoretically separated on 2% agarose gel and visualized by ethidium bromide staining. The DNA size marker (M) was the BioMarker Low (BioVentures Inc.).
patients [11]. Similar to the recent study by Vowels et al [12], we report that Sezary blood T cells are characterized by a Th2-type cytokine profile and extend this observation to include Sezary skin lesions. Our results complement the Vowels et al study, in which they report the production of a Th2 cytokine profile based on biosay of cultured Sezary leukocytes. We confirm that the cytokines expressed at the mRNA level by Sezary syndrome T cells are IL-4, IL-5, and IL-10, matching the murine Th2 profile [1]. Earlier work from our laboratories predicted that Sezary syndrome was likely to be characterized by defective IFNγ expression as Sezary epidermis was found to be lacking intercellular adhesion molecule-1 (ICAM-1) expression, which is transcriptionally regulated by IFNγ [13]. These findings also support those of Parronchi et al [14] in that there appears to be an inhibition of IFNγ by IL-4, as no detectable IFNγ mRNA was found in the blood of Sezary patients, despite the highly sensitive Southern analysis of all PCR products.

In normal adult skin, no detectable IL-2, IL-4, or IL-5 mRNA was present in the epidermis or dermis. The majority of epidermal specimens could be shown to have detectable IFNγ expression, suggesting that the epidermis of normal skin bears some cell(s) that constitutively make low levels of IFNγ mRNA. This trace IFNγ expression may be due to the occasional migration of Th1 cells in the epidermis of normal adult skin or may result from other resident epidermal cell populations such as Langerhans cells [15]. Dermal IFNγ was regularly observed in normal adult skin and could be attributable to resident T cells in the perivascular space as described by Bos et al [16]. Epidermal expression of IL-10 is also reported in this study as a regular finding in normal adult skin and may function to suppress pro-inflammatory cytokine release from resident T cells in the epidermis and dermis. Thus epidermal IL-10 may counterbalance any significant effects of epidermal IFNγ production. Basal expression of IL-10 mRNA has also been recently shown in unstimulated murine keratinocyte cultures [17]. Thus low levels of cytokine expression may be responsible for maintenance of adhesion molecule mediated epidermal and dermal immune cell trafficking and surveillance in normal skin as well as in CTCL and psoriasis.

Our data also confirm that psoriasis is characterized by a Th1-type cytokine profile, as recently suggested by Uyemura et al [3]. Separate epidermal and dermal analysis of psoriasis specimens revealed that, in contrast to CTCL, T-cell cytokines are transcribed in both epidermis and dermis. Thus only specimens of malignant T-cell mediated skin disease (e.g., CTCL) have been shown to demonstrate epidermal selectivity for Th cytokine transcription. The pathogenesis of this phenomenon is unknown but may be due to factors including the unique location of T cells within the epidermis and its rich milieu of keratinocyte-derived cytokines, the process of epidermotropism, and/or compartment-specific reciprocal inhibition of cytokine mRNA transcription [14,18,19].

The differential cytokine response profile in MF (Th1) and Sezary syndrome (Th2) suggests several possible explanations. The first of these is that all malignant T cells in CTCL are of Th2 type and that changes in profiles observed may be due to a predominantly reactive (e.g., benign) phenotype in the skin (Th1) versus the blood (Th2) as suggested recently in an editorial by Rook et al [20]. The predominant Th1-type response in the epidermis of MF may then overwhelm the relatively fewer malignant Th2-type cells to yield an effective anti-tumor response, allowing MF to remain indolent. The lack of detectable Th2-type cytokine mRNAs in the epidermis could be explained by transcriptional feedback inhibition by IL-2 and IFNγ [14], as the use of RT-PCR with Southern analysis could have theoretically detected 1 cell/specimen expressing Th2 cytokine mRNAs. Similar pathways resulting in the extracutaneous inhibition of Th1-type cytokines by IL-4, IL-5, and IL-10 could also explain the cytokine profile in the blood of Sezary syndrome patients, as the malignant Th2 clone dominates the circulatory compartment. The effect here would be for the Th2 cytokines to inhibit appropriate cell-mediated immune responses to the tumor cells (as observed in Sezary syndrome) and favor a more rapidly progressive, fatal disease process. Although this is still highly speculative, it could explain why MF patients treated with cyclosporin have been reported to have rapid worsening of their disease [21], as this immune modulator inhibits IL-2 function, thus favoring Th2 cytokines and suppression of cell-mediated immunity. Although data are not presented in this report, this model would predict that those patients who have increasing tumor cell density (i.e., tumor-stage MF) or who progress from MF to Sezary syndrome would be expected to increase.

Figure 3. RT-PCR analysis of T-helper cytokine mRNAs in normal skin. A) PCR analysis of cytokines mRNA isolated from the epidermis (E) and dermis (D) of a representative normal adult skin biopsy from the buttocks. RNA samples were PCR amplified using primers specific to IL-2, IL-4, and IL-10. PCR products were electrophoretically separated on 2% agarose gel and visualized by ethidium bromide staining. B) PCR analysis of cytokines mRNA isolated from the epidermis (E) and dermis (D) from two specimens of normal skin. RNA samples were PCR amplified using primers specific for IFNγ. PCR products were electrophoretically separated on 2% agarose gel and then Southern blotted using a 32P-labeled IFNγ-specific oligonucleotide probe as no bands could be detected by ethidium bromide staining.

Figure 4. RT-PCR analysis of T-helper cytokine mRNAs in psoriasis. PCR analysis of cytokines mRNA isolated from the epidermis (E) and dermis (D) of an untreated psoriatic plaque. RNA samples were PCR amplified using primers specific to IL-2, IL-4, IL-10, and IFNγ. PCR products were electrophoretically separated on 2% agarose gel and visualized by ethidium bromide staining.
pected to go through a transition stage from Th1 to Th2 that would parallel progression of their disease. If Th cytokines do not fluctuate in the numbers of copies transcribed per cell, then this transition stage would be characterized by relatively comparable levels of Th1 and Th2 cytokines, negating any transcriptional inhibition. However, if the rate of cytokine mRNA production changes with disease progression (either due to increased transcription or decreased mRNA turnover), then a minority of very active Th2 cells could produce sufficient quantities of IL-4, IL-5, and IL-10 to shut off Th1 and IFN-γ production. This may explain why some of the Sezary patients studied with as few as 7% circulating malignant cells showed a "pure" Th2 mRNA phenotype in their blood.

A second possibility is that compartment specific (epidermis versus dermis versus blood) cytokine class switches occur in CTCL patients. In this model, malignant T cells in the epidermis of MF would be predicted to begin as Th1 cells. Only after migration out of the skin would they switch to Th2 cytokines in the circulatory compartment as Sezary syndrome T cells. These malignant Th2 cells would then be required to re-infiltrate the skin, to yield a Th2 phenotype for the Sezary epidermis. Although no CTCL data is available to support this model, clonal murine T cells have been reported to produce either class of cytokines depending on environmental (i.e., thymic) stimuli [22]. A third explanation for MF expression of a Th1 cytokine profile and Sezary expression of a Th2 profile is the possibility that these two diseases are completely unrelated and that their Th cytokine productions are therefore unrelated. Although the weight of accumulated immunopathologic data would argue that these diseases are closely related, their disparate clinical courses does support such a hypothesis [12,20,23].

In summary, we report that CTCL demonstrates clear-cut differences in Th-helper cell cytokine mRNA profiles between the skin and blood of patients with MF versus Sezary syndrome. An epidermal Th1 phenotype is seen in the skin of MF lesions, analogous to that seen in psoriasis [2], whereas a Th2 phenotype is seen in Sezary syndrome in the epidermis and blood. Interrelation between types of CTCL seems to involve the differential expression of these cytokines. Distinctive Th-helper cell cytokine profiles associated with the epidermis versus dermis versus peripheral blood of patients with CTCL and psoriasis may be related to the pathophysiology of these T-cell-mediated disorders.

REFERENCES


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