

CD4/CD8 double-negative epidermotropic cutaneous T-cell lymphoma: An immunohistochemical variant of mycosis fungoides

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Background: Mycosis fungoides (MF) is an epidermotropic cutaneous T-cell lymphoma in which the tumor cells express a mature T-helper memory phenotype, ie, CD3⁺, CD4⁺, CD8⁻, CD45RO⁺, with a T-cell receptor (TCR) of the α/β heterodimer. A minority of patients have an unusual immunohistochemical profile consisting of a CD4⁻, CD8⁺ mature T-cell phenotype. An aberrant CD4/CD8 double-negative (DN) immunophenotype in patients with early MF has rarely been reported.

Objectives: We sought to evaluate the frequency of CD4/CD8 DN immunophenotype in patients with early MF, and to study their clinical, histopathologic, and immunohistochemical features, and the course of their disease.

Methods: Our departmental archives were searched for patients with early-stage MF and CD4/CD8 DN immunophenotype.

Results: Of the 140 patients with early MF immunophenotyped in our laboratory, 18 (12%) showed CD4 and CD8 expression in less than 10% of their intraepidermal T cells on fresh-frozen and paraffin-embedded samples. The group included 13 male and 5 female patients; 14 adults and 4 children; and 15 Jews and 3 Arabs. In all, 8 had classic MF and 10 had unusual clinical variants (5 hypopigmented, 3 localized, 1 ichthyosiform, 1 purpuric). All received skin-targeted therapies and all had an indolent course (mean follow-up 3.5 years). Histopathology revealed early MF. Results of immunohistochemical analysis of the intraepidermal lymphocytes were as follows: CD3⁺, CD4⁻, CD8⁻ in all patients; CD7⁻ in all of 17; CD45RO⁺ in 15 of 16; T-cell–restricted intracellular antigen-1⁺ in 11 of 15; CD30⁺ in 2 of 16; and CD56⁺ in 2 of 16. A β F1⁺/ δ ⁻ phenotype, indicating a TCR of the α/β heterodimer, was found in 8 of 16; β F1⁻/ δ ⁺ phenotype, indicating a TCR of the γ/δ heterodimer, in 1 of 16; β F1⁻/ δ ⁻ in 5 of 16; and no determinable phenotype in 2 of 16. The TCR γ gene was clonally rearranged in 10 of 16 patients.

Limitation: This was a single-center case series.

Conclusions: There is a subgroup of patients with early MF that exhibit a CD4/CD8 DN immunophenotype. In our region, this aberrant immunophenotype is not as rare as reflected in the literature, is overrepresented in the unusual clinical variants of MF, and does not seem to have prognostic significance. Like CD4⁺ MF, the tumor cells represent memory T cells and in many cases express α/β TCR, but unlike CD4⁺ MF, they have a mostly cytotoxic phenotype. We suggest that CD4/CD8 DN MF should be recognized as another immunohistochemical variant of this lymphoma. (J Am Acad Dermatol 2006;55:276-84.)

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Mycosis fungoides (MF) is an epidermotropic cutaneous T-cell lymphoma (CTCL) in which the tumor cells express a mature T-helper memory phenotype, ie, CD3⁺, CD4⁺, CD8⁻, CD45RO⁺,¹ with a T-cell receptor (TCR) of the α/β heterodimer.² A minority of patients have an unusual immunohistochemical profile consisting of a CD4⁻, CD8⁺ mature T-cell phenotype.³⁻⁸ Although partial loss of one or more T-cell–associated antigens is a common finding in tumor-stage

Abbreviations used:

CTCL:	cutaneous T-cell lymphoma
DN:	double negative
EORTC:	European Organization for Research and Treatment of Cancer
MF:	mycosis fungoides
TCR:	T-cell receptor

MF,⁹⁻¹² an aberrant phenotype, and specifically, loss of both CD4 and CD8 antigens, has hardly been reported in early-stage MF.^{11,13-17} Several reports have described CD4/CD8 double-negative (DN) CTCLs that were not MF, which were characterized by an aggressive clinical course and, usually, γ/δ TCR expression.^{4,18,19} Some cases fell within the spectrum of CD56⁺ (natural killer cell) lymphomas,^{4,18} and many of the tumors expressed cytotoxic intracytoplasmic granules, which are markers for cytotoxic cells.^{4,20}

In recent years, we have encountered several patients with early-stage MF who exhibited an unusual CD4/CD8 DN phenotype. These cases prompted us to evaluate the frequency of the CD4/CD8 DN phenotype in patients in our department with a diagnosis of early-stage MF and to study their clinical, histopathologic, and immunohistochemical features. In addition, we sought to investigate whether this tumor immunophenotype has any prognostic implications.

On the basis of our findings, we propose that CD4/CD8 DN MF should be recognized as an immunohistochemical variant of this CTCL.

METHODS

Patients with early-stage MF who were CD4⁻, CD8⁻ were identified by review of our departmental archives of 1997 to 2004. Patients were considered to lack CD4 and CD8 when less than 10% of their intraepidermal T cells expressed these markers.

In all cases, biopsy specimens had been obtained from untreated skin lesions at the time of diagnosis or relapse. The diagnosis of MF was based on the clinical and histopathologic criteria of the European Organization for Research and Treatment of Cancer (EORTC),¹ and stage was determined according to the TNM system. Clinical data on patient age, sex, and ethnic origin, time to diagnosis, morphology of eruption, treatment, and disease course were retrieved from the files.

Immunohistochemical studies done on frozen tissues were performed using the avidin-biotin complex immunoperoxidase technique (ABC Vectastain, Vector Laboratories Inc, Burlingame, Calif). Immunohistochemical studies done on formalin-fixed

paraffin-embedded sections were performed using: (1) streptavidin-biotin (LSAB+ kit, Dako, Carpinteria, Calif) as the detection system for CD4, CD7, CD8, CD30, and CD56; and (2) avidin-biotin (ES automated system, Ventana Medical System, Tucson, Ariz) for CD3 and CD45RO. Details of the antibodies are shown in Table I. Immunohistochemical staining of CD4 and CD7 was done only on frozen tissues from 1997 to 2001, and also on paraffin-embedded tissue from 2001 to 2004. For this study, restaining on paraffin sections was done in all cases found to be CD4/CD8 DN on frozen tissues in 1997 to 2001.

Polymerase chain reaction studies were performed on DNA extracted from frozen tissue of each patient to determine the gene rearrangement of the TCR, as previously described.²¹

RESULTS

Of the 140 patients with early-stage MF immunophenotyped in our laboratory, 18 (12%) were found to lack both CD4 and CD8.

Clinical features

The clinical features of the patients with a DN phenotype are shown in Table II. The group included 13 male and 5 female patients, of whom 14 were adults and 4 children. In all, 15 were Jewish and 3 Arabic. Age at diagnosis ranged from 11 to 77 years (mean: approximately 40 years), and duration of disease before diagnosis ranged from 0.5 to 20 years (mean: 7.5 years). Eight patients had classic Alibert-Bazin type MF (Fig 1, A), and 10 presented with unusual clinical variants: hypopigmented MF in 5 (Fig 1, B); localized MF in 3 (Fig 1, C), including one patient with pagetoid reticulosis (Fig 1, D); ichthyosiform MF in one (Fig 1, E); and purpuric MF in one. All received skin-targeted therapies, and all had an indolent clinical course without evidence of disease progression after a mean follow-up of 3.5 years (range: 0.5-20 years).

Histopathologic, immunohistochemical, and genotypic findings

In all patients, hematoxylin and eosin findings were diagnostic of early MF (Figs 2, A; 3, A; and 4, A). One patient fulfilled the EORTC histopathologic criteria of pagetoid reticulosis,¹ namely hyperplastic epidermis with marked epidermotropism of large atypical pagetoid lymphocytes, together with clinical features of a psoriasiform plaque on the extremity (index finger).

Table III summarizes the immunophenotype of the intraepidermal mononuclear cells. All patients exhibited a CD3⁺, CD4⁻, CD8⁻ phenotype by immunoperoxidase study on both paraffin-embedded

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