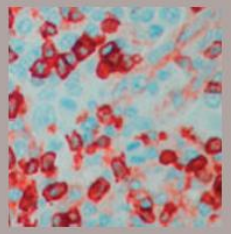
ISTITUTO DI EMATOLOGIA
"L. E A. SERÀGNOLI"

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA,
DIAGNOSTICA E SPERIMENTALE

2012...2015.
T-Cell Lymphomas:
We are illuminating
the darkest of tunnels



Bologna,
ROYAL HOTEL CARLTON
April 27-29, 2015

Presidents: Stefano A. Pileri
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CTCL: Histology

Marco Santucci

Division of Pathological Anatomy
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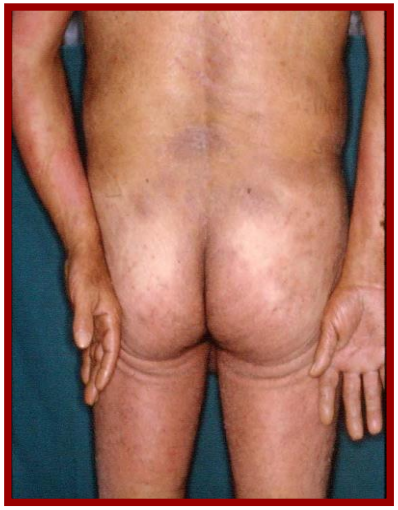
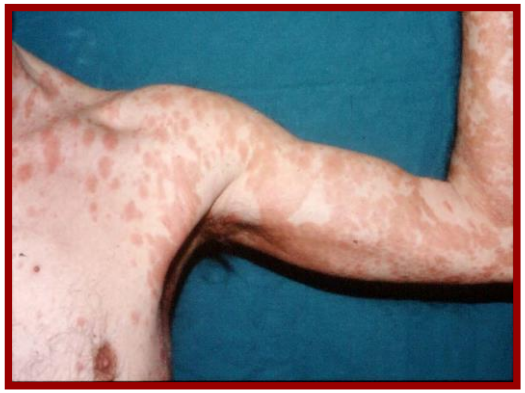
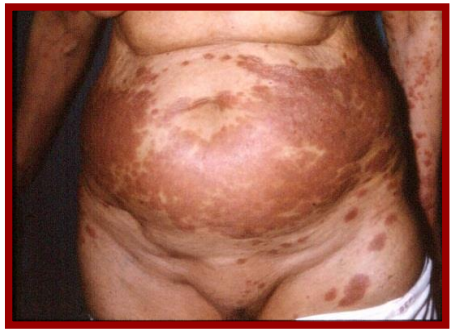
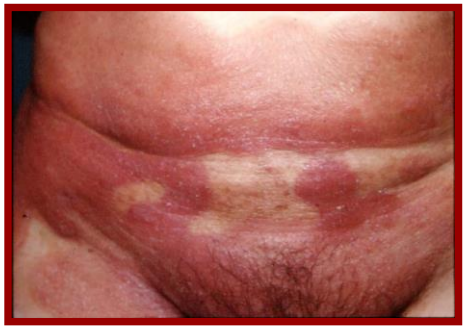
PATCH STAGE



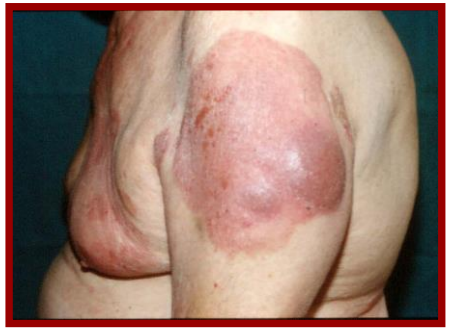


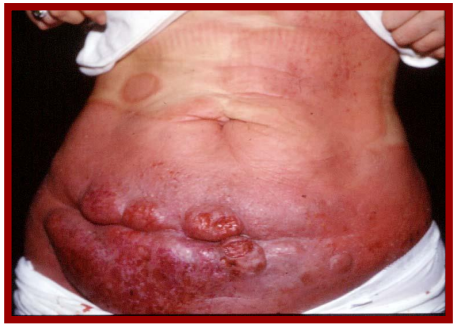
PLAQUE STAGE



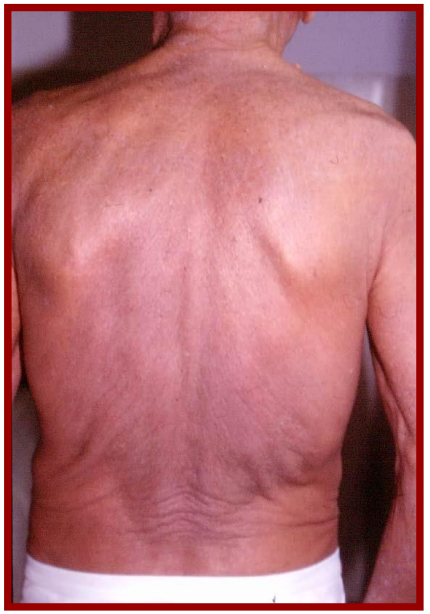


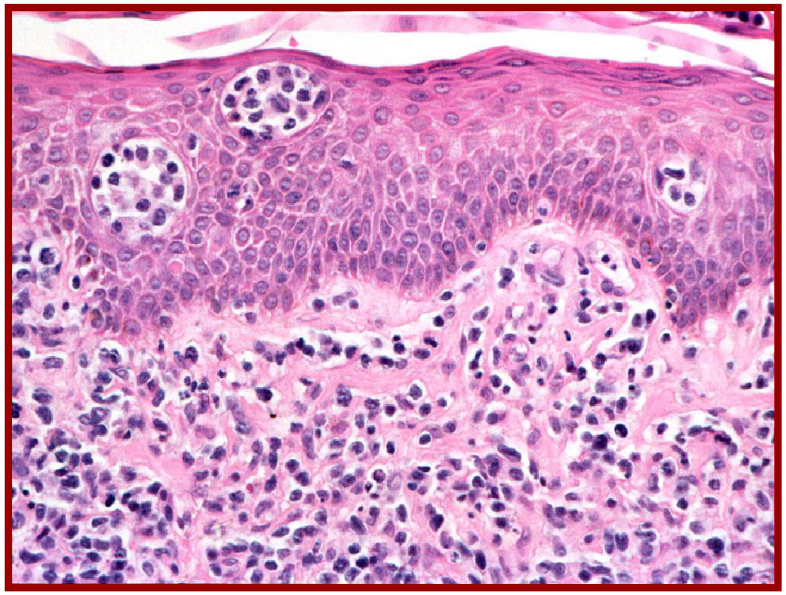
TUMOR STAGE





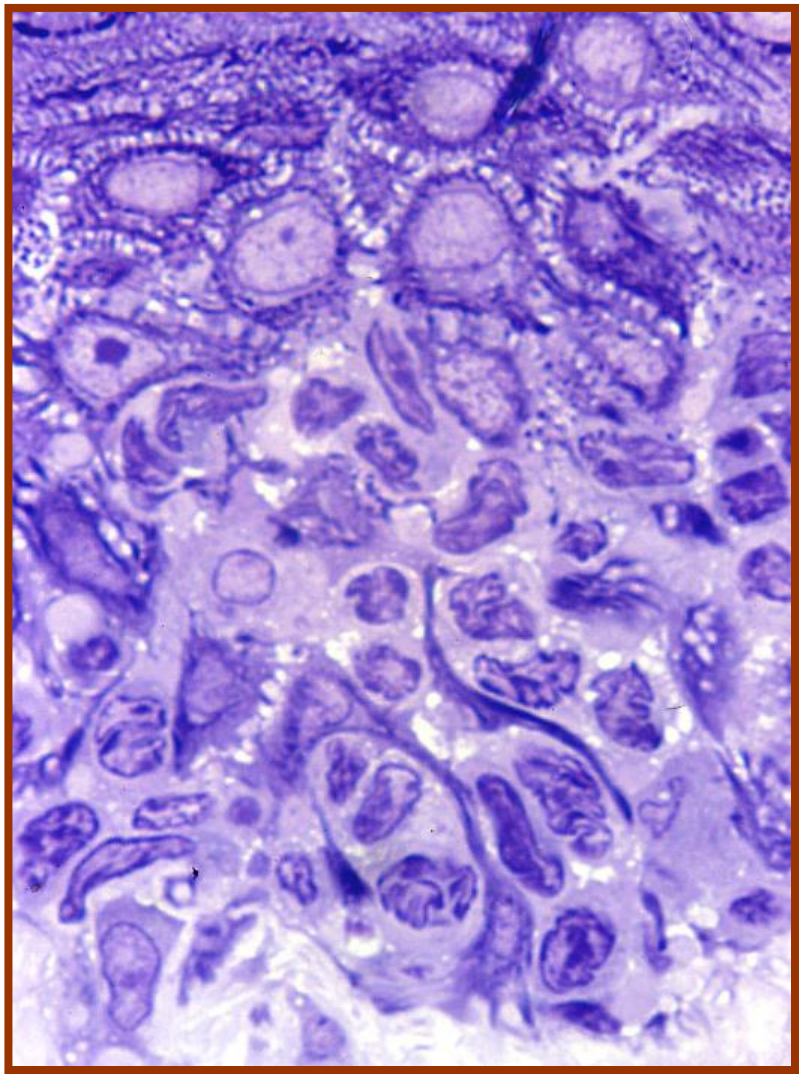
ERYTHRODERMA

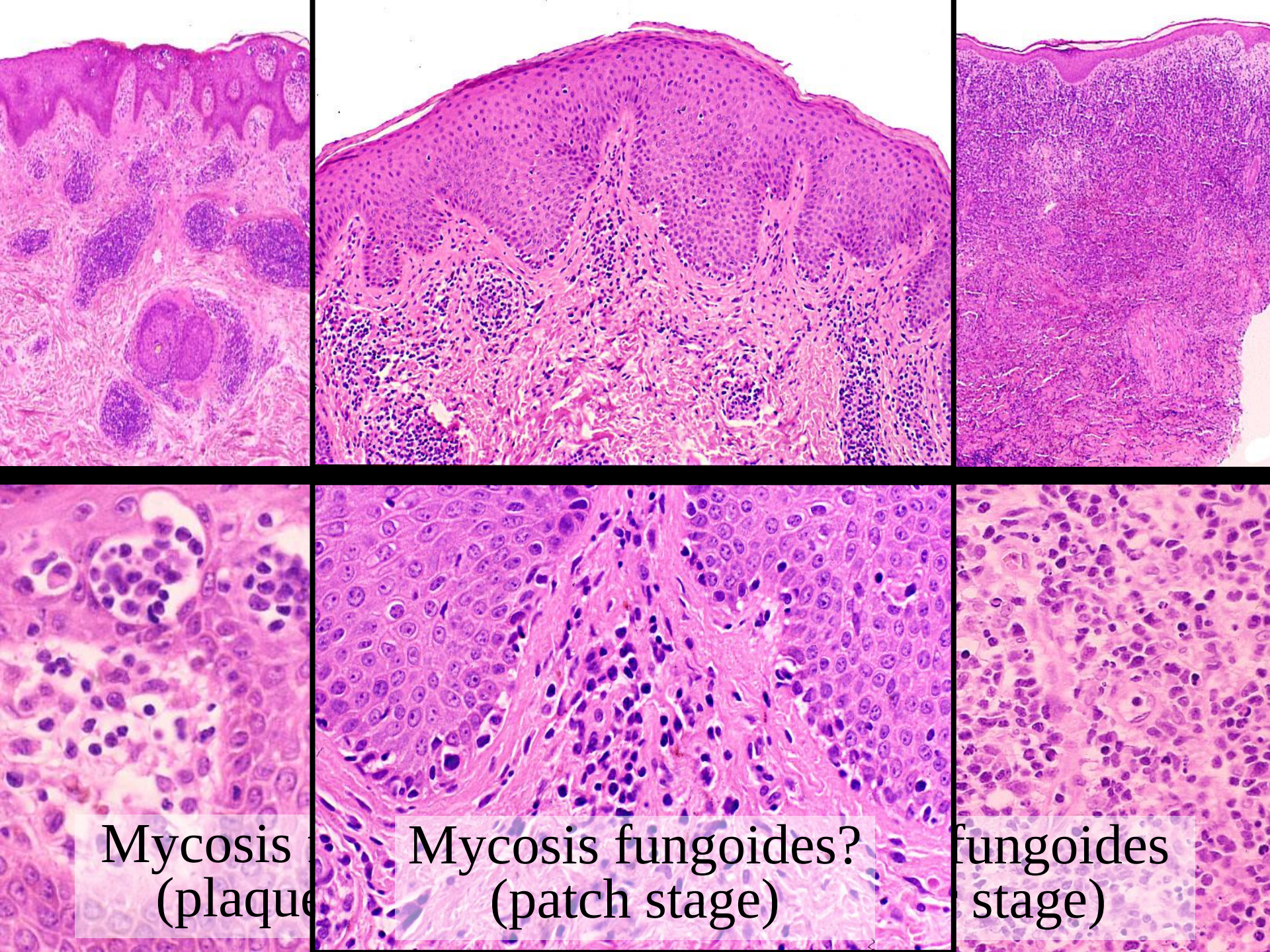




Cerebriform Nuclei

Nuclei with deep indentations resembling the sulci on the surface of the brain that, in histologic sections, have a roundish-to-oval shape with a quite smooth contour




Mycosis
(plaque
Mycosis fungoides?
(patch stage)
fungoides
stage)

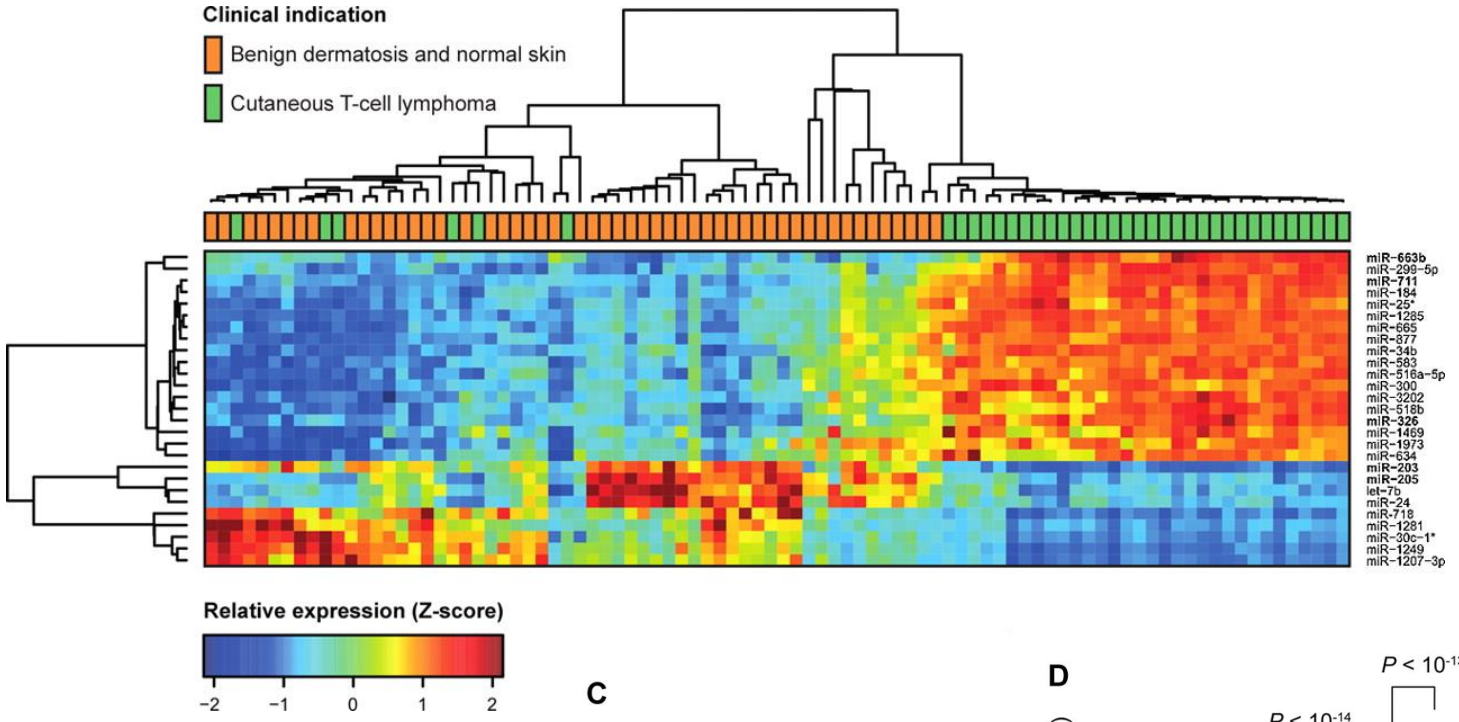
Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL)

*Ulrik Ralfkiaer,[1,2] *Peter H. Hagedorn,[3] Nannie Bangsgaard,[4] Marianne B. Løvendorf,[3,4] Charlotte B. Ahler,[3] Lars Svensson,[3] Katharina L. Kopp,[1,5] Marie T. Vennegaard,[5] Britt Lauenborg,[5] John R. Zibert,[3] Thorbjørn Krejsgaard,[5] Charlotte M. Bonefeld,[5] Rolf Søkilde,[1,5] Lise M. Gjerdrum,[6] Tord Labuda,[3] Anne-Merete Mathiesen,[1,5] Kirsten Grønbæk,[2] Mariusz A. Wasik,[7] Malgorzata Sokolowska-Wojdylo,[8] Catherine Queille-Roussel,[9] Robert Gniadecki,[6] Elisabeth Ralfkiaer,[10] Carsten Geisler,[5] Thomas Litman,[1,5] Anders Woetmann,[1,5] Christian Glue,[11] Mads A. Røpke,[3] Lone Skov,[4] and Niels Odum[1,5]

[1]Department of Biology, University of Copenhagen, Copenhagen, Denmark; [2]Department of Hematology, State University Hospital, Copenhagen, Denmark; [3]LEO Pharma A/S, Ballerup, Denmark; [4]Department of Dermato-Allergology, Gentofte University Hospital, University of Copenhagen, Copenhagen, Denmark; [5]Department of International Health, Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark; [6]Department of Dermatology, Bispebjerg University Hospital, Copenhagen, Denmark; [7]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; [8]Department of Dermatology University of Gdansk, Gdansk, Poland; [9]Centre de Pharmacologie Clinique Appliquée à la Dermatologie, Hopital l'Archet, Nice, France; [10]Department of Pathology, State University Hospital, Copenhagen, Denmark; and [11]Exiqon A/S, Vedbæk, Denmark

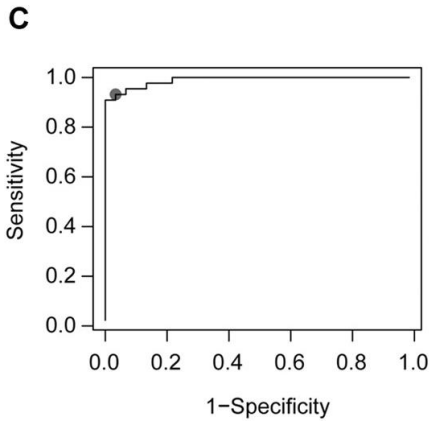
Cutaneous T-cell lymphomas (CTCLs) are the most frequent primary skin lymphomas. Nevertheless, diagnosis of early disease has proven difficult because of a clinical and histologic resemblance to benign inflammatory skin diseases. To address whether microRNA (miRNA) profiling can discriminate CTCL from benign inflammation, we studied miRNA expression levels in 198 patients with CTCL, peripheral T-cell lymphoma (PTL), and benign skin diseases (psoriasis and dermatitis). Using microarrays, we show that the most induced (miR-326, miR-663b, and miR-711) and repressed (miR-203 and miR-205) miRNAs distinguish CTCL from benign skin diseases with > 90% accuracy in a training set of 90 samples and a test set of 58 blinded samples. These miRNAs also distinguish malignant and benign lesions in an independent set of 50 patients with PTL and skin inflammation and in experimental human xenograft mouse models of psoriasis and CTCL. Quantitative (q)RT-PCR analysis of 103 patients with CTCL and benign skin disorders validates differential expression of 4 of the 5 miRNAs and confirms previous reports on miR-155 in CTCL. A qRT-PCR–based classifier consisting of miR-155, miR-203, and miR-205 distinguishes CTCL from benign disorders with high specificity and sensitivity, and with a classification accuracy of 95%, indicating that miRNAs have a high diagnostic potential in CTCL. (*Blood*. 2011;118(22): 5891-5900)

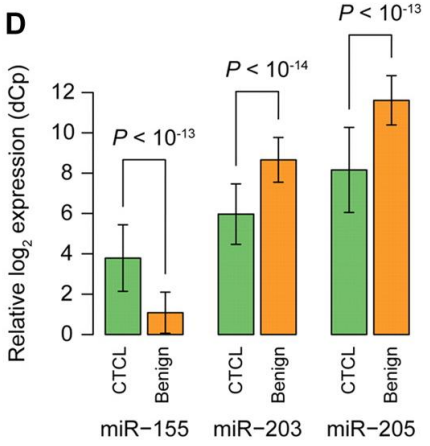
Expression profiles for highly significant miRNAs.



91% sensitivity at 97% specificity

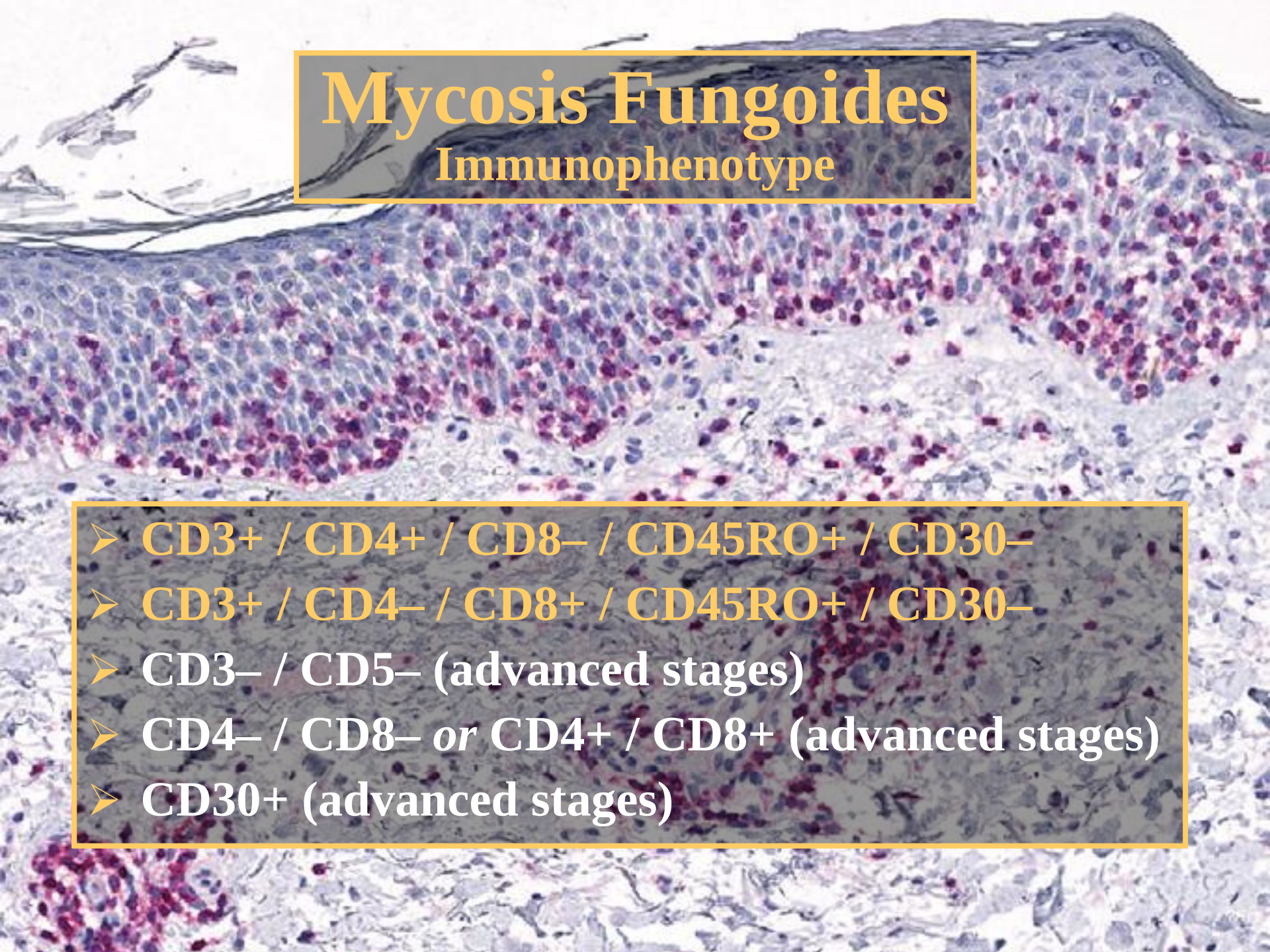
95% classification accuracy





Ralfkiaer U et al. Blood 2011;118:5891-5900

blood



Mycosis Fungoides
Immunophenotype

- CD3+ / CD4+ / CD8– / CD45RO+ / CD30–
- CD3+ / CD4– / CD8+ / CD45RO+ / CD30–
- CD3– / CD5– (advanced stages)
- CD4– / CD8– *or* CD4+ / CD8+ (advanced stages)
- CD30+ (advanced stages)

Follicular center helper T-cell (TFH) marker positive mycosis fungoides/Sezary syndrome

Howard J Meyerson[1], Amad Awadallah[1], Peter Pavlidakey[1], Kevin Cooper[2], Kord Honda[2] and John Miedler[1]

[1]*Department of Pathology, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH, USA and* [2]*Department of Dermatology, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH, USA*

We identified 11 patients with CD10(+) cutaneous T-cell lymphoma by flow cytometry. All cases were CD4(+) and CD8(−). Three patients had extensive lymphadenopathy, systemic symptoms and an aggressive clinical course consistent with angioimmunoblastic T-cell lymphoma or peripheral T-cell lymphoma. However, 8 of the 11 patients had a prolonged disease course with gross morphology, histology and tumor cell phenotype indistinguishable from mycosis fungoides or Sezary syndrome. Immunohistochemical studies confirmed CD10 expression in seven of the eight cases and revealed the lymphoma cells were Bcl-6(+), PD-1(+), and EBV(−). Two had significant expression of CXCL-13(+). The findings indicate that lymphoma cells from mycosis fungoides or Sezary syndrome may express follicular center helper T-cell markers CD10, Bcl-6, and PD-1 and occasionally CXCL-13. The expression of these markers in some cases of mycosis fungoides/Sezary syndrome suggests follicular center helper T-cell differentiation and may lead to confusion in distinguishing mycosis fungoides/Sezary syndrome from other follicular center helper T-cell marker positive T-cell lymphomas with cutaneous manifestations.

Modern Pathology (2013) **26,** 32–43; doi:10.1038/modpathol.2012.124; published online 24 August 2012

Keywords: Bcl-6; CD10; cutaneous T-cell lymphoma; flow cytometry; follicular helper T-cell; mycosis fungoides; Sezary syndrome

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Volume 34, Number 2, Part 1

Mycosis fungoides expressing γ/δ T-cell receptors

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Primary cutaneous T-cell lymphoma (CTCL) expressing γ/δ T-cell receptors (TCRs) is rare. From the few cases reported,[1-7] it is not possible to establish it as a separate clinicopathologic entity,[6,8] although a more aggressive course has been suggested.[9] We report an additional case of primary γ/δ CTCL.

CASE REPORT

A 68-year-old man had a spreading erythematous eruption of mildly scaly patches and plaques that had appeared 1 year earlier. A biopsy specimen confirmed the diagnosis of plaque-stage mycosis fungoides. Within 4 months ulcerated nodules developed. A biopsy specimen revealed typical features of mycosis fungoides with many hyperchromatic cerebriform cells in both the epidermis and the dermis (Fig. 1).

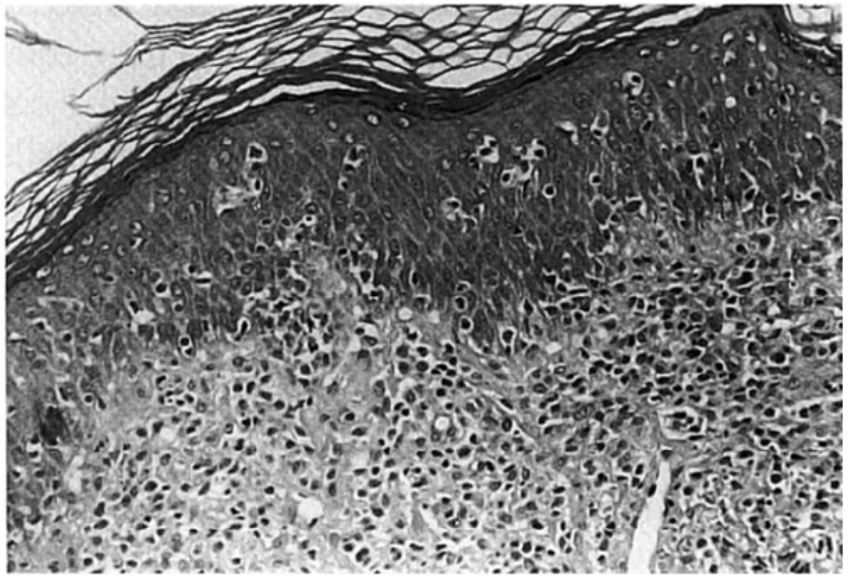


Fig. 1. Typical features of mycosis fungoides. (Hematoxylin-eosin stain; original magnification ×200.)

TCR-γ Expression in Primary Cutaneous T-cell Lymphomas

Socorro Maria Rodríguez-Pinilla, MD, PhD,† Pablo L. Ortiz-Romero, MD, PhD,‡ Verónica Monsalvez, MD,‡ Itziar Eraña Tomás, MD,§ Manuel Almagro, MD,‖ Amparo Sevilla, MD,¶ Gloria Camacho, MD,# María Isabel Longo, MD,** Águeda Pulpillo, MD,†† Julio Alexander Diaz-Pérez, MD,‡‡ Santiago Montes-Moreno, MD,*§§ Yolanda Castro, MD,‖‖ Begoña Echevarría, MD,¶¶ Izaskun Trébol, MD,## Carlos Gonzalez, MD,*** Lydia Sánchez, Bsc,††† Alberto Puime Otín, MD,† Luis Requena, MD, PhD,‡‡‡ Jose L. Rodríguez-Peralto, MD, PhD,§§§ Lorenzo Cerroni, MD, PhD,‖‖‖ and Miguel Ángel Piris, MD, PhD*§§*

Abstract: Primary cutaneous γδ T-cell lymphomas (PCGD-TCLs) are considered a subgroup of aggressive cytotoxic T-cell lymphomas (CTCLs). We have taken advantage of a new, commercially available antibody that recognizes the T-cell receptor-γ (TCR-γ) subunit of the TCR in paraffin-embedded tissue. We have analyzed a series of 146 primary cutaneous T-cell lymphomas received for consultation or a second opinion in the CNIO Pathology Department. Cases were classified according to the World Health Organization 2008 classification as mycosis fungoides (MF; n = 96), PCGD-TCLs (n = 5), pagetoid reticulosis (n = 6), $CD30^+$ primary cutaneous anaplastic large cell lymphomas (n = 5), primary cutaneous $CD8^+$ aggressive epidermotropic CTCLs (n = 3), primary cutaneous CTCL, not otherwise specified (n = 4), and extranodal nasal-type NK/T-cell lymphomas primarily affecting the skin or subcutaneous tissue (n = 11). Sixteen cases of the newly named lymphomatoid papulosis type D (LyP-D; n = 16) were also included. In those cases positive for TCR-γ, a further panel of 13 antibodies was used for analysis, including TIA-1, granzyme B, and perforin. Clinical and follow-up data were recorded in all cases. Twelve cases (8.2%) were positive for TCR-γ, including 5 PCGD-TCLs, 2 MFs, and 5 LyP-Ds. All 5 PCGD-TCL patients and 1 MF patient died of the disease, whereas the other MF patient and all those with LyP-D were alive. All cases expressed cytotoxic markers, were frequently $CD3^+/CD8^+$, and tended to lose CD5 and CD7 expressions. Eight of 12 and 5 of 11 cases were $CD30^+$ and $CD56^+$, respectively. Interestingly, 5/12 TCR-γ-positive cases also expressed TCR-BF1. All cases analyzed were negative for Epstein-Barr virus–encoded RNA. In conclusion, TCR-γ expression seems to be rare and is confined to cytotoxic primary cutaneous TCLs. Nevertheless, its expression is not exclusive to PCGD-TCLs, as TCR-γ protein can be found in other CTCLs. Moreover, its expression does not seem to be associated with bad prognosis by itself, as it can be found in cases with good and bad outcomes.

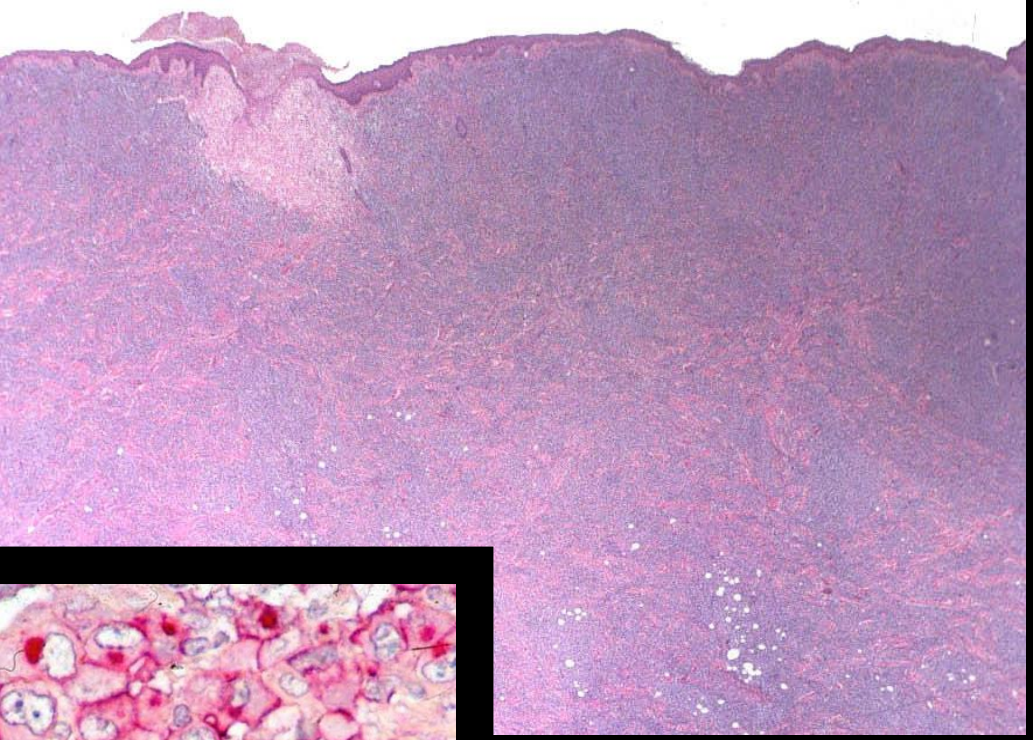
Key Words: TCR-γ, CTCL, prognosis

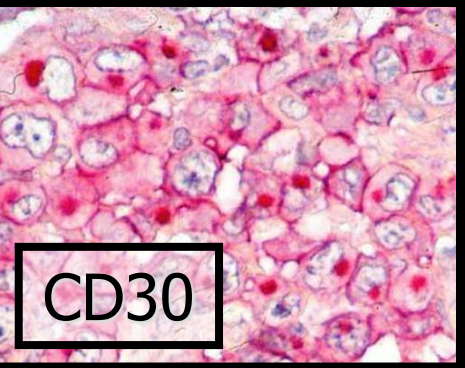
(*Am J Surg Pathol* 2013;37:375–384)

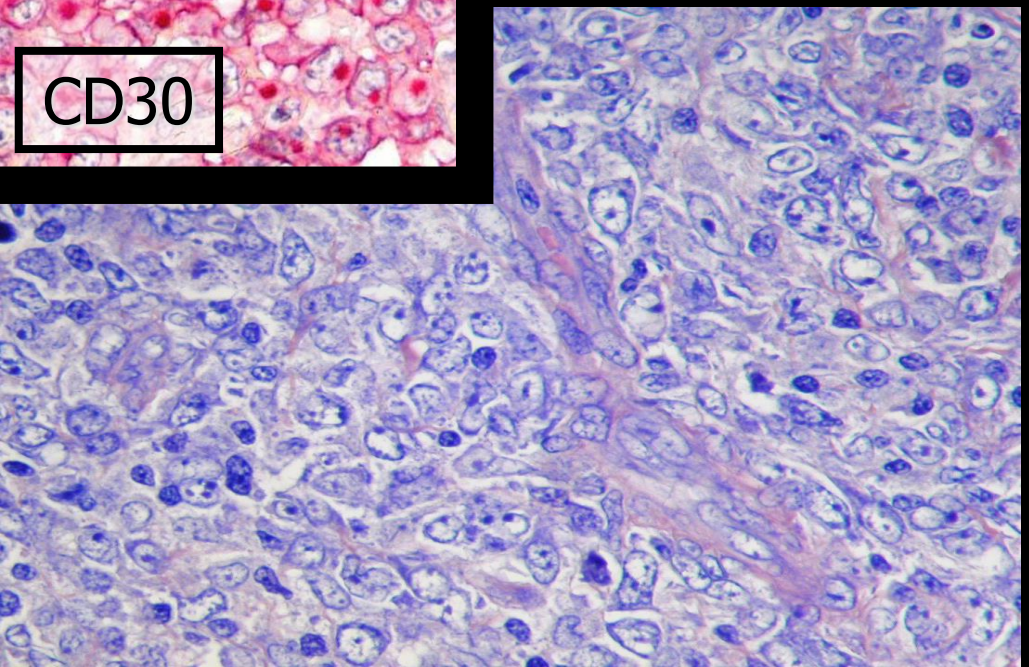
TABLE 2. Clinical Characteristics of Primary Cutaneous TCLs Expressing TCR-γ

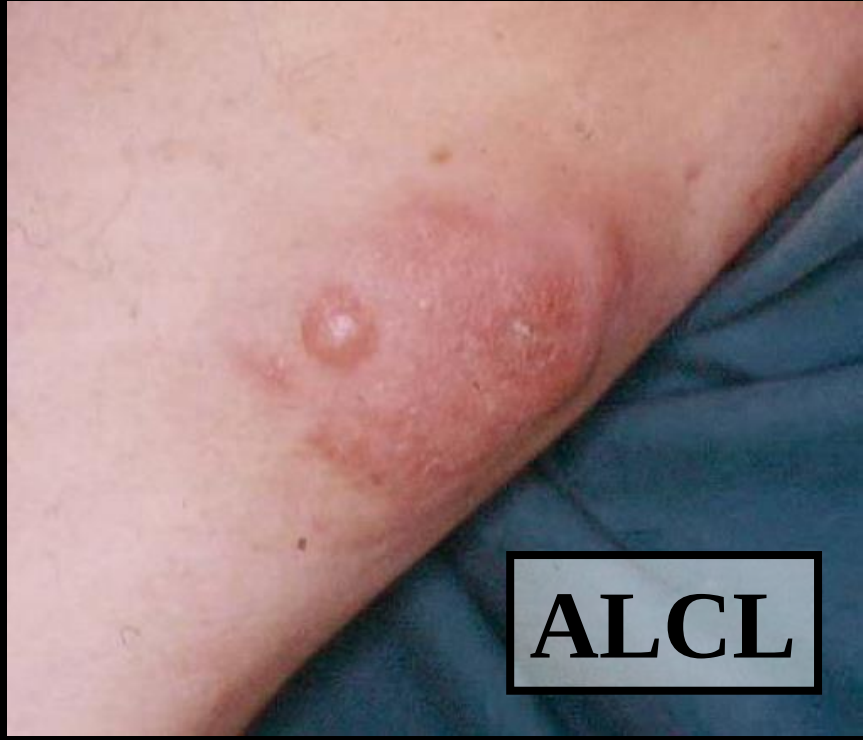
Case	Diagnosis	Sex/ Age	Presenting Skin Lesion	Location	Type of Lesion (Biopsy)	Extent of Cutaneous Involvement	Treatments	Status	Overall Survival (mo)
1	PCGD-TCL	M/29	Nodule	Trunk and limbs	Nodule	Multifocal	Polychemotherapy	DOL	9
2	PCGD-TCL	M/87	Subcutaneous nodule	Trunk and limbs	Nodule	Multifocal	Chlorambucil + prednisone	DOL	4
3	PCGD-TCL	F/70	Subcutaneous nodule	Trunk and limbs	Nodule	Multifocal	Methotrexate, BXT, CHOP, autologous BMT	DOL	15
4	PCGD-TCL	M/64	Ulcerated nodule	Leg and forehead	Tumor	2 tumors	PUVA, RT, CHOP	DOL	16
5	PCGD-TCL	M/51	Ulcerated plaques	Generalized	Plaque	Multifocal	Interferon, chlorambucil + prednisone	DOL	2
6	MF tumoral	F/60	Patches/ plaques	Generalized	Tumor	Multifocal	PUVA, BXT, RT, Ontak, CHOP, photopheresis	DOL	66
7	MF with large cells	M/48	Patches/ plaques	Generalized	Plaque	Multifocal	Methotrexate, BXT, PUVA	A+	> 44
8	LyP-D	F/24	Papules self-healing	Limbs	Papule	Multifocal	PUVA	A−	> 36
9	LyP-D	F/47	Papules self-healing	Trunk and limbs	Papule	Multifocal	PUVA + local steroids	A−	204
10	LyP-D	F/18	Papules self healing	Trunk and limbs	Papule	Multifocal	Not treated	A−	24
11	LyP-D	F/12	Papules self-healing	Trunk and limbs	Papule	Multifocal	Not treated	A−	> 36
12	LyP-D	M/26	Papules self-healing	Trunk and limbs	Papule	Multifocal	Not treated	A−	4

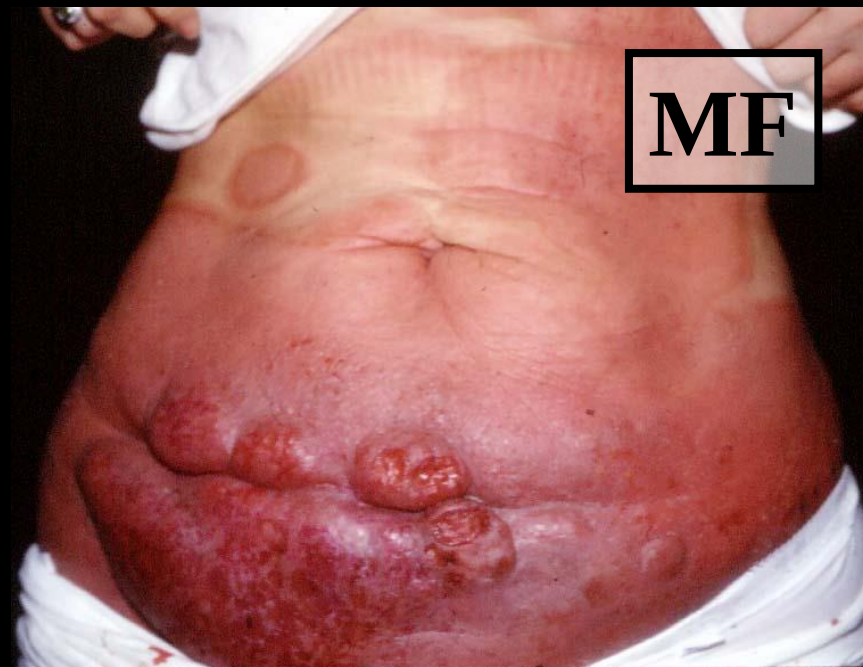
A− indicates alive without disease; A+, alive with disease; DOL, died of lymphoma.




CD30




ALCL


MF

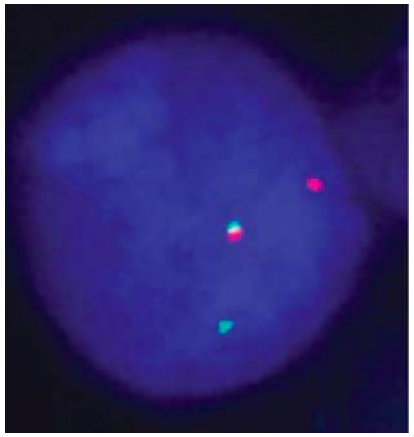
Specificity of *IRF4* translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies

David A Wada[1,2], Mark E Law[1], Eric D Hsi[3], David J DiCaudo[4], Linglei Ma[5], Megan S Lim[5], Aieska de Souza[6], Nneka I Comfere[2], Roger H Weenig[7], William R Macon[1], Lori A Erickson[1], Nazan Özsan[8], Stephen M Ansell[9], Ahmet Dogan[1] and Andrew L Feldman[1]

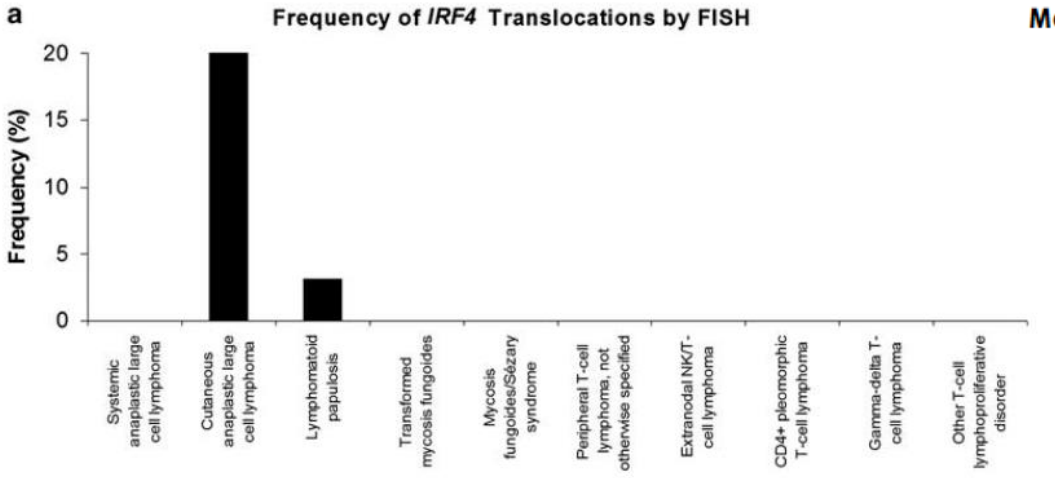
[1]*Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA;* [2]*Department of Dermatology, Mayo Clinic, Rochester, MN, USA;* [3]*Department of Clinical Pathology, Cleveland Clinic Foundation, Cleveland, OH, USA;* [4]*Department of Dermatology, Mayo Clinic, Scottsdale, AZ, USA;* [5]*Department of Pathology, University of Michigan, Ann Arbor, MI, USA;* [6]*Department of Dermatology, NYU Lagone Medical Center, New York, NY, USA;* [7]*Associated Skin Care Specialists, PA, Fridley, MN, USA;* [8]*Department of Pathology, Ege University, Izmir, Turkey and* [9]*Division of Hematology, Mayo Clinic, Rochester, MN, USA*

Current pathologic criteria cannot reliably distinguish cutaneous anaplastic large cell lymphoma from other CD30-positive T-cell lymphoproliferative disorders (lymphomatoid papulosis, systemic anaplastic large cell lymphoma with skin involvement, and transformed mycosis fungoides). We previously reported *IRF4* (interferon regulatory factor-4) translocations in cutaneous anaplastic large cell lymphomas. Here, we investigated the clinical utility of detecting *IRF4* translocations in skin biopsies. We performed fluorescence *in situ* hybridization (FISH) for *IRF4* in 204 biopsies involved by T-cell lymphoproliferative disorders from 182 patients at three institutions. In all, 9 of 45 (20%) cutaneous anaplastic large cell lymphomas and 1 of 32 (3%) cases of lymphomatoid papulosis with informative results demonstrated an *IRF4* translocation. Remaining informative cases were negative for a translocation (7 systemic anaplastic large cell lymphomas; 44 cases of mycosis fungoides/Sézary syndrome (13 transformed); 24 peripheral T-cell lymphomas, not otherwise specified; 12 CD4-positive small/medium-sized pleomorphic T-cell lymphomas; 5 extranodal NK/T-cell lymphomas, nasal type; 4 gamma-delta T-cell lymphomas; and 5 other uncommon T-cell lymphoproliferative disorders). Among all cutaneous T-cell lymphoproliferative disorders, FISH for *IRF4* had a specificity and positive predictive value for cutaneous anaplastic large cell lymphoma of 99 and 90%, respectively ($P=0.00002$, Fisher's exact test). Among anaplastic large cell lymphomas, lymphomatoid papulosis, and transformed mycosis fungoides, specificity and positive predictive value were 98 and 90%, respectively ($P=0.005$). FISH abnormalities other than translocations and IRF4 protein expression were seen in 13 and 65% of cases, respectively, but were nonspecific with regard to T-cell lymphoproliferative disorder subtype. Our findings support the clinical utility of FISH for *IRF4* in the differential diagnosis of T-cell lymphoproliferative disorders in skin biopsies, with detection of a translocation favoring cutaneous anaplastic large cell lymphoma. Like all FISH studies, *IRF4* testing must be interpreted in the context of morphology, phenotype, and clinical features.

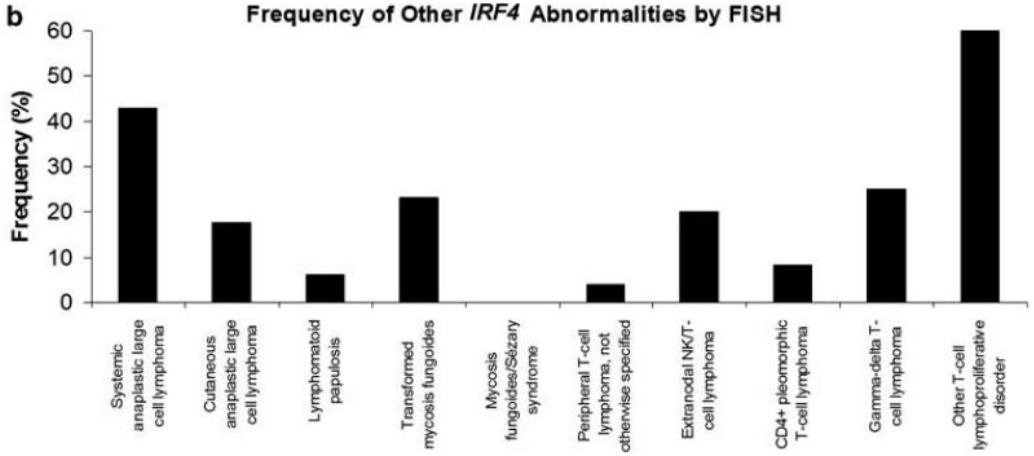
Modern Pathology (2011) **24,** 596–605; doi:10.1038/modpathol.2010.225; published online 17 December 2010



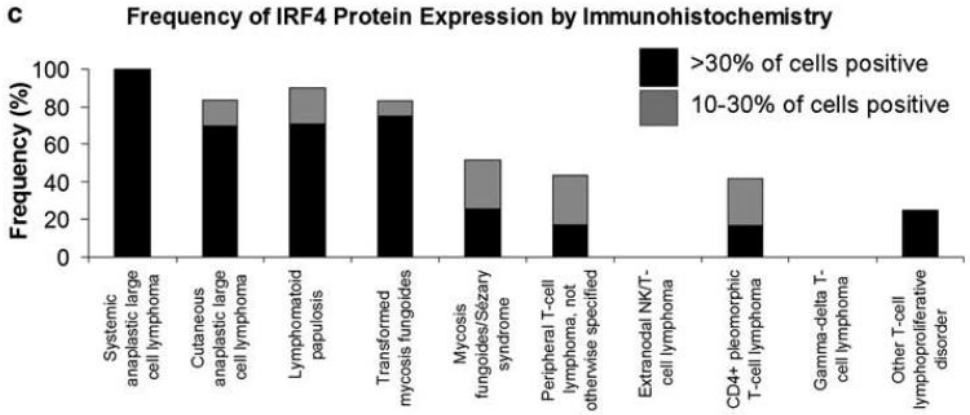
a


Frequency of IRF4 Translocations by FISH
Frequency (%)
0
5
10
15
20
Systemic anaplastic large cell lymphoma
Cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Transformed mycosis fungoides
Mycosis fungoides/Sézary syndrome
Peripheral T-cell lymphoma, not otherwise specified
Extranodal NK/T-cell lymphoma
CD4+ pleomorphic T-cell lymphoma
Gamma-delta T-cell lymphoma
Other T-cell lymphoproliferative disorder

b


Frequency of Other IRF4 Abnormalities by FISH
Frequency (%)
0
10
20
30
40
50
60
Systemic anaplastic large cell lymphoma
Cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Transformed mycosis fungoides
Mycosis fungoides/Sézary syndrome
Peripheral T-cell lymphoma, not otherwise specified
Extranodal NK/T-cell lymphoma
CD4+ pleomorphic T-cell lymphoma
Gamma-delta T-cell lymphoma
Other T-cell lymphoproliferative disorder

c


Frequency of IRF4 Protein Expression by Immunohistochemistry
>30% of cells positive
10-30% of cells positive
Frequency (%)
0
20
40
60
80
100
Systemic anaplastic large cell lymphoma
Cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Transformed mycosis fungoides
Mycosis fungoides/Sézary syndrome
Peripheral T-cell lymphoma, not otherwise specified
Extranodal NK/T-cell lymphoma
CD4+ pleomorphic T-cell lymphoma
Gamma-delta T-cell lymphoma
Other T-cell lymphoproliferative disorder

STUDY

Lymphomatoid Papulosis

Reappraisal of Clinicopathologic Presentation and Classification Into Subtypes A, B, and C

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Objectives: To analyze clinicopathologic features of lymphomatoid papulosis and delineate the characteristics of histopathologic variants (types A, B, and C).

Design: Retrospective nonrandomized study.

Setting: University-based dermatologic referral center.

Patients: Eighty-five patients with lymphomatoid papulosis. Clinical data and 1 or more biopsy specimens were available for review in all cases. When possible, immunophenotypic and molecular analyses were carried out.

Results: Of these patients, 78 presented only 1 histopathologic subtype of lymphomatoid papulosis (64 had type A, 3 had type B, and 11 had type C). The last 7 patients presented more than 1 subtype (1 had A and B, 5 had A and C, and 1 had A, B, and C). Two patients had regional lymphomatoid papulosis, an unusual clinical presentation characterized by groups of lesions localized to 1 anatomic region. We observed, we believe for the first time, that some histopathologic patterns, ie, follicular mucinosis (n=1), syringotropic infiltrates (n=1), epidermal vesicle formation (n=2), and syringosquamous metaplasia (n=1), were associated with lymphomatoid papulosis. A distribution along hair follicles, or follicular lymphomatoid papulosis, was observed in 5 biopsy specimens. A bandlike rather than a wedge distribution of the infiltrate was seen in 5 specimens from patients with lymphomatoid papulosis type A. Of 8 patients who had associated lymphoid malignancies, 4 had Hodgkin disease and 4 had mycosis fungoides.

Conclusions: Lymphomatoid papulosis is a cutaneous disorder with multiple clinicopathologic features. Differentiating between mycosis fungoides and anaplastic large cell lymphoma may be very difficult and sometimes impossible. In the spectrum of $CD30^+$ cutaneous lymphoproliferative disorders, boundaries between these 2 entities are not clear-cut.

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LyP type D

A Variant of Lymphomatoid Papulosis Simulating Primary Cutaneous Aggressive Epidermotropic CD8+ Cytotoxic T-cell Lymphoma. Description of 9 Cases

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Abstract: Lymphomatoid papulosis (LyP) is a recurrent, self-healing eruption belonging to the spectrum of cutaneous CD30+lymphoproliferative disorders. Three main histologic subtypes of LyP are recognized: type A (histiocytic), type B (mycosis fungoides—(MF)-like), and type C (anaplastic large cell lymphoma–like). We reviewed 26 biopsies from 9 patients (M:F = 6:3, median age: 29; mean age 27,2; age range 10 to 38) who presented with clinical features typical of LyP but with histopathologic aspects that resembled primary cutaneous aggressive epidermotropic CD8+cytotoxic T-cell lymphoma. In all but 1 case atypical lymphoid cells showed expression of CD30, and in 8 of 9 cases a T-cell cytotoxic phenotype could be observed (βF1+, CD3+, CD4−, CD8+). Expression of at least 1 cytotoxic marker (TIA-1, granzyme B) was observed in all cases. Polymerase chain reaction analysis of the T-cell receptor genes revealed a monoclonal rearrangement in 2 of 5 cases tested. Follow-up data available for 8 patients (mean follow-up time: 84 mo, median: 32.5 mo; range: 1 to 303 mo) revealed that none of them developed systemic involvement or signs of other cutaneous lymphomas. This cytotoxic variant of LyP may be histopathologically indistinguishable from primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, and may be the source of pitfalls in the diagnosis and classification. We propose the term LyP type D for this unusual variant of the disease. Accurate clinicopathologic correlation is required in this setting, with crucial implications regarding prognosis and management of patients.

Key Words: lymphomatoid papulosis, primary cutaneous aggressive epidermotropic CD8+cytotoxic T-cell lymphoma, mycosis fungoides, cytotoxic lymphoma, cutaneous T-cell lymphoma

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LyP type E

Angioinvasive Lymphomatoid Papulosis

A New Variant Simulating Aggressive Lymphomas

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Abstract: Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders. Clinically, LyP is characterized by a variable number of self-healing papulo-nodular lesions, with the typical waxing and waning course. Histologically, 4 types (A, B, C, and D) have been delineated. Angioinvasive growth and large ulcers are rare findings in LyP and simulate aggressive lymphoma. We retrospectively analyzed the clinicopathologic and molecular features of angioinvasive LyP in a series of 16 patients. This new form of LyP is characterized by oligolesional papules that rapidly ulcerate and evolve into large necrotic eschar-like lesions with a diameter of 1 to 4 cm and an angiocentric and angiodestructive infiltrate of small-sized to medium-sized atypical lymphocytes expressing CD30 and frequently CD8. As in other forms of LyP, the lesions underwent spontaneous regression after a few weeks. Recurrences were common, but the prognosis was excellent with no extracutaneous spread or disease-related deaths. Complete remission occurred in 9 of 16 patients (56%). This LyP variant should be distinguished from aggressive forms of angiocentric and angiodestructive and cytotoxic T-cell lymphomas. We propose the term LyP type E for this clinically and histologically unusual variant.

Key Words: lymphoma, skin, CD8, CD30, lymphomatoid papulosis, cytotoxic lymphoma, angiotropic

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LyP types (A, B, C, and D) have been identified. Type A is characterized by the presence of large pleomorphic or anaplastic $CD30^+$ T cells scattered or in small clusters within the background of eosinophilic and neutrophilic granulocytes, histiocytes, and small lymphocytes. Type B shows epidermotropic infiltrates of small-sized to medium-sized lymphoid cells, with variable extent of CD30 expression. In type C, a nodular dense infiltrate of cohesive sheets of pleomorphic or anaplastic $CD30^+$ cells is present, and it usually contains only a few eosinophilic or neutrophilic granulocytes.[3–7] Recently, type D has been described, which displays an epidermotropic infiltrate of $CD8^+$ and $CD30^+$ small-sized to medium-sized lymphoid cells.[8] Within the same patient, different lesions may show different histologic types, either synchronously or metachronously.[9] The $CD30^+$ lymphoid cells may express CD4, CD8, or CD56, with CD4 immunoreactivity being the most common phenotype.[10,11] Independent of its histologic pattern and the immunophenotype, LyP is clinically characterized by a variable number of self-healing papulo-nodular lesions, with the typical waxing and waning course. The individual lesions undergo spontaneous regression within a few weeks, sometimes accompanied by ulceration on top of the lesions and occasionally leaving behind varioliform scars. Despite the

LyP type F?

Chromosomal Rearrangements of 6p25.3 Define a New Subtype of Lymphomatoid Papulosis

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Abstract: Lymphomatoid papulosis (LyP) is an indolent cutaneous lymphoproliferative disorder with clinical and pathologic features overlapping those of both reactive conditions and aggressive lymphomas. Recurrent genetic abnormalities in LyP have not been previously identified. Here, we describe the clinical, immunophenotypic, and genetic characteristics of cutaneous lymphoproliferative lesions showing distinctive and previously undescribed histologic features in 11 patients. All patients were older adults (67 to 88 y) with predominantly localized lesions and clinical presentations suggesting benign inflammatory dermatoses or low-grade epithelial tumors. Histologically, lesions showed a biphasic growth pattern, with small cerebriform lymphocytes in the epidermis and larger transformed lymphocytes in the dermis. All had a T-cell immunophenotype. The pathologic features raised the possibility of an aggressive T-cell lymphoma such as transformed mycosis fungoides. However, no patient developed disseminated skin disease or extracutaneous spread. Untreated lesions regressed spontaneously. All cases harbored chromosomal rearrangements of the *DUSP22-IRF4* locus on 6p25.3. The overall findings suggest that these cases represent a newly recognized LyP subtype characterized by 6p25.3 rearrangements. The benign clinical course in all 11 patients despite pathologic features mimicking an aggressive lymphoma emphasizes the importance of clinicopathologic correlation, incorporating molecular genetic analysis when possible, during the evaluation of cutaneous lymphoproliferative disorders.

Key Words: lymphomatoid papulosis, cutaneous CD30-positive T-cell lymphoproliferative disorder, T-cell lymphoma, chromosomal translocation, fluorescence in situ hybridization, DUSP22, genetics

(*Am J Surg Pathol* 2013;37:1173–1181)

Lymphomatoid papulosis (LyP) is a chronic, recurring CD30-positive T-cell lymphoproliferative disorder (TLPD) that presents as multifocal papular lesions on the trunk, buttocks, and extremities of patients ranging in age from 4 to 88 years.[1,2] Five subtypes currently are recognized and/or have been proposed on the basis of their histologic and immunophenotypic features.[3–8] The most frequent, type A, is characterized by a dermal infiltrate of large transformed lymphocytes in a mixed inflammatory background.[9] Type B lesions have a predominantly intraepidermal lymphocytic infiltrate mimicking mycosis fungoides (MF). Type C lesions have sheets of large transformed lymphocytes in the dermis, with or without significant epidermotropism.[5] Type D LyP is a CD8-positive cytotoxic T-cell variant with epidermotropism.[6] Kempf et al[8] recently proposed another oligolesional, ulcerative, angioinvasive variant (type E).

We report 11 elderly patients with localized skin lesions clinically suggestive of inflammatory dermatoses, infections, or low-grade epithelial skin tumors. Pathologic findings raised the possibility of an aggressive lymphoid malignancy and consisted of a combination of pagetoid reticulosis–like intraepidermal lymphocytosis and a cohesive, nodular dermal infiltrate of highly proliferative CD30-positive tumor cells. However, all lesions showed

Chromosomal Rearrangements of 6p25.3 Define a New Subtype of Lymphomatoid Papulosis.
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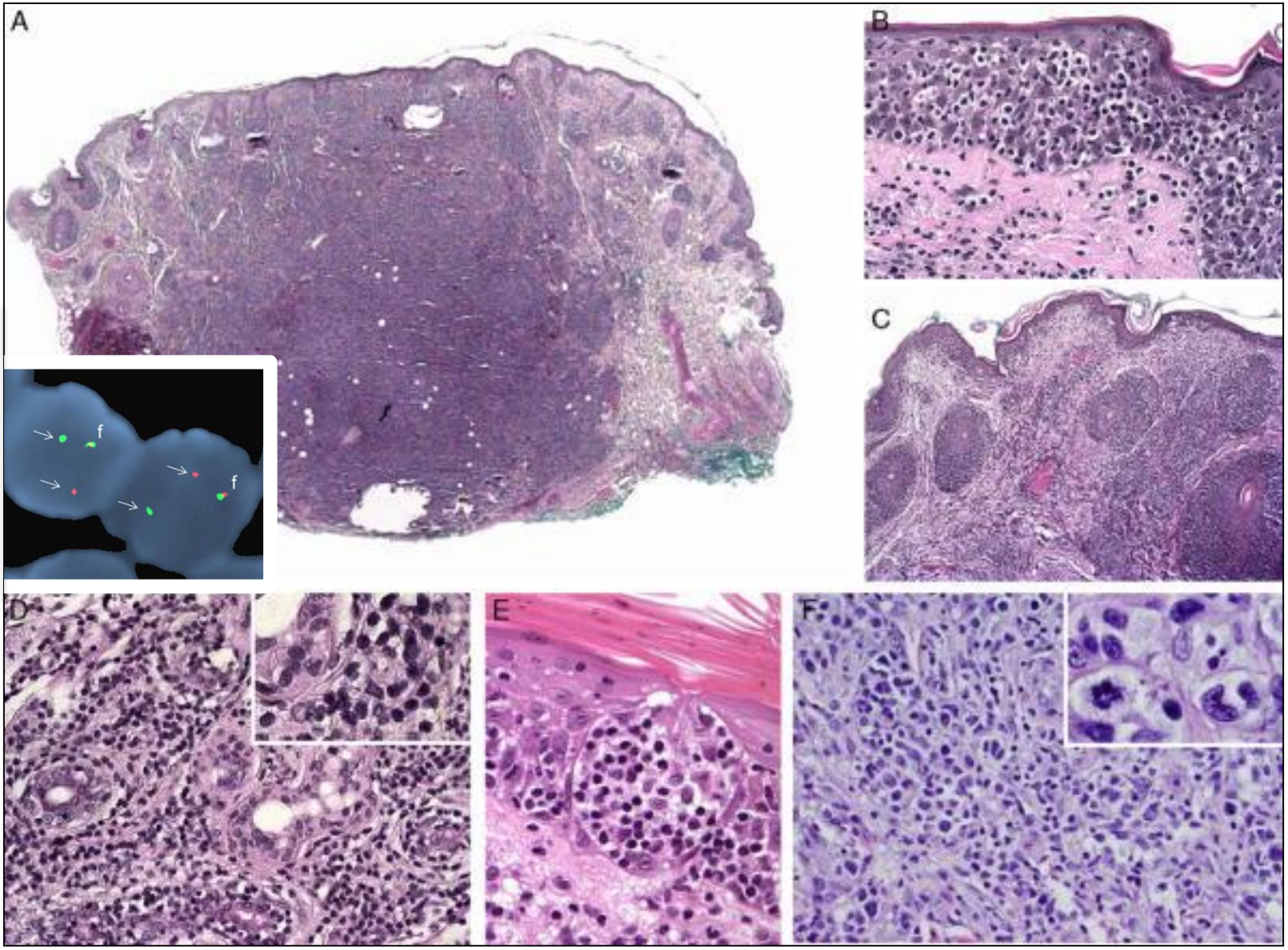

Histopathology

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Primary cutaneous anaplastic large cell lymphomas with 6p25.3 rearrangement exhibit particular histological features

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Intralymphatic Cutaneous Anaplastic Large Cell Lymphoma/Lymphomatoid Papulosis

Expanding the Spectrum of CD30-positive Lymphoproliferative Disorders

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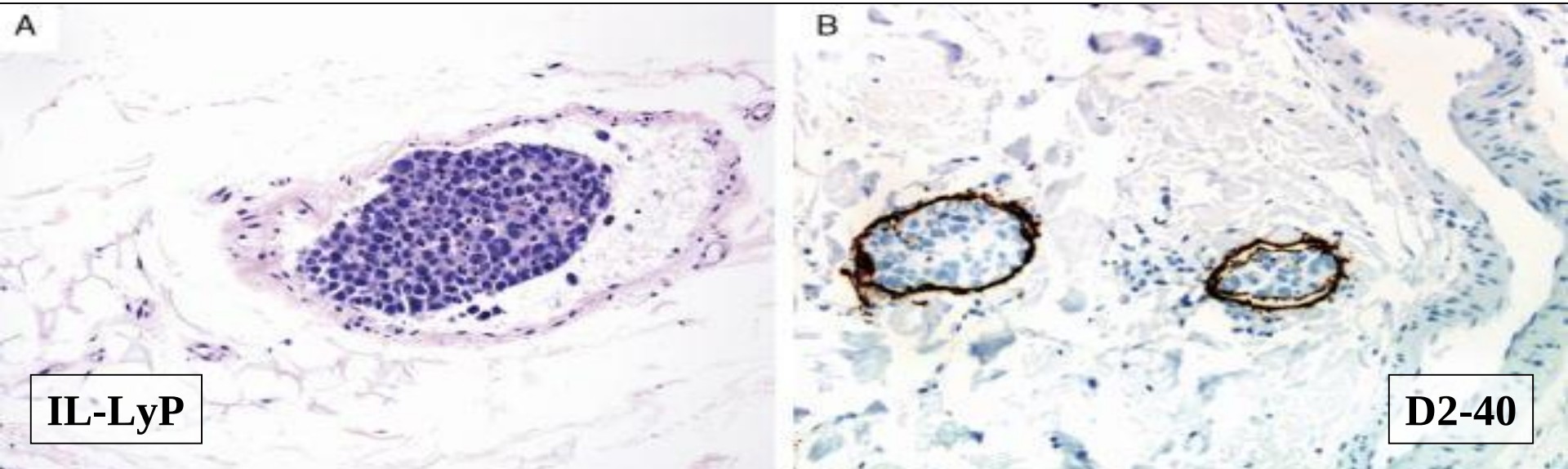

Cytotoxic T-cell and NK-cell Lymphomas

Current Questions and Controversies

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Abstract: The cytotoxic T-cell and natural killer (NK)-cell lymphomas and related disorders are important but relatively rare lymphoid neoplasms that frequently are a challenge for practicing pathologists. This selective review, based on a meeting of the International Lymphoma Study Group, briefly reviews T-cell and NK-cell development and addresses questions related to the importance of precise cell lineage (αβ-type T cell, γδ T cell, or NK cell), the implications of Epstein-Barr virus infection, the significance of anatomic location including nodal disease, and the question of further categorization of enteropathy-associated T-cell lymphomas. Finally, developments subsequent to the 2008 World Health Organization Classification, including the recognition of indolent NK-cell and T-cell disorders of the gastrointestinal tract are presented.

Key Words: cytotoxic T-cell lymphoma, γδ T cells, natural killer cells, enteropathy-associated T-cell lymphoma

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TABLE 3. Recently Recognized Cytotoxic T-cell and NK-cell Lesions Not Included in the 2008 WHO Classification

Indolent $CD8^+$ cytotoxic cutaneous T-cell lymphoproliferative diseases of the ear, face, and other acral sites
NK-cell enteropathy/lymphomatoid gastropathy
Indolent T-cell lymphoproliferative disease of the GI tract
Breast implant–associated ALK^- anaplastic large cell lymphoma

Primary Cutaneous CD4+ Small/Medium-sized Pleomorphic T-cell Lymphoma Expresses Follicular T-cell Markers

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Abstract: Cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (CSTCL) is a cutaneous T-cell lymphoma defined by a predominance of small-to-medium–sized CD4+ pleomorphic T cells, with a favorable clinical course. Cases are also characterized by the presence of a rich infiltrate of reactive B cells. Recently, it has been reported that follicular helper T cells (T_{FH} cells) display a distinct gene expression profile, positive for PD-1, CXCL13, and BCL-6. We report for the first time the expression of PD-1 and other T_{FH} cell markers in CSTCLs and discuss its biologic significance. Sixteen CSTCLs were included in this study, and also 20 reactive inflammatory conditions, 10 primary cutaneous marginal zone, 10 follicular center lymphomas, and 5 primary CD30+ cutaneous lymphomas. They were immunohistochemically analyzed for a large panel of markers. Double immunoperoxidase labeling of paraffin sections was performed for PD-1, OCT-2, and BCL-6. Clonal Ig and T-cell receptor rearrangements and Epstein-Barr virus-encoded RNA expression were also evaluated. Morphologic and clinical data were reviewed. Histologic examination showed a dense polymorphic lymphoid infiltrate throughout the dermis. Atypical large CD4+ cells were positive for PD-1, CXCL13, and BCL-6 in all cases, and were attached in small clusters, or formed rosettes around CD30/OCT-2+ B blast cells. Epstein-Barr virus was not apparent in any of the cases. A dominant T-cell clone was identified in 14 cases, whereas polymerase chain reaction IgH gene rearrangement studies showed that all cases were polyclonal. None of the patients had lymphadenopathy or showed any evidence of systemic disease, nor did they have any previous history of mycosis fungoides or drug reactions. F_{TH} cell markers are not exclusive to angioimmunoblastic lymphadenopathy but may also be seen in neoplastic cells of CSTCLs. Moreover, these findings suggest that B-cell stimulation by F_{TH} could also take place in some cutaneous T-cell lymphomas.

Key Words: cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma, PD-1, CD10, BCL-6, CXCL13

(*Am J Surg Pathol* 2009;33:81–90)

Expression of Programmed Death-1 in Primary Cutaneous CD4-Positive Small/Medium-Sized Pleomorphic T-Cell Lymphoma, Cutaneous Pseudo-T-Cell Lymphoma, and Other Types of Cutaneous T-Cell Lymphoma

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Abstract: In this study we investigated whether programmed death-1 (PD-1) could serve as a useful diagnostic marker to differentiate between primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (PCSM-TCL) and cutaneous pseudo-T-cell lymphomas on the one hand and other types of cutaneous T-cell lymphomas (CTCLs) on the other. Formalin-fixed, paraffin-embedded skin biopsies from 26 patients with PCSM-TCL or pseudo-T-cell lymphoma, including 1 patient with a lymphomatoid drug eruption, and 52 skin biopsies from other types of CTCLs were stained for PD-1. In addition, PD-1-positive cases were stained with antibodies against BCL6, CXCL13, and CD10 to determine a possible relationship with follicular helper T (TFH) cells. In all 26 cases of PCSM-TCL or pseudo-T-cell lymphoma, the medium-sized to large-sized atypical T cells consistently expressed PD-1, BCL6, and CXCL13 but not CD10. PD-1 expression was found in only 2 of 21 cases of mycosis fungoides and in only 2 of 16 cases of cutaneous peripheral T-cell lymphoma, unspecified. All 4 patients with an aggressive epidermotropic cytotoxic $CD8^+$ CTCL and all 11 cases with a primary cutaneous $CD30^+$ lymphoproliferative disorder were negative for PD-1. In conclusion, PD-1 is typically expressed by atypical cells in PCSM-TCL and pseudo-T-cell lymphoma but is not expressed or is rarely expressed in other types of CTCLs. Therefore, it may serve as a suitable adjunct in differential diagnosis. Our results demonstrate that the atypical cells in PCSM-TCL and pseudo-T-cell lymphomas share a common TFH phenotype and support the view that most cases classified nowadays as PCSM-TCL are identical to cutaneous pseudo-T-cell lymphomas described previously.

Key Words: cutaneous lymphoma, T-cell lymphoma, PD-1, follicular helper T cell, immunohistochemistry

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Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (PCSM-TCL) is a cutaneous T-cell lymphoma (CTCL) that has been included as a provisional entity and rare subtype of primary cutaneous peripheral T-cell lymphoma, not otherwise specified (PTCL,NOS), in recent cutaneous lymphoma classifications [World Health Organization (WHO)-European Organization for Research and Treatment of Cancer 2005; WHO 2008].[22,24] These PCSM-TCLs characteristically present with a solitary plaque or tumor that is generally localized on the face or the upper trunk and rarely present with multiple papules, plaques, or tumors.[3,10,24] In particular, patients presenting with a solitary skin lesion have an excellent prognosis.[2] Histologically, these lymphomas show nodular-to-diffuse infiltrates with a predominance of $CD3^+$, $CD4^+$, $CD8^-$, $CD30^-$ small-sized to medium-sized pleomorphic T cells and a small proportion (< 30%) of large $CD4^+$ pleomorphic T cells. In most cases there is a considerable admixture with small reactive $CD8^+$ T cells and $CD20^+$ B cells, including some blast cells, histiocytes, and in some cases plasma cells and eosinophils. The clinical presentation, architecture, and cellular composition of these PCSM-TCLs are strikingly similar to those described previously in so-called pseudo-T-cell lymphomas.[16,17] Demonstration of a T-cell clone (common) and loss of pan-T-cell antigens (rare) are nowadays used as diagnostic criteria for PCSM-TCL,[1] but delineation between PCSM-TCL and pseudo-T-cell lymphomas is arbitrary and a matter of debate.

Recently, Rodriguez-Pinilla et al[19] reported that the large atypical $CD4^+$ T cells in PCSM-TCLs express programmed death-1 (PD-1), BCL6 ,and CXCL13. PD-1, which is located on chromosome 2q37, is a member of the CD28/CTLA-4 receptor family that regulates cellular

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ORIGINAL REPORT

Primary Cutaneous Small/Medium CD4$^+$ T-Cell Lymphomas: A Heterogeneous Group of Tumors With Different Clinicopathologic Features and Outcome

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2620-3364/$20.00

ABSTRACT

Purpose
To define the clinical and pathologic characteristics of primary cutaneous small/medium CD4$^+$ T-cell lymphoma (PCSM-TCL) and identify parameters of prognostic significance.

Patients and Methods
We have investigated 24 patients with primary cutaneous lymphomas composed of small/medium mature T-cells with a βF1, CD3, CD4$^+$ and/or noncytotoxic, CD8$^-$ and CD30$^-$ phenotype. The proliferation index and CD8$^+$ infiltrating cells were quantified with an automated image analysis system.

Results
Sixteen patients presenting with solitary or localized plaques or small nodules (< 3 cm) had an indolent course. Only three patients experienced repeated cutaneous relapses, and none of them died as a result of the disease after 1 to 168 months (median, 17 months) of follow-up. The tumors had a low proliferation (median Ki-67, 9% ± 5%) and an intense infiltrate of reactive CD8$^+$ (median, 20% ± 11.7%). Five patients presenting with rapidly evolving large tumors or nodules (≥ 5 cm) had an aggressive disease and died with extracutaneous dissemination 18 to 36 months after diagnosis (median, 23 months). These tumors had a significantly higher proliferation (median Ki-67, 22% ± 11.3%; $P < .05$) and lower number of infiltrating CD8$^+$ (median, 1% ± 3%; $P < .05$) than the previous group. A third group of three patients had a peculiar clinical presentation with multifocal relapsing lesions without extracutaneous dissemination after a long period of follow-up ranging from 41 to 92 months. Histologically, these cases had an intense infiltrate of eosinophils.

Conclusion
PCSM-TCL is a heterogeneous group of tumors with differentiated clinical and pathological characteristics with impact in the outcome of the patients.

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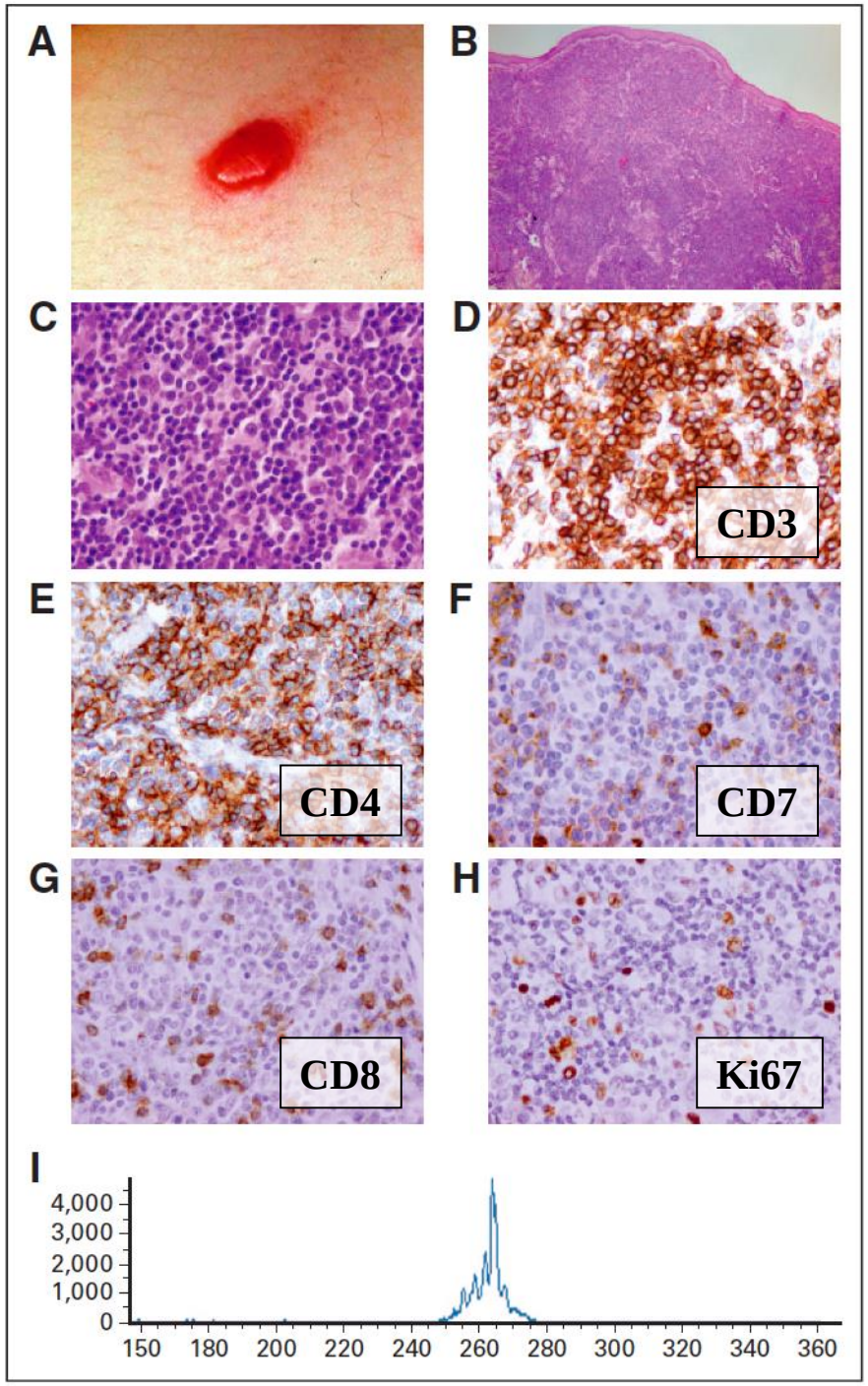

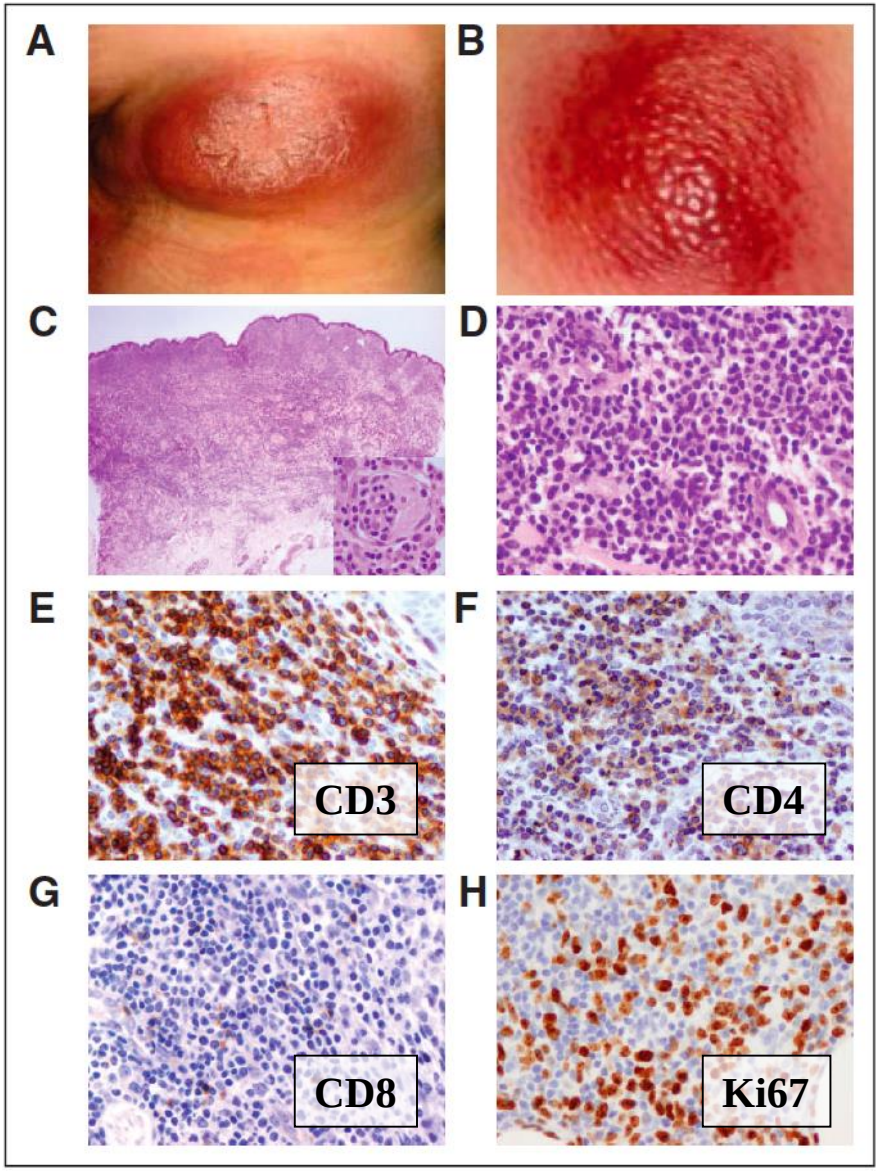

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Histopathology 2010, **56**, 548–555

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Primary cutaneous follicular variant of peripheral T-cell lymphoma NOS. A report of two cases

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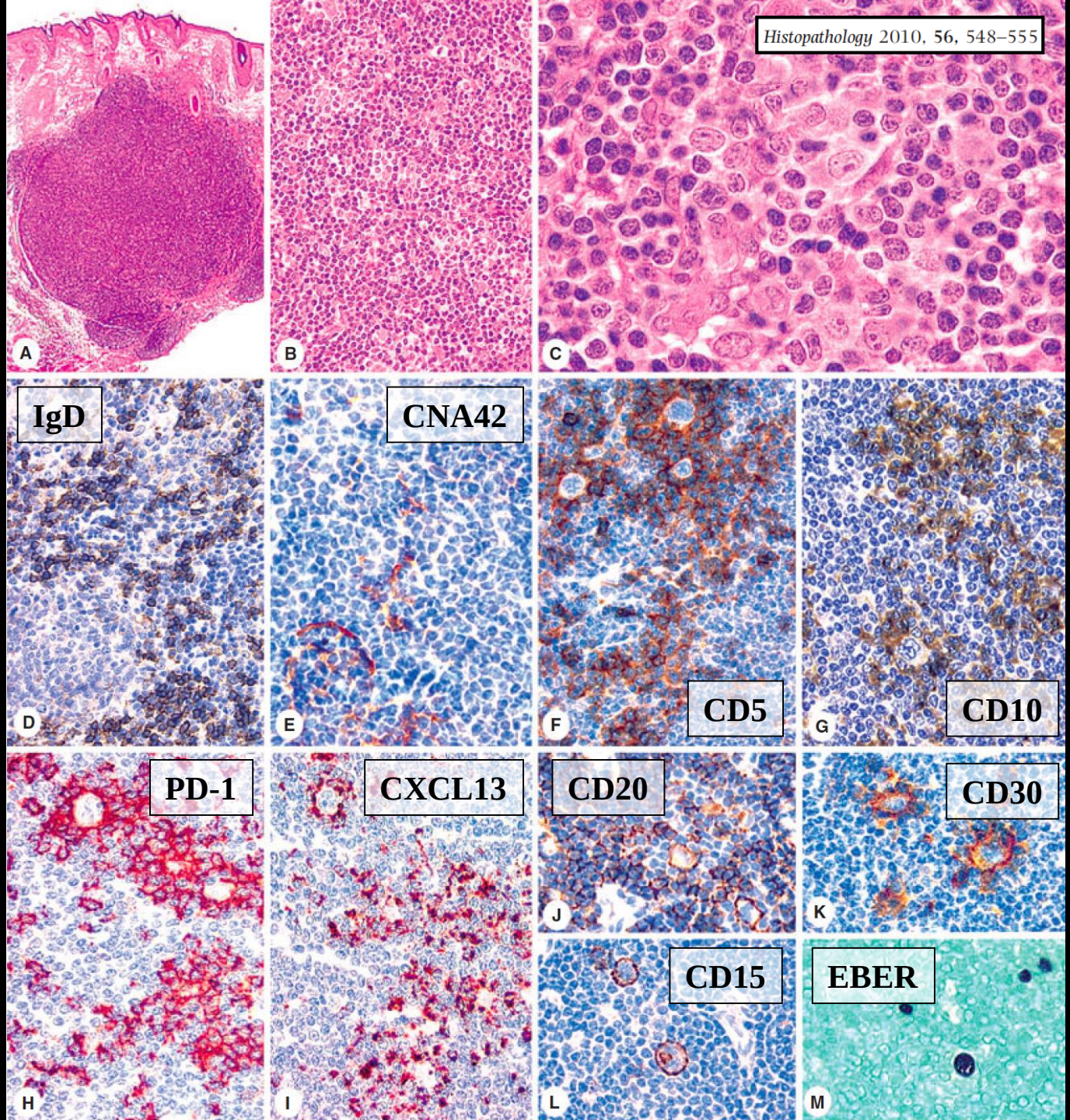
Sir: The World Health Organization (WHO) classification (2008) describes a variant of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) called 'follicular variant' (FV).[1] All cases show primary nodal localization and involve the proliferation of follicular helper T cells (TFH), a subset of normal lymphocytes expressing a particular immunophenotype. We report two cases of this lymphoma, appearing as primary skin tumours.

phoid cells with irregular nuclei (Figures 1B,C and 2B,C), which, in case 1 only, surrounded immunoblasts.

About 50–70% of cells in the dermal sheets were CD20+. GC remnants contained CD10+, Bcl-2–cells in a network of CD21+ and CD23+ follicular dendritic cells. They were surrounded by a hyperplastic IgD+ mantle zone. The pale areas, unstained with B markers, contained cells positive for CD2, CD3, CD4 and CD5, and negative for CD7, CD8, CD56, CD57 and TiA-1. Some cells (Table 1) expressed CD10, Bcl-6, CXCL13 and PD-1 (Figures 1D–M and 2D–G). This phenotype is reminiscent of the 'follicular helper' subset of T cells (TFH). In case 1, immunoblasts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