City of Hope

International Society for Cutaneous Lymphomas ISCL

# 5TH World Congress of Cutaneous Lymphomas


*Enhancing the Ability to Diagnose, Interpret and Apply Best Treatment Options for Cutaneous Lymphomas*

CHALLENGING CASES OF CUTANEOUS LYMPHOMAS| #46

# Molecularly-Annotated Case of CD30+ Gamma-Delta T-Cell Proliferation with Features of Primary Cutaneous Anaplastic Large Cell Lymphoma: a Wolf in Sheep's Clothing?

Robert E. LeBlanc, MD

Associate Professor of Pathology

Department of Pathology & Laboratory Medicine

Dartmouth-Hitchcock Medical Center

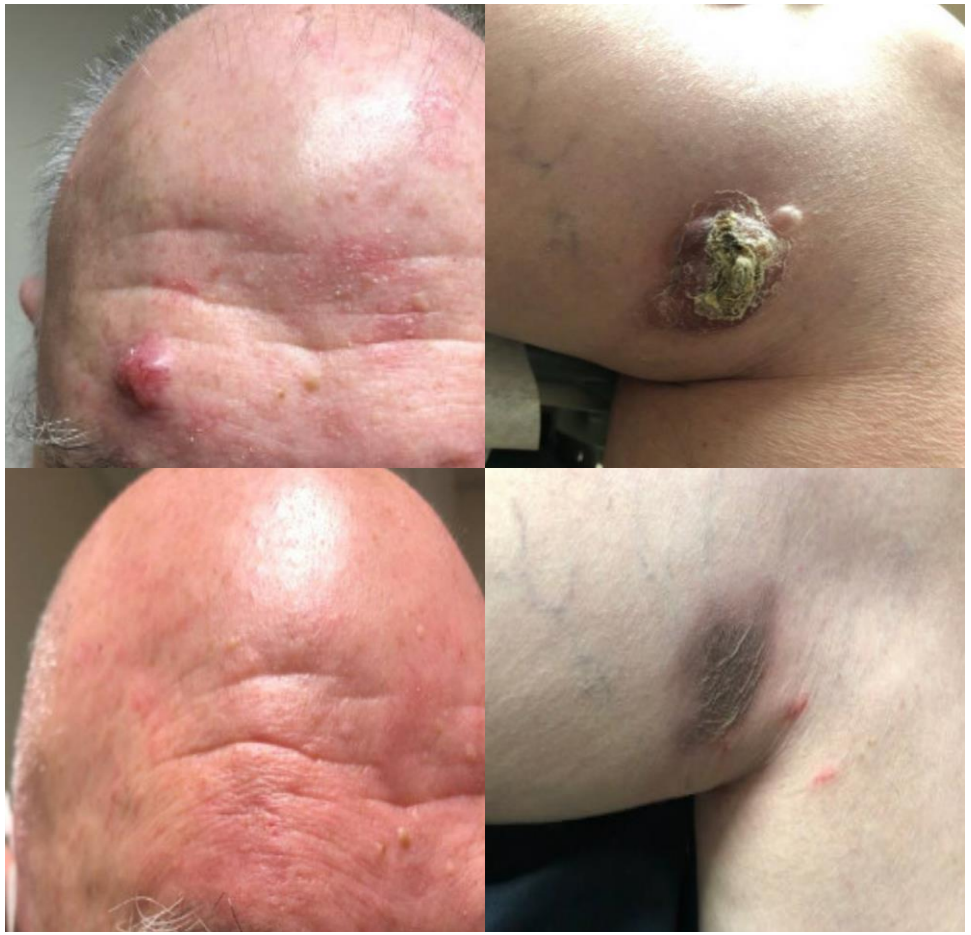
Lebanon, New Hampshire, USA

# Disclosures

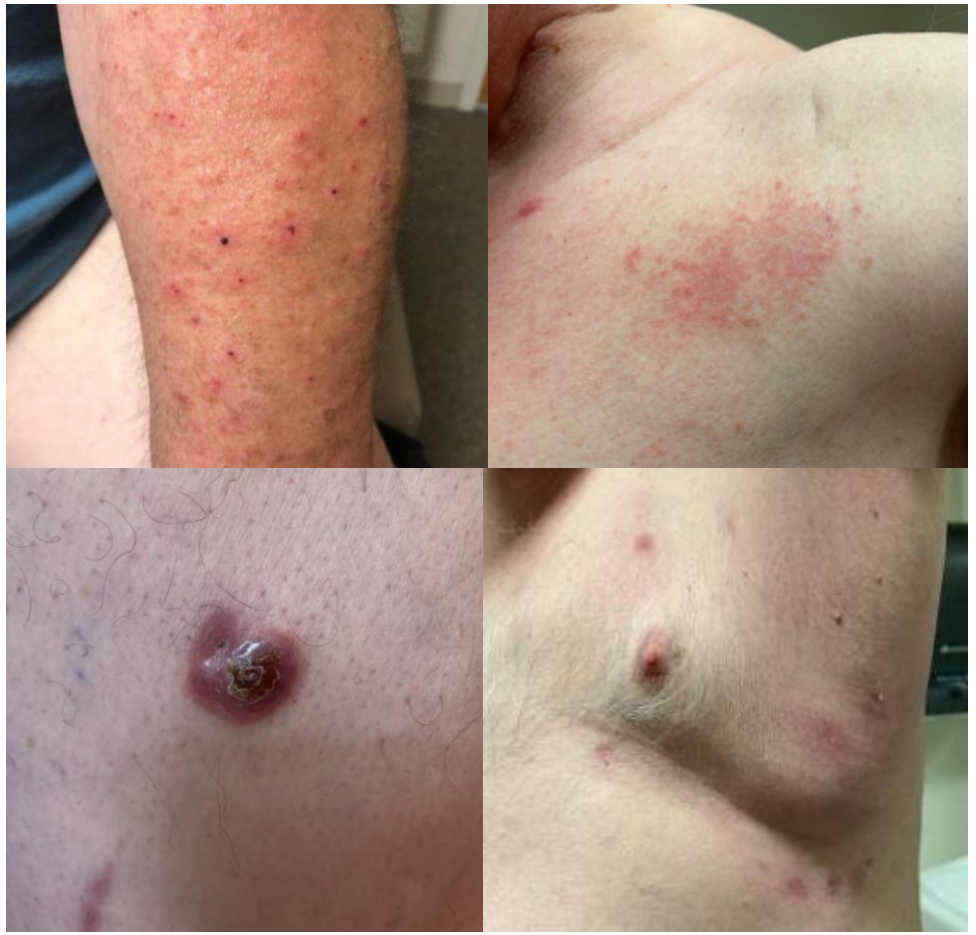
- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

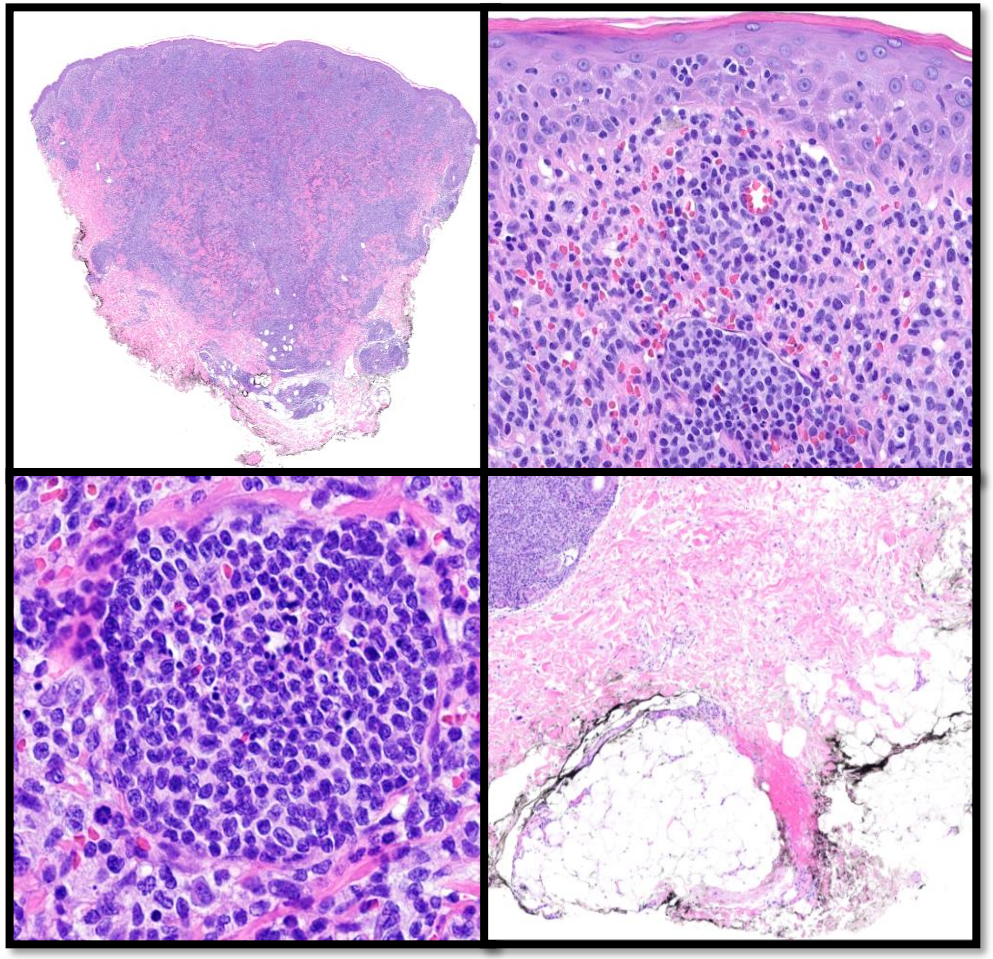
# Clinical Presentation



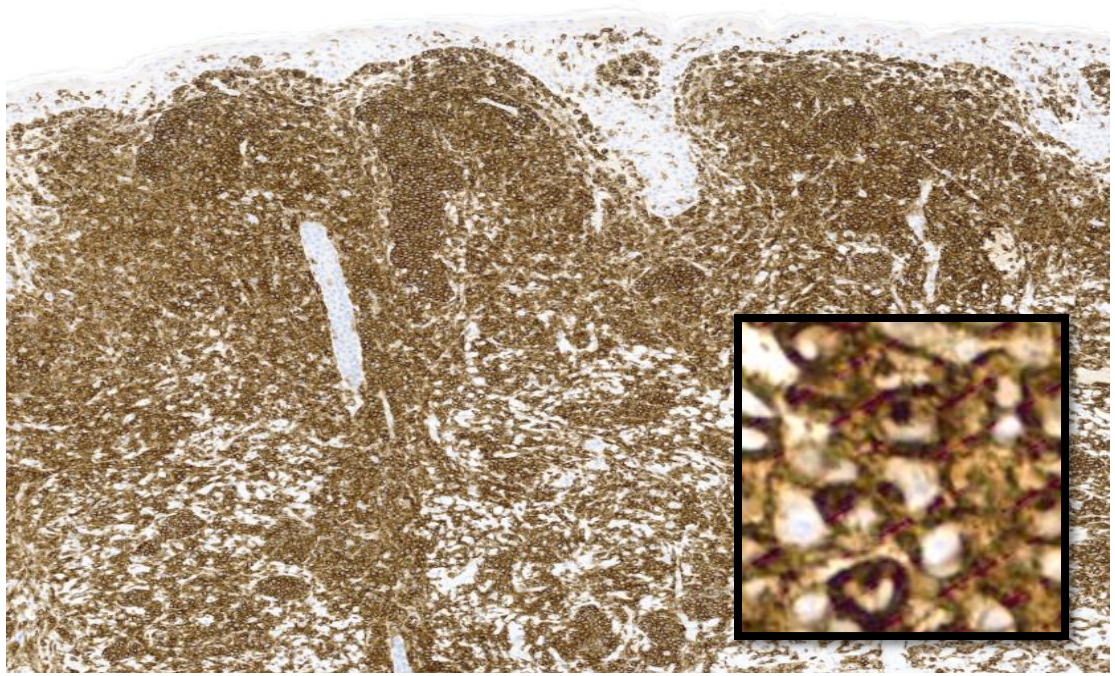
# Clinical Presentation



# Biopsy Findings



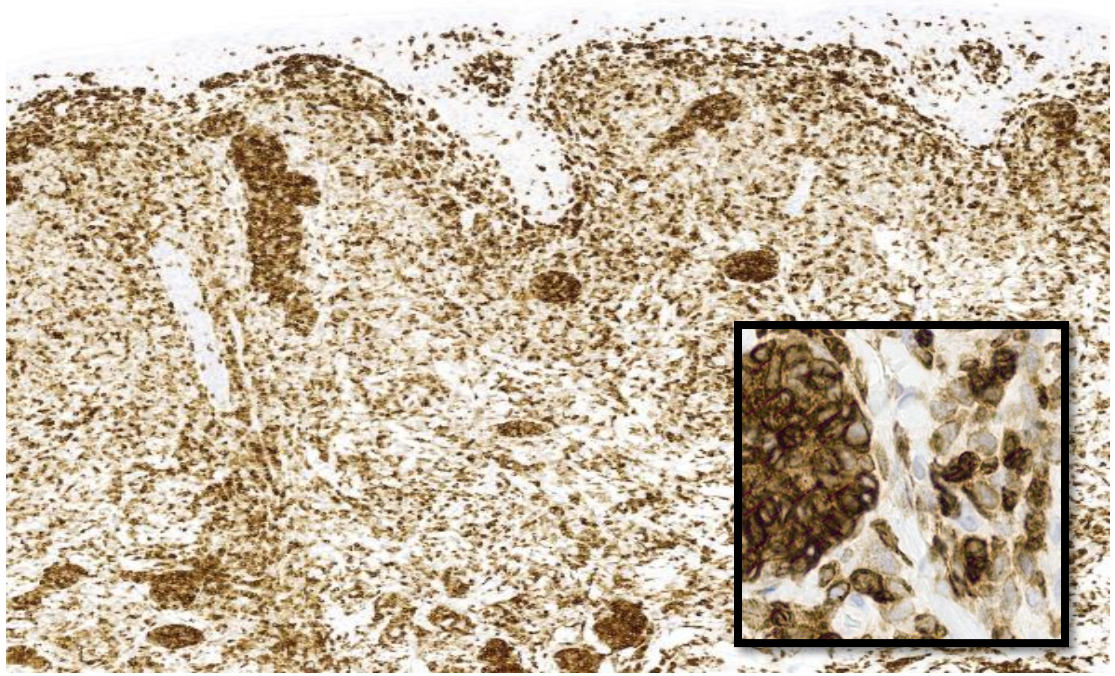
# Biopsy Findings



- CD30
- CD3

- ALK
- EBER
- CD56
- Granzyme
- TIA-1
- CD4
- CD8
- CD2
- CD5
- PAX5

# Biopsy Findings



- CD30
- CD3
- TCR-Gamma

- ALK
- EBER
- CD56
- Granzyme
- TIA-1
- CD4
- CD8
- CD2
- CD5
- PAX5

# Clinical Findings Favoring ALCL/LyP > pcGDTCL

- Indolent, non-ulcerating papules and nodules, spontaneous regression
- No mucosal involvement or lymphadenopathy by physical examination and PET CT
- No fever, sweats, or weight loss
- No peripheral blood lymphocytosis
- No cytopenias
- LDH normal

# Histologic Findings Favoring ALCL/LyP > pcGDTCL

- No panniculitis-like fat involvement or angiodestructive-vasculitis-like features
- Small epidermotropic cells with larger cells in the dermis, more reminiscent of *DUSP22-IRF4*-rearranged CD30+LPD than epidermotropic pcGDTCL
- Widespread distention of dermal blood vessels
- No cytotoxic marker expression
- Loss of many T-cell markers
- Pan CD30 expression

# Ancillary Test Findings

- FISH was negative for rearrangement involving *DUSP22-IRF4*
- Comprehensive genomic profiling revealed no reportable pathogenic mutations
- Comprehensive genomic profiling revealed no gene fusions
- Eight variants of unknown significance were detected
- Copy number profiling revealed aneuploidy

# Additional Ancillary Test Findings

- Copy number profiling revealed aneuploidy
  - Gain 1q loss of 16q loss of 19p13.3 (including *STK11*)
  - Gain 1q is the most frequent alteration reported in pcGDTCL
  - Copy number variations with a median of 4 arm-level events common in pcGDTCL
  - *STK11* (*LKB1*)is a tumor suppressor gene. Germline mutations seen in Peutz-Jeghers syndrome. Sporadic mutations present in malignancies including some renal, lung, and pancreatic cancers.

# Additional Ancillary Test Findings

- Copy number profiling revealed aneuploidy
  - Gain 1q loss of 16q loss of 19p13.3 (including *STK11*)
  - Copy number variations are also seen in pcALCL, although often not arm-level
  - Most frequently include gains involving 7q and 17, and losses involving 6q and 13

# Additional Ancillary Test Findings

- Eight variants of unknown significance were detected
  - *ADGRA2* *EPHA7* *ERBB2* *LRP1B* *NOD1* *RAF1* *RICTOR* *WDR90*
  - Many of the above genes have been found to be mutated in pcGDTCL
  - In general, however, pcGDTCL has been associated with reportable driver mutations involving MAPK, MYC, JAK/STAT and chromatin remodeling pathways, which often includes mutations in consensus cancer genes such as *CDKN2A*, *TP53*, or *ARID1A*
  - *TERT* gain of function mutations are also common

# Additional Ancillary Test Findings

- Eight variants of unknown significance were detected
  - *ADGRA2* *EPHA7* *ERBB2* *LRP1B* *NOD1* *RAF1* *RICTOR* *WDR90*
  - LyP and pcALCL have been associated with JAK/STAT pathway mutations
  - *LRP1B* (tumor suppressor) mutations have been identified in a subset of pcALCL, but it's among the most altered genes in cancer

# Additional Ancillary Test Findings

- FISH was negative for rearrangement involving *DUSP22-IRF4*
- Comprehensive genomic profiling revealed no gene fusions
  - In addition to DUSP22-IRF4 rearrangements, fusions involving JAK/STAT pathway genes have been identified in CD30+LPD
  - Rearrangements involving *TP63* and *JAK2* have been described in pcGDTCL

# Reports of CD30+LPD with a γδ T-cell phenotype

ORIGINAL ARTICLE

## 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 Díaz-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)

Peripheral T-cell lymphomas are a heterogenous group of tumors comprising >20 diseases. Although their molecular pathogenesis is not well understood, T-cell receptor (TCR) signaling is considered an essential component in lymphomagenesis.[1–4]

The TCR is a multimeric complex comprising 2 ligand-binding glycoproteins containing variable regions (αβ or γδ TCR heterodimers) that are expressed on the cell surface in association with 4 CD3 molecules.[5] The αβ TCR/CD3 complex is the most commonly represented among T cells and differs from that of the γδ TCR/CD3 complex. γδ T cells account for <5% of CD3$^+$ cells in peripheral blood but constitute a more prevalent T-cell subset in certain tissues, including skin and intestine. Within lymphoid organs and tissues, they account for 15% of T cells in the spleen, 2% to 4% in lymph nodes, 1% in the thymus cortex, and 3% to 5% in the medulla.[6,7]

From the *CNIO Lymphoma Group; Departments of †Pathology; ‡‡‡Dermatology, Fundación Jiménez Díaz; Departments of ‡Dermatology; §§§Pathology, Hospital Universitario 12 de Octubre; §Pathology Department, Hospital de Torrejón de Ardoz; Departments of **Dermatology; ‖‖Pathology, Hospital Universitario Gregorio Marañón; ***Dermatology Department, Hospital Universitario de Getafe, Getafe; ††Immunohistochemistry Unit, Biotechnology Programme, CNIO, Madrid; ‡Dermatology Department, Hospital Universitario Juan Canalejo, La Coruña; ¶Dermatology Department, Hospital de San Juan, Alicante; #Dermatology Department, Hospital Universitario Reina Sofía, Córdoba; ††Dermatology Department, Hospital Universitario Virgen del Rocío, Sevilla; §§Pathology Department, Hospital Universitario Marqués de Valdecilla, Santander; ¶¶Dermatology Department, Hospital Virgen del Castillo, Murcia; ##Dermatology Department, Hospital Santiago Apostol, Vitoria, Spain; ‡‡UCSD Moores Cancer Center, La Joya, CA; and ‖‖Department of Dermatology, Research Unit Dermatopathology, Medical University of Graz, Graz, Austria.

Conflicts of Interest and Source of Funding: Supported by grants from the Ministerio de Ciencia e Innovación, Spain (RETICC, SAF2008-03871, FIS 08/0856) and the Spanish Association against Cancer (AECC). The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Correspondence: Socorro Maria Rodríguez-Pinilla, MD, PhD, Pathology Department, Fundación Jiménez Díaz, Avd, Reyes Católicos, 2, 28040 Madrid, Spain (e-mail: smrodriguez@fjd.es).





ORIGINAL ARTICLE

## Lymphomatoid Papulosis With T-cell Receptor–Gamma Delta Expression

### *A Clinicopathologic Case-series of 26 Patients of an Underrecognized Immunophenotypic Variant of Lymphomatoid Papulosis*

*Erica Mark, MD,* Werner Kempf, MD,† Joan Guitart, MD,‡ Melissa Pulitzer, MD,§ Christina Mitteldorf, MD,‖ Alexandra Hristov, MD,¶ Carlos Torres-Cabala, MD,# Enrica Marchi, MD, PhD,** Thomas Cropley, MD,†† Socorro Maria Rodriguez Pinilla, MD,‡‡ Teresa Griffin, MD,‡ Rony Fernandez, MD,‡ Stefano Pileri, MD, PhD,§§ Alessandro Pileri, MD, PhD,‖‖¶¶ Valentina Tabanelli, MD,## Lisa Borretta, MD,* Antonio Subtil, MD,*** Jose Antonio Plaza, MD,††† Jose A. Miguel Angel Piris, MD, PhD,‡‡ Andrew L. Feldman, MD,‡‡‡ Lorenzo Cerroni, MD,§§§ and Alejandro A. Gru, MD*††*

**Abstract:** Lymphomatoid papulosis (LyP) has several histopathologic presentations. LyP featuring gamma-delta (γδ) T-cell receptor expression may masquerade as and may be misdiagnosed as aggressive cutaneous T-cell lymphoma, particularly primary cutaneous γδ T-cell lymphoma (PCGDTL) or γδ mycosis fungoides. We performed a clinicopathologic analysis of the largest series of LyP featuring γδ T-cell expression. We identified 26 patients with a diagnosis of LyP with γδ T cells from our institutions, as well as through a comprehensive review of the literature, and characterized these cases. Most cases were treated with topical steroids or not treated at all. The majority of cases showed a CD4$^+$CD8$^+$ phenotype and featured at least one cytotoxic marker. Histopathologic features included an intraepidermal or dermal infiltrate with large cells and frequent angiotropism. One case was initially misdiagnosed as PCGDTL, requiring further therapy. Our case series, the largest international cohort of γδ T cell predominant LyP cases, confirms marked clinicopathologic heterogeneity that may contribute to misdiagnosis, reasserting the need to identify classic clinical features, CD30$^+$ T-cell components, and markers of cytotoxicity when dealing with this differential diagnosis. A limitation of this study includes somewhat limited follow-up, histologic, and immunophenotypic information for some cases.

**Key Words:** CD30$^+$ T-cell lymphoproliferative disorders, cutaneous T-cell lymphoma, dermatopathology, gamma-delta T-cells, immunohistochemistry, lymphomatoid papulosis, mycosis fungoides, primary cutaneous gamma-delta T-cell lymphoma

(*Am J Surg Pathol* 2024;00:000–000)

Lymphomatoid papulosis (LyP) is a subacute CD30$^+$ T-cell lymphoproliferative disorder that manifests clinically as recurrent self-remitting papules or small nodules with diverse histopathologic correlates. This diagnosis is important to achieve, because LyP is clinically troublesome, because specific treatment protocols are available upon recognition of the diagnosis, and because, if incorrectly microscopically evaluated, the findings can

From the *Department of Pathology; **Division of Hematology and Oncology; ††Department of Dermatology, University of Virginia, Charlottesville, VA; †Department of Dermatology, Kempf und Pfaltz Histologische Diagnostik, University of Zurich, Zurich, Switzerland; ‡Department of Dermatology, Northwestern University, Chicago, IL; §Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York City, NY; ‖Department of Dermatology, University Medical Center Göttingen, Venereology and Allergology, Göttingen, Germany; ¶Departments of Pathology and Dermatology, University of Michigan, Ann Arbor, MI; #Departments of Pathology and Dermatology, The University of Texas MD Anderson Cancer Center, Houston, TX; ‡‡Department of Pathology, Fundacion Jimenez Diaz, Madrid, Spain; §§Department of Pathology, European Institute of Oncology IRCCS, Hematopathology Division, Milan; ##Department of Pathology, University of Bologna; ¶¶Department of Surgical and Medical Science, Bologna University, Bologna, Italy; ‖‖Dermatology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna; ***Department of Pathology, University of British Columbia, Royal Jubilee Hospital, Victoria, Canada; †††Departments of Pathology and Dermatology, The Ohio State University, Columbus, OH; ‡‡‡Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, MN; and §§§Department of Dermatology, Medical University of Graz, Graz, Austria.

IRB approval was obtained from the University of Virginia.

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Conflicts of Interest and Source of Funding: A.L.F. receives research funding from Seattle Genetics, is an inventor of technology for which Mayo Clinic holds an unlicensed patent, and has intellectual property licensed to Zeno Pharmaceuticals. A.A.G. is an investigator for StemLine Therapeutics, Innate Pharma, and Dren Bio. He is also consultant for Kyowa Kirin and BluePrints Medicine. For the remaining authors none were declared.

Correspondence: Alejandro A. Gru, MD, 622 West 168th St.VC-15-207, New York, NY 10032. email: aag2222@cumc.columbia.edu





Histopathology

*Histopathology* 2018, **73**, 653–662. DOI: 10.1111/his.13671

## T-cell receptor-δ expression and γδ+ T-cell infiltrates in primary cutaneous γδ T-cell lymphoma and other cutaneous T-cell lymphoproliferative disorders

Melissa Pulitzer,[1] Shamir Geller,[2] Erica Kumar,[1] Denise Frosina,[1] Alison Moskowitz,[2] Steven Horwitz,[2] Patricia Myskowski,[2] Meenal Kheterpal,[2] Alexander Chan,[1] Ahmet Dogan[1] & Achim Jungbluth[1]

[1]*Department of Pathology, and* [2]*Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Date of submission 16 March 2018
Accepted for publication 10 June 2018
Published online *Article Accepted* 12 June 2018

Pulitzer M, Geller S, Kumar E, Frosina D, Moskowitz A, Horwitz S, Myskowski P, Kheterpal M, Chan A, Dogan A & Jungbluth A

(2018) *Histopathology* **73**, 653–662. https://doi.org/10.1111/his.13671

**T-cell receptor-δ expression and γδ+ T-cell infiltrates in primary cutaneous γδ T-cell lymphoma and other cutaneous T-cell lymphoproliferative disorders**

*Aims*: The diagnosis of cutaneous γδ T-cell lymphoma (GDTCL) requires the identification of γδ chains of the T-cell receptor (TCR). Our aim in this study was, by using a new monoclonal antibody (mAb) against TCRδ, to evaluate TCRδ expression in formalin-fixed paraffin-embedded (FFPE) skin tissue from TCRγ+ cutaneous T-cell lymphoma (CTCL), and to assess TCRδ expression within a spectrum of other cutaneous lymphoproliferative disorders (CLPDs).

*Methods and results*: Twelve cases (10 patients) with TCRγ+ CTCL and 132 additional CLPD cases (127 patients) were examined, including mycosis fungoides (MF) ($n$ = 60), cutaneous GDTCL ($n$ = 15), subcutaneous panniculitis-like T-cell lymphoma (SPTCL) ($n$ = 11), and CD30$^+$ lymphoproliferative disorder (LPD) ($n$ = 24). Clone H-41 against TCRδ was used on a Leica Bond-3 automated stainer to label FFPE slides. H-41 immunostaining was graded as percentage infiltrate: high (50–100%), moderate (10–49%), and low (0–9%). In TCRγ+ tumours, 12 of 12 (100%) patients showed TCRδ expression comparable to TCRγ expression. No (0%) TCRγ+ cases were negative for TCRδ. In all CLPDs, TCRδ expression was as follows: GDTCL, 16 of 20 cases (14 of 15 patients) high, two moderate, and two low; MF, 0 of 60 cases high, nine moderate, and 51 low; CD30$^+$ LPD, one of 24 cases high, two moderate, and 21 low; and SPTCL, 0 of 11 cases (0 of 9 patients) high, two moderate, and two low. Three MF-like cases and one SPTCL-like case showed high expression; the remainder showed low expression.

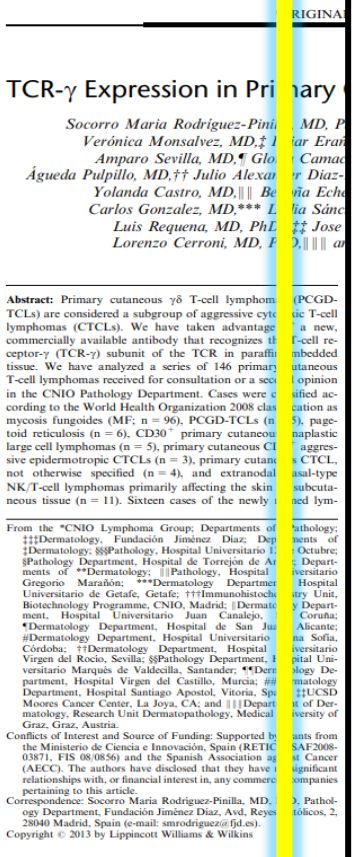
*Conclusions*: mAb H-41 against TCRδ matches TCRγ in immunostaining FFPE tissues from GDTCL, supporting H-41 as a replacement for mAb γ3.20. TCRδ expression in our study suggests that the true occurrence of γδ+ non-GDTCL CTCL/CLPD may be lower than suggested by the recent literature.

Keywords: classification, immunohistochemistry, immunological techniques, lymphoproliferative disorders, T-cell lymphoma

# Reports of CD30+ LPD with a γδ T-cell phenotype

## Take-home messages from case series

- Most LyP subtypes can show gamma-delta expression
- Clinical course and outcomes as expected for LyP
- Papules, variable nodules, variable ulceration
- Variable expression of CD2, CD3, CD5, CD7, CD4, CD8
- Variable expression of cytotoxic markers
- Variable DUSP22-IRF4 rearrangement
- EBER-negative


TCR-γ Expression in Pri ary

Socorro Maria Rodríguez-Pini , MD, P
Verónica Monsalvez, MD,‡ iar Erar
Amparo Sevilla, MD,¶ Glo Camac
Águeda Pulpillo, MD,†† Julio Alexa r Díaz-
Yolanda Castro, MD,‖‖ Be ña Eche
Carlos Gonzalez, MD,*** L ia Sánc
Luis Requena, MD, PhD,‡‡‡ Jose
Lorenzo Cerroni, MD, P ),‖‖‖ a

Abstract: Primary cutaneous γδ T-cell lymphom (PCGD-TCLs) are considered a subgroup of aggressive cyte tic T-cell lymphomas (CTCLs). We have taken advantage a new, commercially available antibody that recognizes th T-cell receptor-γ (TCR-γ) subunit of the TCR in paraffi mbedded tissue. We have analyzed a series of 146 primary utaneous T-cell lymphomas received for consultation or a sec opinion in the CNIO Pathology Department. Cases were c ified according to the World Health Organization 2008 clas cation as mycosis fungoides (MF; n = 96), PCGD-TCLs (n ), page-toid reticulosis (n = 6), CD30+ primary cutaneou naplastic large cell lymphomas (n = 5), primary cutaneous CL aggressive epidermotropic CTCLs (n = 3), primary cutane CTCL, not otherwise specified (n = 4), and extranodal asal-type NK/T-cell lymphomas primarily affecting the skin subcutaneous tissue (n = 11). Sixteen cases of the newly ed lym-

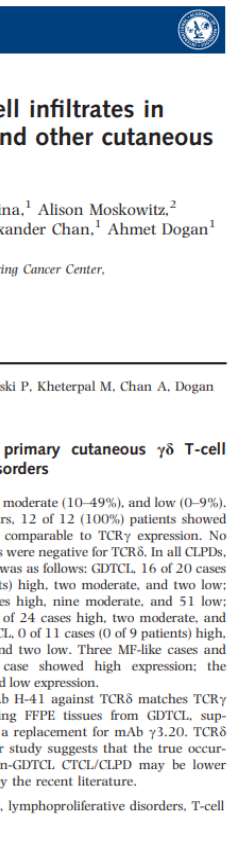
From the *CNIO Lymphoma Group; Departments of athology; ‡‡‡Dermatology, Fundación Jiménez Diaz; Dep ments of ‡Dermatology; §§§Pathology, Hospital Universitario 1 Octubre; §Pathology Department, Hospital de Torrejón de Ar Depart-ments of **Dermatology; ‖‖Pathology, Hospital iversitario Gregorio Marañón; ***Dermatology Departmer Hospital Universitario de Getafe, Getafe; ††Immunohistoche try Unit, Biotechnology Programme, CNIO, Madrid; ‡Dermato Depart-ment, Hospital Universitario Juan Canalejo, Coruña; ¶Dermatology Department, Hospital de San Ju Alicante; #Dermatology Department, Hospital Universitario a Sofia, Córdoba; ††Dermatology Department, Hospital iversitario Virgen del Rocio, Sevilla; §§Pathology Department, H ital Universitario Marqués de Valdecilla, Santander; ¶¶Derm logy Department, Hospital Virgen del Castillo, Murcia; ## matology Department, Hospital Santiago Apostol, Vitoria, Spa ‡‡UCSD Moores Cancer Center, La Joya, CA; and ‖‖Depart of Dermatology, Research Unit Dermatopathology, Medical iversity of Graz, Graz, Austria.

Conflicts of Interest and Source of Funding: Supported b ants from the Ministerio de Ciencia e Innovación, Spain (RETIC SAF2008-03871, FIS 08/0856) and the Spanish Association ag t Cancer (AECC). The authors have disclosed that they have ignificant relationships with, or financial interest in, any commerc ompanies pertaining to this article.

Correspondence: Socorro Maria Rodriguez-Pinilla, MD, Pathology Department, Fundación Jiménez Diaz, Avd, Reyes tólicos, 2, 28040 Madrid, Spain (e-mail: smrodriguez@fjd.es).



Am J Surg Pathol • Volume 37, Number 3, March 13


d γδ+ T-cell infiltrates in nphoma and other cutaneous ders

r,[1] Deni Frosina,[1] Alison Moskowitz,[2] Kheterpal[2] Alexander Chan,[1] Ahmet Dogan[1]

morial Sl Kettering Cancer Center,

orwitz S, yskowski P, Kheterpal M, Chan A, Dogan

111/his.1 571

infiltra s in primary cutaneous γδ T-cell proliferative disorders

high (5 00%), moderate (10–49%), and low (0–9%). In TCRγ tumours, 12 of 12 (100%) patients showed TCRδ e ression comparable to TCRγ expression. No (0%) TC + cases were negative for TCRδ. In all CLPDs, TCRδ ex ession was as follows: GDTCL, 16 of 20 cases (14 of 1 patients) high, two moderate, and two low; MF, 0 50 cases high, nine moderate, and 51 low; CD30+ D, one of 24 cases high, two moderate, and 21 low; d SPTCL, 0 of 11 cases (0 of 9 patients) high, two mo rate, and two low. Three MF-like cases and one SP L-like case showed high expression; the remaind showed low expression.

Conclusi : mAb H-41 against TCRδ matches TCRγ in imm ostaining FFPE tissues from GDTCL, supporting 41 as a replacement for mAb γ3.20. TCRδ expressi in our study suggests that the true occurrence o δ+ non-GDTCL CTCL/CLPD may be lower than su ested by the recent literature.

logical te niques, lymphoproliferative disorders, T-cell

# Reports of CD30+LPD with a γδ T-cell phenotype

CLINICAL AND LABORATORY INVESTIGATIONS
BJD British Journal of Dermatology

## γδ T-cell-rich variants of pityriasis lichenoides and lymphomatoid papulosis: benign cutaneous disorders to be distinguished from aggressive cutaneous γδ T-cell lymphomas

M.E. Martinez-Escala,[1] M. Sidiropoulos,[1] J. Deonizio,[1] P. Gerami,[1] M.E. Kadin[2] and J. Guitart[1,3]

[1]Department of Dermatology, Northwestern University Feinberg School of Medicine, 676 North St. Clair Street, Suite 1600, Chicago, IL 60611, U.S.A.
[2]Department of Dermatology, Boston University, Roger Williams Medical Center, Providence, RI, U.S.A.
[3]Department of Dermatology, Robert H. Lurie Cancer Center, Chicago, IL, U.S.A.

**Correspondence**
Joan Guitart.
E-mail: j-guitart@northwestern.edu

**Accepted for publication**
15 August 2014

**Funding sources**
None.

**Conflicts of interest**
None declared.

DOI 10.1111/bjd.13364

**Summary**

*Background* T cells with a γδ phenotype have been associated with aggressive lymphomas. Yet, inflammatory skin disorders and low-grade lymphoproliferative disorders have rarely been described with a predominant γδ T-cell infiltrate.

*Objectives* To review our experience and determine the clinical relevance of the γδ T-cell phenotype in lymphomatoid papulosis (LyP) and pityriasis lichenoides (PL).

*Methods* A retrospective dermatopathology file review looking for LyP and PL characterized by a γδ T-cell phenotype was performed. Clinical manifestations and course, histological features and molecular data were analyzed.

*Results* Six of 16 cases of LyP and four of 23 cases diagnosed as PL during a 5-year period (2009–14) were identified. The median follow-up for the whole group was 16 months (range 3–64), showing an indolent clinical course in all cases.

*Conclusions* The detection of a predominantly γδ T-cell phenotype in papular lymphoid-rich infiltrates in the absence of other lesions is not associated with a clinically aggressive course. γδ T-cell-rich variants of LyP and PL may reflect a spectrum of related conditions. This is a single academic centre retrospective chart review of a relatively small sample.

**What's already known about this topic?**

- Most lymphoid-rich inflammatory skin conditions are composed of T cells expressing αβ T-cell receptors (TCRs) and, in general, TCR γδ T-cell infiltrates of the skin are associated with aggressive cutaneous lymphomas.

**What does this study add?**

- Regardless of the presence or absence of lymphoid atypia, a subset of γδ T-cell-rich cutaneous lymphoid infiltrates are self-limited and indolent. Pityriasis lichenoides and lymphomatoid papulosis may present as a predominant γδ T-cell infiltrate.

*J Cutan Pathol* 2015: 42: 1012–1017
doi: 10.1111/cup. 12601
John Wiley & Sons. Printed in Singapore



Journal of Cutaneous Pathology

## Atypical cutaneous γδ T cell proliferation with morphologic features of lymphoma but with clinical features and course of PLEVA or lymphomatoid papulosis

Reactive lymphoid infiltrates of the skin composed predominantly of gamma-delta (γδ) T cells are not well described in the literature. Herein we report a case of an otherwise healthy 4-year-old male who presented with a waxing and waning papular rash characterized by small, discrete crusted papules spread across his trunk, face and extremities. Clinical evaluation revealed no evidence of systemic disease. Microscopic examination revealed a dermal, perivascular infiltrate of highly atypical lymphocytes with a γδ T cell phenotype, worrisome for primary cutaneous γδ T cell lymphoma. The clinical course, however, was that of a reactive condition and prompted consideration of a diagnosis of pityriasis lichenoides et varioliformis acuta (PLEVA) and lymphomatoid papulosis (LyP). In many ways, this case defies current classification schemes and seems to expand the spectrum of reactive γδ T cell infiltrates of the skin.

*Keywords:* T lymphocytes, atypical features, CUTANEOUS LYMPHOMAS, hematopathology,

King RL, Yan AC, Sekiguchi DR, Choi JK. Atypical cutaneous γδ T cell proliferation with morphologic features of lymphoma but with clinical features and course of PLEVA or lymphomatoid papulosis.
J Cutan Pathol 2015; 42: 1012–1017. © 2015 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

**Rebecca L. King[1], Albert C. Yan[2], Debora R. Sekiguchi[1] and John K. Choi[1]**

[1]Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA and
[2]Department of Dermatology Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Rebecca L. King, MD,
Mayo Clinic, 200 First Street SW, Hilton 8,
Hematopathology, Rochester, MN 55905, USA
Tel: +240 535 2768
Fax: +507 284 5115
e-mail: rebecca.king98@gmail.com

Accepted for publication June 16, 2012

*J Cutan Pathol* 2013: 40: 896–902
doi: 10.1111/cup.12091
John Wiley & Sons. Printed in Singapore



Journal of Cutaneous Pathology

## Indolent course of cutaneous gamma-delta T-cell lymphoma

Cutaneous gamma-delta T-cell lymphoma (γδTCL) is a rare malignancy that typically displays an aggressive clinical course. We present an unusual case of a 57-year-old woman with a 3-year history of lower extremity nodules. Histopathologic, immunophenotypic and molecular genetic studies revealed a clonal, predominantly pannicular gamma-delta T-cell infiltrate, leading to a diagnosis of cutaneous γδTCL. The clinical course was characterized by rapid improvement within months of starting systemic corticosteroids, with relapse in ulcerations but no new lesions more than 3 years after onset of disease. Our case and seven previously reported patients with indolent and relatively localized cutaneous γδTCL provide evidence that not all cases of this entity carry a poor prognosis. This indolent subset adds complexity to treatment of cutaneous γδTCL.

*Keywords:* connective tissue disease panniculitis, gamma-delta T-cell lymphoma, panniculitic lymphoma

Endly DC, Weenig RH, Peters MS, Viswanatha DS, Comfere NI. Indolent course of cutaneous gamma-delta T-cell lymphoma.
J Cutan Pathol 2013; 40: 896–902. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

**Dawnielle C. Endly[1], Roger H. Weenig[2], Margot S. Peters[3,4], David S. Viswanatha[4] and Nneka I. Comfere[3,4]**

[1]College of Osteopathic Medicine, Midwestern University, Glendale, AZ, USA,
[2]Associated Skin Care Specialists, Dermatopathology Associates, Fridley, MN, USA,
[3]Department of Dermatology, Mayo Clinic, Rochester, MN, USA, and
[4]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Nneka I. Comfere, MD,
Department of Dermatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
Tel: +507 284 2511
Fax: +507 284 2072
e-mail:comfere.nneka@mayo.edu

Accepted for publication December 16, 2012

Cutaneous gamma-delta T-cell lymphoma (γδTCL) represents less than 1% of primary cutaneous lymphomas and currently is a provisional entity in the subset of peripheral T-cell lymphomas (TCLs), unspecified in the current World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification of lymphoid neoplasms.[1] Composed of a clonal population of mature gamma-delta T cells with a cytolytic phenotype, γδTCL was previously designated as a subcutaneous panniculitis-like T-cell lymphoma (SPTCL) subset. The new distinction was made after γδTCL was recognized to have a distinctively adverse prognosis with 11% 5-year survival rate compared with 82% for SPTCL.[2] In contrast with the lymphocytes of SPTCL that express CD8 but not CD56 or CD4, γδTCL is characterized by expression of CD56 but not CD8 and CD4. Cytolytic protein expression is present in both variants of subcutaneous TCL.[1]

Lupus erythematosus (LE) panniculitis continues to represent a clinicopathologic challenge with respect to its distinction from the two subcutaneous T-cell lymphoma variants.[3,4] Shared presentations of LE panniculitis and subcutaneous T-cell lymphomas include erythematous to violaceous dermal or subcutaneous nodules that may ulcerate, and histopathologic features of interface changes, hyaline fat necrosis and lobular pannicular infiltration by cytolytic lymphocytes that exhibit adipocyte rimming, karyorrhexis and atypia.[5] We present a case of cutaneous γδTCL that followed an indolent clinical course and review the literature regarding similar cases.

### Case report

A 57-year-old woman was referred to our dermatology department with a 3-year history of tender, ulcerating nodules of the legs associated with swelling of the ankles. Past medical history included chronic lower extremity ulcers of unknown etiology dating back to 1997, which healed after skin grafting; persistent patches of 'parapsoriasis'

# Reports of CD30+LPD with a γδ T-cell phenotype

CLINICAL AND LABORATORY INVESTIGATIONS
BJD British Journal of Dermatology

## γδ T-cell-rich variants of pityriasis lichenoides and lymphomatoid papulosis: benign cutaneous disorders to be distinguished from aggressive cutaneous γδ T-cell lymphomas

M.E. Martinez-Escala,[1] M. Sidiropoulos,[1] J. Deonizio,[1] P. Gerami,[1] M.E. Kadin[2] and J. Guitart[1,3]

[1]Department of Dermatology, Northwestern University Feinberg School of Medicine, 676 North St. Clair Street, Suite 1600, Chicago, IL 60611, U.S.A.
[2]Department of Dermatology, Boston University, Roger Williams Medical Center, Providence, RI, U.S.A.
[3]Department of Dermatology, Robert H. Lurie Cancer Center, Chicago, IL, U.S.A.

**Correspondence**
Joan Guitart.
E-mail: j-guitart@northwestern.edu

**Accepted for publication**
15 August 2014

**Funding sources**
None.

**Conflicts of interest**
None declared.

DOI 10.1111/bjd.13364

**Summary**

Background T cells with a γδ phenotype have been associated with aggressive lymphomas. Yet, inflammatory skin disorders and low-grade lymphoproliferative disorders have rarely been described with a predominant γδ T-cell infiltrate.

Objectives To review our experience and determine the clinical relevance of the γδ T-cell phenotype in lymphomatoid papulosis (LyP) and pityriasis lichenoides (PL).

Methods A retrospective dermatopathology file review looking for LyP and PL characterized by a γδ T-cell phenotype was performed. Clinical manifestations and course, histological features and molecular data were analyzed.

Results Six of 16 cases of LyP and four of 23 cases diagnosed as PL during a 5-year period (2009–14) were identified. The median follow-up for the whole group was 16 months (range 3–64), showing an indolent clinical course in all cases.

Conclusions The detection of a predominantly γδ T-cell phenotype in papular lymphoid-rich infiltrates in the absence of other lesions is not associated with a clinically aggressive course. γδ T-cell-rich variants of LyP and PL may reflect a spectrum of related conditions. This is a single academic centre retrospective chart review of a relatively small sample.

**What's already known about this topic?**

- Most lymphoid-rich inflammatory skin conditions are composed of T cells expressing αβ T-cell receptors (TCRs) and, in general, TCR γδ T-cell infiltrates of the skin are associated with aggressive cutaneous lymphomas.

**What does this study add?**

- Regardless of the presence or absence of lymphoid atypia, a subset of γδ T-cell-rich cutaneous lymphoid infiltrates are self-limited and indolent. Pityriasis lichenoides and lymphomatoid papulosis may present as a predominant γδ T-cell infiltrate.

J Cutan Pathol 2015: 42: 1012–1017
doi: 10.1111/cup. 12601
John Wiley & Sons. Printed in Singapore



Journal of

J Cutan Pathol 2013: 40: 896–902
doi: 10.1111/cup.12091
John Wiley & Sons. Printed in Singapore



Journal of
Cutaneous Pathology

| Patient no. | Sex/age (years) | Ethnicity | Clinical presentation | Distribution | Treatment | Status | Length of follow-up (months) | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| 1 | M/26 | U | Crusted papules | Generalized | U | U | U | PL |
| 2 | F/3 | W | Crusted papules | Generalized | Oral ATB | AWD | 14·1 | PL |
| 3 | F/33 | W | Crusted and eroded papules | Generalized | Topical steroids | AWOD | 2·3 | PL |
| 4 | M/13 | W | Crusted papules hypo- and hyperpigmentation | Trunk, upper and lower extremities | Oral ATB, NB-UVB | AWD | 29·1 | PL |
| 5 | F/53 | W | Papules, overlap with eczematous patches | Trunk and lower extremities | NB-UVB | AWOD | 62·6 | LyP |
| 6 | M/57 | W | Crops of papules | Upper and lower extremities | None | AWD | 33·0 | LyP |
| 7 | M/48 | W | Papules | Upper and lower extremities | Topical steroids | AWOD | 13·6 | LyP |
| 8 | M/71 | U | Single lesion | Left lower extremity | Surgical excision | AWOD | 22·0 | LyP |
| 9 | F/30 | W | Papules, some eroded | Trunk, upper and lower extremities | Oral ATB | AWOD | 14·9 | LyP |
| 10 | F/44 | U | Solitary papule | Neck | Surgical excision | AWOD | 1·0 | LyP |

M, male; F, female; U, unknown; W, white; ATB, antibiotics; NB-UVB, narrowband ultraviolet B; AWD, alive with disease; AWOD, alive without disease; PL, pityriasis lichenoides; LyP, lymphomatoid papulosis.

# Reports of CD30+LPD with a γδ T-cell phenotype



8. de Carvalho N, Farnetani F, Ciardo S, et al. Reflectance confocal microscopy correlates of dermoscopic patterns of facial lesions help to discriminate lentigo maligna from pigmented nonmelanocytic macules. *Br J Dermatol*. 2015;173:128–133.
9. El Shabrawi-Caelen L, Kerl H, Cerroni L. Melan-A: not a helpful marker in distinction between melanoma in situ on sun-damaged skin and pigmented actinic keratosis. *Am J Dermatopathol*. 2004;26:364–366.
10. Buonaccorsi JN, Prieto VG, Torres-Cabala C, et al. Diagnostic utility and comparative immunoistochemical analysis of MITF-1 and SOX10 to distinguish nelanoma in situ and actinic keratosis: a clinicopathological and immunohistochemical study of 70 cases. *Am J Dermatopathol*. 2014;36:124–130.

## The First Case of Gamma-Delta Primary Cutaneous Anaplastic Large Cell Lymphoma?

***To the Editor:***

We have read with much interest the report by Meawad et al[1] on a case of a primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) mimicking ALK-1 negative anaplastic large cell lymphoma (ALCL).

It caught our attention that the tumor cells showed many features which are characteristic of ALCL such as hallmark cells, anaplasia, pleomorphism, and CD30 positivity. Lack of ALK expression is also typical of primary cutaneous ALCL.[2] Nevertheless, the authors made the diagnosis of PCGD-TCL based on the panniculitic pattern, the rimming, and mainly on the immunostaining for T-cell receptor (TCR)-delta.

We would like to remark that prominent involvement of the subcutaneous fat is identified in some cases of primary cutaneous ALCL.[3] We are also aware that, to the best of our knowledge, no cases of gamma-delta ALCL have been published so far, although Pulitzer et al[4] reported one case of a "CD30 lymphoproliferative disorder borderline" which showed an intense and diffuse TCR delta expression. In addition, there are cases of gamma-delta lymphomatoid papulosis, which is another CD30$^+$ lymphoproliferative disorder closely related to primary cutaneous ALCL.[5]

The current case was negative for CD4 and CD8. This is not a handicap for the diagnosis of primary cutaneous ALCL, because only one-third of cases are positive for CD4, and negativity for CD4 and CD8 is seen in almost half of the cases.[3] In addition, most of PCGD-TCL are CD30 negative, and when positive, they usually show low-medium expression of the marker.[6]

Primary cutaneous ALCL usually presents with eosinophils,[3] which are rarely seen in PCGD-TCL. Although it is not sharply appreciated, Figure 2b seems to show some eosinophils accompanying the tumoral cells.

Regarding the clinical presentation, lesions of PCGD-TCL often are ulcerated, involvement of mucosae is frequent, B symptoms occur in most cases, and lactate dehydrogenase is normally elevated. In addition, involvement of soft tissue and lymph nodes by the PCGD-TCL are usually present at the time of diagnosis.[7] None of these features were reported in the case report of the authors.

Multiple lesions are not uncommon in CD30 positive lymphomas: Although most frequent in lymphomatoid papulosis, such presentation has also been described in some cases of primary cutaneous ALCL,[3] so much so that the latter can sometimes clinically mimic the former.

Cases of PCGD-TCL have been described after treatment with etanercept, but this drug has also been associated with primary cutaneous ALCL.[8]

We believe that the current case would better fit into the diagnosis of TCR delta positive primary cutaneous ALCL. Therefore, we agree that this case is extraordinary, as in our opinion, it represents the first well-documented case of gamma-delta primary cutaneous ALCL.

The good response to treatment is also more in consonance with primary cutaneous ALCL. However, long-term follow-up will probably give us more reliable information on the prognosis of this lymphoma, and we believe that the entire scientific community would be grateful if the authors could keep us informed.

**Ana Taibo, MD***
**David Cassarino, MD, PhD†**
**Angel Fernandez-Flores, MD, PhD‡§¶**
*Department of Dermatology, University Hospital of A Coruña, A Coruña, Spain
†Departments of Pathology and Dermatology, Los Angeles Medical Center (LAMC), Southern California Kaiser Permanente, Los Angeles, CA
‡Department of Histopathology, University Hospital El Bierzo, Ponferrada, Spain
§Department of Cellular Pathology, Hospital de la Reina, Ponferrada, Spain
¶Research Department, Institute for Biomedical Research of A Coruña (INIBIC), University of A Coruña (UDC), A Coruña, Spain

### REFERENCES

1. Meawad H, Song JY, Ulrickson ML, et al. Primary cutaneous gamma-delta T-cell lymphoma mimicking anaplastic lymphoma kinase-1-negative anaplastic large cell lymphoma: a case report. *Am J Dermatopathol*. 2022;44:62–65.
2. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood* 2011;118:4024–4035.
3. Cerroni L. Cutaneous anaplastic large cell lymphoma. In: Cerroni L, ed. *Skin Lymphoma*. 5th ed. Oxford, UK: Wiley Blackwell; 2020:150–166.
4. Pulitzer M, Geller S, Kumar E, et al. T-cell receptor-δ expression and γδ+ T-cell infiltrates in primary cutaneous γδ T-cell lymphoma and other cutaneous T-cell lymphoproliferative disorders. *Histopathology* 2018;73:653–662.
5. Cerroni L. Lymphomatoid papulosis. In: Cerroni L, ed. *Skin Lymphoma*. 5th ed. Oxford, UK: Wiley Blackwell; 2020:134–149.
6. Alberti-Violetti S, Maronese CA, Venegoni L, et al. Primary cutaneous gamma-delta T cell lymphomas: a case series and overview of the literature. *Dermatopathology (Basel)*. 2021;8:515–524.
7. Cerroni L. Primary cutaneous γ/δ T-cell lymphoma. In: Cerroni L, ed. *Skin Lymphoma*. 5th ed. Oxford, UK: Wiley Blackwell; 2020:201–207.
8. De Angelis F, Di Rocco A, Minotti C, et al. Atypical presentation of anaplastic large T-cell lymphoma mimicking an articular relapse of rheumatoid arthritis in a patient treated with etanercept. A case report and literature review. *Leuk Res*. 2012;9:e199–201.

The authors declare no conflicts of interest.
Ethics approval: Approved.








## Primary Cutaneous Gamma-Delta T-Cell Lymphoma Mimicking anaplastic lymphoma kinase-1-Negative Anaplastic Large Cell Lymphoma: A Case Report

*Hany Meawad, MD, MSc,* Joo Y. Song, MD,* Matthew L. Ulrickson, MD,† and Dennis D. Weisenburger, MD**

**Abstract:** Primary cutaneous gamma-delta T-cell lymphoma is a rare and aggressive neoplasm, representing less than 1% of all cutaneous T-cell lymphomas. In this article, we report the case of a 49-year-old woman who presented with a history of generalized skin rash and a recent mass on the left upper extremity, as well as right inguinal soft tissue swelling and splenomegaly. Histologic examination of the mass revealed a diffuse subcutaneous infiltrate of large anaplastic and CD30-positive lymphoid cells with rimming of the adipocytes. This case demonstrates unusual cytologic features in primary cutaneous gamma-delta T-cell lymphoma that mimic the features of anaplastic lymphoma kinase-1-negative anaplastic large-cell lymphoma.

**Key Words:** primary cutaneous gamma-delta T-cell lymphoma, anaplastic large-cell lymphoma

(*Am J Dermatopathol* 2022;44:62–65)

### INTRODUCTION

Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) is a rare and aggressive neoplasm that was identified as a distinct entity in the 2008 World Health Organization classification.[1] This entity primarily affects the skin and is composed of clonal and activated cytotoxic gamma-delta T cells. The entity includes cases that were previously designated as "subcutaneous panniculitis-like T-cell lymphoma" but was separated from cases with the alpha-beta phenotype because PCGD-TCL has a worse survival, a higher incidence of necrosis and ulceration, and a higher frequency of hemophagocytic syndrome.[2] Patients with PCGD-TCL usually present with plaques which ulcerate and form necrotic nodules that rapidly increase in size and occur most frequently on the extremities. Development of mucosal lesions and involvement of other extranodal sites are frequently observed. However, the bone marrow, lymph nodes, and spleen are not typically involved at the time of initial presentation.[2] Two distinct molecular subtypes of PCGD-TCL have been identified. The Vdelta-1 subtype classically involves the epidermis and dermis, whereas the Vdelta-2 subtype is characterized by panniculitis and a more aggressive clinical course.[3] Noticeable subcutaneous involvement can also occur in other T-cell neoplasms with a predilection for the skin, such as subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and extranodal natural killer (NK)/T-cell lymphoma.[4,5]

Although epidermal involvement with skin ulceration and concomitant hemophagocytic syndrome are commonly seen in PCGD-TCL, these findings are not considered pathognomonic of the disease and accurate diagnosis depends on careful morphologic and immunophenotypic characterization that includes T-cell receptor (TCR)-delta expression by immunohistochemistry or flow cytometry.[2,6]

### CASE REPORT

A 49-year-old White woman, with a history of rheumatoid arthritis treated with etanercept and methotrexate, presented with mild neutropenia. Bone marrow biopsy at the time was hypercellular at 75% with no significant dysplasia or evidence of lymphoma. She was noted to have mild splenomegaly at 12 cm. A clinical diagnosis of Felty syndrome was made, and she was managed with oral methotrexate and intermittent rituximab with stable blood counts.

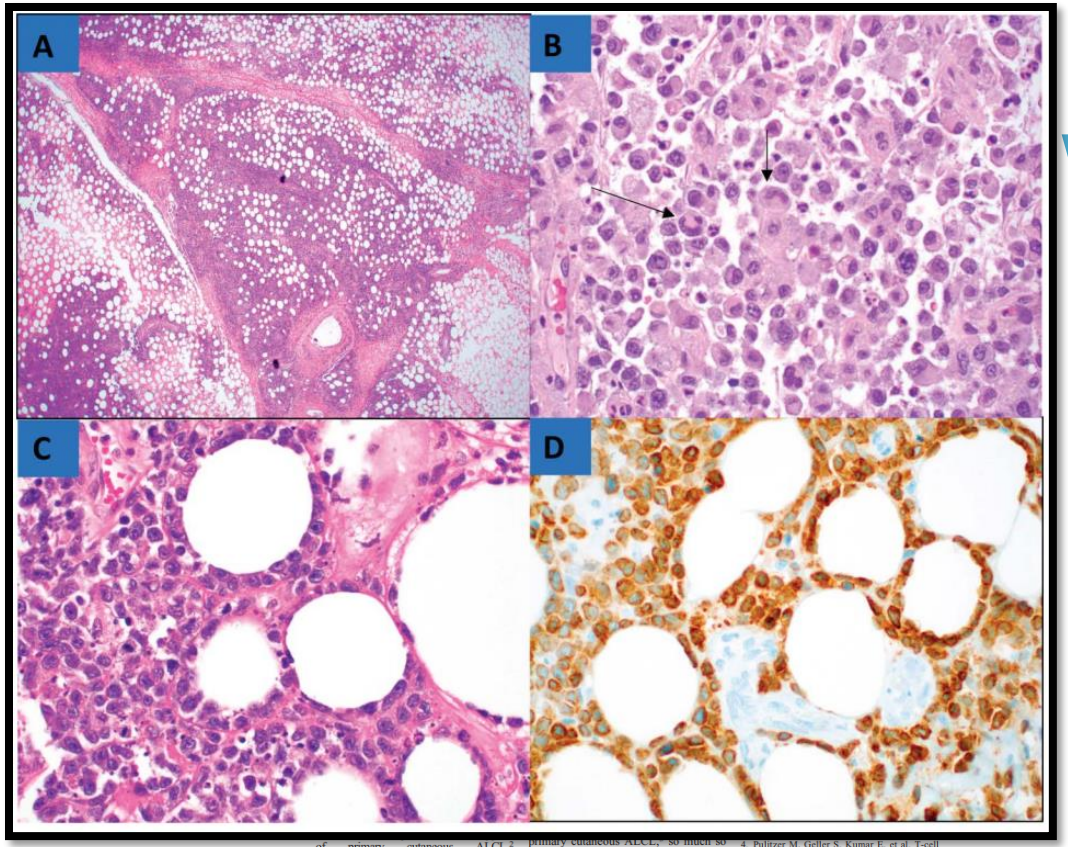
Three years later, she developed the onset of multiple cutaneous nodules, initially in the left upper extremity and then few nodules overlying the right lower quadrant of the abdomen and right lower extremity as seen in Figure 1A. These lesions were tender, mildly erythematous, and 2–3 cm in size. Ultrasound of the lesions suggested fat necrosis. Her spleen remained 11 cm in size, and computed tomography scan of the abdomen and pelvis did not reveal any significant adenopathy. Repeat bone marrow biopsy was negative for evidence of lymphoma.

She underwent excision of these subcutaneous nodules and splenectomy. Positron emission tomography scan staging shortly after these procedures identified multiple fluorodeoxyglucose-avid cutaneous nodules in the extremities and lower abdomen without significant adenopathy, as seen in Figures 1B–D.

Histologic examination of biopsies of the mass lesions showed infiltration of the subcutaneous fat by sheets of large anaplastic lymphoid cells with irregular nuclear contours, open chromatin, and prominent nucleoli. Many "hallmark cells" were also present, along with frequent mitotic figures. Rimming and necrosis of fat cells were also observed. No significant epidermotropism was noted. Immunohistochemistry performed on paraffin sections showed strong expression of CD3 on the large cells without expression of CD4, CD8, or CD5. There was also expression of

From the *Department of Pathology, City of Hope Comprehensive Cancer Center, Duarte, CA; and †Department of Hematology, Stem Cell Transplant and Cellular Therapy, Banner MD Anderson Cancer Center, Gilbert, AZ.
The authors declare no conflicts of interest.
Correspondence: Hany Meawad, MD, MSc, Department of Pathology, City of Hope Comprehensive Cancer Center, 1500 E. Duarte Road, Duarte, CA 91010 (e-mail: Hameawad@coh.org).

# with a γδ T-cell phenotype




of primary cutaneous ALCL.[2] Nevertheless, the authors made the diagnosis of PCGD-TCL based on the panniculitic pattern, the rimming, and mainly on the immunostaining for T-cell receptor (TCR)-delta.

We would like to remark that prominent involvement of the subcutaneous fat is identified in some cases of primary cutaneous ALCL.[3] We are also aware that, to the best of our knowledge, no cases of gamma-delta ALCL have been published so far, although Pulitzer et al[4] reported one case of a "CD30 lymphoproliferative disorder

The authors declare no conflicts of interest.
Ethics approval: Approved.




primary cutaneous ALCL, so much so that the latter can sometimes clinically mimic the former.

Cases of PCGD-TCL have been described after treatment with etanercept, but this drug has also been associated with primary cutaneous ALCL.[8]

We believe that the current case would better fit into the diagnosis of TCR delta positive primary cutaneous ALCL. Therefore, we agree that this case is extraordinary, as in our opinion, it represents the first well-documented case of gamma-delta primary cutaneous ALCL.

The good response to treatment is also more in consonance with primary cutaneous ALCL. However, long-term follow-up will probably give us more reliable information on the prognosis of

4. Pulitzer M, Geller S, Kumar E, et al. T-cell receptor-δ expression and γδ+ T-cell infiltrates in primary cutaneous γδ T-cell lymphoma and other cutaneous T-cell lymphoproliferative disorders. *Histopathology* 2018;73:653–662.
5. Cerroni L. Lymphomatoid papulosis. In: Cerroni L, ed. *Skin Lymphoma*. 5th ed. Oxford, UK: Wiley Blackwell; 2020:134–149.
6. Alberti-Violetti S, Maronese CA, Venegoni L, et al. Primary cutaneous gamma-delta T cell lymphomas: a case series and overview of the literature. *Dermatopathology (Basel)*. 2021;8:515–524.
7. Cerroni L. Primary cutaneous γδ T-cell lymphoma. In: Cerroni L, ed. *Skin Lymphoma*. 5th ed. Oxford, UK: Wiley Blackwell; 2020:201–207.
8. De Angelis F, Di Rocco A, Minotti C, et al. Atypical presentation of anaplastic large T-cell lymphoma mimicking an articular relapse of rheumatoid arthritis in a patient treated with etanercept. A case report and literature review. *Leuk Res*. 2012;9:e199–201.



EXTRAORDINARY CASE REPORT

## Primary Cutaneous Gamma-Delta T-Cell Lymphoma Mimicking anaplastic lymphoma kinase-1-Negative Anaplastic Large Cell Lymphoma: A Case Report

*Hany Meawad, MD, MSc,* Joo Y. Song, MD,* Matthew L. Ulrickson, MD,† and Dennis D. Weisenburger, MD**

**Abstract:** Primary cutaneous gamma-delta T-cell lymphoma is a rare and aggressive neoplasm, representing less than 1% of all cutaneous T-cell lymphomas. In this article, we report the case of a 49-year-old woman who presented with a history of generalized skin rash and a recent mass on the left upper extremity, as well as right

have been identified. The Vdelta-1 subtype classically involves the epidermis and dermis, whereas the Vdelta-2 subtype is characterized by panniculitis and a more aggressive clinical course.[3] Noticeable subcutaneous involvement can also occur in other T-cell neoplasms with a predilection for the skin, such as subcutaneous panniculitis-like T-cell lym-

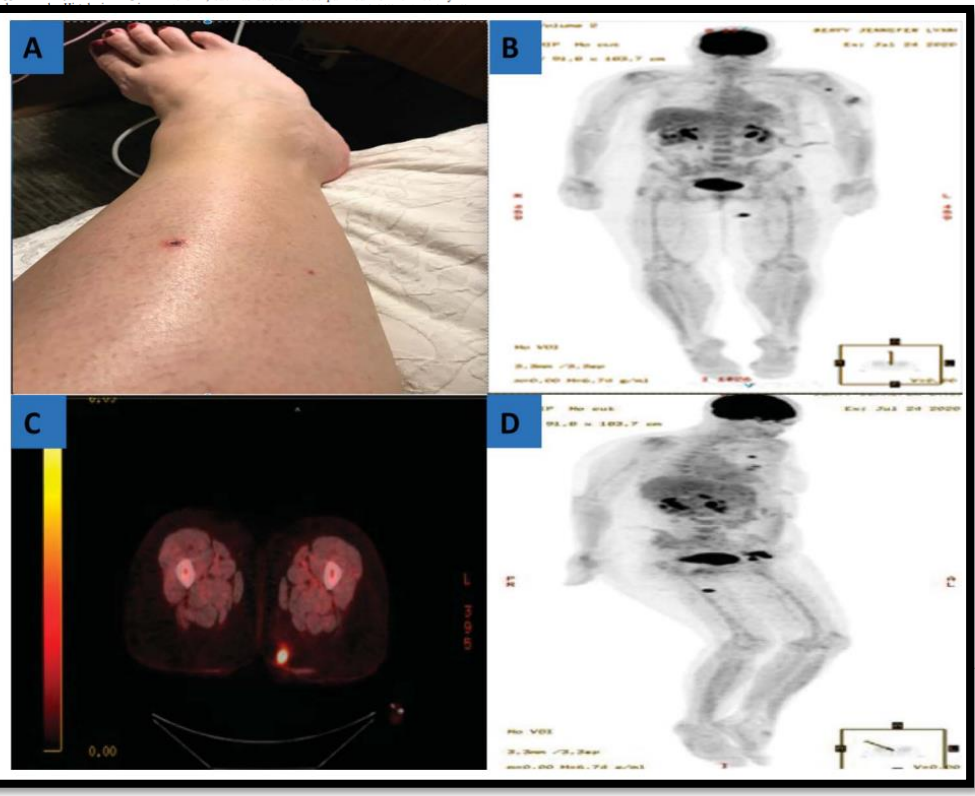



**FIGURE 1.** A, Skin lesion on the right lower extremity. B–D, Positron emission tomography scan staging at diagnosis reveals multiple fluorodeoxyglucose-avid subcutaneous lesions at the left upper extremity, left posterior medial thigh, and lower abdomen.

# Reports of CD30+LPD with a γδ T-cell phenotype



## DUSP22-IRF4 Rearranged CD30-Positive Primary Cutaneous Lymphoproliferative Disorder With Gamma/Delta Phenotype

*Yasmin H. Fattah, MD,* David Crasto, DO,* Shuo S. Liu, MD, PhD,* Yuliya Linhares, MD,† Franz Kerdel, DO,‡ Andrew Hanly, MD,§ and Laszlo J. Karai, MD, PhD§*

**Abstract:** CD30-positive primary cutaneous lymphoproliferative disorders (CD30+PCLPD) are a heterogeneous group of cutaneous T-cell lymphoma (CTCL) that includes lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma. They exist as a clinical and pathological spectrum, which display significant overlap and variability. The diagnosis is made based on correlation between clinical and histopathologic findings. LyP with 6p25.3 rearrangement subtype represents <5% of LyP cases and is defined by DUSP22-IRF4 rearrangement on 6p25.3 locus. The reported cases express the alpha/beta T-cell receptor and follow an indolent clinical behavior typical of LyP. The same rearrangement is detected in 28% of anaplastic large cell lymphoma. We hereby present an extraordinary case of CD30+PCLPD with DUSP22-IRF4 rearrangement and novel expression of gamma/delta T-cell immunophenotype in a young patient. Although the gamma/delta T-cell immunophenotype has been described in many other T-cell lymphomas, this is the first reported association with CD30+PCLPD with DUSP22-IRF4 rearrangement.

**Key Words:** CD30+ primary cutaneous lymphoproliferative disorders, C-ALCL, LyP with DUSP22-IRF4 rearrangement, γδ T cells

(*Am J Dermatopathol* 2023;45:831–834)

### INTRODUCTION

CD30-positive lymphoproliferative disorders (CD30+PCLPDs) are the second most common group of cutaneous lymphomas, after mycosis fungoides, accounting for 30% of cases.[1,2] They include lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (C-ALCL), which display a spectrum of morphologic features.[3,4] C-ALCL is characterized by the appearance of necrotic and/or ulcerated papulonodular eruption, which may be solitary or grouped, favoring the head/neck region, along with the upper extremity. Median age of onset is the sixth decade of life. Most cases are anaplastic lymphoma kinase-1 negative.[5,6] LyP is a monoclonal disorder that arises from a single transformed T cell and is characterized by multifocal crops of recurrent papulonodular lesions that favor the trunk and extremities, with a median age of onset of 45 years.[7] LyP histological spectrum is classified by the World Health Organization into (A through E) subtypes based on morphologic features and stratified with either CD4-positive or CD8-positive T cells of alpha/beta (αβ) or gamma/delta (γδ) immunophenotype. In 2013, the new subtype of LyP with 6p25.3 rearrangement was described[8] and subsequently recognized in 2018 by the World Health Organization classification of LyP as a sixth subtype of LyP.[9]

We hereby present a novel case of CD30+PCLPD with DUSP22-IRF4 rearrangement demonstrating γδ phenotype in a young patient that had an unusual clinical course. We illuminate the complexity of classifying such a case under the current spectrum of CD30+PCLPDs, which suggests that this might be an outlier and possibly a new subtype of CD30+PCLPD with unique histology and prognosis.

### CASE REPORT

A 41-year-old African American woman presented to the dermatology clinic with a recent development of lesions on her extremities. She reported that the individual lesions had increased in size since their appearance, rendering significant worry and ultimately prompting her to seek medical consultation. Otherwise, she was without any active medical problems and denied any additional signs or symptoms suggestive of systemic disease. Physical examination demonstrated 2 skin-colored papules, approximately 8–10 mm in diameter, one on the flexural aspect of the left forearm, and the other on thigh, sharply demarcated from the surrounding uninvolved skin (Fig. 1A). The remainder of her physical examination was unremarkable, including axillary and inguinal lymph node examination. An initial punch biopsy of the left arm lesion was performed followed by a subsequent diagnostic excision for more thorough and accurate evaluation. The pathologic findings were remarkable for dermal based, atypical lymphocytic infiltrate, with Grenz zone and no epidermotropism (Figs. 1B, C). The atypical lymphocytes are medium to large in size, with no involvement or destruction of the follicular or adnexal structures, permeating through the collagen bundles with infiltration of the subcutaneous tissue (Figs. 1D–F). A polymorphic reactive inflammatory milieu was not identified. The lymphocytes were atypical T cells with mostly retained CD3 (Fig. 2A), strongly positive CD30 (Fig. 2B), completely lost CD5, high Ki-67 proliferative index, and partial loss of CD2 (Fig. 2C). Interestingly, the malignant T cells had a double-negative CD4 (Fig. 2D), and CD8 immunophenotype (Fig. 2E) and were positive for gamma T-cell receptor (TCR) (Fig. 2F). Cytotoxic T-cell markers TIA-1 and Granzyme B were negative.

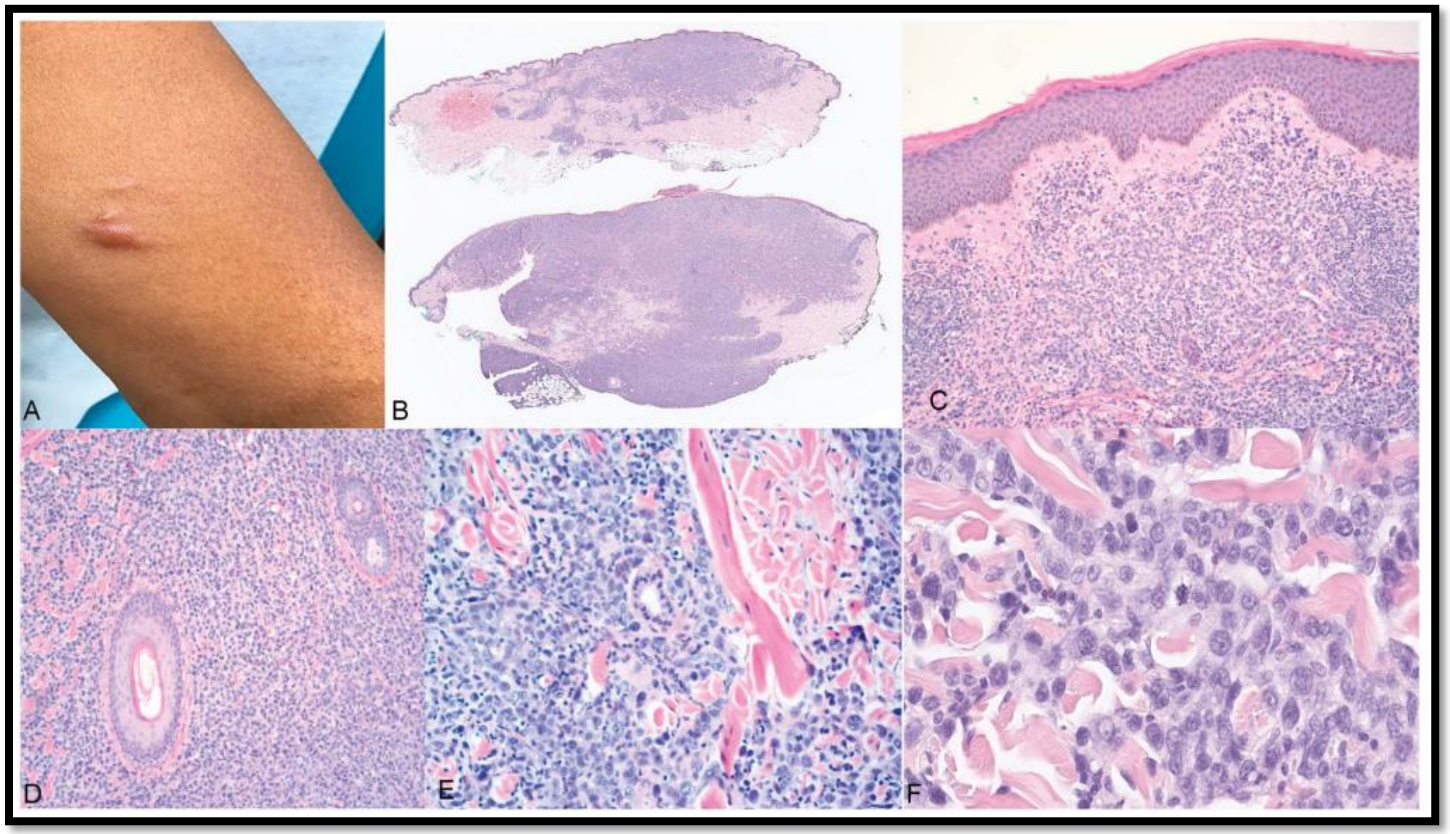
From the *Department of Dermatology, Larkin Community Hospital, South Miami, FL; †Department of Oncology, Baptist Hospital, Miami, FL; ‡Skin Center of South Miami, South Miami, FL; and §Global Pathology, Sonic Health Care USA, Miami Lakes, FL.

The authors declare no conflicts of interest.

Correspondence: Laszlo Karai, MD, PhD, 16250 NW, 59th Ave, Suite 201, Miami Lakes, FL 33014 (e-mail: lkarai1@yahoo.com).







# Summary

- Our patient's clinical presentation and histopathologic findings over 3 years of follow-up support the possibility of gamma-delta-positive pcALCL with extensive LyP-like lesions
- While two arm-level copy number variations including gain of 1q raise alternative concern for pcGDTCL, the absence of consensus cancer gene mutations in MAPK, MYC, and JAK/STAT pathways would be unusual for pcGDTCL
- No rearrangements or fusions were identified
- The diagnosis is not unambiguous; therefore, our patient will be managed conservatively and followed closely

# Collaborators

Joi B. Carter, MD

Dept. of Dermatology, Dartmouth-Hitchcock Medical Center

Erick Lansigan, MD

Dept. of Hematology, Dartmouth-Hitchcock Medical Center

David Weiner

Perelman School of Medicine, University of Pennsylvania

City of Hope

International Society for Cutaneous Lymphomas ISCL

Thank you!

# Thank you!

City of Hope®

International Society for Cutaneous Lymphomas
ISCL

# References


- Bastidas Torres AN, Melchers RC, Van Grieken L, Out-Luiting JJ, Mei H, Agaser C, Kuipers TB, Quint KD, Willemze R, Vermeer MH, Tensen CP. Whole-genome profiling of primary cutaneous anaplastic large cell lymphoma. Haematologica . 2022 Jul 1;107(7):1619-1632.

- Daniels J, Doukas PG, Escala MEM, Ringbloom KG, Shih DJH, Yang J, Tegtmeyer K, Park J, Thomas JJ, Selli ME, Altunbulakli C, Gowthaman R, Mo SH, Jothishankar B, Pease DR, Pro B, Abdulla FR, Shea C, Sahni N, Gru AA, Pierce BG, Louissaint A Jr, Guitart J, Choi J. Cellular origins and genetic landscape of cutaneous gamma delta T cell lymphomas. Nat Commun . 2020 Apr 14;11(1):1806.

- Endly DC, Weenig RH, Peters MS, Viswanatha DS, Comfere NI. Indolent course of cutaneous gamma-delta T-cell lymphoma. J Cutan Pathol . 2013 Oct;40(10):896-902.

- Fadl A, Bennani NN, Comfere N, Durani U, Greipp PT, Feldman AL. Primary cutaneous gamma/delta T-cell lymphoma with simultaneous JAK2 and TP63 rearrangements: a new double-hit? Histopathology . 2023 Sep;83(3):492-495.

- Fattah YH, Crasto D, Liu SS, Linhares Y, Kerdel F, Hanly A, Karai LJ. DUSP22-IRF4 Rearranged CD30-Positive Primary Cutaneous Lymphoproliferative Disorder With Gamma/Delta Phenotype. Am J Dermatopathol . 2023 Dec 1;45(12):831-834.

- King RL, Yan AC, Sekiguchi DR, Choi JK. Atypical cutaneous γδ T cell proliferation with morphologic features of lymphoma but with clinical features and course of PLEVA or lymphomatoid papulosis. J Cutan Pathol . 2015 Dec;42(12):1012-1017.

- Martinez-Escala ME, Sidiropoulos M, Deonizio J, Gerami P, Kadin ME, Guitart J. γδ T-cell-rich variants of pityriasis lichenoides and lymphomatoid papulosis: benign cutaneous disorders to be distinguished from aggressive cutaneous γδ T-cell lymphomas. Br J Dermatol . 2015 Feb;172(2):372-9.

- Maurus K, Appenzeller S, Roth S, Brändlein S, Kneitz H, Goebeler M, Rosenwald A, Geissinger E, Wobser M. Recurrent Oncogenic JAK and STAT Alterations in Cutaneous CD30-Positive Lymphoproliferative Disorders. J Invest Dermatol . 2020 Oct;140(10):2023-2031.

# References


- Meawad H, Song JY, Ulrickson ML, Weisenburger DD. Primary Cutaneous Gamma-Delta T-Cell Lymphoma Mimicking anaplastic lymphoma kinase-1-Negative Anaplastic Large Cell Lymphoma: A Case Report. Am J Dermatopathol . 2022 Jan 1;44(1):62-65.

- Pulitzer M, Geller S, Kumar E, Frosina D, Moskowitz A, Horwitz S, Myskowski P, Kheterpal M, Chan A, Dogan A, Jungbluth A. T-cell receptor-δ expression and γδ+ T-cell infiltrates in primary cutaneous γδ T-cell lymphoma and other cutaneous T-cell lymphoproliferative disorders Histopathology . 2018 Oct;73(4):653-662.

- Rodríguez-Pinilla SM, Ortiz-Romero PL, Monsalvez V, Tomás IE, Almagro M, Sevilla A, Camacho G, Longo MI, Pulpillo Á, Diaz-Pérez JA, Montes-Moreno S, Castro Y, Echevarría B, Trébol I, Gonzalez C, Sánchez L, Otín AP, Requena L, Rodríguez-Peralto JL, Cerroni L, Piris MÁ., TCR-gamma expression in primary cutaneous T-cell lymphomas. Am J Surg Pathol. 2013 Mar;37(3):375-84.

- Szuhai K, van Doorn R, Tensen CP, Van Kester. Array-CGH analysis of cutaneous anaplastic large cell lymphoma. Methods Mol Biol . 2013:973:197-212.

- Taibo A, Cassarino D, Fernandez-Flores A. The First Case of Gamma-Delta Primary Cutaneous Anaplastic Large Cell Lymphoma? Am J Dermatopathol . 2022 Oct 1;44(10):786-787.

**HEMATOLOGICAL MALIGNANCY DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATION**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *ABL1* | *ACTB* | *ADGRA2 (GPR124)* | *AKT1* | *AKT2* | *AKT3* | *ALK* | *AMER1 (FAM123B or WTX)* | |
| *APC* | *APH1A* | *AR* | *ARAF* | *ARFRP1* | *ARHGAP26 (GRAF)* | | *ARID1A* | *ARID2* |
| *ASMTL* | *ASXL1* | *ATM* | *ATR* | *ATRX* | *AURKA* | *AURKB* | *AXIN1* | *AXL* |
| *B2M* | *BAP1* | *BARD1* | *BCL10* | *BCL11B* | *BCL2* | *BCL2L2* | *BCL6* | *BCL7A* |
| *BCOR* | *BCORL1* | *BIRC3* | *BLM* | *BRAF* | *BRCA1* | *BRCA2* | *BRD4* | *BRIP1* |
| *BRSK1* | *BTG2* | *BTK* | *BTLA* | *CAD* | *CALR** | *CARD11* | *CBFB* | *CBL* |
| *CCN6 (WISP3)* | *CCND1* | *CCND2* | *CCND3* | *CCNE1* | *CCT6B* | *CD22* | *CD274 (PD-L1)* | *CD36* |
| *CD58* | *CD70* | *CD79A* | *CD79B* | *CDC73* | *CDH1* | *CDK12* | *CDK4* | *CDK6* |
| *CDK8* | *CDKN1B* | *CDKN2A* | *CDKN2B* | *CDKN2C* | *CEBPA* | *CHD2* | *CHEK1* | *CHEK2* |
| *CIC* | *CIITA* | *CKS1B* | *CPS1* | *CREBBP* | *CRKL* | *CRLF2* | *CSF1R* | *CSF3R* |
| *CTCF* | *CTNNA1* | *CTNNB1* | *CUX1* | *CXCR4* | *DAXX* | *DDR2* | *DDX3X* | *DNM2* |
| *DNMT3A* | *DOT1L* | *DTX1* | *DUSP2* | *DUSP9* | *EBF1* | *ECT2L* | *EED* | *EGFR* |
| *ELP2* | *EMSY (C11orf30)* | *EP300* | *EPHA3* | *EPHA5* | *EPHA7* | *EPHB1* | *ERBB2* | *ERBB3* |
| *ERBB4* | *ERG* | *ESR1* | *ETS1* | *ETV6* | *EXOSC6* | *EZH2* | *FAF1* | *FANCA* |
| *FANCC* | *FANCD2* | *FANCE* | *FANCF* | *FANCG* | *FANCL* | *FAS (TNFRSF6)* | *FBXO11* | *FBXO31* |
| *FBXW7* | *FGF10* | *FGF14* | *FGF19* | *FGF23* | *FGF3* | *FGF4* | *FGF6* | *FGFR1* |
| *FGFR2* | *FGFR3* | *FGFR4* | *FHIT* | *FLCN* | *FLT1* | *FLT3* | *FLT4* | *FLYWCH1* |
| *FOXL2* | *FOXO1* | *FOXO3* | *FOXP1* | *FRS2* | *GADD45B* | *GATA1* | *GATA2* | *GATA3* |
| *GID4 (C17orf39)* | *GNA11* | *GNA12* | *GNA13* | *GNAQ* | *GNAS* | *GRIN2A* | *GSK3B* | *GTSE1* |
| *HDAC1* | *HDAC4* | *HDAC7* | *HGF* | *H1-2 (HIST1H1C)* | | *H1-3 (HIST1H1D)* | | |
| *H1-4 (HIST1H1E)* | | *H2AC6 (HIST1H2AC)* | | *H2AC11 (HIST1H2AG)* | | *H2AC16 (HIST1H2AL)* | | |
| *H2AC17 (HIST1H2AM)* | | *H2BC4 (HIST1H2BC)* | | *H2BC11 (HIST1H2BJ)* | | *H2BC12 (HIST1H2BK)* | | |
| *H2BC17 (HIST1H2BO)* | | *H3C2 (HIST1H3B)* | | *HNF1A* | *HRAS* | *HSP90AA1* | *ICK* | *ID3* |
| *IDH1* | *IDH2* | *IGF1R* | *IKBKE* | *IKZF1* | *IKZF2* | *IKZF3* | *IL7R* | *INHBA* |
| *INPP4B* | *INPP5D (SHIP)* | *IRF1* | *IRF4* | *IRF8* | *IRS2* | *JAK1* | *JAK2* | *JAK3* |
| *JARID2* | *JUN* | *KAT6A (MYST3)* | *KDM2B* | *KDM4C* | *KDM5A* | *KDM5C* | *KDM6A* | *KDR* |
| *KEAP1* | *KIT* | *KLHL6* | *KMT2A (MLL)* | *KMT2C (MLL3)* | *KMT2D (MLL2)* | *KRAS* | *LEF1* | *LRP1B* |
| *LRRK2* | *MAF* | *MAFB* | *MAGED1* | *MALT1* | *MAP2K1* | *MAP2K2* | *MAP2K4* | *MAP3K1* |
| *MAP3K14* | *MAP3K6* | *MAP3K7* | *MAPK1* | *MCL1* | *MDM2* | *MDM4* | *MED12* | *MEF2B* |
| *MEF2C* | *MEN1* | *MET* | *MIB1* | *MITF* | *MKI67* | *MLH1* | *MPL* | *MRE11 (MRE11A)* |
| *MSH2* | *MSH3* | *MSH6* | *MTOR* | *MUTYH* | *MYC* | *MYCL (MYCL1)* | *MYCN* | *MYD88* |
| *MYO18A* | *NCOR2* | *NCSTN* | *NF1* | *NF2* | *NFE2L2* | *NFKBIA* | *NKX2-1* | *NOD1* |
| *NOTCH1* | *NOTCH2* | *NPM1* | *NRAS* | *NSD2 (WHSC1 or MMSET)* | | *NT5C2* | *NTRK1* | *NTRK2* |
| *NTRK3* | *NUP93* | *NUP98* | *P2RY8* | *PAG1* | *PAK3* | *PALB2* | *PASK* | *PAX5* |
| *PBRM1* | *PC* | *PCBP1* | *PCLO* | *PDCD1* | *PDCD11* | *PDCD1LG2 (PD-L2)* | | *PDGFRA* |
| *PDGFRB* | *PDK1* | *PHF6* | *PIK3CA* | *PIK3CG* | *PIK3R1* | *PIK3R2* | *PIM1* | *PLCG2* |
| *POT1* | *PPP2R1A* | *PRDM1* | *PRKAR1A* | *PRKDC* | *PRSS8* | *PTCH1* | *PTEN* | *PTPN11* |
| *PTPN2* | *PTPN6 (SHP-1)* | *PTPRO* | *RAD21* | *RAD50* | *RAD51* | *RAF1* | *RARA* | *RASGEF1A* |
| *RB1* | *RELN* | *RET* | *RHOA* | *RICTOR* | *RNF43* | *ROS1* | *RPTOR* | *RUNX1* |
| *S1PR2* | *SDHA* | *SDHB* | *SDHC* | *SDHD* | *SERP2* | *SETBP1* | *SETD2* | *SF3B1* |
| *SGK1* | *SMAD2* | *SMAD4* | *SMARCA1* | *SMARCA4* | *SMARCB1* | *SMC1A* | *SMC3* | *SMO* |
| *SOCS1* | *SOCS2* | *SOCS3* | *SOX10* | *SOX2* | *SPEN* | *SPOP* | *SRC* | *SRSF2* |
| *STAG2* | *STAT3* | *STAT4* | *STAT5A* | *STAT5B* | *STAT6* | *STK11* | *SUFU* | *SUZ12* |
| *TAF1* | *TBL1XR1* | *TCF3 (E2A)* | *TCL1A (TCL1)* | *TENT5C (FAM46C)* | *TET2* | *TGFBR2* | *TLL2* | *TMEM30A* |
| *TMSB4XP8 (TMSL3)* | | *TNFAIP3* | *TNFRSF11A* | *TNFRSF14* | *TNFRSF17* | *TOP1* | *TP53* | *TP63* |
| *TRAF2* | *TRAF3* | *TRAF5* | *TSC1* | *TSC2* | *TSHR* | *TUSC3* | *TYK2* | *U2AF1* |
| *U2AF2* | *VHL* | *WDR90* | *WT1* | *XBP1* | *XPO1* | *YY1AP1* | *ZMYM3* | *ZNF217* |
| *ZNF24 (ZSCAN3)* | *ZNF703* | *ZRSR2* | | | | | | |

## HEMATOLOGICAL MALIGNANCY DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *ALK* | *BCL2* | *BCL6* | *BCR* | *BRAF* | *CCND1* | *CRLF2* | *EGFR* | *EPOR* |
| *ETV1* | *ETV4* | *ETV5* | *ETV6* | *EWSR1* | *FGFR2* | *IGH* | *IGK* | *IGL* |
| *JAK1* | *JAK2* | *KMT2A (MLL)* | *MYC* | *NTRK1* | *PDGFRA* | *PDGFRB* | *RAF1* | *RARA* |
| *RET* | *ROS1* | *TMPRSS2* | *TRG* | | | | | |

## HEMATOLOGICAL MALIGNANCY RNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *ABI1* | *ABL1* | *ABL2* | *ACSL6* | *AFDN (MLLT4 or AF6)* | *AFF1* | *AFF4* | *ALK* | |
| *ARHGAP26 (GRAF)* | | *ARHGEF12* | *ARID1A* | *ARNT* | *ASXL1* | *ATF1* | *ATG5* | *ATIC* |
| *BCL10* | *BCL11A* | *BCL11B* | *BCL2* | *BCL3* | *BCL6* | *BCL7A* | *BCL9* | *BCOR* |
| *BCR* | *BIRC3* | *BRAF* | *BTG1* | *CAMTA1* | *CARS1 (CARS)* | *CBFA2T3* | *CBFB* | *CBL* |
| *CCND1* | *CCND2* | *CCND3* | *CD274 (PD-L1)* | *CDK6* | *CDX2* | *CEP43 (FGFR1OP)* | *CHIC2* | *CHN1* |
| *CIC* | *CIITA* | *CLP1* | *CLTC* | *CLTCL1* | *CNTRL (CEP110)* | *COL1A1* | *CREB3L1* | *CREB3L2* |
| *CREBBP* | *CRLF2* | *CSF1* | *CTNNB1* | *DDIT3* | *DDX10* | *DDX6* | *DEK* | *DUSP22* |
| *EGFR* | *EIF4A2* | *ELF4* | *ELL* | *ELN* | *EML4* | *EP300* | *EPOR* | *EPS15* |
| *ERBB2* | *ERG* | *ETS1* | *ETV1* | *ETV4* | *ETV5* | *ETV6* | *EWSR1* | *FCGR2B* |
| *FCRL4* | *FEV* | *FGFR1* | *FGFR2* | *FGFR3* | *FLI1* | *FNBP1* | *FOXO1* | *FOXO3* |
| *FOXO4* | *FOXP1* | *FSTL3* | *FUS* | *GAS7* | *GLI1* | *GMPS* | *GPHN* | *H4C9 (HIST1H4I)* |
| *HERPUD1* | *HEY1* | *HIP1* | *HLF* | *HMGA1* | *HMGA2* | *HOXA11* | *HOXA13* | *HOXA3* |
| *HOXA9* | *HOXC11* | *HOXC13* | *HOXD11* | *HOXD13* | *HSP90AA1* | *HSP90AB1* | *IGH* | *IGK* |
| *IGL* | *IKZF1* | *IL21R* | *IL3* | *IRF4* | *ITK* | *JAK1* | *JAK2* | *JAK3* |
| *JAZF1* | *KAT6A (MYST3)* | *KDSR* | *KIF5B* | *KMT2A (MLL)* | *LASP1* | *LCP1* | *LMO1* | *LMO2* |
| *LPP* | *LYL1* | *MAF* | *MAFB* | *MALT1* | *MDS2* | *MECOM* | *MLF1* | *MLLT1 (ENL)* |
| *MLLT10 (AF10)* | *MLLT3* | *MLLT6* | *MN1* | *MNX1* | *MRTFA (MKL1)* | *MSI2* | *MSN* | *MUC1* |
| *MYB* | *MYC* | *MYH11* | *MYH9* | *NACA* | *NBEAP1 (BCL8)* | *NCOA2* | *NDRG1* | *NF1* |
| *NF2* | *NFKB2* | *NIN* | *NOTCH1* | *NPM1* | *NR4A3* | *NSD1* | *NSD2 (WHSC1 or MMSET)* | |
| *NSD3 (WHSC1L1)* | *NTRK1* | *NTRK2* | *NTRK3* | *NUMA1* | *NUP214* | *NUP98* | *NUTM2A* | *OMD* |
| *P2RY8* | *PAFAH1B2* | *PAX3* | *PAX5* | *PAX7* | *PBX1* | *PCM1* | *PCSK7* | *PDCD1LG2 (PD-L2)* |
| *PDE4DIP* | *PDGFB* | *PDGFRA* | *PDGFRB* | *PER1* | *PHF1* | *PICALM* | *PIM1* | *PLAG1* |
| *PML* | *POU2AF1* | *PPP1CB* | *PRDM1* | *PRDM16* | *PRRX1* | *PSIP1* | *PTCH1* | *PTK7* |
| *RABEP1* | *RAF1* | *RALGDS* | *RAP1GDS1* | *RARA* | *RBM15* | *RET* | *RHOH* | *RNF213* |
| *RNF217-AS1 (STL)* | | *ROS1* | *RPL22* | *RPN1* | *RUNX1* | *RUNX1T1 (ETO)* | *RUNX2* | *SEC31A* |
| *SEPTIN5 (SEPT5)* | *SEPTIN6 (SEPT6)* | *SEPTIN9 (SEPT9)* | *SET* | *SH3GL1* | *SLC1A2* | *SNX29 (RUNDC2A)* | | *SRSF3* |
| *SS18* | *SSX1* | *SSX2* | *SSX4* | *STAT6* | *SYK* | *TAF15* | *TAL1* | *TAL2* |
| *TBL1XR1* | *TCF3 (E2A)* | *TCL1A (TCL1)* | *TEC* | *TET1* | *TFE3* | *TFG* | *TFPT* | *TFRC* |
| *TLX1* | *TLX3* | *TMPRSS2* | *TNFRSF11A* | *TOP1* | *TP63* | *TPM3* | *TPM4* | *TRIM24* |
| *TRIP11* | *TTL* | *TYK2* | *USP6* | *YPEL5* | *ZBTB16* | *ZMYM2* | *ZNF384* | *ZNF521* |

***ADGRA2 (GPR124)***
NM_032777.9:
c.3010_3011delinsAA
(p.G1004K)
chr8:37698866-37698867

***EPHA7***
NM_004440.3: c.2024A>C
(p.Q675P)
chr6:93967903

***ERBB2***
NM_004448.2: c.3484C>T
(p.P1162S)
chr17:37884013

***LRP1B***
NM_018557.2: c.9415C>A
(p.P3139T)
chr2:141242922

***NOD1***
NM_006092.2: c.434T>C
(p.L145P)
chr7:30492599

***RAF1***
NM_002880.3: c.94A>G
(p.I32V)
chr3:12660127

***RICTOR***
NM_152756.3: c.2719C>T
(p.R907C)
chr5:38953634

***WDR90***
NM_145294.4: c.2417G>A
(p.G806D)
chr16:707165