



## Case Report

# Mature T-Cell Lymphoma/Leukemia with a Novel Skap1: Jak2 Fusion

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## Introduction

The recent WHO/ICC-classifications recognize six subgroups of primary leukemic mature T-cell neoplasms, namely aggressive-mature-NK-cell-leukemia, Sezary-Syndrome (SS), T-Cell-Prolymphocytic Leukemia (T-PLL), Adult-T-Cell Lymphoma/leukemia (ATLL), T-Large Granular-Lymphocytic Leukemia (LGLL) and chronic lymphoproliferative disorder of NK-cells [1,2]. In most instances the diagnosis of these rare

disorders is straightforward since they are distinct from one another [1,2].

We present a leukemic mature T-cell neoplasm with cutaneous involvement undergoing Complete Remission (CR) after Alemtuzumab treatment, with peculiar clinical and molecular features not fitting into any of the currently defined subgroups [1,2].

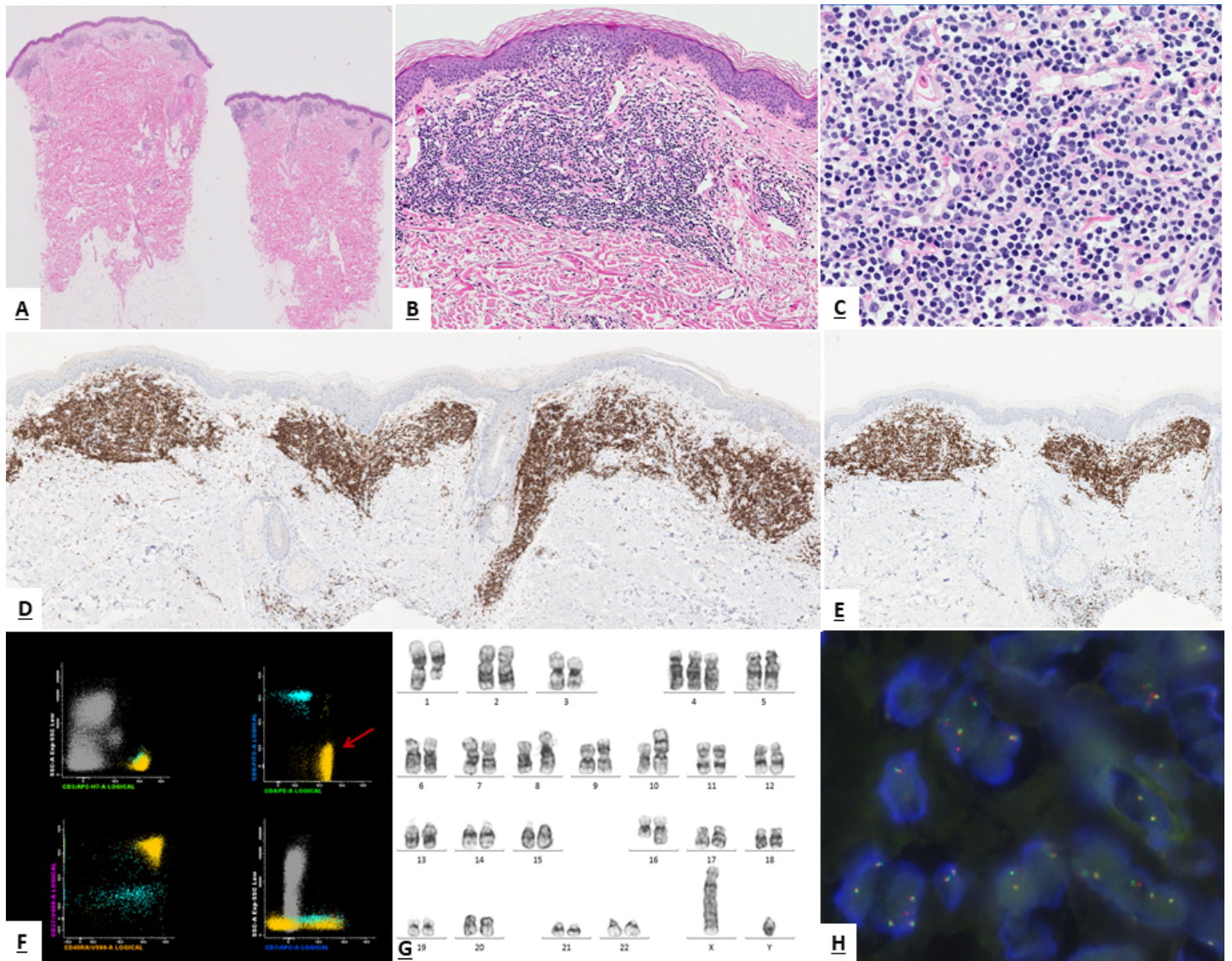
## Case Report

A 55-year-old man complained of an erythematous, butterfly-pattern, non-pruritic rash on his face present for one year and subsequently spreading to his neck and back (Figure 1, A-B-C).



Figure 1A-1C: Clinical appearance of skin erythematous rash at onset. C. Resolution of skin lesions after treatment with alemtuzumab.

A skin biopsy showed a dense band-like infiltrate of atypical small to intermediate-sized lymphocytes without epidermotropism (Figure 2A-2I). The neoplastic cells were CD3/CD4/CD2/CD5/PD1/TCRBF1/CD25/FOXP3 positive (Figure 2D-E) and TdT/CD34/CD117/MNDA/CD7/TCL1/CD30/TIA1/granzymeB/perforin/CD56/CD57/CD20/TCRG/ICOS negative. Epstein - Barr Virus Encoded Small RNA (EBER) by in-situ-hybridization was negative.



**Figure 2A-I:** Skin biopsy specimen: (A) Panoramic view with Hematoxylin-eosin (10x), (B and C) Band-like infiltrate of small to intermediate-sized lymphoid cells, with no significant epidermotropism. (Hematoxylin-eosin staining, 20 and 40x, respectively). (D) Immunohistochemical study for CD3 and PD1 (E). Bone marrow aspirate showing neoplastic lymphocytes (red arrows).(G.) Flow cytometry study, 1) Cellular complexity/CD3; 2)CD8/CD4; 3)CD27/CD45RA; and 4)Cellular complexity/CD7 (H). Cytogenetic study (conventional Karyotype). I. FISH break apart study for JAK2 gene.

Total body CT showed neither lymphadenopathy nor organomegaly. Blood tests revealed a lymphocyte count of 7,300 cells/mm<sup>3</sup>, not associated with leukocytosis or eosinophilia. On peripheral blood and bone marrow smears these cells were small and showed round hyperchromatic nuclei (Figure 2F).

Serum-lactate-dehydrogenase levels and B-2-microglobulin levels were normal, and tests for Human-T-Cell Lymphotropic Virus (HTLV1/2), Human Immunodeficiency Virus (HIV) and Epstein - Barr virus (EBV) were negative.

Polymerase-Chain-Reaction (PCR) of the T-cell-receptor gamma gene demonstrated an identical clonal-rearrangement on skin and blood.

By flow cytometry 79.03% (5,733 cel/μl) of the cells on peripheral blood were CD45<sup>++</sup>/CD3<sup>++</sup>/CD4<sup>+</sup>/CD2<sup>+</sup>/CD5<sup>+</sup>/CD7<sup>+</sup>bimodal/CD45Ra<sup>+</sup>/CD52<sup>+</sup>/CD27<sup>+</sup>/CCR7<sup>+</sup>/CD25<sup>+</sup>/PD1<sup>+</sup>het/CD38<sup>+</sup>het/CD8-CD10-/CD26-/CD30-/CD56-/HLADR- (Figure 2G). Bone marrow was also involved.

Conventional cytogenetic studies on blood and bone-marrow showed a complex karyotype with the following formula: 47X,Y,der(X)t(X;?)(q28;?),t(1;10)(q23;p14),t(3;16)(p22;q23),+4,ins(8)(q21q24),add(9)(p24)[5]/46,XY[15] (Figure 2H). RNA-Fusion-Panel (Illumina) studies on a skin specimen showed a fusion between SKAP1 (chr17 46,423,267) and JAK2 (chr9 5,081,724) (Score: 0.775) genes. JAK2-rearrangement was validated using FISH break-apart probe (Figure 2I). Next-Generation Sequencing (NGS) with a customized T-cell panel found no further somatic mutations. Treatment with prednisolone was ineffective and was replaced by Alemtuzumab, achieving CR after 60 months of follow-up (Figure 1C).

## Discussion

We present an intriguing case resembling T-PLL and non-erythrodermic-SS, in which a final diagnosis of unclassified leukemic-mature T-cell neoplasms was made.

Neoplastic cells expressed CD4/CD25/PD1/FOXP3; showed a band-like skin infiltration pattern and were CD7 negative. These data have been described in SS and ATLL patients [3]. The latter was excluded due to negativity for HTLV1. CD25 expression is seen in T-PLL cases, while PD1 is usually negative [4]. No data regarding FOXP3 expression has been reported in T-PLL cases. CD52 is typically overexpressed in T-PLL but can be seen in other T-cell-lymphomas, including SS [5]. On the other hand, phenotype by flow-cytometry could match T-PLL or SS [6] but the morphology of neoplastic cells on blood smears excluded SS and resembled small-cell-variant of T-PLL.

Cytogenetics abnormalities in chromosome 14(inv(14)(q11q32), t(14;14)(q11;q32) or t(X;14)) juxtaposing TCRA/D and

TCL1 / TCL1B/ MTCP1 genes were not found by karyotyping or FISH studies and TCL1 was negative by immunohistochemistry. Although TCL1 expression is one of the three major criteria for T-PLL, Staber et al described a TCL1- negative subgroup [7]. Other than alterations on chromosome 8, none of the usual 11q (ATM), 12p, 22q, 17 deletions or abnormalities of chromosome 6 were found.

The patient presented a complex karyotype and MYC gene alterations (8q24) with no mutations in JAK-STAT-pathway genes, but a JAK2-gene rearrangement. SS cells are characterized by a complex karyotype with frequent gains in 8q (MYC) [3]; and fusion transcripts [8]. JAK2-gene fusions have been described in CD4-positive CTCLs

[9,10]. However, SKAP1-gene as fusion partner has not been previously reported in lymphomagenesis. Those CTCL cases lacked genomic complexity and involved patients were younger than the average for mycosis fungoides, responded poorly to conventional therapeutic regimens and suffered histological progression with CD30-positive large T-cells in skin and lymph nodes [10].

T-PLL manifests with leukocytosis, lymphadenopathy, extranodal-involvement, hepatosplenomegaly and B-symptoms. In one-third of the patients there are cutaneous manifestations typically involving the face. Staber et al. [7] suggested that no “indolent”-T-PLL cases exist although Stengel et al. [11] described two different prognostic subgroups based on their molecular background. Our patient is alive and well after 2-years on Alemtuzumab therapy, skin involvement being the sole criterion for this treatment [7]. Alemtuzumab is also effective in SS patients [5], a disorder characterized by erythroderma and lymphadenopathy, even though rare forms without erythroderma have been reported [12, 13]. The latter usually complained of pruritus and eventually evolved into conventional SS.

We report an extraordinary case with an unexpected novel gene fusion and excellent clinical outcome. Further cases within this spectrum need to be collected to elucidate whether they constitute a distinct entity.

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## Authorship

FJ Díaz de la Pinta and SM Rodríguez Pinilla wrote the manuscript and reviewed the literature.

FJ Díaz de la Pinta, SM Rodríguez Pinilla, N Carvajal García, C Serrano, R Manso, C Soto and RN Salgado performed cytogenetics,

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molecular, cytological and histopathological investigations for an accurate diagnosis.

R Córdoba, L Requena and J Torre cared for the patient and contributed clinical data for the manuscript.

### Competing interests

Competing interests: the authors have no competing interests

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