

# Silent T-cell receptor cutaneous T-cell lymphoma associated to a clonal plasma cell proliferation

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## Abstract

Within T-cell lymphomas (TCL) there are 2 entities expressing gamma-delta TCR: hepatosplenic gamma-delta T-cell lymphoma (HSGDTL) and the primary cutaneous gamma-delta T-cell lymphoma (PCGDTL). PCGDTL is a rare form of T-cell lymphoma with specific tropism for skin that have a dismal prognosis. Although even rarer, there have been reports of TCL with loss of expression of the TCR, which have been termed peripheral TCL TCR-silent type. We report the case of a cutaneous TCR-silent type lymphoma associated to a clonal plasma cell proliferation with an ominous outcome that led to a lot of discussion in its classification. Due to the aggressiveness of the disease and the scant evidence about therapy in this strange entity the outcome was fatal. We report a unique case of a TCR-silent cutaneous TCL with an exceptional histopathology, prolonged clinical evolution and a subsequent plasma cell clonal expansion.

## Introduction

Peripheral T-cell lymphomas (PTCLs) are a group of complex entities, comprising less than 10% of non-Hodgkin lymphomas. PTCLs are subclassified based on histologic, immunophenotypic, and genetic findings. PTCLs frequently involve the skin, either as primary or secondary manifestation of the disease. Most of these cutaneous T-cell lymphomas (CTCLs) express an alpha-beta T-cell receptor (TCR) while only 2-4% express a gamma-delta TCR. The WHO classification recognizes only two distinct entities of gamma-delta T-cell lymphoma: the hepatosplenic gamma-delta T-cell lymphoma (HSGDTL) and the primary cutaneous gamma-delta T-cell lymphoma (PCGDTL).<sup>1,2</sup>

PCGDTL is a rare form of T-cell lym-

phoma with specific tropism for skin that exhibits an aggressive clinical behavior. They are resistant to chemotherapy and/or radiation, and have a poor prognosis with a 5-year overall survival of 10%. Although even rarer, there have been reports of PTCLs with loss of expression of the TCR, which have been termed PTCL TCR-silent type.<sup>3,4</sup>

## Case Report

A 72-year-old male with a previous heart transplant in 2000 was diagnosed with a PCGDTL. At the time of diagnosis, he was receiving immunosuppressive drugs. In a control in September 2014 he presented with 2 nodular lesions about 2 cm in the anterior and lateral surfaces of his lower limbs. The skin biopsy revealed a diffuse cell infiltration of the dermis (predominantly of perivascular and peri-adnexal). The tissue was composed by a medium-size lymphoid population with irregular nuclei and prominent nucleoli. Some cells occasionally had large cytoplasm. The immunohistochemical (IHC) stains showed a predominant T-cell population (CD2, CD3 and CD5 positive) with an intense and diffuse expression of CD8. There was a loss of CD7 expression. *In situ* hybridization for mRNA of Epstein-Barr virus (EBERs) was negative. Staining for TCR beta-F1 chain was also negative. TCR gamma and delta proteins expression studied by IHC in paraffin-embedded tissue were no assessable. The Ki67 index was 50%. TCR molecular studies showed a gamma rearrangement with a predominant peak at 208 bp. Thus, the patient was diagnosed with a PCGDTL. The complete blood count and PET-CT were normal (Figure 1).

The patient received 4 cycles of COP chemotherapy (cyclophosphamide-vincristine-prednisone) reaching a stable disease followed by radiotherapy (30 Gy) that eliminated skin infiltration.

Two months later, new nodular lesions appeared above the previously irradiated field. The new skin biopsy showed atypical T cells (CD2+, CD3+ and CD5+) with loss of CD7 expression and diffuse expression of CD8. The beta-F1 staining remained negative; IHC for gamma and delta TCR proteins were negative. The study of TCR-gamma rearrangement showed the same monoclonal peak than the previous biopsy. The previous diagnosis was revised and a new diagnosis of CTCL TCR silent subtype was established. A new PET-CT did not show disease dissemination. The patient received 4 cycles of gemcitabine-oxali-

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platin, with no response. Radiotherapy was administered (20 Gy) with temporal remission of the disease. At the end of treatment, a new PET-CT reported the presence of an adenopathy at the left external iliac chain. The lymph node biopsy showed a dense plasma cell infiltrate with lambda light chain restriction (Figure 2).

Plasma cells were EBERs negative. The study of B-cell receptor rearrangement showed a monoclonal peak in the FR3 region. The serum/urine protein electrophoresis and bone marrow biopsy were normal.

On October 2015, a new follow-up PET-CT showed a diffuse infiltration of the skull, left humerus, and right femur. A biopsy of one of the bone lesions showed the presence of infiltration of the inter-trabecular spaces by a proliferation of medium-size lymphoid cell, occasional mitotic figures and apoptotic bodies. IHC stains showed a T-cell population CD3+ CD5+ and CD7-; CD8 was positive on some atypical cells. CD4 and CD138 were negative

In summary, we report a complex case of a CTCL with an exceptional histopathology, prolonged clinical evolution and a subsequent plasma cell clonal expansion.

## Discussion

In this report, we describe an infrequent form of disseminated CTCL with loss of expression of the TCR (TCR silent type) associated with a clonal plasma cell expansion. The most frequent TCR is made up of alpha and beta chains. The other form comprises gamma and delta chains, which are expressed approximately on 4% of T-cells.

Gamma-delta T-cells tend to concentrate in the mucosa, lymphoid tissues and epithelial barriers as well as in the red pulp of the spleen. These T-cells develop from CD4-/CD8- thymic precursors in the bone marrow and, unlike alpha-beta T-cells, they typically lack the major histocompatibility complex restriction. In contrast to TCR alpha-beta cells, these cells usually have a CD4-/CD8- phenotype.<sup>5</sup>

The 2016 WHO classification recognizes two main types of gamma-delta PTCL namely, gamma-delta hepatosplenic T-cell lymphoma and primary cutaneous gamma-delta T-cell lymphoma (PCGDTL).<sup>6</sup>

PCGDTL is a lymphoma composed of a clonal proliferation of mature, activated gamma delta T-cells with a cytotoxic phenotype. PCGDTL represents approximately 1% of all CTCL.

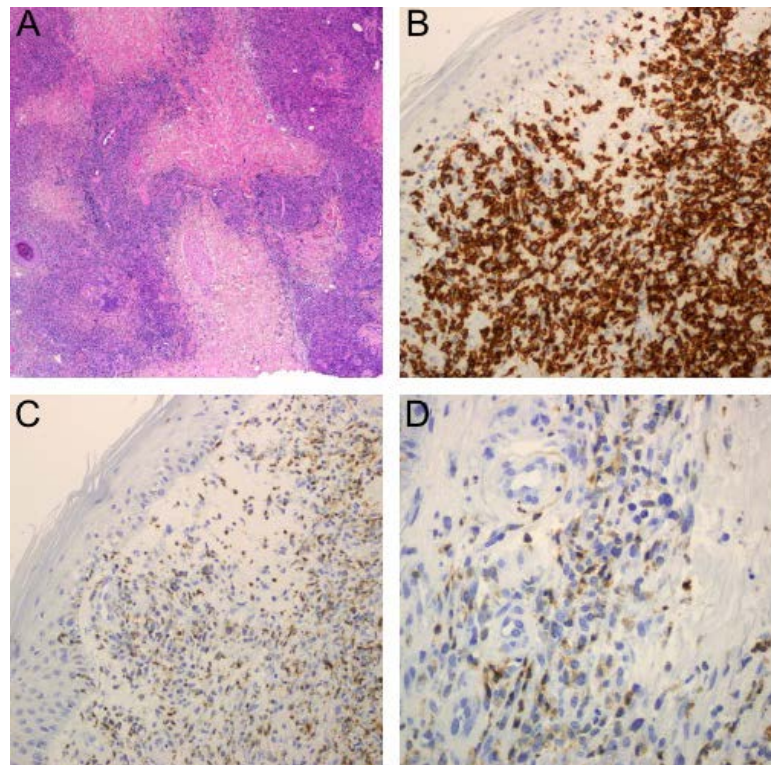
The disease may be predominantly epidermotropic and presents with patches and plaques. The lesions are most often located on the extremities. Dissemination to mucosal and other extranodal sites is frequently observed, but involvement of lymph nodes, spleen or bone marrow is uncommon.

Cells of PCGDTL have a beta-F1-, CD3+, CD2+, CD5-, CD7+/-, CD56+ phenotype with strong expression of cytotoxic proteins. But some cases with CD5+ have been reported.<sup>7,8</sup> Most, lack both CD4 and CD8, although CD8 may be expressed in some cases. The cells are strongly positive for delta TCR with appropriate detection methods. If staining for delta TCR cannot be performed, the absence of beta-F1 may be used to establish the diagnosis. TCR beta may be either rearranged or deleted, but it is not expressed. Epstein-Barr virus is usually negative.<sup>9</sup>

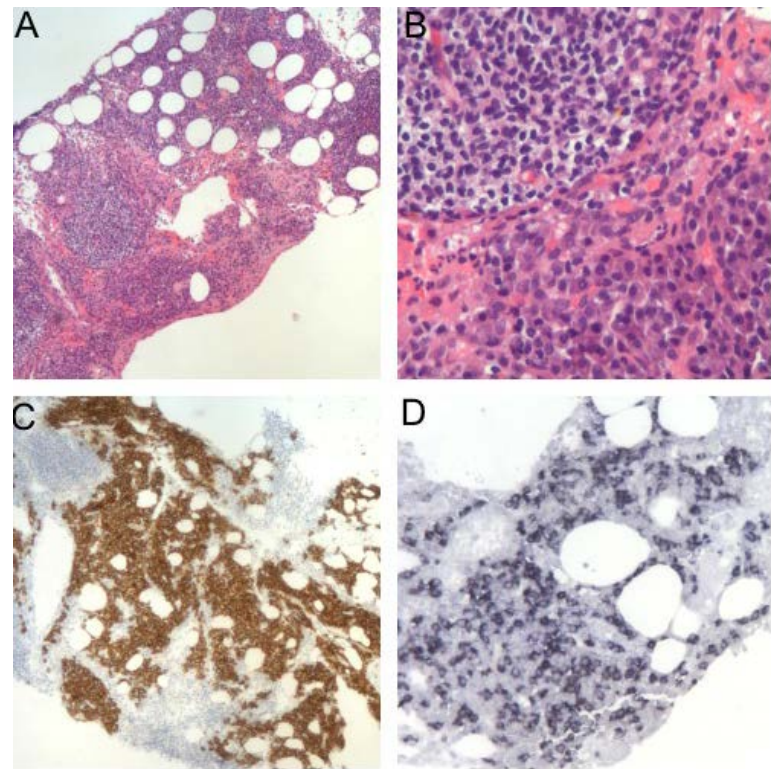
Prognosis of PCGDTL is poor, with a median survival of 15 months and a 5-year overall survival of 10%.<sup>2</sup>

With the histopathology, IHC, and because of the gamma-delta TCR studies were not assessable the patient was diagnosed with a PCGDTL. The second skin biopsy showed negative beta-F1 and a negative gamma and delta TCR. These new findings lead us to reconsider our first diagnosis as a TCR silent type lymphoma.

These PCGDTL that lacks a TCR



**Figure 1.** A) Skin biopsy showing a diffuse lymphoid infiltration of the dermis (original magnification  $\times 10$ ). B) Immunohistochemical stain for CD3 highlighting medium and occasionally large neoplastic T cells (original magnification  $\times 10$ ). C, D) Diffuse negative immunohistochemical stain for TCR beta-F1 chain of neoplastic population (original magnification  $\times 10$  and  $\times 40$ ).



**Figure 2.** A, B) Loss of lymph node architecture. Two different cell populations: a lymphoid population accompanied by clusters of mature plasma cells (original magnification  $\times 4$  and  $\times 20$ ). C) Immunohistochemical stain for CD138 highlighting extensive infiltration by mature plasma cells (original magnification  $\times 4$ ). D) Lambda light chain restriction (original magnification  $\times 10$ ).

expression by IHC studies have been designated as “TCR silent PTCL”. It has been proposed that the TCR silent phenotype represents a common phenomenon of “TCR instability” in different tumor types, rather than representing a distinct entity. In favor to this hypothesis there is a previous report of a TCR alpha-beta hepatosplenic T-cell lymphoma that evolved to a TCR silent phenotype.<sup>10,11</sup>

The lack of TCR expression may represent a phenotypic aberration in PTCL, usually found at the time of progression. This finding indicates that the lack of beta TCR chain expression cannot be used to infer a gamma-delta T-cell origin with certainty. A first explanation could be that the  $\beta$ F1 - TCR- $\gamma\delta$ - cases represent a more ‘immature’ step, before or during cytoplasmic CD3 expression. A second hypothesis is that some cases may represent neoplasms of NK cells. This is supported by another report showing that NKH-1 is preferentially expressed on peripheral T-cell lymphomas with CD3-/ $\beta$ F1- phenotype, which seems to be the usual phenotype of “true” NK cells.<sup>5</sup>

Regardless of whether it is a separate entity or a transition due to disease progression, our case is even more unique because it is associated with a clonal plasma cells proliferation.

The coexistence of PTCLs and B-cell clonality occurs in 9 to 16% of cases and represents a diagnostic dilemma. This finding is more frequent in immature T cell lymphoid neoplasms.<sup>12</sup>

There are some possible explanations for the detection of coexisting B and T clones. The first is the so-called lineage infidelity of a single clone that results of the recombination of TCR and IGH genes in the same clone. The second is the presence of two different clones’ coexistence, which may happen in up to 35% of PTCL cases.<sup>12,13</sup> Another possibility is that tumoral cells could secrete factors that might produce a second neoplasia, in this case a new lymphoma.<sup>14</sup> B-cell expansions are ranging from isolated or small clusters of large activated B-cells to focally confluent transformed B-cells that may obscure the T-cell proliferation.

A recent study described that EBV-negative B-cell proliferations associated with PTCL had a marked plasma cell differentiation. Nevertheless, EBV-negative prolifera-

tions associated with T-cell lymphomas are uncommon and not well characterized.<sup>15</sup>

## Conclusions

In summary, we show a CTCL TCR silent associated with an EBV-negative clonal plasma cell proliferation, which represents an example of the heterogeneity of the PTCLs. The clonal plasma cell expansion in addition to the presence of bone disease may lead to a misdiagnosis of multiple myeloma making the diagnosis of a TCR-silent PTCL a real challenge.

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