

## Clinically and genetically atypical T-cell prolymphocytic leukemia underlines the relevance of a multidisciplinary diagnostic approach

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Prolymphocytic leukemia (PLL) is a rare clonal lymphoproliferative disorder of mature lymphocytes. The disease originates from B lymphocytes in approximately 80% of cases and from T lymphocytes in 20% of cases.<sup>1</sup> B-PLL and T-PLL are both characterized by an aggressive clinical course with splenomegaly, and a high WBC count. However, generalized lymphadenopathy and cutaneous involvement are rare in B-PLL, while present in ~25% of cases with T-PLL.<sup>1,2</sup> We report a patient with T-PLL with an unusual clinical presentation and relatively indolent clinical course in whom a translocation was found, which was previously described in B-PLL.

A 61-year-old man presented with a 2-year history of asymptomatic red raised skin lesions, starting with a few lesions on the back, and gradually progressing until it became almost generalized. On a lesional skin biopsy taken at another clinic 4 months after the first symptoms developed, an initial diagnosis of lichen nitidus was suggested. The patient had no history of skin diseases. There was no pruritus, fever, night sweats, or weight loss. Dermatological examination at our hospital demonstrated numerous erythematous non-scaling papules on the trunk, extremities and behind the ears (Figure 1). The face, palms, and soles were not involved. General physical examination demonstrated cervical and inguinal lymphadenopathy but no hepatosplenomegaly.

Computed tomography (CT) showed generalized lymphadenopathy and mild splenomegaly.

Laboratory examination revealed a white blood cell (WBC) count of 61X10<sup>9</sup>/L, with 85% lymphocytes, 11% neutrophils, 1% eosinophils, and 3% monocytes. The hemoglobin (Hb) level was 15.2 g/dL and platelet count 98 x 10<sup>9</sup>/L. Biochemistry revealed a slightly elevated lactate dehydrogenase (LDH) level of 567 U/L. Serological analysis of human T cell leukemia virus type 1 (HTLV-I) was negative. Peripheral blood smear showed 91% medium sized lymphoid cells with light grey, sometimes vacuolated cytoplasm, but without cytoplasmic granules (Figure 2A). The nucleus was round or oval shaped and some nuclei showed indentation. An occasional nucleolus was present. The bone marrow smears showed all hematopoietic cell lineages at different stages of maturation and infiltration with lymphoid cells, morphologically similar to the peripheral blood lymphoid cells.

Histologic examination of a later skin biopsy showed various patches of non-epidermotropic dermal infiltrates, composed of lymphocytes admixed with Langerhans cells and histiocytes (Figure 2B). The lymphocytes were only slightly enlarged and barely demonstrated atypical features such as nuclear polymorphism. Immunohistochemistry demonstrated that the infiltrate was mainly composed of CD2, CD3<sup>+</sup>, CD4<sup>+</sup>, CD5<sup>+</sup>, CD7<sup>+</sup>, CD8<sup>+</sup>, CD56<sup>+</sup>, CD30<sup>+</sup>, ALK1<sup>+</sup>, TCL1<sup>+</sup> T cells (Figure 2B; insert). Examination of a bone marrow biopsy demonstrated focal infiltration of small to medium-sized T cells with similar morphology and immunophenotype as those found in skin and peripheral blood.

Immunophenotypic analysis of peripheral blood revealed a large population (83% of total leukocytes) of aberrant T cells with the immunophenotype CD3<sup>+</sup> dim /CD2<sup>+</sup>/CD4<sup>+</sup>/CD5<sup>+</sup>/CD7<sup>++</sup>/CD8<sup>+</sup>/CD25<sup>+</sup>/TCRαβ<sup>+</sup>/CD16<sup>-</sup>/CD56<sup>-</sup>/CD57<sup>-</sup>/CD30<sup>-</sup>/CD52<sup>-</sup>/CD11b<sup>-</sup>/CD1a<sup>-</sup>/CD10<sup>-</sup>/TdT<sup>-</sup> (Figure 2C; red dots). The normal T-cell population represented 1% of total T lymphocytes (Figure 2C; blue dots). B-cell markers (CD19, CD20, CD79a) were negative. TCR Vβ flowcytometric analysis demonstrated that 98% of CD3<sup>+</sup> dim cells reacted with a TCR-Vβ16 antibody (Figure 2C; red dots). Flowcytometric analysis confirmed bone marrow localization of this aberrant T-cell population. The immunophenotypical findings in peripheral blood and bone marrow were most compatible with a diagnosis of T-cell prolymphocytic leukemia (T-PLL). PCR based GeneScan analysis of T-cell receptor (TCR) genes demonstrated identical clonal TCRγ (TCRG) and TCRβ (TCRB) gene rearrangements in peripheral blood and skin biopsy samples (Figure 2D), while the immunoglobulin heavy-chain (IGH) genes were polyclonally rearranged. These results indicate the presence of clonally identical T-cell populations in peripheral blood and skin.

Cytogenetic analysis of PB cells using standard cytogenetic techniques and classification according to the International System for Human Cytogenetic Nomenclature ISCN 2005, revealed an aberrant karyotype: 46,X,-Y,t(6;12)(q15;p13),-12,+mar1,+mar2[7]/46,XY[15] (Fig 3A). Fluorescence in situ hybridization (FISH) using whole chromosome paints (WCP) demonstrated the presence of Y sequences in the large marker chromosome as suggested by the QFQ banded karyogram (Figure 3A; top). FISH also showed that chromosome 12 sequences were present on the large marker chromosome harbouring the Y sequences (described as: der(2)t(2;Y)t(2;12)) and on the small marker chromosome (Figure 3B; arrows). FISH with WCP for chromosome 6 (green), and 12 (red) confirmed the t(6;12), with the 6q

Figure 1. Photograph of the thorax and abdomen of the patient showing disseminated erythematous papules.

typical, and molecular genetic analysis, the diagnosis of T-PLL was made according to WHO Classification criteria.<sup>6</sup> Revision of the initial skin biopsy demonstrated a lymphocytic infiltrate with non-specific reactive changes, likely to be compatible with early manifestation of T-PLL. Revision of a lymph node (LN) biopsy (at first suggested to contain a reactive lymphocytic infiltrate), showed a slightly disturbed architecture and involvement with neoplastic T-PLL cells.

The clinical presentation and the so far indolent clinical course of our patient are remarkable. T-PLL is considered to be an aggressive leukemia with a poor prognosis and a median overall survival of less than 7.5 months.<sup>2</sup> Interestingly, our patient is in good clinical condition 32 months after onset of the erythematous papules. He has a mild thrombopenia, and a moderate but stable leukocytosis. Because of the indolent course of his disease, no treatment was initiated. The patient is monitored close-

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**Figure 2.** A. Peripheral blood (PB) smear demonstrating medium sized lymphoid cells with light grey, non-granular vacuolated cytoplasm (MGG; magnification x 630) B. Histology of skin lesion. Skin biopsy specimen demonstrates the patchy dermal infiltrate of lymphoid cells admixed with histiocytes and Langerhans cells (HE; magnification x 100). The vast majority of cells are positive for CD3 (insert) (Magnification x 400). C. Immunophenotype of T-PLL cells (shown in red) and normal T-cells (shown in blue) present in PB at diagnosis. The T-PLL cells are CD2-/CD3+ dim/strong CD7+/Vb16+. D. GeneScan analysis of PCR products. TCRB gene rearrangement analysis was performed using multiplex tube B of the BIOMED-2 multiplex PCR protocol.<sup>11</sup> Identical monoclonal TCRB gene rearrangements were detected in skin and PB samples. Polyclonal TCRB gene rearrangements can be detected in a PB sample from a healthy donor.

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breakpoints being more centromeric than in the karyotypic results (Figure 3B; arrowheads). Based on the banding pattern, the breakpoint on the long arm of chromosome 6 was determined to be in 6q15. FISH using WCP for chromosome 6 and 12 showed that there was hardly any chromosome 6 WCP present below the centromeric region of the der(6) showing that the estimated breakpoint on 6q was in fact more centromeric than determined by banding.

FISH analysis with ETV6 (located on 12p13) exon 1a and 5-8 probes showed only one ETV6 signal, present on the very tip of the long arm of the large marker chromosome, suggesting further intrachromosomal rearrangements. The absence of the other signal is indicative for an ETV6 deletion, which has been reported as a recurrent genetic event in T-PLL.<sup>3</sup> This also indicates that the seemingly balanced t(6;12) is in fact accompanied by a small deletion of chromosome 12p13 sequences.

In the Mitelman Database (<http://cgap.nci.nih.gov/Chromosomes/Mitelman>) eleven cases with various hematological malignancies were found to contain translocations involving the 6q1 and 12p1 regions. Interestingly, five of these had been diagnosed with B-cell prolymphocytic leukemia (B-PLL) and t(6;12)(q15;p13).<sup>4</sup> As the chromosomes of the case presented here look exactly like the ones detected in these B-PLL cases, t(6;12)(q15;p13) seems not specific for B-PLL, but may rather be considered as a marker for PLL in general. Notably, the most common cytogenetic aberrations in T-PLL, i.e. (inv(14)(q11q32) and t(14;14)(q11;q32)5, could not be detected in our patient.

Based on histo- and cytomorphology, immunopheno-

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**Figure 3.** A. Partial karyogram showing chromosome 6, 12 and markers present in QFQ-banding (top), or RBA-banding (bottom) in PB cells. B. Partial metaphase spread hybridized with WCP 6 (green) and WCP12 (red), showing both derivatives of the t(6;12) (arrowheads). The large marker and the small marker are shown to contain chromosome 12 sequences (arrows). The dim green fluorescent signals are secondary signals.

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ly. Although patients diagnosed with T-PLL may present with an indolent clinical course<sup>7</sup>, cutaneous manifestation of the disease at presentation generally is a feature of initially progressive disease.<sup>7,8</sup> Moreover, one of the characteristics of the progression phase of patients with initially indolent disease is the development of skin lesions.<sup>7,9</sup>

This case demonstrates that skin lesions can be the initial presentation of T-PLL and that a skin biopsy is essential in revealing the underlying disease. However, as prolymphocytoid features of T-PLL cells can be difficult to detect in routinely stained sections of extramedullary biopsy specimens,<sup>10</sup> extensive histopathological examination, cytomorphological, flow cytometric, and molecular (cyto)genetic analysis all contribute to reach the diagnosis. This case therefore exemplifies the importance of a multidisciplinary team approach in correctly diagnosing mature T-cell malignancies.

Y. Sandberg,<sup>1</sup> K.L. Wu,<sup>2</sup> F. Heule,<sup>3</sup> R.R. van den Bos,<sup>3</sup> K.H. Lam,<sup>4</sup>  
A.W. Langerak,<sup>1</sup> V.H. van der Velden,<sup>1</sup> K. van Lom,<sup>2</sup>  
H.B. Beverloo<sup>5</sup>

Departments of <sup>1</sup>Immunology, <sup>2</sup>Hematology, <sup>3</sup>Dermatology,  
<sup>4</sup>Pathology, and <sup>5</sup>Clinical Genetics, University Medical Center  
Rotterdam, Erasmus MC, Rotterdam, The Netherlands

Correspondence (and reprint request): Dr. A.W. Langerak, PhD,  
department of Immunology,  
erasmus MC, University Medical Center  
Dr. Molewaterplein, 503015 GE Rotterdam, The Netherlands  
Tel.: 31-10-408.8089, Fax: 31-10-408.9456  
E-mail: a.langerak@erasmusmc.nl

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