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Malignant Lymphomas

Application of cross-species color banding (RxFISH) in the study of T-prolymphocytic leukemia

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ABSTRACT

Background and Objectives. **Cross-species color banding (RxFISH) is a new FISH technology based on the use of differentially labeled gibbon chromosome probes to obtain a specific color banding pattern for each human chromosome. The aim of the study was to test the RxFISH technique for better characterization of complex karyotypes in patients with T-prolymphocytic leukemia (T-PLL).**

Design and Methods. **The study evaluated the cross-species color banding technique in four patients affected with T-PLL previously studied by conventional cytogenetics.**

Results. **All patients showed an abnormal karyotype and three of them had a complex karyotype. The involvement of 14q11 in all four cases, the gain of 8q in three cases and a loss of chromosome 10, 15 and 17 and a gain of chromosome 21 in two cases were noted. The RxFISH technique identified from 2 to 7 not previously recognized aberrations per case and confirmed the inv(14)(q11q32).**

Interpretation and Conclusions. **To our knowledge, this is the first application of RxFISH to characterize chromosomal rearrangements in T-cell neoplasms. RxFISH gave rapid and easy identification of chromosome rearrangements that were difficult to recognize by conventional cytogenetics. Using this new technology we identified 15 rearrangements not detected by conventional cytogenetics.**

Key words: cytogenetics, *in situ* hybridization, T-PLL, cross-species color banding, RxFISH.

Peripheral T cell neoplasms are malignant T-cell lymphoid disorders that, as described in the REAL classification,[1] comprise among other entities, T-cell chronic lymphocytic leukemia/T-prolymphocytic leukemia (T-CLL/T-PLL), T-cell and NK-type large granular lymphocyte leukemia (LGLL) and mycosis fungoides/Sézary syndrome (MF/SS). The World Health Organization has proposed a classification for lymphomas similar to that of the REAL with minor modifications and reassesement of provisional categories such as the consideration of T-PLL instead of T-CLL/PLL.[2] The cytogenetic data-base on T-cell neoplasms from Western countries, as compared with that on B-cell neoplasms, is still limited due to the low incidence of these pathologies.[3] The karyotype of T-cell lymphoid disorders is often complex showing multiple rearrangements.[4-13] The most significant findings are involvement of chromosome 14 at 14q11, most often as an inversion inv(14) (q11q32), t(14;14)(q11;q32) or t(X;14)(q28;q11).[5,6,8,10-13] Chromosome 8 abnormalities, usually as i(8)(q10) or t(8;8)(p21;q11), are also commonly observed in T-cell neoplasms.[9-13]

Recently, a new technology, introduced as cross-species color banding (or RxFISH for Rainbow cross-species FISH), has been developed. It consists in a DNA probe set that permits the visualization and analysis of color banded chromosomes.[14-18] RxFISH is based on the use of fluorescent *in situ* hybridization with DNA probes derived from bivariate fluorescence activated flow sorting of primate chromosomes. Probes used come from two gibbon species (*Hylobates concolor* and *Hylobates syndactylus*) previously characterized as having both extensively rearranged chromosomes and a high degree of homology to the target human DNA. Combination labeling of the probe set (3 fluorophores generating 7 colors) and its subsequent application to metaphase spreads in a single fluorescent *in situ* hybridization assay permits the generation of a distinctive color-banding pattern throughout the genome. The addition of colors in the karyotype has simplified chromosome identification compared to the analysis of classical banding based on grey values.

We report the results of peripheral blood cytogenetic studies in four cases of T-PLL using conventional cytogenetics and RxFISH technologies. To our knowledge, this is the first application of the mentioned technology to characterize chromosomal rearrangements in T-cell neoplasms. The application of cross-species color banding gave rapid and easy identification of chromosome rearrangements that were difficult to recognize by conventional cytogenetics.

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Design and Methods

Patients

Four patients with T-PLL diagnosed in our institution have been studied. Diagnoses were made in all cases according to standard clinical, cytologic and immunologic criteria (Table 1). Immunologic studies were performed on peripheral blood smears using a panel of monoclonal antibodies that included CD2, CD3, CD4, CD5, CD7, CD8, CD16, CD19 and CD 56. Three patients had a mature T-cell phenotype ($CD2^+$, $CD3^+$ and $CD4^+$) and one patient coexpressed CD4 and CD8 (case #1).

Conventional cytogenetics

Conventional cytogenetic (CC) studies were performed in all patients at diagnosis prior to any treatment. Chromosome analyses were carried out on lymphoid cells from 72-hour peripheral blood cultures. Phytohemagglutinin (PHA) was used as a mitogen. Cultures were incubated for 72 hours at 37ºC and harvested after exposure to the antimitotic colcemid for 30 minutes. After having treated the cultures with hypotonic solution for 30 minutes, 3 to 5 fixative changes were performed before the slides, were prepared. G-banding was performed after having aged the slides in a slide warmer at 100ºC for 1 hour. The slides were stained with Wright's solution. Karyotypes were described according the International System for Human Cytogenetic Nomenclature (ISCN).[19]

Cross-species color banding FISH

In order to characterize the complex karyotypes of four T-PLL patients the RxFISH color chromosome analysis FISH kit (Applied Imaging, Santa Clara, CA, USA) was used according to the instructions supplied by the manufacturer with modifications. Briefly, metaphase slides were prepared the same day and aged for 2 hours in a 60ºC oven. Ten microliters of RxFISH color chromosome probe per case were prewarmed for 5 minutes at 37ºC, then denatured at 65ºC for 10 minutes and placed in a 37ºC waterbath for at least 10 minutes (but used within two hours). Preparations were dehydrated in 100% ethanol at room temperature for 5 minutes and allowed to air dry. They were then denatured by incubation in a 70% formamide/2XSSC solution for 1.5 minutes at 75ºC. Immediately, slides were quenched in ice cold 70% ethanol for 2 minutes and dehydrated using 70%, 90% (twice) and 100% ethanol series for 2 minutes each at room temperature. Slides were allowed to air dry. Ten microliters of the denatured RxFISH probes were applied to each slide, which was covered by a coverslip. Slides were incubated for a least 12 hours in a moist chamber at 37ºC. Post-hybridization washes consisted in one change of five minutes in a 2×SSC solution, two changes of five minutes each in a 50% formamide/2×SSC solution, one wash of five minutes in a 2×SSC solution and one wash of ten minutes in a 4×SSC/0.05% Tween-20 solution at 45ºC. Slides were stained in a Coplin jar containing DAPI (4,6-diamino-2-phenylindole)/2×SSC (0.1 µg/mL) (Sigma, St. Louis, MO, USA) for at least two minutes at room temperature. Finally, they were mounted on Cytofluor AF1 mounting media and covered by a coverslip. Results were analyzed in a Nikkon Eclipse 600 fluorescent microscope using an automated filter wheel. Image acquisition was performed with an RxFISH CytoVision System (Applied Imaging, Santa Clara, CA, USA). A minimum of 20 metaphases per case were studied by two different observers.

Table 1. Clinical and analytical data in four patients with T-PLL.

Case	Diagnosis	Age/sex	Hb ($x10^9$ g/L)	WBC ($x10^9$ g/L)	Platelets ($x10^9$ g/L)	Atypical lymph in PB (%)
1	T-PLL	42/M	14.6	12.2	144	70
2	T-PLL	94/F	9.4	13.4	279	27
3	T-PLL	89/F	13.6	24.1	203	73
4	T-PLL	72/M	14.5	12.9	118	29

Abbreviations: T-PLL: chronic prolymphocytic leukemia; PB: peripheral blood; WBC: white blood cell count.

Results

Conventional cytogenetics and cross-species color banding

All patients had analyzable metaphases with an abnormal karyotype, and three of them had a complex karyotype. The most frequently involved chromosomes in decreasing order of frequency were: 8,14, 12, 15, 17 and 21. The involvement of 14q11 was noted in all four cases (and in two of them as a translocation t(X;14)(q28;11) or t(X;14;14)(q28;q11;q11)), as was the the gain of 8q in three cases and a loss of chromosome 10, 15 and 17 and a gain of chromosome 21 in two cases. The application of RxFISH allowed identification of novel aberrations not detected by conventional cytogenetics. In case #1, for which there were very good quality metaphases with large chromosomes and well defined G-bands, RxFISH revealed only one new cytogenetic abnormalitiy over the 12 previously described by conventional cytogenetics. However, cases #2 and 3 had poorly defined chromosomal bands and in both cases, RxFISH technology detected a larger number of chromosomal aberrations (7/15 in cases #2 and 3). In case #4, RxFISH confirmed the presence of an additional copy of chromosome 8 and inversion of chromosome 14 affecting the common region in T-cell neoplasms, but no new aberrations were detected. The detailed cytogenetic results detected by conventional techniques and by RxFISH are shown in Table 2. Table 3 shows cytogenetic abnormalities identified by RxFISH but not detected by conventional cytogenetics.

Discussion

Peripheral T-cell neoplasms have been poorly cytogenetically studied due to the relative scarcity of these disorders in Western countries. The detection of a complex karyotype is very common, chromosomes 1, 2, 4, 6, 8, 10, 13, 14, 17 and 21 being the most frequently involved.[4-13] In our series, the most frequent chromo-

Table 2. Cytogenetic findings in four patients with T-PLL. A comparison between conventional cytogenetics and RxFISH techniques.

Case	Conventional cytogenetic findings	Cross-species color banding FISH (RxFISH) findings
1	46,XY[10]/43,X,-Y, der(X)(14qter→14q11::Xp22→Xq28::14q11→14qter), dic(5;13)(p15;p13),i(8)(q10), der(11)t(11;15)(q21;q13),del(12)(p13), del(14)(q11),add(18)(q23),dic(21;21)(p13;p13),+ac[10]	43,X,-Y, der(X)(14qter→14q11::Xp22→Xq28::14q11→14qter) dic(5;13)(p15;p13),i(8)(q10),der(11)t(11;15)(q21;q13), del(12)(p13),del(14)(q11),der(18)t(13;18)(q22;q23), dic(21;21)(p13;p13),+ac [10]
2	46,XX[5]/44»45,XX, der(1), der(2), der(5)t(1;5)(q25;q35),-9, -10, -13, add(14)(p11), add(15)(q26), i(17)(q10),der(20)t(13;20)(q11;q13),+21,+mar, +ac [9]/ 45,XX, der(2), der(3), del(5)(q13), +der(8), -9, -10, add(14)(p11), -15, -17, i(17)(q10),+21, +mar [6].	44»45,XX,der(2)t(2;12)(p25;q11),der(5)t(1;5)(q25;q35),-9,-10, -13, der(14)t(6;14)(p21;p11), der(15)t(8;15)(q?;q26), der(17)t(13;17)(q?;q25),i(17)(q10), add(20)(q13), +21/ 44»45,XX,der(2)t(2;12)(p25;q11), der(3)(1qter→1q32::3q22→3q29::3p26→3qter) del(5)(q13),+der(8)(8pter→8q21::4q25→4q35::8p21→8pter), -9,-10, der(14)t(6;14)(p21;p11), -15,-17,i(17)(q10),+21.
3	46,XX [16]/41,XX,t(X;14)(q28;q11),-6,t(7;11)?, add(8)(q24),-10, der(12)t(12;?),-15,add(15)(p11),-17,-21,-22,+mar [9]	41,XX,t(X,14)(q28;q11), +der(4)(4pter→4q21::Xq?→Xq?::14q11→14qter),-6,-7, ider(8)(3pter→3p21::8q23→8q10::8q10→8qter),-10, der(11)t(11;17)(q11;q11), der(12)(Xqter→Xq26::12p13→12q24::?), -15,i(15)(q10),-17, der(21)t(10;21)(q11;p11),-22.
4	47,XY,+8,inv(14)(q11q32) [20]	47,XY,+8,inv(14)(q11q32)

somal abnormalities were gain of 8q (as i(8q) or +8), monosomies 10, 15 and 17, involvement of 14q11, t(X;14) (q28;q11), t(X;14;14) and trisomy 21 or i(21)(q10). Similarities exist among cytogenetic findings in T-PLL, LGLL and SS. In a series of 21 patients with T-PLL, 71% had abnormalities involving 14q11 and 81% had aberrations of chromosome 8q[13]. As Pawson *et al.*[20] reported and as we have found, inv(14) is not specific to T-PLL and trisomy 8, including i(8q), occurs preferentially in patients with T-PLL, being rare in SS patients. In most cases of SS, karyotypic changes are complex. Structural changes involving chromosomes 1, 6 and 14 and loss of chromosome 10 are very frequent.[4-10,21] In contrast to the above mentioned T-cell malignancies, LGLL usually shows few chromosomal abnormalities and it is very rare to find complex karyotypes.[11]

Table 3. Cytogenetic abnormalities detected by cross-species color banding (RxFISH) not previously detected by conventional cytogenetics.

Case	RxFISH findings
1	der(18)t(13;18)(q22;q23)
2	der(2)t(2;12)(p25;q11) der(3)(1qter→1q32::3q22→3q29::3p26→3qter) der(8)(8pter→8q21::4q25→4q35::8p21→8pter) der(14)t(6;14)(p21;p11) der(15)t(8;15)(q?;q26) der(17)t(13;17)(q?;q25) add(20)(q13)
3	der(4)(4pter→4q21::Xq?→Xq?::14q11→14qter) -7 ider(8)(3pter→3p21::8q23→8q10::8q10→8qter) der(11)t(11;17)(q11;q11) der(12)(Xqter→Xq26::12p13→12q24::?) i(15)(q10) der(21)t(10;21)(q11;p11)

Since its introduction, conventional cytogenetic analysis has depended on chromosome banding techniques. In some cases, chromosomes are not large enough to detect small rearrangements and in others, bands have a poor morphology that renders the interpretation of the karyotype difficult. In addition, especially in lymphoid disorders, karyotypes are often very complex with multiple rearrangements and unidentified chromosomes (marker chromosomes). The first FISH technologies allowed particular aberrations to be defined using locus-specific or painting probes. In 1996, multicolor-FISH (M-FISH)[22] and spectral karyotyping (SKY)[23] were introduced, for the first time allowing visualization of the genome in multicolor. These techniques *paint* each pair of chromosomes in a single assay with a different color. Both techniques have demonstrated their usefulness in the study of the karyotype of neoplastic cells.[24-26] However, intrachromosomal rearrangements cannot be visualized, by M-FISH or SKY, despite these techniques being more powerful for determining the identity of small marker chromosomes. Recently, the development of a new cross-species color banding technique has refined karyotype analysis allowing the detection of rearrangements that involve the same chromosome, such as translocations with both homologs, inversions or insertions between homologs. It has been demonstrated its utility in the study of neoplasias.[27,28] In our study, this technique, RxFISH identified 1 to 7 previously unrecognized aberrations per case (Table 3). Among those newly identified aberrations, three had previously been described in Mitelman's catalog:[21] a t(13;17) (q14;q25) was described by Johnson *et al.*[29] in a patient with SS, confirming the simi-

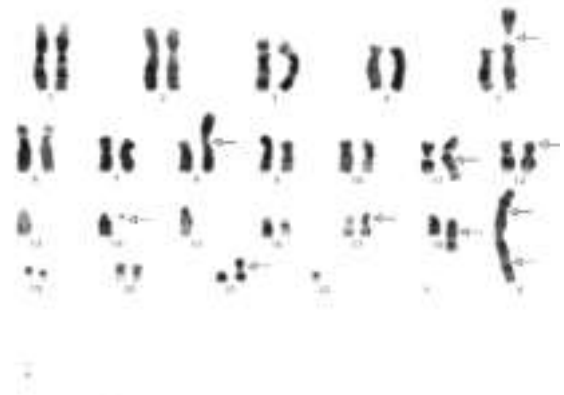

Figure 1. Conventional karyotype 43,X, -Y, der(X)(14qter→14q11::Xp22→Xq28::14q11→14qter), dic(5;13)(p15;p13), i(8)(q10), der(11)t(11;15)(q21;q13), del(12)(p13), del(14)(q11), add(18)(q23), dic(21;21)(p13;p13), +ac from patient 1.

Figure 2. RxFISH karyotype 43,X,-Y, der(X)(14qter→14q11::Xp22→Xq28::14q11→14qter),dic(5;13)(p15;p13), i(8)(q10), der(11)t(11;15)(q21;q13), del(12)(p13), del(14)(q11), der(18)t(13;18)(q22;q23), dic(21;21)(p13;p13),+ac from patient #1.

Figure 3. Conventional karyotype 44, XX, der(1), der(2), -4, der(5)t(1;5) (q25;q35), -9, -10, add(12)(p13), -13, add(14)(p11), add(15)(q26), i(17)(q10), der(20)t(13;20)(q11;q13), +21, +mar, +ac from patient #2 (random loss of chromosome 4).

larity between T-PLL and SS at a cytogenetic level; a t(8;15)(q12;q26) was descibed in a complex karyotype from a splenic marginal zone B-cell lymphoma[30] and an i(15)(q10) in a complex karyotype from a diffuse large cell lymphoma[31] both being aberrations described in B-cell neoplasms rather than T-cell disorders.

In addition, RxFISH confirmed the inv(14)(q11q32) that could not be identified by the M-FISH or SKY technique. Nevertheless, one of the limitations of RxFISH appears when chromosomal rearrangements involve regions painted a similar color (for example, 8q is indistinguishable from 21q, 6q has a similar color to 13q, 17q or chromosome X) due to the lower number of bands (no more than 100 bands per haploid karyotype) in comparison with conventional cytogenetics.[19] In all cases it is worth going back to the conventional karyotype or studying the

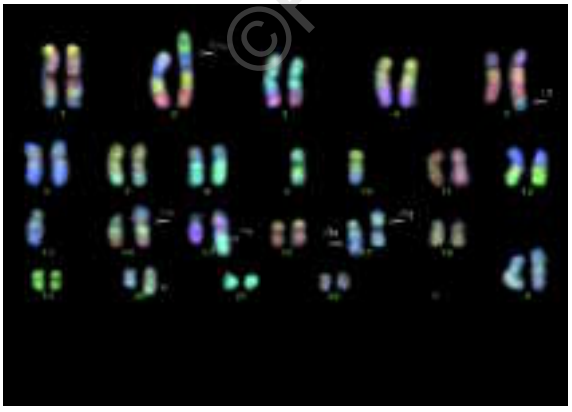

Figure 4a. RxFISH karyotype (corresponding to the clone represented in Figure 3) 43,XX, der(2)t(2;12)(p25;q11), der(5)t(1;5)(q25;q35), -9, -10, -13, der(14)t(6;14)(p21;p11), der(15)t(8;15)(q?;q26), der(17)t(13;17)(q?;q25), i(17)(q10), add(20)(q13) (acentric loss in imaging process).

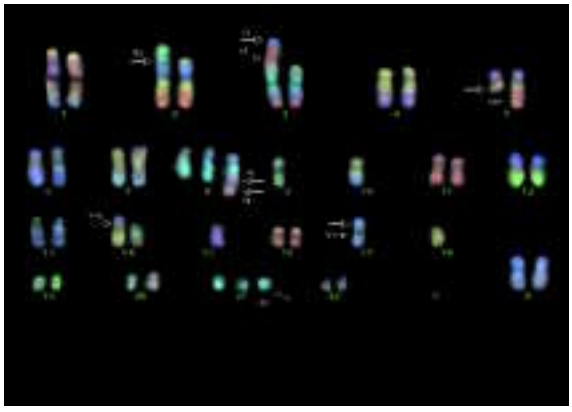

Figure 4b. RxFISH karyotype (corresponding to a different clone) 43,XX, der(2)t(2;12) (p25;q11),der(3)(1qter→1q32::3q22→3q29::3p26→3qter), del(5)(q13), +der(8)(8pter→8q21::4q25→4q35::8p21→8pter),-9,-10, der(14)t(6;14)(p21;p11), -15,-17,i(17)(q10),-18, +21 from patient 2 (random loss of chromosome 18 and acentric loss in imaging process).

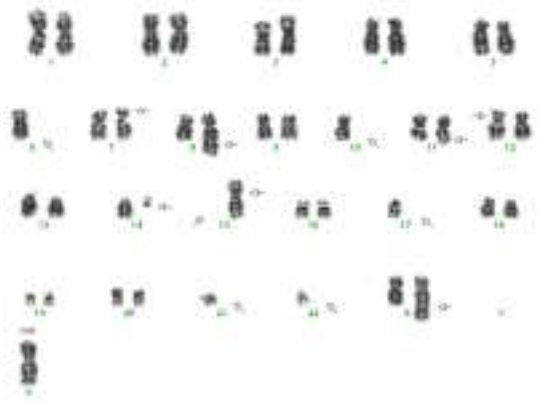

Figure 5. Conventional karyotype 41, XX, t(X;14)(q28;q11), -6, t(7;11)?, add(8)(q24), -10, der(12)t(12;?), -15, add(15)(p11), -17, -21, -22, +mar from patient 3.

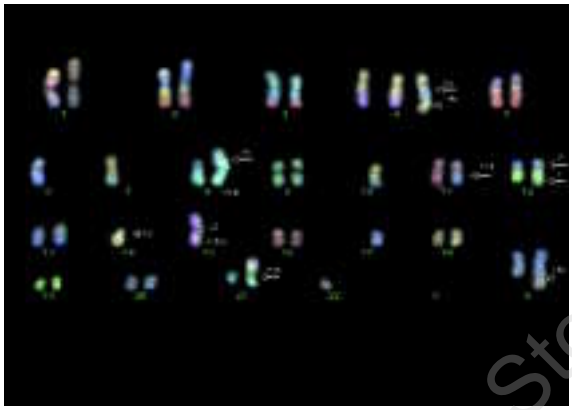

Figure 6. RxFISH karyotype 41,XX,t(X,14)(q28;q11), +der(4)(4pter→4q21::Xq?→Xq?::14q11→14qter), -6, -7, ider(8) (3pter→3p21::8q23→8q10::8q10→8qter), -10, der(11)t(11;17)(q11;q11), der(12)(Xqter→Xq26::12p13→12q24::?), -15,i(15)(q10),-17, der(21)t(10;21)(q11;p11),-22 from patient #3.

same cell in black and white (DAPI in black and white). The combination of G-banding and RxFISH would yield additional information beyond that obtained by either technique used alone.

In our series of patients, slides were made from fixative (Carnoy)-stored material (from 1995 until now) and in all of them the resolution (brightness of fluorescence and quality of bands) was good enough to analyze all samples easily. In all cases, it is important to have metaphase spreads without cytoplasm to allow better penetration of the probe into the cell. In such cases, colors are brighter. As the cross-species color banding technique depends on the finding of metaphase spreads, it is important to have a large number of cells in metaphase per slide. It is recommended that at least 15 metaphases per slide are analyzed.

To conclude, the application of RxFISH technology is very useful in T-cell lymphoid disorders because

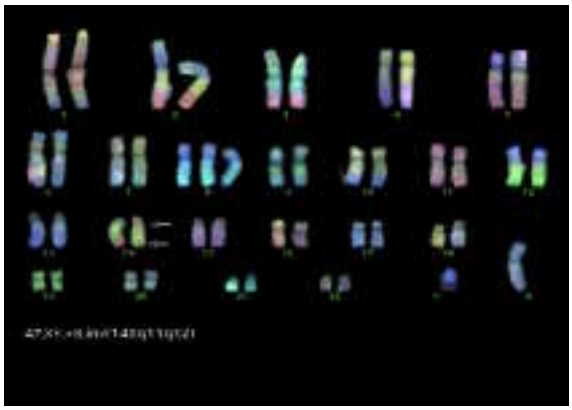

Figure 7. RxFISH karyotype 47, XY, +8, inv(14)(q11q32) from patient #4.

of the case of obtaining a large number of metaphases per case with very good quality chromosomes. The routine application of conventional cytogenetics combined with RxFISH techniques may lead to the identification of new recurring chromosomal abnormalities in T-cell lymphoid disorders. It will be interesting to apply this new technology to B-cell lymphoid disorders which usually show poor chromosome morphology.

Contributions and Acknowledgments

BE had the main responsibility for writing the paper. FS was responsible for conventional cytogenetic studies with BE. BE, MS and ELL performed RxFISH analyses of the samples. EA and CB were responsible for the clinical management and clinical data acquisition. SS, SW and LF performed the morphologic, histologic and immunophenotypic studies at diagnosis. FS, SW and LF reviewed the article to obtain the final form in which it was submitted. BE and FS were responsible for all aspects of this study.

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All the authors gave their critical contribution and approved the final version of the manuscript. The authors are listed in an order reflecting their individual contribution to the article.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Potential implications for clinical practice

- Cytogenetic studies in patients with T-PLL allow better identification of this entity which is inusual in Western countries.
- RxFISH technology may lead to better identification of new recurring chromosomal abnormalities in T-cell lymphoid disorders.

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