

Review Article

Isolated Trisomy 3 in Chronic Lymphocytic Leukemia: A Case Report of an Aggressive Clinical Presentation with High Tumor Burden and Classic Matutes Score

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Abstract: Background: Chronic lymphocytic leukemia (CLL) is the most frequent B-cell lymphoproliferative disorder in adults. Although its cytogenetic landscape is dominated by 13q deletion, trisomy 12, 11q deletion, and 17p deletion, rarer numerical abnormalities such as trisomy 3 are occasionally identified. The clinical impact and prognostic value of trisomy 3 remain poorly characterized. **Case Presentation:** A 71-year-old male presented with progressive asthenia and intermittent headaches lasting for several weeks. Physical examination revealed a tumor syndrome combining splenomegaly and peripheral lymphadenopathy. Laboratory evaluation demonstrated major hyperleukocytosis at 180000/ μ L associated with anemia (hemoglobin 8.0g/dL) and thrombocytopenia (platelets 75000/ μ L), categorizing the disease as Binet stage C (Rai stage IV). Peripheral blood smear showed a lymphocytosis composed of monotonous mature small lymphocytes with the presence of Gumprecht shadows. Flow cytometry immunophenotyping on whole blood confirmed the diagnosis of classic CLL with a Matutes score of 5. Conventional R-banding karyotype revealed a trisomy of chromosome 3. FISH analysis excluded the presence of targeted deletions of the *TP53* (17p13) and *ATM* (11q22.3) genes. **Conclusion:** This case illustrates an aggressive initial presentation of CLL associated with an isolated trisomy 3, despite an immunophenotypic profile highly concordant with typical CLL. Systematic investigation and characterization of these rare chromosomal aberrations are essential to better define their pathophysiological role.

Keywords: Chronic Lymphocytic Leukemia, Trisomy 3, Matutes Score, Hyperleukocytosis, Cytogenetics, FISH.

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1. INTRODUCTION

Chronic lymphocytic leukemia (CLL) is characterized by the progressive accumulation of mature-appearing B lymphocytes in peripheral blood, bone marrow, and secondary lymphoid organs. Cytogenetic and molecular characterization plays a major role in risk stratification and therapeutic management decisions.

Recurrent chromosomal aberrations identified by fluorescence *in situ* hybridization (FISH) are present in more than 80% of patients at diagnosis [1].

- **13q14 deletion (del(13q)):** The most frequent abnormality, carrying a favorable prognosis when isolated.

- **Trisomy 12:** Associated with occasionally atypical morphology and an intermediate prognosis.
- **11q22-23 deletion (del(11q) / *ATM* gene):** Associated with marked lymphadenopathy and an aggressive disease course.
- **17p13 deletion (del(17p) / *TP53* gene):** A marker of ultra-high risk and resistance to conventional chemoimmunotherapy.

Beyond this standard panel, conventional R-banding karyotyping allows the detection of rarer or more complex structural or numerical chromosomal abnormalities. Isolated trisomy 3 is an unusual chromosomal abnormality in CLL, more frequently reported in other B-cell lymphoid malignancies such as

marginal zone lymphomas. Here, we report the case of a 71-year-old patient presenting with a highly aggressive *de novo* CLL associated with trisomy 3 in the absence of high-risk *TP53* and *ATM* deletions [2, 3].

2. Clinical Observation (Case Presentation)

2.1 History and Physical Examination

A 71-year-old male, with no known hematological history, consulted a specialist for the evaluation of a constitutional syndrome combining marked asthenia and intermittent headaches evolving over one month.

Clinical Examination Revealed:

- **Peripheral Tumor Syndrome:** Painless, mobile bilateral cervical, axillary, and inguinal lymphadenopathies.
- **Splenomegaly:** Measured at 4 cm below the left costal margin.
- **Absence of hepatomegaly** or signs of active acute infection.

2.2 Hematological Evaluation

The complete blood count performed urgently showed marked involvement of all three hematopoietic cell lineages:

- **Leukocytes:** 180 000/ μ L (major hyperleukocytosis) with absolute lymphocytosis.
- **Hemoglobin:** 8.0 g/dL (normochromic normocytic anemia).
- **Platelets:** 75 000/ μ L (moderate-to-severe thrombocytopenia).

Examination of the May-Grünwald-Giemsa (MGG)-stained peripheral blood smear showed a monotonous proliferation of small, mature-appearing lymphocytes with clumped chromatin and scanty cytoplasm, accompanied by an abundant presence of Gumprecht shadows (smudge cells), strongly pointing toward a CLL-type lymphoproliferative disorder (Figure 1).

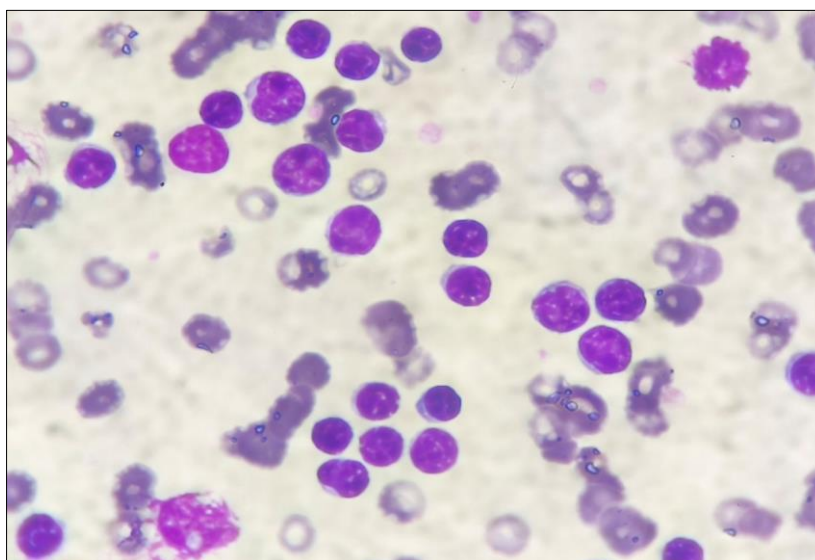


Figure 1: MGG-stained blood smear (x1000) showing lymphocytes and Gumprecht shadows

2.3 Flow Cytometry Immunophenotyping: [4, 5]

Multiparameter flow cytometry on whole blood demonstrated a monoclonal B-cell population

representing the majority of leukocyte events (Figures 2,3,4). The detailed immunophenotypic profile was established as follows:

Marker	Expression Level	Matutes Score Contribution
CD45	Bright positive	—
CD19	Positive	—
CD20	Positive (low/moderate intensity)	—
CD5	Positive	+1
CD23	Positive	+1
CD200	Positive	—
sIg (Lambda light chain)	Low intensity monotypy	+1
FMC7	Negative	+1
CD79b	Negative	+1
CD10	Negative	—
Matutes Score	5 / 5 (Classic CLL)	Total: 5

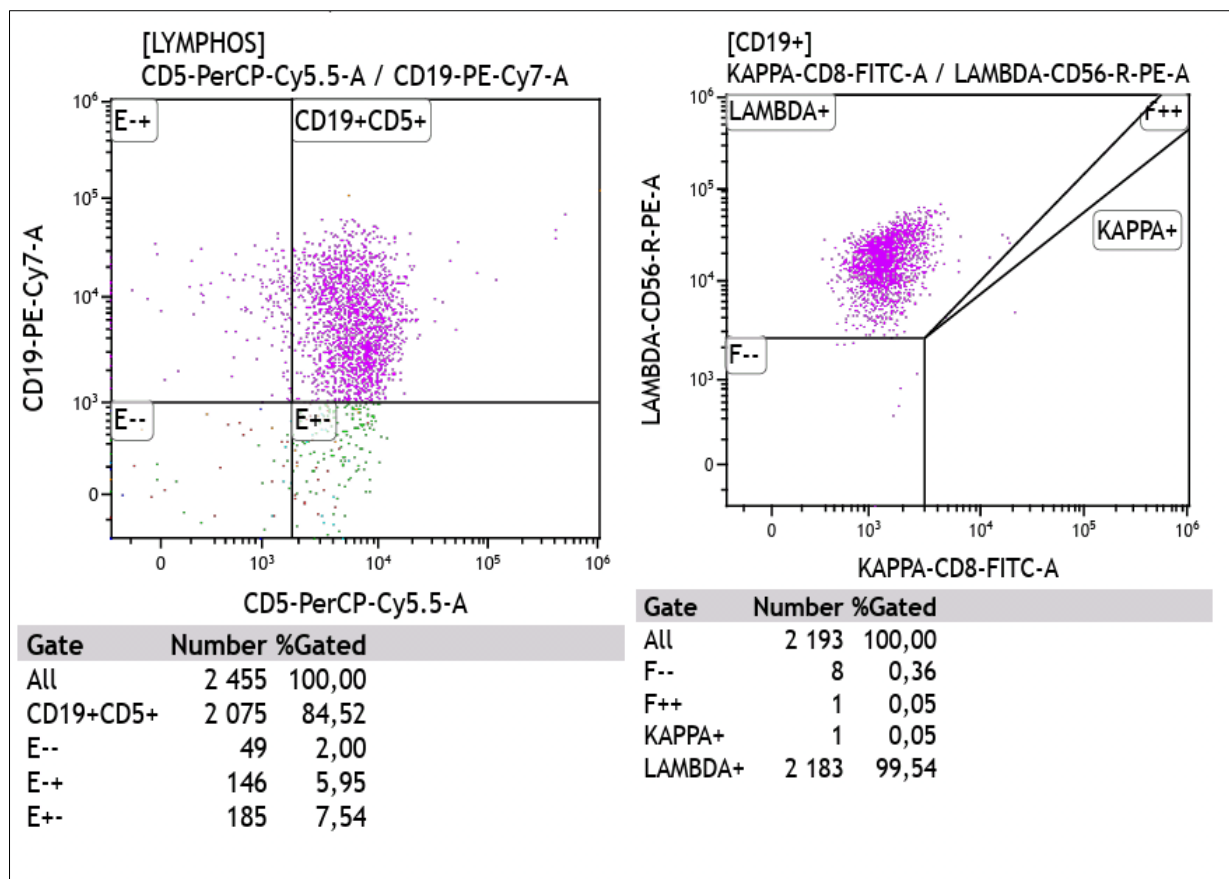


Figure 2: CD19+/CD5+ and Lambda monotypy

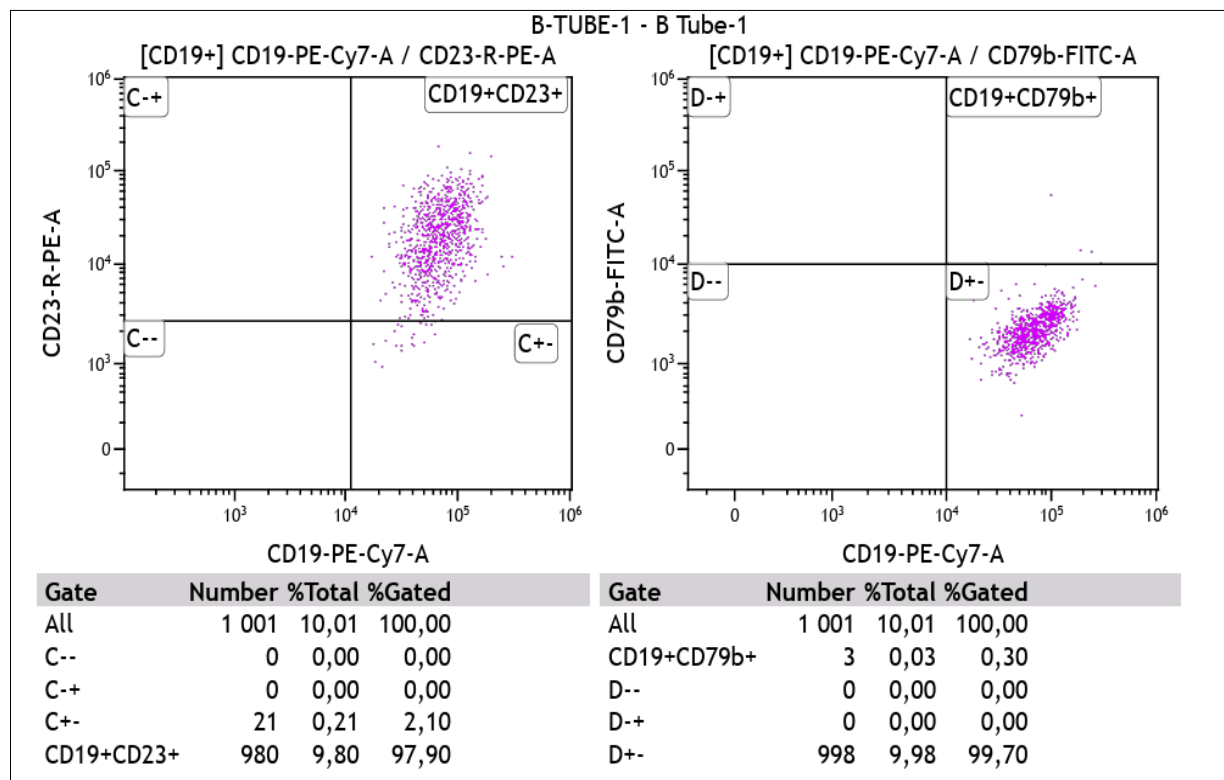


Figure 3: CD19+/CD23+ and CD19+/CD79b-

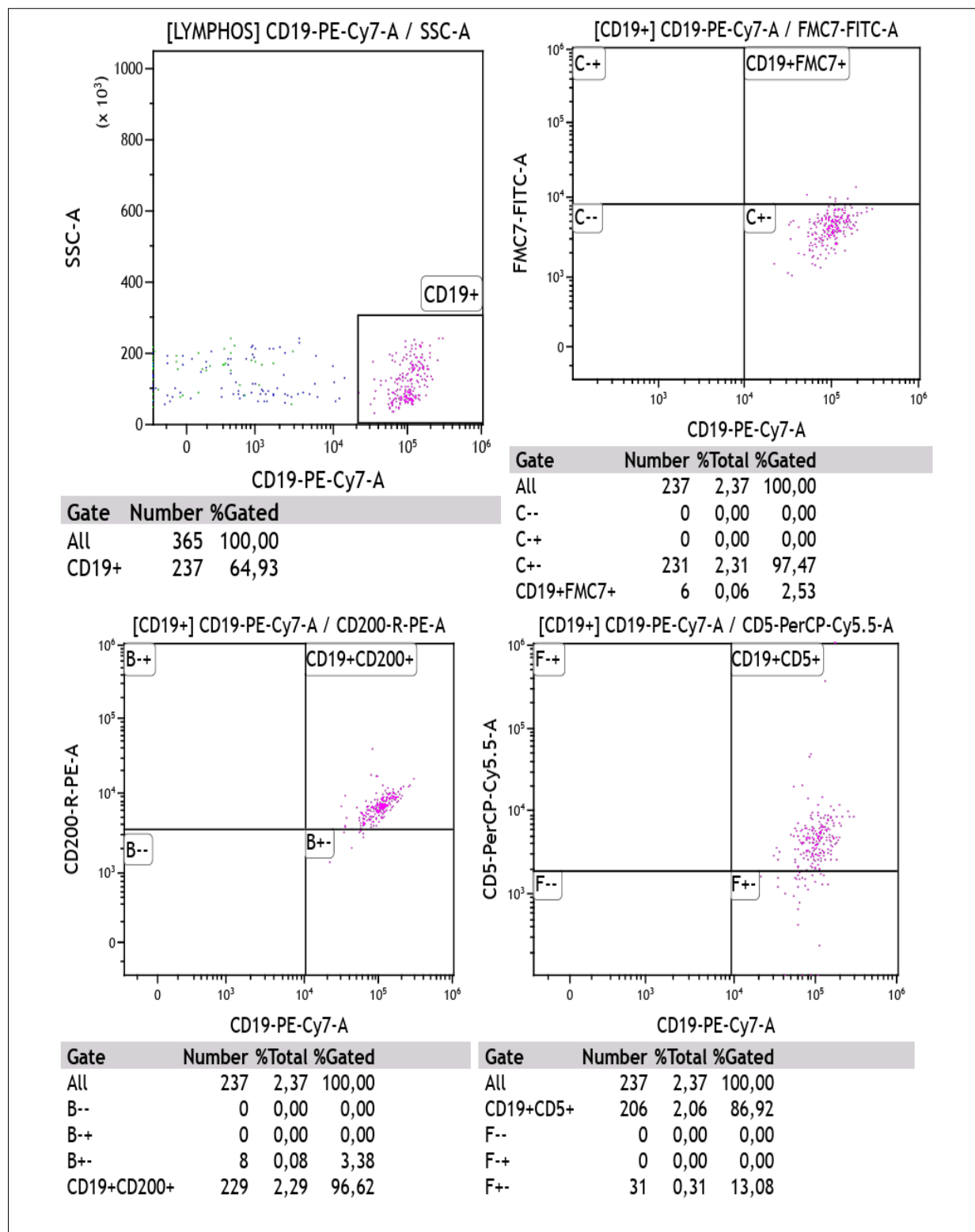


Figure 4: CD19+/FMC7- and CD19+/CD200+

2.4 Cytogenetic and Molecular Studies

- **Conventional Karyotype (R-banding):** Metaphase analysis of stimulated peripheral blood lymphocyte cultures revealed a numerical chromosomal abnormality: an isolated trisomy 3 in the leukemic clone: **47, XY, +3** (Figure 5).

- **Fluorescence In Situ Hybridization (FISH):** Specific probe panels were tested to screen for high-risk abnormalities: **TP53 probe (17p13):** No deletion detected.
- **ATM probe (11q22.3):** No deletion detected.

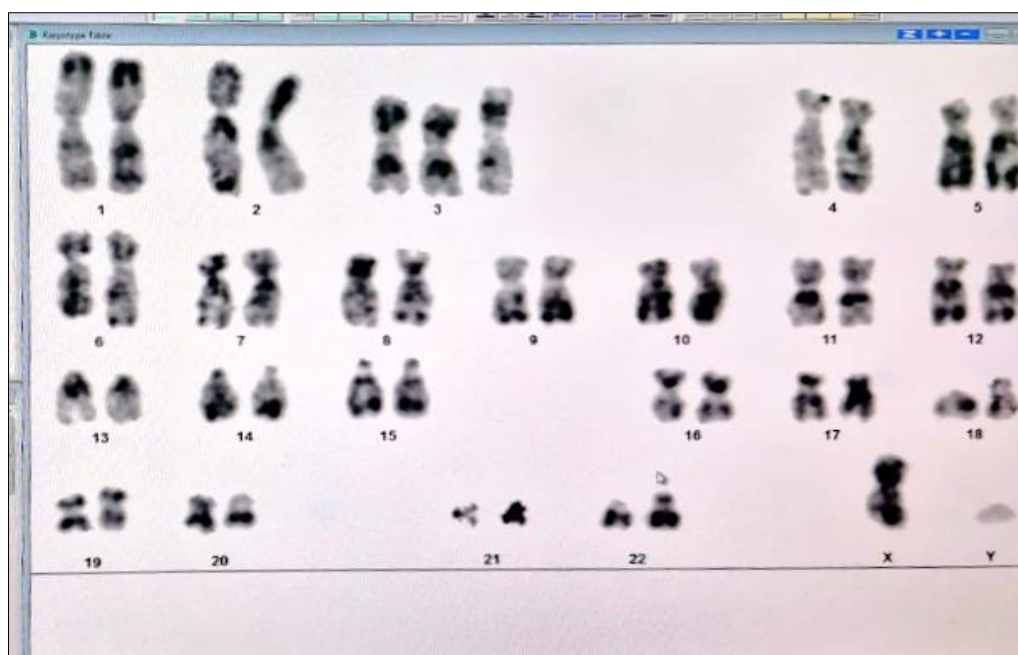


Figure 5: Karyotype R-banding 47, XY, +3

3. DISCUSSION

Chronic lymphocytic leukemia is characterized by considerable clinical heterogeneity. Some patients present with indolent disease requiring no treatment for several years, whereas others develop an aggressive form characterized by early bone marrow failure and high tumor burden.

3.1 Trisomy 3 in Lymphoid Malignancies

While trisomy 12 constitutes the second most frequent numerical abnormality in CLL (present in approximately 15% to 20% of patients), trisomy of chromosome 3 remains a rare genetic event. In the literature, trisomy 3 is preferentially associated with marginal zone B-cell lymphomas (notably MALT lymphoma and splenic marginal zone lymphoma). When reported in CLL, it most frequently occurs within complex karyotypes or as a secondary event during clonal evolution [6].

3.2 Immunophenotypic Correlation and Tumor Burden

The major interest of this case lies in the contrast between:

1. **A perfect Matutes score of 5/5:** Confirming the most typical immunological form of CLL and ruling out mantle cell lymphoma or leukemic marginal zone lymphoma.
2. **An initially aggressive clinical presentation:** Characterized by major hyperleukocytosis (180 000/ μ L) and bicytopenic bone marrow failure (anemia at 8.0g/dL and thrombocytopenia at 75,000/ μ L), classifying the patient immediately as Binet stage C. [7]

3.3 Potential Role of Genes Located on Chromosome 3
Chromosome 3 harbors several oncogenes and key regulators of the cell cycle and lymphoid survival, notably:

- ***PIK3CA* (3q26.32):** A key component of the PI3K/AKT/mTOR signaling pathway essential for B-cell proliferation.
- ***BCL6* (3q27.3):** A transcription factor involved in controlling B-cell differentiation.
- ***NFKB1* (3p24.1):** A subunit of the NF- κ B pathway promoting apoptosis resistance.

The acquisition of a third copy of chromosome 3 could result in a gene dosage effect that increases the expression of these survival factors, thereby promoting the rapid progression and high tumor burden observed in this patient [8].

3.4 Therapeutic Management in the Era of Targeted Therapies

Due to the presence of anemia and thrombocytopenia (Binet stage C), an immediate therapeutic indication is established. The absence of *TP53* deletion (17p) on FISH is a favorable element regarding treatment selection. However, assessing the mutation status of *IGHV* genes as well as searching for *TP53* point mutations represent the next required steps. The use of Bruton's tyrosine kinase inhibitors (BTKi, such as acalabrutinib or zanubrutinib) or BCL-2 inhibitors (venetoclax in combination with an anti-CD20 antibody) constitutes the treatment of choice for this form with high tumor burden [9].

4. CONCLUSION

This case describes an aggressive initial presentation of chronic lymphocytic leukemia with a

classic immunophenotypic profile (Matutes score = 5), associated with a rare chromosomal abnormality: isolated trisomy 3. Systematic screening by conventional karyotyping beyond the standard FISH panel is crucial to identify these unusual rearrangements and to enrich international cytogenetic registries in order to establish their precise prognostic value.

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