



## Double hit B cell precursor leukemia/lymphoma in a patient with a prior diagnosis of follicular lymphoma: a diagnostic and therapeutic dilemma

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Dear Editor,

Follicular lymphoma (FL) transformation into a high-grade TdT+ entity resembling acute lymphoblastic leukemia (ALL) has been reported. Diagnosis and treatment of these rare cases of poor prognosis are challenging [1].

A 53-year-old female was admitted to our hospital because of acute leukemia suspicion. One year before, a diagnosis of stage IV FL was established elsewhere. At the moment of diagnosis, a PET/CT revealed increased uptake in most lymph node territories and in the spleen, left kidney, and both iliac crests; however, bone marrow examination was not performed. A core needle biopsy of the renal mass showed a diffuse, pseudo-nodular infiltrate of centrocytes and centroblasts (grade 2). Phenotype was CD20+, CD79a+, CD10+, Bcl2+, Bcl6+, CD23+, Mum1-, Cyclin-D1-, VEB-, CD30-, CD15-, cMyc-, and p53-. In situ hybridization (FISH)

showed t(14;18)(q32;q21) (Fig. 1A.1–4). After receiving R-CHOP × 6, she achieved complete response (CR).

At admission to our hospital (3 months after CR), she complained of vomits, abdominal pain, and fever and presented a frail condition in the physical exam. A tomography evidenced hepatosplenomegaly without lymphadenopathies. Gastroscopy revealed patchy gastroduodenal infiltrates with pseudopolyps (< 6 mm). Biochemistry showed LDH 1649 U/L. Notably, hemogram showed pancytopenia (hemoglobin 76 g/L, platelets 22 × 10<sup>9</sup>/L, WBC 0.9 × 10<sup>9</sup>/L) with an 11% of blastoid cells in blood smear (Fig. 1B.1–2).

Bone marrow aspirate had no yield (dry-tap). Either touch imprint cytology (Fig. 1B.3), trephine biopsy (Fig. 1C.1–2), or gastroduodenal biopsies (Fig. 1C.3) showed a massive infiltration by mid-sized blastoid cells. Phenotype was CD19+, CD10+, CD20-, CD22+, Pax5+, Bcl2+, Bcl6-, c-Myc+, TdT+, CD45+, CD34-, and IgS-. Ki67:80% (Fig. 1C.4).

FISH in peripheral blood and gastric tissue showed t(14;18)(q32;q21)/*BCL2-IGH* and 8q24/*MYC* rearrangement (Fig. 1D.1). Karyotype in peripheral blood (Fig. 1D.2) was 46,XX,t(8;22)(q24;q11),t(14;18)(q32;q21)[16]/46,idem,add(15)(q24)[4]. Lymphoblastic transformation of FL was clonally confirmed.

A diagnosis of double hit (DH) B cell precursor leukemia/lymphoma was established. High risk-ALL chemotherapy (PETHEMA LAL-AR/2011) was initiated, with minimally transient response. However, by day + 40, the patient was readmitted with LDH of 29.000 U/L and WBC of 25.1 × 10<sup>9</sup>/L (> 90% blasts). As salvage therapy, PETHEMA BURKIMAB-13 regimen was initiated, but 5 days later, during pre-phase, she died because of a massive spleen rupture.

According to WHO 2016 classification, TdT is a pivotal discriminator between ALL (TdT+) and aggressive B cell lymphomas (TdT-). Besides, DH/TH lymphomas have been integrated into the high-grade B cell lymphoma (HGBCL) category [2].

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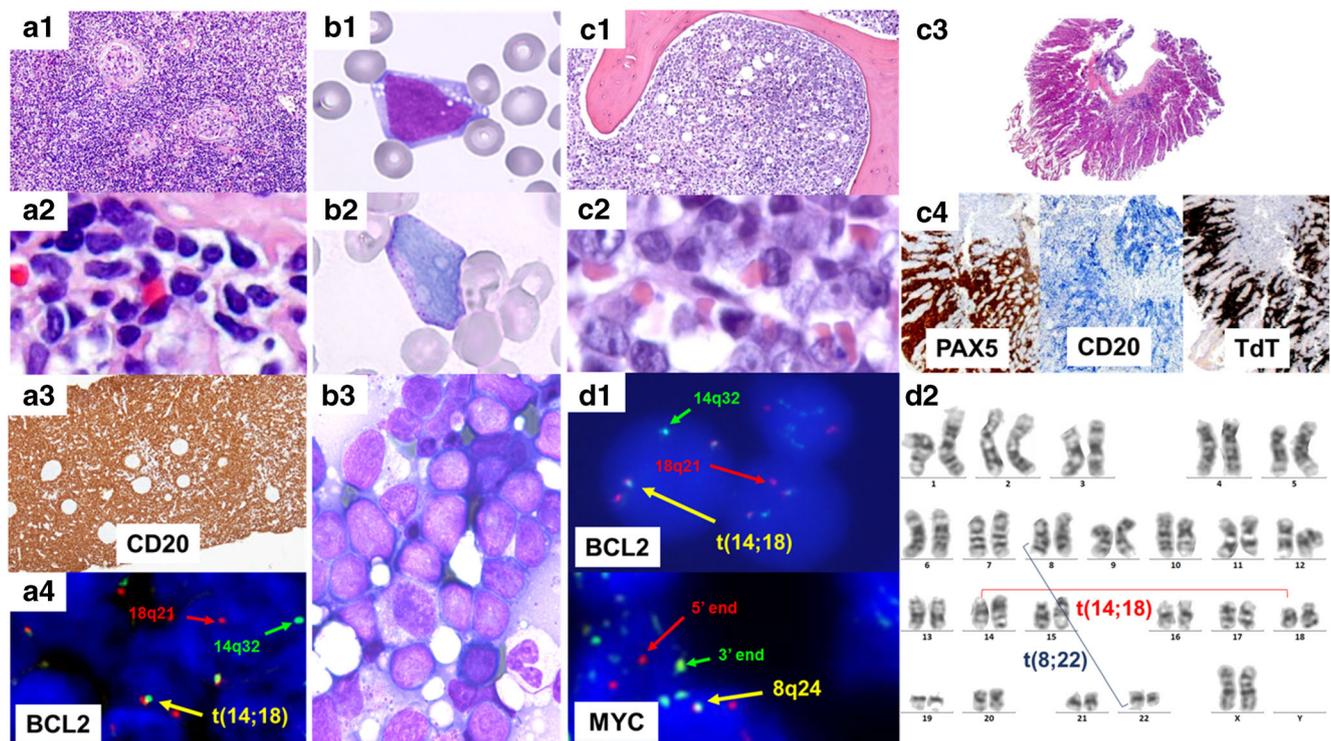
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**Fig. 1** Follicular lymphoma (previous diagnosis). **A.1-2:** Core needle biopsy of the renal mass (hematoxylin-eosin,  $\times 200$  and  $\times 1000$ , respectively) showed a diffuse, pseudo-nodular infiltrate of centrocytes and centroblasts (grade 2). **A.3:** Positive immunohistochemistry for CD20. Phenotype was CD20+, CD79a+, CD10+, Bcl2+, Bcl6+, CD23+, Mum1-, Cyclin-D1-, VEB-, CD30-, CD15-, cMyc-, and p53-. **A.4:** Positive in situ hybridization for t(14;18)(q32;q21)/BCL2-IGH (Dual-Color/Dual-Fusion probe). Cytological findings of lymphoblastic transformation. **B.1:** Blood smear (May-Grünwald-Giemsa,  $\times 1000$ ) showed 11% mid-sized blastoid cells. **B.2:** Cytoplasmic PAS-positive inclusions (Periodic-Acid-Schiff,  $\times 1000$ ). **B.3:** Bone marrow touch imprint cytology (May-Grünwald-Giemsa,  $\times 1000$ ) revealed massive blastic infiltration. **Histological findings of lymphoblastic transformation. C.1-2:**

Bone marrow trephine biopsy (hematoxylin-eosin,  $\times 100$  and  $\times 1000$ , respectively) confirmed massive infiltration. **C.3:** Gastric biopsy (hematoxylin-eosin,  $\times 40$ ) also showed disease extension. **C.4:** Immunohistochemistry in gastric tissue for Pax5 (positive), CD20 (negative), and TdT (positive). Phenotype was CD19+, CD10+, CD20-, CD22+, Pax5+, Bcl2+, Bcl6-, c-Myc+, TdT+, CD45+, CD34- and IgS-. Ki67:80%. Cytogenetic findings of lymphoblastic transformation. **D.1:** Positive in situ hybridization for t(14;18)(q32;q21)/BCL2-IGH (dual-color/dual-fusion probe) and for 8q24/MYC rearrangement (Break-Apart probe). **D.2:** Karyotype in peripheral blood confirmed double hit (BCL2 and MYC rearrangement): 46,XX,t(8;22)(q24;q11),t(14;18)(q32;q21)[16]/46,idem,add(15)(q24)[4].

Exceptional cases of either DH/TH-HGBCL with aberrant expression of TdT or transformation of FL to B-ALL have been reported [1, 3, 4]. Interestingly, most of these second groups of cases possess a DH condition (*MYC* and *BCL2* rearrangements) [1, 5]. Then the lymphoblastic transformation of FL is thought to have occurred due to a gain of *MYC* rearrangement at an early stage of FL lymphomagenesis (immature B-precursor carrying t(14;18)(q32;q21) in the bone marrow) [1, 5, 6]. As illustrated in our case, prognosis and outcomes are poor, so intensive or novel induction/consolidation strategies should be explored [7–9].

To conclude, the integration of biological, genetic, and clinical data of these such rare and aggressive cases suggests that, in the end, both entities might be included in the same category of high-grade TdT+ lymphoid neoplasms and differentiated from canonical HGBCL or de novo ALL subgroups. Finally, these evidences would also imply that the current WHO stratification proposal based on TdT should be reconsidered.

## Compliance with ethical standards

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from the patient included in the study.

**Conflict of interest** The authors declare that they have no conflict of interest.

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