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Double transformation of relapsing juvenile myelomonocytic leukemia to refractory acute myeloid leukemia

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Introduction

Juvenile myelomonocytic leukemia (JMML) is a clonal, hematopoietic disorder of childhood of which the clinical manifestation is leukocytosis, thrombocytopenia and overproduction of monocytes. It is the only pediatric entity classified by the World Health Organization (WHO) as a myelodysplastic syndrome/myeloproliferative neoplasm overlap syndrome [1, 2]. The incidence of JMML is 1.2 cases per 1,000,000 children and the disease is most often diagnosed at the age of two [3].

The WHO diagnostic criteria for JMML are [1, 3]:

I. Clinical and hematological features (all of these are mandatory if JMML is to be diagnosed):
   - absence of Philadelphia chromosome (*BCR/ABL* rearrangement);
   - peripheral blood monocyte count ≥1 × 10^9/L;
   - peripheral blood and bone marrow blast count <20%;
   - splenomegaly.

II. Gene features (the presence of just one of these is sufficient):
   - somatic mutations in *PTPN11* or *KRAS* or *NRAS* (germline mutations need to be excluded);
   - clinical diagnosis of neurofibromatosis-1 (NF-1) or *NF1* mutation;
   - germline *CBL* mutation and loss of heterozygosity of *CBL*.

III. For patients without a gene feature, in addition to the clinical and hematological features listed under criterion I, the following criteria must be met:
   - monosomy 7 or any other chromosomal abnormality, or at least two of the following criteria:
   - myeloid or erythroid precursors on peripheral blood smear;
   - fetal hemoglobin (HbF) increased for age;
   - granulocyte macrophage colony-stimulating factor (GM-CSF) hypersensitivity in colony assay;
   - white blood cells >10 × 10^9/L;
   - hyperphosphorylation of STAT5.

The characteristic feature of JMML is hyperactivation of the RAS pathway, induced by five main mutations which can occur either as somatic (*PTPN11* in 38%; *NRAS* in 18%; *KRAS* in 14%) or as germline (*NF1* in 5–10%; *CBL* in 12–18%) lesions in hematopoietic cells [1, 4, 5]. *RAS* mutations can provoke uncontrolled proliferation of cancer cells [6]. There have also been evident 'all-negative' (sometimes called 'quintuple-negative') JMML cases with the absence of the main genes mutations and lack of NF-1 clinical manifestation [1, 2, 4, 5, 7].

In c.49% of cases, the RAS pathway mutation is followed by secondary molecular alteration, which include mutations in the components of polycomb repressive complex 2, *SETBP1, JAK3*, spliceosome-related genes (*ZRSR2*) and monosomy 7 [1].

A transformation from JMML to acute myeloid leukemi (AML) occurs in one third of cases [1]. Subsequently, there

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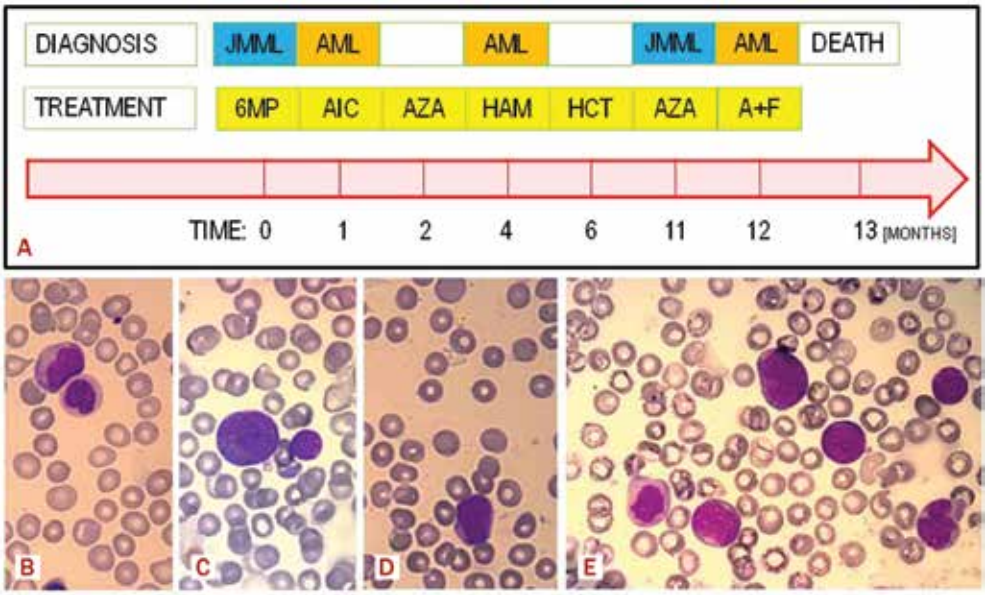

Figure 1A. Timeline of clinical course [juvenile myelomonocytic leukemia (JMML), acute myeloid leukemia (AML), mercaptopurine (6MP), cycles of AML-BFM-2004 protocol (AIC/HAM); allogeneic hematopoietic cell transplantation (HCT); azacytidine (AZA), cytarabine + fludarabine (A + F)]; **B.** Monocyte and granulocyte (BM, bone marrow) hematological smears (×1,000); **C.** Monocyte (PB, peripheral blood) hematological smears (×1,000); **D.** Myeloblast, hematological smears (×1,000); **E.** Three myeloblasts, two monocytes and lymphocyte

are documented factors associated with a higher transformation risk. *RRAS*-mutation, the presence of two or more RAS-activating mutations, and a secondary molecular alteration (*EZH2, ASXL1, SETBP1, JAK3, ZRSR2*, monosomy 7) characterizes cases with an increased risk of progression to AML [1, 3].

Case description

A 6-year-old boy was diagnosed with JMML (Figure 1A). Clinically, the patient developed a significant hepatosplenomegaly. Primary tests revealed: increased percentage of monocytes, increased level of HbF (18.6%), blasts in peripheral blood smear (below 20%), and 10–14% blasts in myelogram (Figure 1B–E). Genetic tests revealed the presence of heterozygotic mutation of *PTPN11* gene. The patient was qualified to allogeneic hematopoietic cell transplantation (allo-HCT), and cytoreductive mercaptopurine treatment was initiated immediately. During the therapy, his clinical condition worsened, with features of secondary hemophagocytic syndrome. Then JMML transformation to AML-M6 [blasts: peripheral blood (PB) 30%, bone morrow (BM) 35%] occurred, confirmed in the reference center. The boy received a first cycle (AIC) of AML-BFM-2004 protocol, with blasts clearance. Due to poor tolerance of chemotherapy, he was switched to azacitidine treatment, but after two cycles, myeloblasts were found in the bone marrow. Another cycle-(HAM) of AML-BFM-2004 protocol was administered, and then the patient underwent allo-HCT from a matched unrelated donor preceded by European Working Group of Myelodysplastic Syndrome (EWOG-MDS) conditioning BuCyMel + rATG. Hematological and molecular remission and full donor chimerism was achieved, but hepatosplenomegaly persisted. The boy received another cycle of azacytidine. After the first cycle, six months after HCT, mixed donor chimerism and molecular JMML relapse were confirmed, with *PTPN11* mutation in 36% of granulocytes and the presence of myeloblasts in BM. Two cycles of cytoreductive chemotherapy with cytarabine/fludarabine were applied, which were followed by prolonged myelosuppression and numerous infectious complications. The patient died a few days later in leukemic bone marrow progression with symptoms of pneumonia and multiorgan failure.

Our case report demonstrates a complicated clinical course of relapsing JMML, with conversion to AML both in initial and relapsed JMML. The explanation for incomplete clinical remission was probably splenomegaly not returning to normal size despite chemotherapy and conditioning before allo-HCT. Furthermore, this case proves that transformation can occur at any moment throughout the course of the disease — before or after allo-HSCT. Relapsing and aggressive course of JMML requires regular bone marrow biopsies with frequent evaluation of myeloblasts level in order to adjust treatment depending on the current diagnosis (JMML or AML). Frequent evaluation of myeloblasts quantity is essential for all patients with JMML in order to administer AML chemotherapy as soon as possible. Stratifying the transformation risk may help in finding the most suitable therapy plan for patients with an aggressive course of disease. Nevertheless, dealing with relapsing

JMML remains a considerable challenge, and the prognosis is poor. Further investigation into both the clinical and the molecular risk factors of AML progression is needed in order to adjust JMML therapy to make it more effective in the most aggressive cases.

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Authors' contributions
KC, TS — design of study. RD, MRP, KC, MK, BKR — provision of clinical data. All authors — analysis of clinical data. TS, JS — literature search and analysis of data. TS, JS — writing of manuscript: TS, JS. Critical revision and final approval: all authors

Conflict of interests
None.

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Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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