Leukemia Research Reports 17 (2022) 100289

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

B/T mixed phenotype acute leukemia with high hyperdiploidy and lineage switch to B-cell acute leukemia

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ARTICLE INFO

Keywords:
B/T mixed phenotype acute leukemia
Moroccan female
High hyperdiploidy
Poor outcome
Lineage switch

ABSTRACT

Acute leukemias are often of myeloid or lymphoid origin. However, some acute leukemias revealed an undefined differentiation into a single lineage. Mixed phenotype acute leukemia (MPAL) is an uncommon diagnosis were blasts can share B/T/myeloid phenotype. Here, we report a rare case of a 17-year-old Moroccan female diagnosed with B/T mixed phenotype acute leukemia and a high hyperdiploid karyotype who relapsed after one year of complete remission with a lineage switch to B-cell acute lymphoblastic leukemia. This case report corroborates the disclosed findings about the high occurence of abnormal karyotypes and poor prognosis of MPAL.

1. Introduction

Mixed phenotype acute leukemia (MPAL) indicates a rare subgroup of acute leukemias with leukemic blasts showing myeloid and lymphoid markers [1]. It is categorized by the 2008 and 2016 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors as acute leukemias of ambiguous lineage [2, 3]. The bilineal MPAL is characterized by the coexistence of distinct blast populations with different immunophenotypes, while the biphenotypic MPAL denotes the coexpression of markers of more than one lineage in a single blast population [4, 5]. These leukemias constitute 2–5% of acute leukemia cases [6, 7] and can also be screened as a B/myeloid, T/myeloid, B/T/myeloid, or B/T lymphoid phenotypes [8]. MPAL are often linked to unfavorable outcomes [9]. Previous studies have shown that MPAL patients respond poorly to chemotherapy with high rates of relapse and that it can be caused by the associated cytogenetic disorders [10, 11].

Leukemic cell lineage switch represents a rare phenomenon where acute leukemia converts to a different lineage upon relapse compared with that during the initial diagnosis [12, 13]. Most of reported cases involve switchs from lymphoid to myeloid leukemia [14, 15]. Myeloid leukemia may exceptionally convert to lymphoid leukemia [16]. In this study, we aim to report an uncommon case of a 17-year-old girl with B/T lymphoid acute leukemia and high-hyperdiploidy which should be to the best of our knowledge, the first reported case of a lineage switch at relapse from B/T mixed phenotype leukemia to B cell leukemia.

2. Case presentation

In October 2016, the female patient was hospitalized in hemato-oncology department of children'hospital in Rabat, Morocco at the age of 17. She presented during 2 months, skin pallor, asthenia, progressive weight loss and amenorrhea. The initial hemoglobin was 5.7 g/dL, white blood cells were 3220/μL, and platelets were 118 000/μL. Bone marrow aspiration analysis showed 80% of small uniform blasts with reduced cytoplasm, no granulation and a myeloperoxidase (MPO) cytochemical negativity. Flow cytometric immunophenotyping revealed that cells were sCD3(91.4%), cCD3(83.3%), $CD4^{dim}$(20.1%), $CD5^{dim}$(23.8%), CD8(30.8%), CD10(94.4%), CD19(91.2%), CD22 (91.3%), CD34(84%), HLA-DR.(74.4%), cCD79a(96.7%), and TdT (89.7%). The patient was considered as a B/T mixed phenotype acute leukemia case according to the WHO 2008/2016 classification. Further, cytogenetic analysis showed:

56~60,XX,+4,+5,+8,+9,+11 × 2,+12,+13,+18,+20,+21 × 2,+22 × 2[cp5]/46,XX[17].

Intensive chemotherapy was administrated based on MARALL-06 protocol for high risk acute lymphoblastic leukemia (ALL) [17].

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https://doi.org/10.1016/j.lrr.2022.100289
Received 28 June 2021; Received in revised form 3 November 2021; Accepted 14 January 2022
Available online 15 January 2022

Prednisone, Vincristine, L-Asparaginase, and Daunorubucin were used for remission-induction therapy. Then, the patient received treatment with Aracytine, Cyclophosphamide and 6-Mercaptopurine during the consolidation phase of chemotherapy. Maintainance therapy began in late 2017 with repeated cycles of 6-mercaptopurine, vincristine, methotrexate, and dexamethasone. The patient achieved the complete remission in September 2019.

One year later, the patient presented with asthenia and fever. She also showed a left-sided facial hemiparesis. Her complete blood count revealed a hemoglobin level of 8.5 g/dL, a white blood cell count of 2220/μL, and a platelet count of 14,000/μL. The bone marrow examination yielded 53% of relapsed lymphoblasts, and karyotyping demonstrated 46, XX [25]. Flow cytometry of the bone marrow aspirate disclosed a switch to the B-lineage ALL with positive expressions of CD10 (72%), CD19 (71%), CD20 (15%) and cIgM (82%). Weak or negative signals of T lineage markers (CD3 0%, CD7 1%, CD8 0%, cCD3 0%) and myeloid lineage markers (CD117 2%, CD13 3%, CD14 2%, CD15 4%, CD33 0%, CD42a 1%, CD61 1%, CD64 0%, cMPO 0%) were detected.

The patient achieved a first complete remission within 2 months of induction therapy, with a full recovery from the facial hemiparesis. She is undergoing a salvage regimen for childhood relapsed ALL, which involves R1 (Dexamethasone, vincristine, metothrexate, folinic acid, aracytine, L-asparaginase, 6-mercaptourine) and R2 (Dexamethasone, vincristine, metothrexate, folinic acid, L-asparaginase, ifosfamide, daunorubicine, 6-mercaptopurine) blocks according to the asparaginase-based COOPRALL-07 trial, before being subjected to the allogeneic hematopoietic stem cell transplantation (allo-HSCT).

DNA sequencing of the patient revealed the GG genotype of *P53* Pro72Arg polymorphism (rs1042522), and the homozygous dominant genotype of the rare *P53* Arg213Arg polymorphism (rs1800372). No variation was detected in *NRAS, KRAS*, or *PAX5* genes.

3. Discussion

The co-expression of both B and T cell lineage markers on leukemic blasts marks the B/T subgroup of MPAL and may designate a high-risk entity of acute leukemia [5]. MPAL patients are confirmed to harbored complex chromosomal aberrations. At diagnosis, our patient showed a 56~60 hyprdiploid karyotype with trisomies of chromosomes 4, 5, 8, 9, 11, 12, 13, 18, 20, 21, and 22. In a cohort of 9 B/T MPAL cases, Xiaoli Mi and colleagues indicated that four cases had a hyperdiploid karyotype with a chromosome count variying from 47 to 51 [5]. The study of Estella Matutes and colleagues has revealed that 20% of the 76 MPAL patients with karyotypic description exhibited the t(9;22)/(pH+), and 32% had a complex karyotype. Hyperdiploidy was underrepresented (2 cases), while 11q23/MLL rearrangements and normal karyotypes were at 8% and 13% respectively [18]. The t(9;22) (q34;q11) and 11q23 (MLL) abnormalities are the most observed cytogenetic disorders in MPAL and are classified as separate subgroups [3]. Cytogenetic aberrations associated with MPAL can also comprise trisomies of chromosomes 4, 19 and 21, polysomies of chromosome 8, monosomies of chromosomes 5 or 7, deletions in 1p32, 5q, 6q, 7q, and 12p or hypodiploidy [19].

The adverse prognosis of MPAL has been attributed to the commonly associated cytogenetic disorders and genetic alterations [10, 11, 20]. Moreover, the intrinsic chemoresistance of primitive mixed phenotype blasts due to slow replication, adaption to therapy by switching phenotype, and high levels of expressed multidrug resistance proteins may explain the unfortunate outcomes of MPAL patients [21]. At relapse, the patient had experienced a rare lineage switch from B/T mixed phenotype leukemia to B cell acute lymphoblastic leukemia. Diverse studies have documeted leukemic cell lineage conversions such as T-ALL to MPAL [22], T-ALL to B-ALL [15] or ALL to acute myeloid leukemia (AML) [23, 24]. The lineage switch may implicate either a relapse of an original population of resistant cells with heterogeneity at the morphological level or the evolution of a new leukemic clone. Otherwise, hematopoietic progenitors may have a high potency to be plastic and change cell fate reversibly through epigenetic or transcription factors modifications in response to inductive environmental signals [25, 26]. The exact mechanism of the switching still remains not well clarified.

The patient was also found to harbor two polymorphisms of *P53* gene while no variant was identified in *RAS* genes or *PAX5* which is a deciding factor in B-cell commitment. P53 mutations are well known to be mainly responsible for over half of human tumors [27]. Furthermore, polymorphisms in this gene are implicated in the pathogenesis of cancer. The Pro72Arg (rs1042522) occurs in the proline-rich domain and may modulate the biological functions of *P53* gene, through changes in pathways of either apoptosis or cell cycle arrest [28]. Moreover, the silent Arg213Arg (rs1800372) may confer an effect on mRNA splicing, stability or translation [29]. The mutational status of B/T MPAL was reported to be highly similar to that of T-ALL, with variations involving *PHF6, JAK-STAS, RAS* or *NOTCH-1* [5]. These mutations can also confer the poor outcome in B/T lymphoid leukemia.

In conclusion, the present study reports a very rare case of lineage switching from B/T mixed phenotype leukemia with high hyperdiploidy to B-cell lymphoblastic leukemia and highlights the poor outcome observed in MPAL.

Funding

The genetic study was performed in Genetics Unit of Military Hospital Mohammed V of Rabat, Morocco.

Author contributions

Hanaa Skhoun: performed the genetic study, wrote the paper and was involved in the literature search. Pr Mohammed Khattab: made the diagnosis, and examined the patient. **Dr Aziza Belkhayat and Dr Zahra Takki Chebihi**: performed the cytogenetic analysis in BIOLAB laboratory. **Pr Nadia Dakka** : participated in writing the paper. **Pr Jamila El Baghdadi** : supervised the genetic study, directed the research work, revised and approved the final version of the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank the patient and the staff of the Pediatric Hematology and Oncology Center in the Children's Hospital of Rabat for their esteemed collaboration.

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