CASE REPORT

A prognostic approach on a case of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia with monosomy-7

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Abstract
In this work, we present the first case of a Ph-positive ALL Moroccan girl with t(9;22)(q34;q11) and monosomy-7. She was diagnosed with Ph-positive ALL based on bone marrow examination, immunophenotyping, and cytogenetic analysis. She relapsed after treatment with the persistence of the Ph chromosome and the appearance of a monosomy-7.

KEYWORDS
ALL, childhood, monosomy-7, patient outcome, Philadelphia-Positive

1 | INTRODUCTION

Chromosomal analysis allows the identification of cytogenetic abnormalities which are the hallmark of hematological cancers.1 In acute leukemias, these aberrations are important for classification and prognosis assessment. Cytogenetic abnormalities involved in acute myeloid leukemia (AML) are strikingly heterogenous. The t(15;17)(q22;q21) translocation characterizes the acute promyelocytic leukemia with favorable outcome. It leads to the generation of PML-RARA fusion protein that provokes transcription inhibition and aberrant differentiation of myeloid cells.2,3 The 11q23 abnormalities are interesting recurrent cytogenetic aberrations in AML, resulting from chromosomal translocation between 11q23 and several translocation partners. MLL fusion gene affects various genes such as HOX, inducing leukemogenesis.2 MLL rearrangements are generally associated with poor outcome. Important cytogenetic disorders in AML can also include t(8;21)(q22;q22): RUNX1-RUNX1T1 rearrangement and trisomy-6 with favorable prognosis or t(7;11) (p15;p15): NUP98-HOXA9 rearrangement with poor effects on survival.2,4

The well-known t(9;22)(q34;q11) translocation engenders a shortened chromosome 22 named the Philadelphia (Ph) chromosome that juxtaposes the ABL1 gene which is a proto-oncogene tyrosine-protein kinase located on
the long arm of chromosome 9 to the \textit{BCR} (breakpoint cluster region) gene on the long arm of chromosome 22.\textsuperscript{5} The \textit{BCR-ABL1} fusion gene on the Ph chromosome is a characteristic feature of chronic myeloid leukemia (CML) (95%),\textsuperscript{6} but it also occurs in 2\% to 5\% of pediatric acute lymphoblastic leukemia (ALL).\textsuperscript{7} Prognosis of children with Ph-positive ALL is very poor.\textsuperscript{8–10} However, treatment regimens combining Imatinib as a tyrosine kinase inhibitor (TKI) and chemotherapy, followed by hematopoietic stem cell transplantation (HSCT) have a major potential to improve the outcome.\textsuperscript{8,10,11} Additional cytogenetic aberrations to \(t(9;22)\) are commonly detected in Ph-positive ALL and may impact the treatment.\textsuperscript{12,13} The complete or partial loss of chromosome 7 has been shown to be markedly associated with unfavorable prognosis in pediatric Ph-positive ALL.\textsuperscript{14,15} Therefore, we sought to report the case of an 8-year-old female patient with Ph-positive ALL and secondary chromosomal abnormalities who presented a monosomy-7 at relapse.

2 | CASE HISTORY/EXAMINATION

An 8-year-old female patient was admitted to the children’s hospital of Rabat in October 2013 because of bone pain, polyarthralgia, petechiae, and fever. She also presented hepatosplenomegaly and cervical, inguinal and axillary adenopathies that were bilateral and painless. Peripheral hematological tests showed a low hemoglobin and platelet rates (Table 1).

2.1 | Differential diagnosis, investigations, and treatment

Bone marrow assessment revealed 90\% of blasts with L1 morphology, according to the FAB classification and the flow cytometric immunophenotyping confirmed the diagnosis of B-ALL (cells were positive for CD19, CD22, CD10, CD34, partial CD20 and CD45). Cytogenetic analysis was performed in BIOLAB laboratory in Rabat, for chromosomal analysis by convention G-banding and molecular cytogenetic methods. Karyotype showed a clone with a duplicated Philadelphia chromosome [26.9\%], a complex clone with a monosomy-X, a trisomy-5, and a monosomy-10 in addition to the duplicated Philadelphia chromosome [34.6\%] and a normal diploid clone [38.5\%] with no chromosomal disorders detected within the resolution of the metaphasic karyotype:

\[
46,XX,t(9;22)(q34;q11),d(22)\]

Fluorescence in situ hybridization (FISH) for \textit{MLL} gene rearrangements, \textit{ETV6-RUNXI}, and \textit{BCR-ABL} confirmed the presence of the duplicated Philadelphia chromosome.

The therapeutic approach had consisted of combining chemotherapy with imatinib to improve the long-term outcome. Intensive chemotherapy was started according to MARALL-06 protocol for high-risk group.\textsuperscript{16} Leukocyte level started to decrease (2.55 \( \times 10^9/L \)), and the patient achieved an initial complete remission after the induction therapy. Imatinib Mesylate (two 100 mg capsules a day) was administrated conjointly to chemotherapy. The patient was subsequently treated with Cytarabine (ara-C), Cyclophosphamide, and 6-Mercaptopurine during the consolidation therapy. Intensification cycles were frequently disturbed because of recurrent episodes of febrile neutropenia and mucositis. Repeated cycles of 6-mercaptopurine, vincristine, methotrexate, and prednisone were administrated for maintenance phase. In November 2016, bone marrow and cerebrospinal fluid analysis confirmed the complete remission (Absence of blasts). Imatinib therapy was recommended to be continued.

The genetic study was carried out in Genetics Unit of the Military Hospital in Rabat. 2 ml of peripheral blood was collected from the patient into an EDTA containing
Genomic DNA was isolated based on the conventional phenol-chloroform method with the aim of investigating the mutational status of $P53$, $NRAS$, $KRAS$, and $PAX5$ genes. This research work was approved by the Ethics Committee for Biomedical Research in Faculty of Medicine and Pharmacy of Rabat. Informed consent was provided by the parents of the patient.

Hotspot exons of the studied genes were amplified by polymerase chain reaction (PCR). Amplified PCR products were confirmed using 2% agarose gel electrophoresis and purified with Sephadex® G-50 Superfine, (GE Healthcare, 100 g). Purified PCR products were sequenced for sense and/or anti-sense using ABI Big Dye terminator cycle sequence kit V3.1 (Applied Biosystems) and ABI 3500 genetic analyzer (Applied Biosystems). Sequence results were analyzed by Sequencing Analysis v5.4 Software. Our findings revealed that this patient harbored the Arg/Arg genotype of $P53$ Pro72Arg polymorphism (rs1042522), and the heterozygous genotype of the rare $P53$ Arg213Arg polymorphism (rs1800372). No variant was found in $NRAS$, $KRAS$, and $PAX5$ exons.

### 2.2 Outcome and follow-up

After 14 months, the patient returned with bone pain, arthralgia, asthenia, and fever. She also showed skin purpura and submandibular lymphadenopathy. She was noted to present 27.42 $10^9$/L, 101 g/L, 16 $10^9$/L for white blood cells, hemoglobin, and platelets, respectively, in January 2018. Relapse was diagnosed by bone marrow aspirate (77% of blasts) and immunophenotyping. Further, the cerebrospinal fluid examination showed a value of 62% of blasts indicating a central nervous system relapsed ALL.
Cytogenetics demonstrated the persistence of the duplicated Ph chromosome with an additional monosomy-7 in 23 out of the 30 examined metaphases:

\[ \text{46,XX,}\_7,\text{der}(9)t(9;22)(q34;q11)t(9;?) (p22)?),+der(22)t(9;22)[23]/46.XX[7] \] (Figure 2) (Table 1).

The patient died by the end of 2019, after receiving cycles of granisetron, vincristine, 6-mercaptopurine, prednisone, and imatinib.

### 3 | DISCUSSION

The hybrid oncogenic protein BCR-ABL1 is responsible for the persistently elevated tyrosine kinase activity that perturbs cell proliferation, differentiation, and survival pathways. In ALL, t(9;22) often occurs in patients diagnosed with B-ALL, and most cases express the p190 

\[ \text{BCR-ABL1} \]

transcript. Ph-positive ALL patients show an aggressive leukemia with poor prognosis and high relapse rates due to standard therapies resistance.

In addition to Ph chromosome, our patient showed the der(22), trisomy-5, and losses of chromosomes 10, and X. It had been previously reported that secondary cytogenetic disorders are detected in approximately two thirds of cases with Ph-positive ALL including additional copy of the derivative chromosome 22, loss of chromosome 7, del(7p), del(9p), trisomy-8, and hyperdiploidy. According to the study of Heerema NA et al., additional disorders were revealed in 153 of the 249 Ph-positive ALL children (61%), and frequently aberrant chromosomes were 9, 22, 7, 8, and 14. Moreover, the loss group was found to have the worst leukemia-free survival \( (p = 0.013) \). Aldoss et al. have also disclosed the poor outcome of these additional cytogenetic abnormalities in adult patients with Ph-positive ALL considering that the 3 years leukemia-free survival was superior in the Ph-only patients than the additional chromosomal abnormalities patients (79.8% versus 39.5%, \( p = 0.01 \)). Thus, the occurrence of chromosomal aberrations conjointly with Ph chromosome seems to have a remarkable deleterious influence on outcomes. This finding was not consistent with the study of Cristina Motlló et al., where no differences were observed in outcome related to the presence or not of additional chromosomal abnormalities to t(9;22). In CML, secondary chromosomal aberrations to Ph chromosome also denote the poor outcome. These abnormalities comprise monosomy-7, trisomy-8, trisomy-21, loss of chromosome X in women, and loss of chromosome Y in men.

Molecular genetics have been well established in cancer diagnostics, and prediction of response to therapeutic approaches. We performed a genetic study in order to identify the mutational status of our Ph-positive ALL patient, which revealed the heterozygous genotypes of P53 Pro72Arg and Arg213Arg polymorphisms. P53 is the most altered gene in human cancers. Somatic mutations of this gene are identified in almost 38% to 50% of all types of cancer (eg, ovarian, esophageal, colorectal, head and neck, larynx, and lung cancers) and about 5% of ALL. Germline mutations are demonstrated as the main drivers of Li-Fraumeni syndrome, which predisposes to a diverse range of inherited rare cancers. Mutations in other genes such as RAS, PAX5, PTEN, EGFR, or MSH6 are involved as predictive markers for poor prognosis in cancers such as pediatric B and T ALL, AML, gastric adenocarcinoma, glioblastoma, and brain tumors.

The reported case had relapsed within the first year following the achievement of remission and died after receiving intensive chemotherapy combined with imatinib. These unfortunate results can be explained by the appearance of a monosomy-7 in addition to the persistent Ph chromosome. Additional -7 was delineated to be the most associated disorder to Ph chromosome with unfavorable outcomes. In a group of 13 children with partial or complete -7 conjointly to the t(9;22), Russo et al. have found that the event-free survival for children with Ph chromosome and -7 ALL was worse compared with that of children with Ph-negative ALL and children with Ph-positive ALL. These conclusions were also approved by Heerema et al.

Children with Ph-positive ALL respond inadequately to intensive therapy, but those with monosomy-7 in addition to the Ph chromosome appear to have poorer outcome. Monosomy-7 or structural abnormalities involving the deletion of 7p have been identified to increase the risk of treatment failure in Ph-positive cases, and suggestion was made that a tumor suppressor gene on chromosome 7 may contribute to the poor outcome of those patients. Furthermore, several genes on chromosome 7 are associated with leukemia. Deletions of IKZF1 (IKAROS Family Zinc Finger 1) which is a pivotal locus for ALL at 7p12.2 are frequently identified in BCR-ABL1-positive pediatric B-ALL with poor outcome. As well, deleted segments in the long arm of chromosome 7 are implicated in myeloid disorders including cases of pediatric acute myeloid leukemia (AML) with poor prognosis.

### 4 | CONCLUSION

The treatment of Ph-positive ALL has considerably improved due to the incorporation of tyrosine kinase inhibitors combined with chemotherapy. However, remission durations remain short. The presence of additional cytogenetic disorders to t(9;22)(q34;q11), especially the monosomy-7 unfavorably affects the outcome. The risk stratification of ALL based on cytogenetic and molecular
profiling at diagnosis is required to predict patients’ prognosis. Hence, the detection of losses involving chromosome 7 may identify a higher risk group of Ph-positive ALL who should undergo specific therapeutic regimens to reduce the likelihood of relapse.

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CONFLICT OF INTEREST
None declared.

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

CONSENT
Written consent was obtained from the parents of the child for publication of the case. This study does not contain any personal information that could lead to the identification of the patient.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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