Rare cytogenetic abnormalities and their clinical relevance in pediatric acute leukemia of Saudi Arabian population

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Abstract

Background: Childhood Acute Leukemia (AL) is characterized by recurrent genetic aberrations in 60% of AML cases and 90% of ALL cases. Insufficient data exists of rare cytogenetic abnormalities in AL. Therefore, we tested rare cytogenetic abnormalities occurring in childhood AL and its effect on clinical prognosis in patients diagnosed at our institution from 2010 to 2017.

Results: Among 150 cases of AL, we detected 9 cases with rare chromosomal abnormalities. We found two hypodiploid (2n-) cases: 2n-,t (5;14)(q31;q32) and t (3;11;19)(q21;q23;q13.1) in ALL patients. AML patients showed t (7;14)(q22;q32), t (11;17)(p15;q11), t (12;17)(q15;p23) and t (11;20)(p15;q11). Both t (1;15)(q10;q10) and t (17;19)(q21;p13.3) occurred in a case with biphenotypic AL. Complete remission (CR) status was attained in 3 patients and 6 patients never attained CR or relapsed/demised.

Conclusion: The study highlighted that rare cytogenetic abnormalities are associated with a poor prognosis. This finding is not well reported in the literature suggesting that ongoing cytogenetic studies for rare abnormalities associated with pediatric leukaemia are warranted.

Keywords: Acute leukemia, Rare chromosomal abnormalities, Outcome, Pediatric

Background

Leukemia is the most common form of pediatric cancer occurring in one-third of childhood malignancies [1]. Acute Leukemia (AL) is a clonal hematological disorder which occurs following a genetic alteration. Acute Lymphoblastic Leukemia (ALL) occurs more frequently in the pediatric age group compared to Acute Myeloid Leukemia (AML) [1].

Cytogenetic investigations using G-banding and fluorescence in-situ hybridization (FISH) is an essential tool for diagnosis, prognosis and targeted therapy. Chromosomal abnormalities are grouped into three prognostic categories: favorable, intermediate and adverse [2]. Some of these abnormalities are common and others are rare. Rare cytogenetic abnormalities that have been described in the literature include aberrations of chromosomes 3, del (5q), -5 and -7 [3].

While common recurrent cytogenetic abnormalities in AL have been well risk-stratified, the prognostic significance of many rare cytogenetic abnormalities in ALL and AML remains uncertain [4].

There is a paucity of data on the prevalence and clinical outcome of rare cytogenetic abnormalities in the Saudi Arabian population. In this study we have examined rare cytogenetic abnormalities in childhood AL and the clinical outcome.

Materials and methods

Patients

We reviewed 150 cases with a diagnosis of childhood pediatric acute leukemia at Prince Sultan Military Medical City in Riyadh, Saudi Arabia from 2010 to 2017.
The diagnosis in all cases was based on morphology, flow cytometry, immunohistochemistry and genetic studies. This study included patients between 1 and 18 years of age (pediatric age group in Saudi Arabia). The medical records were reviewed for all data (Tables 1 and 2).

Cytogenetic analysis and FISH
Standard cytogenetic preparations were made from bone marrow and/or peripheral blood. Cytogenetic analysis was carried out on G-banding chromosomal preparations in a total of 20 metaphases. Karyotypes were interpreted and reported according to the International System for Cytogenetic Nomenclature [5].

Fluorescence in situ hybridization (FISH) was performed on double stranded DNA in fixed chromosomes using fluorescent probes which bind complementary sequences of mRNA in a sequence of hybridization steps to achieve signal amplification of the target which is viewed using a fluorescent microscope.

The panel of probes used to detect ALL specific abnormalities in our institute are BCR-ABL: t (9;22), RUNX1-ETV6: t (12;21), MLL gene rearrangements: (11q23), MYC gene rearrangements:(8q24) and TCF3/ PBX1: t (1;19).

The multiprobe AML panel includes: RUNX1/ RUNX1T1: t (8;21), PML /RARα: t (15;17), CBFβ gene break apart: 16q22, MLL gene break apart, TPS3 gene and the cen(8, 22q11.2).

Results
In our cohort of 150 cases of acute leukemia, we detected 9 cases with rare non-recurrent chromosomal abnormalities of which 4 cases were ALL, 4 cases were AML and one case was biphenotypic AL (B/Myeloid).

Two cases with hypodiploidy (2n-), t (5;14) (q31;q32) and t (3;11;19)(q21;q23;q13.1) were detected in ALL. The AML patients were found to harbor t (7;14) (q22; q32), t (11;17)(p15;q21), t (11;20)(p15;q11), t (12;17)(q15; q23) and t (11;20)(p15;q11). Both t (1; 15) (q10; q10) and t (17; 19) (q21; p13.3) were detected in the case with biphenotypic AL. The demographic, hematological and cytogenetic data of these 9 cases are summarized in Table 1 & Table 2 and Figs. 1, 2, 3, 4, 5, 6, 7. Complete remission (CR) status was achieved in 3 patients. The

| Parameter | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|-----------|--------|--------|--------|--------|--------|
| Age (years) | 4 | 7 | 11 | 18 | 3 |
| Gender | Female | Female | Male | Male | Male |
| Clinical | Cervical Lymphadenopathy and leucocytosis | Fever, abdominal distention, hepatosplenomegaly | Vomiting, diarrhoea, lower limb weakness | Epistaxis, ecchymosis skin lesions | Fever, lymphadenopathy and hepatomegaly |
| WBC (10⁹/L) | 137 | 18 | 100.8 | 221 | 18.8 |
| HB (g/dl) | 5.2 | 4.8 | 7.2 | 11 | 8.7 |
| PLT (X10⁹/L) | 9 | 53 | 109 | 34 | 239 |
| PB blasts | 80% | 60% | No blasts | 40% blasts on PB and 70% blasts on BM | Hypercellular Blasts 75% Myelomonocytic proliferation with M4 AML |
| Bone marrow aspirate | Hypercellular Blasts 90% B-ALL phenotype | Hypercellular Blasts 80% B-ALL phenotype | 40% blasts and 50% eosinophils | 40% blasts on PB and 70% blasts on BM | Hypercellular Blasts 75% Myelomonocytic proliferation with M4 AML |
| Blasts | 90% | 60% | 40% | 70% | 75% |
| Disease | B-ALL | B-ALL | B-ALL | T-ALL | AML FAB M4 |
| Cytogenetic analysis (karyotype/ FISH) | 46, XX,1-, 8-, 9-, 11-, 12-, 19-, and 22- in 80% of cells | 2n,44, XX, 4-, (8), t (12; 17). ETV/RUNX 1. Loss of der (12-) MLY gene rearrangement. | Negative: PDGFRα PDGFRβ FGFR1 | 46,XY,t(3;11;19) (p21;q23;q13.1). MLL gene rearranged; extra MYC gene | 48,XY,+ 8,+ 8,t(11;17) (p15;q21) (14)/47, idem-Y |
| Chemotherapy | Very high risk ALL chemotherapy protocol (COG AALL0331) and intensive consolidation | Standard risk chemotherapy protocol (COG AALL0331). High risk protocol COG AALL0232 with high dose methotrexate for maintenance | Dana Farber then FLAG-Ida salvage chemotherapy high dose | MRC AML12 protocol. | |
| Survival | Partial remission | Complete remission status achieved | Complete remission | Relapsed and demised | Death due to multiorgan failure |
remaining 6 patients never attained CR, relapsed or demised.

**Acute lymphoblastic leukemia cases**

**Case 1**
This 4 year old B-ALL patient was negative for ALL panel specific abnormalities with a normal female karyotype (46, XX) (Fig. 1). Hypodiploidy (2n-) with loss of -1, -8, -9, -11, -12, -19 and -22 was detected in 80% of the studied cells by FISH (Figs. 2, 3, 4, 5). Thereafter, cryptic abnormalities were identified (not detected by the initial karyotyping (Fig. 1). The interesting finding in this case was that the diagnostic karyotype was normal but the FISH showed 2n-. This indicated that FISH revealed the cryptic cytogenetic abnormality which was not detected by GTG-banding karyotype.

The patient was classified on very high risk ALL chemotherapy protocol (COG AALL0031). During induction chemotherapy the patient developed a gluteal ulcer and recurrent infections with positive blood cultures which we treated with antibiotic therapy. The post induction BM aspirate revealed 6% of blasts with the immunophenotype presentation compatible with partial remission. The patient received 2 weeks of extended induction chemotherapy. The BM aspirate on day 43 showed morphological remission. Cytogenetics was negative for all detected tumoral clones except for the 2n- which persisted. The patient then received intensified consolidation phase chemotherapy and is currently awaiting BM transplant.

**Case 2**
This 7 year old B-ALL patient harbored the classical ETV6 /RUNX1 rearrangement in the majority of analyzed cells. However, a clonal evolution with loss of der (12)- and the MYC gene rearrangement was detected in 20% of cells. The karyotype showed 44, XX; del (12;17)(q15;q23), del(7) (p15), inv. (8)(q22q24) with (2+) and(19+). 46,XY,der(15)(t;1;15) (q10;q10),der(17) (t17;19)(q21;p13.3) 46,XY,del(11)(p13),add(21)(p11)

The patient was classified on standard risk chemotherapy protocol (COG AALL0331). The post induction BMA showed CR. The clinical decision was to continue the chemotherapy protocol in consideration of the mild 2n-. Hypodiploidy (2n- < 45 chromosomes is uncommon. Despite improved treatment outcome of childhood ALL, patients with hypodiploid ALL have a dismal prognosis [6–8].

**Table 2** Demographic data cases 6–9

| Parameter | Case 6 | Case 7 | Case 8 | Case 9 |
|-----------|--------|--------|--------|--------|
| Age (years) | 14 | 18 | 5 | 4 |
| Gender | Male | Male | Male | Male |
| Clinical | Melena stools, fatigue | Leucocytosis, anaemia, thrombocytopenia no organomegaly | Generalized ecchymosis, bruises, epistaxis and hepatomegaly | Fever, malaise failure to thrive |
| WBC (10^9/L) | 16.5 | 33 | 16.1 | 100 |
| HB (g/dl) | 10.1 | 8.2 | 6.7 | 7.8 |
| PLT (X10^9/L) | 20 | 67 | 14 | 101 |
| PB blasts | 30% | 70% | 40% | 70% |
| Bone marrow aspirate | 90% blasts with AML MO morphology | 70% blasts | 40% blasts With dysplasia | 90% blasts comprised of two distinct populations |
| Blasts | 90% | 70% | 40% | 90% |
| Disease | AML MO | AML M2 | AML M7 | B/MYELOID |
| Cyto genetic analysis (karyotype/ FISH) | 46,XY,t(7;14) (q22;q32) | 46,XY,t(11;20) (p15;q11), add(21)(p11) | t(12;17)(q15;q23), del(7) (p15), inv. (8)(q22q24) with (2+) and(19+) | 46,XY,der(15)(t;1;15) (q10;q10),der(17) (t17;19)(q21;p13.3) |
| Chemotherapy | Received induction (3 + 7) for AML then high risk MAC/G protocol | AML induction chemotherapy (3 + 7) protocol. Allogeneic stem cell transplant with steroid refractory graft vs host disease treated with ATG | MRC AML12 Protocol | Received 7 chemotherapy cycles |
| Survival | Refractory disease and demised secondary to chemotherapy side effects | Complete remission | Patient demised | Not attain remission Status. Relapsed for MUD transplant |

**Case 3**
This 11 year old patient presented with vomiting, diarrhea and generalized weakness for 3 weeks. The full blood
count detected leukocytosis with marked eosinophilia. The BM was hypercellular with eosinophilia (50%) (Fig. 7) and blasts (40%) (Fig. 8) with B-ALL immunophenotype. The cytogenetic and molecular analysis detected t (5; 14) (q31; q32) by FISH. RT-PCR was negative for *PDGFRA*, *PDGFRB*, and *FGFR1* gene abnormalities. We diagnosed the patient with concurrent B-ALL and hypereosinophilia. The patient was classified on steroid therapy and on high-risk chemotherapy at the time of diagnosis. Post induction chemotherapy analysis showed morphological(
3% blasts/ no eosinophil’s in the BM) and molecular (negative IGH gene rearrangements) remission. The patient is currently in CR status on high dose methotrexate therapy for maintenance.

The t (5, 14) in association with eosinophilia has not been frequently reported in the literature. A single case report of a 6 year old boy presenting with hypereosinophilia and associated Loeffler endocarditis has been previously recorded [8]. Three months following his initial hypereosinophilia this patient developed cutaneous B-lymphoblastic lymphoma. Reanalysis of apparently uninvolved BM revealed a single, previously unidentified.

t (5; 14) (q31; q32) positive cell. IL3 / IGH @ fusion were demonstrated in cutaneous lymphoma cells. Our patient also showed the IL3/IGH gene translocation strengthening the association of IL3 hypersecretion and hypereosinophilia [8].

Acute myeloid leukemia cases

Case 5
This 3 year old AML M4 patient showed t (11; 17) (p15; q21), tetrasomy (4n) of chromosome 8 and two extra copies of MYC in 85 and 70% of the studied cells (Fig. 12).

The patient was classified on the first cycle of MRC AML12 protocol. On day 5 post chemotherapy the patient developed neutropenia and persistent high grade fever. The patient was given Vancomycin and Amikacin following blood cultures and Meropenem for a urinary tract infection. Prophylactic fluconazole was started. On the final chemotherapy cycle the patient developed bloody diarrhea and abdominal distention. The abdominal ultrasound and CT Abdomen revealed a severe typhilitis. Despite intensive care support, the patient demised following cardiopulmonary arrest and multi-organ failure one month after admission.

Only 3 cases of pediatric AML with the t (11; 17) (p15; q21) have been previously reported: two AML M4 cases (aged 3 and 4 years) one AML M0 case [9–11]. Another MDS case with isolated t (11; 17) (p15; q21) after neuroblastoma chemotherapy has been reported in an 8 years old girl [12]. In adults, the translocation has been reported in one case [12].
Chromosomal analysis detected the karyotype 46, XY, t (7; 14) (q22; q32). FISH was negative for AML panel specific abnormalities. After initiation of induction chemotherapy the patient developed persistent neutropenia with klebsiella infection and did not attain remission status. He was classified on high risk MAC/G protocol. He continued to have chemotherapy related side effects such as afebrile neutropenia, severe mucositis and multiple resistant bacterial and fungal infections. The patient failed to recover or attain remission status and subsequently demised. This is rare

**Fig. 6** Case 2 showing complex karyotype: 46,XX,-4,-8,t (12;17)

**Fig. 7** Case 3 hematoxylin and eosin stain shows prominent eosinophilia

**Fig. 8** Case 3 shows CD34+ blasts on immunohistochemistry
presentation of AML MO with t (7, 14) in a patient with previous HL.

Secondary leukemia’s as in this patient commonly manifest with abnormalities of chromosome 7 and 5, however, the t (7; 14) (q22; q32) commonly occurs in T-ALL and rarely in AML [13, 14].

**Case 7**

This 18 year old patient was diagnosed as AML (M2) both morphologically and immunophenotypically. Aberrant expression of CD7 occurred on a cellular subpopulation. Cytogenetic analysis showed 46, XY; t (11, 20) (p15; q11) and add (21) (p11) (Fig. 13). The patient
started the first cycle of AML induction chemotherapy (3 + 7) protocol and achieved CR.

This t (11; 20) (p15; q11) is a rare chromosomal translocation which has a poor prognosis [15, 16]. Our case responded well to 3 + 7 protocol (3 doses of Daunorubicin+7 days of cytosine arabinoside) and attained CR. The patient then had allogeneic stem cell transplant and later developed steroid refractory graft versus host disease which was treated with ATGA.

Case 8
This 5 year old patient presented with anemia and thrombocytopenia. He received IVIG infusion as ITP (immune thrombocytopenic purpura) was suspected, but no improvement occurred. A BM aspirate immunophenotype was compatible with AML (FAB; M7). The cytogenetic analysis revealed a complex karyotype t (12;17)(q15;q23) and 48,XY,+2,del (7)(p15), inv.(8)(q22q24), t (12;17) (q15;q23) and trisomy 19. FISH reported \textit{PML/RARA}; \textit{RUNX1} / \textit{RUNX1T1}; (5′CBFB, (3′CBFB,5′CBFB con 3′CBFB) / (5′MLL,3′MLL con 3′MLL). In addition, a tumoral clone with extra chromosome (2+) and (19+), del (7p), inv.(8) and t (12; 17) (Fig. 14) was detected.

The patient was treated on MRC AML12 Protocol but did not attain remission and subsequently demised. This very rare t (12; 17) has been reported in three adults and one child with secondary AML [17, 18]. Interestingly, the four published cases have been female and have additional aberrations. Our patient is male and the translocation is also part of a complex karyotype.

Case 9
This 4 year old patient was diagnosed as biphenotypic acute leukemia (B /Myeloid). Morphology of two morphologically diverse populations of cells immunophenotypically expressed myeloid markers (CD13, CD33 and MPO) and B cell markers (CD10, CD19, CD79a, and TdT).

The cytogenetic analysis revealed the presence of a cell line with der t (1;15)) (1q10; 15q10) and t (17q21; 19p13.3). The FISH panel was negative for all gene abnormalities.

Fig. 12 Case 5 Karyotype shows t (11;17), tetrasomy of chromosome 8 and extra copy of \textit{MYC} gene
We diagnosed a biphenotypic (B/Myeloid) leukemia with the rare t (1; 15) present in the AML clone and t (17; 19) present in the B-ALL clone. The patient was classified on MRC AML12 protocol. The post induction BM showed persistent disease (60% blasts). A second ADE was given and the BM showed a regenerating marrow with 5% clonal blasts. A third cycle of the protocol MACE and fourth cycle CLASP were given and samples were taken for matched unrelated donor transplant. During the fourth chemotherapy cycle, the patient developed septic shock and the protocol was changed to a fifth chemotherapy cycle MidAC. A month after completing this cycle, the patient presented with fever, bone aches and neutropenia with circulating blasts. The BM aspirate showed relapse with 60% blasts. The patient was classified on FLAG-IDA (the sixth chemotherapy protocol). However, the patient remained refractory. In addition, the patient developed febrile neutropenia and was started on antibiotics, antifungal therapy and a 7th course of chemotherapy. A matched unrelated donor transplant was planned by the treating physicians in view of the persistent refractory disease.

**Discussion**
Cytogenetic investigations for chromosomal abnormalities are important tools for classification and prognostic determination in AL [19]. Response to chemotherapy in AL depends on the cytogenetic characteristics and patient’s age [2]. Leukemia’s with adverse cytogenetic abnormalities and older patients are associated with a poor prognosis [3].

While studies showing the prognostic significance of rare cytogenetic abnormalities in adults have been reported in large cohorts [5], there is a paucity of data showing this association in the pediatric population.

We studied a large series of pediatric patients with acute leukaemia in Saudi Arabia through GTG-banding and FISH techniques. We found that 9 of these cases harbored rare (non-recurrent) chromosomal abnormalities. We analyzed them and found correlations with regard to clinical presentation, outcome and cytogenetic abnormalities.

**Conclusion**
Our results confirm that rare cytogenetic chromosomal abnormalities in pediatric AL are associated with a poor
outcome. Data confirming these findings are sparsely reported in the literature suggesting that ongoing cytogenetic studies are warranted in larger groups of AL to identify rare and novel chromosomal abnormalities that may contribute to diagnosis and prognosis in pediatric patients with AL and help in the development of targeted therapeutic drugs.

Abbreviations
AL: Acute leukemia; ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; BM: Bone marrow; ChlVPP/ABVVP: Chlorambucil, vinblastine, procarbazine, doxorubicin, bleomycin, vincristine and etoposide; CLASP: Cytarabine plus L-asparaginase; COG: Children’s Oncology Group; CR: Complete remission; FISH: Fluorescence in situ hybridization; FLAG: Fludarabine + high dose AraC + GCSF; IDA: Idarubicin; MACE: Amsacrine + AraC + etoposide; MidAC: Mitoxantrone and AraC; MRC: Medical Research Council; RT-PCR: Reverse transcription polymerase chain reaction

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Ethics and approval and consent to participate
Ethics for this study complies with the Declaration of Helsinki and is conducted under the auspices of the Saudi Arabian Pediatric Hematology/Oncology Society (SAPHOS).

Authors’ contributions
All authors contributed to this manuscript accordingly. All authors read and approved the final manuscript

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Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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