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Case Series

Acute myeloid leukemia with rare cytogenetic abnormalities

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ABSTRACT

Acute myeloid leukemia (AML) is a clonal hematologic disorder frequently linked to genetic alterations, accounting for approximately 31% of adult leukemia cases. Recent updates in the World Health Organization (WHO) and International Consensus Classification (ICC) have redefined AML into categories based on genetic abnormalities, emphasizing the role of cytogenetics in diagnosis, prognosis, and treatment. Cytogenetic and molecular analyses are increasingly supplementing conventional morphology and immunophenotype assessments.

In AML, cytogenetic abnormalities are categorized into favorable, intermediate, and adverse risk groups. While common cytogenetic markers have been extensively studied, rare cytogenetic abnormalities in AML remain less understood, often posing challenges in prognostic evaluation and treatment strategies. This study presents a case series of seven AML patients, each exhibiting rare cytogenetic abnormalities that are not well-defined in the WHO's 5th edition classification of hematopoietic and lymphoid tissues.

We retrospectively analyzed these cases, where AML diagnosis was confirmed through morphology, flow cytometry, immunohistochemistry, and molecular studies. Cytogenetic investigations included G-banding and fluorescence in-situ hybridization (FISH). The molecular studies performed as part of the AML multigene panel revealed notable genetic variations, including rare translocations and polysomies.

This study highlights the significance of cytogenetic analysis in identifying rare abnormalities, which can influence risk stratification and treatment decisions. However, due to the limited literature and understanding of these rare cytogenetic events, more research is essential for optimizing patient outcomes.

1. Introduction

Acute Leukaemia is a clonal hematological disorder which is attributed to an underlying genetic alteration. Acute myeloid leukaemia accounts for nearly 31% of all adult leukemia.[1] World health organization (WHO) and international consensus classifications (ICC) have provided classifications recently. The major breakthroughs in the classification of AML being separation into AML with defining genetic abnormalities from AML defined by differentiation has had a significant impact on diagnosis. The diagnosis of AML is gradually shifting from morphology and immunophenotype to cytogenetics and more advanced molecular methods.[2]

The role of cytogenetics in AML has become more eminent which includes establishing specific defining cytogenetic abnormalities, prognostication, and unraveling the unexpected/rare structural and numerical aberrations.[3]

Cytogenetic investigations performed using G-banding and fluorescence in-situ hybridization (FISH), is an essential platform for diagnosis, prognosis, follow-up and targeted therapy. Chromosomal abnormalities are grouped into three prognostic categories: favorable, intermediate, and adverse.[4] Some of these abnormalities are common and

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others are rare. While defined cytogenetic/ molecular abnormalities in AML have been well risk-stratified, the treatment modification and prognostic significance of many of the rare cytogenetic abnormalities of AML remains uncertain.

Hereby, we present a case series of 7 cases highlighting the role of identification of rare cytogenetic abnormalities in AML.

2. Case Series

2.1. Case 1

An 18-year-old male was diagnosed with acute monocytic leukemia based on morphology in peripheral blood and bone marrow aspirate. Flow cytometric analysis of the blast population was also consistent with a monoblastic cell population and aberrant CD4 expression. The AML multigene panel was negative. Cytogenetic analysis performed showed .48,XY,-3,+8,+8,der(12)t(3;12)(q21;p12)+mar/46,XY.(Figure 1) This case was given a final diagnosis of AML with a polysomy of 8.

Although trisomy 8 is one the most common chromosomal abnormalities observed in hematological malignancies,[5] polysomy 8 is a rare, non-random numerical abnormality associated with myeloid malignancies such as acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and rarely myeloproliferative neoplasms (MPN). Trisomy 8 was undetectable at diagnosis with conventional cytogenetics in 75% of all reported cases. In nearly all cases that were further examined with FISH, a concurrent trisomy 8 clone was also detected. It has been suggested that tetrasomy 8 occurred after trisomy 8 by serial clonal evolution from a normal karyotype to tetrasomy 8.[6]

2.2. Case 2

A 46-year-old male was diagnosed with AML with few monocytoid cells, based on morphology in peripheral blood and bone marrow aspirate. Flow cytometric analysis of the blast population was consistent with myeloid lineage along with aberrant CD7 expression. The AML multigene panel was negative. Cytogenetic analysis performed showed 46, XX,t(6;11)(p22;p15)/46, XX.(Figure 2) This case was given a final diagnosis of AML with t(6,11)(p22;p15).

This is a novel karyotype identified in AML with an M4 phenotype and aberrant CD7 expression. A review of the literature does not provide any related articles for this specific translocation. However, there was a case report and review of literature on AML- M2 phenotype with a sole cytogenetic abnormality of t(6;11)(q15;q23), with a FISH MLL rearrangement. This translocation in myeloid leukemia is now classified under AML with KMT2A rearrangement of defining genetic abnormalities. This case, however, had a poor prognosis.

2.3. Case 3

A 60-year-old male was diagnosed with AML, based on morphology in peripheral blood and bone marrow aspirate with a prior history of CML. Flow cytometric analysis of the blast population was consistent with monocytic lineage along with aberrant CD4 expression. BCR- ABL1 gene transcripts were identified in PCR done as AML- multigene panel. The AML multigene panel was negative. Cytogenetic analysis performed showed 46,XY,t(1;21) (p32;q22), t(2;3)(p16;q29)/ 46,XY, t(2;3)(p16;q29).(Figure 3)

This karyotype is the seventh case of AML in the medical literature with a t(1;21). They usually have bone marrow with extensive myelofibrosis also identified in our case, and the differential diagnoses are panmyelosis with myelofibrosis (APMF), myelodysplastic syndrome with myelofibrosis (MDS-MF), and acute megakaryoblastic leukemia with myelofibrosis (AMKL-MF) due to the overlapping clinical and morphological features.[7]

They usually harbor RUNX1–PRDM16 transcript which can be identified by RT-PCR.[8] Their behavior is uncertain, however, showed poor prognosis in the reported cases with relapses.

2.4. Case 4

A 29-year-old female was diagnosed with AML on morphology seen in peripheral blood and bone marrow aspirate. Flow cytometric analysis of the blast population was consistent with monocytic lineage along with aberrant CD7 expression. The AML multigene panel was negative. Cytogenetic analysis performed showed 46,X,-X,der (1)t(1;3)(p36;q21), del(5)(q22q35), der(6)t(1;6)(q21;p21),+mar.

There has been one case reported AML with t(1;3) had associated thrombocytosis. This is a complex karyotype with the reported cases having poor prognosis. This case is a novel karyotype identified AML with monocytic differentiation.[9] The case with t(1:3) can be identified in myeloid and lymphoid neoplasms, namely chronic myeloid leukemia, myelodysplastic neoplasm, AML, acute lymphoid leukemia, and non-Hodgkin lymphomas. They have been reported to have a poor prognosis.

2.5. Case 5

A 21-year-old female was diagnosed with acute myeloid leukemia with erythroblastic hyperplasia on morphology seen in peripheral blood and bone marrow aspirate. Flow cytometric analysis of the blast population was consistent with erythroid lineage along with aberrant CD7 expression and was diagnosed as acute erythroid leukemia. FISH performed to look for Trisomy 8, del 5q, del 7q

turned out to be negative. The AML multigene panel was negative. Cytogenetic analysis performed showed 46, XX,t(3;5)(q25;q31)/46, XX.

This cytogenetic has a mention in the 5^{th} edition of the WHO classification of hematological malignancies under the category of AML with other defined genetic alterations.[10] AML with t(3;5)(q25.1;q34) have NPM1/MLF1 rearrangement and have been reported mostly as a sole karyotypic abnormality in younger patients. However, it should also be considered in elderly patients with complex chromosomal abnormalities. They can be identified in patients with AML and MDS.[11] Their prognosis and biology are however, still not established.

2.6. Case 6

A 33-year-old female was diagnosed with AML on morphology seen in peripheral blood and bone marrow aspirate. Flow cytometric analysis of the blast population was consistent with monocytic lineage. The AML multigene panel was negative. Cytogenetic analysis performed showed 46, XX,t(11;20)(p15;q11).(Figure 4)

The t(11;20)(p15;q11) is associated with AML that are treatment related or with myelodysplastic neoplasms. The breakpoint on chromosome 11p15 targets the NUP98 gene and on chromosome 20q11 occurs within the gene encoding human DNA topoisomerase I (TOP1) which results in a chimeric mRNA encoding the NUP98 FXFG gene and repeats which is fused to the body of DNA topoisomerase I. These results indicate that NUP98 is a recurrent target in therapy-related malignancies and that TOP1 is a previously unrecognized target for chromosomal translocations.[12]

2.7. Case 7

A 16-year-old male was diagnosed with acute monocytic leukemia based on morphology in peripheral blood and bone marrow aspirate. Flow cytometric analysis of the blast population was also consistent with a monoblastic cell population exhibiting CD64 and CD14 positivity. The AML multigene panel was negative. Cytogenetic analysis performed showed . 48,XX,t(1,11)(q21;q23),+10+11+19+21[7].(Figure 5) This case was given a final diagnosis of AML with KMT2A rearrangement.

KMT2A/MLL gene rearrangements in chromosome 11q23 are associated with lymphoid and myeloid leukemia. However, MLL/KMT2A gene can harbor translocations with numerous genes, the most common ones are resulting from the translocations t(9;11)(p22;q23), t(6;11)(q27;q23), t(11;19)(p13.1;q23), and t(10;11)(p12;q23), respectively.[13,14] This translocation is however, extremely uncommon and has case reports to be identified in chronic myeloid leukemia[15] and congenital AML.[16] They are known to have a worse prognosis in neonates compared to young adults.

2.8. Case 8

A 3-year-old girl child was diagnosed with AML with monocytic differentiation on morphology seen in peripheral blood and bone marrow aspirate. Flow cytometric analysis of the blast population was consistent with monocytic lineage along with aberrant CD7 and absence of markers of immaturity (HLA-DR and CD34). A suspicion of promyelocytic leukemia was considered and we did a PML-RARA fusion by FISH which turned out to be negative. The AML multigene panel was negative. Cytogenetic analysis performed showed 47, XX,t(11,19)(q23;p13.1),+mar(15). (Figure 6) A final diagnosis of AML with KMT2A rearrangement was given in his case.

As discussed in the previous case, this case also harbors KMT2A gene rearrangement with t(11,19)(q23;p13). This translocation is more predominantly identified in acute lymphoid neoplasms, though KMT2A can be identified in myeloid/lymphoid or mixed-lineage neoplasms. KMT2A rearrangements are also associated with adverse outocmes, especially in children.[17] During replication, topoisomerase inhibitors slow down the ligation of free DNA ends and stabilize double-strand breaks. Free ends of DNA can readily recombine with DNA from another chromosome, potentially leading to certain gene fusions like KMT2A/MLL–MLL3.[18] This gives the validation for these rearrangements also being associated with therapy-related AML. Case 8 and Case 9 had translocations with the 11q23, however, did not harbour MLL gene rearrangements, which can be attributed to the heterogeneity to 11q23 breakpoint.

2.9. Case 9

A 36-year-old female was diagnosed with AML on morphology seen in peripheral blood and bone marrow aspirate. Flow cytometric analysis of the blast population was consistent with myeloid lineage along with aberrant CD7 and CD19 expression. The AML multigene panel was negative. Cytogenetic analysis performed showed 47, XX,t(8;22)(p11:q13),+19. FISH performed with break apart probe for FGFR1 is positive corresponding to the cytogenetics. (Figure 7)

The t(8;22) which results in BCR-FGFR1 fusion transcripts is usually identified in myeloid and as well as lymphoid neoplasms, specifically the leukemic blast crisis of chronic myeloid leukemias.[19] Montenegro-Garreaud et al. reported a patient with the (8;22) translocation, with no FGFR1 rearrangements, who achieved complete morphologic, immunophenotypic, and cytogenetic remission after allogeneic stem cell transplant.[20] Based on the biological profile of the cytogenetic abnormality they have been known to have poor prognosis.

A large clinical trial conducted by Grimwade et al. on 5876 young adults with AML has evaluated various cytogenetic abnormalities in determining prognosis including rare recurring chromosomal abnormalities.[21] They have found varied cytogenetic abnormalities including rare ones, like t(3;5), t(6;11). But have not described the other abnormalities as reported in our series. The authors have mentioned about lack of consensus regarding informed clinical decision-making in cases with cytogenetic analysis showing rarer karyotypic abnormalities, so more case reports and further studies are essential in assessing the outcome of such patients.

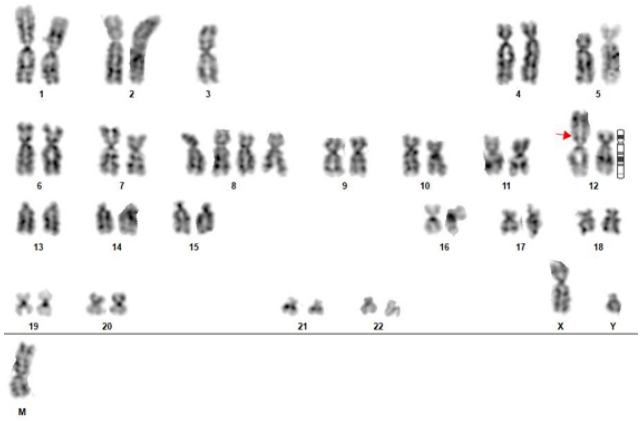

Figure 1: Conventional cytogenetics of Case 1 with 48,XY,-3,+8,+8,der(12)t(3;12)(q21;p12)+mar

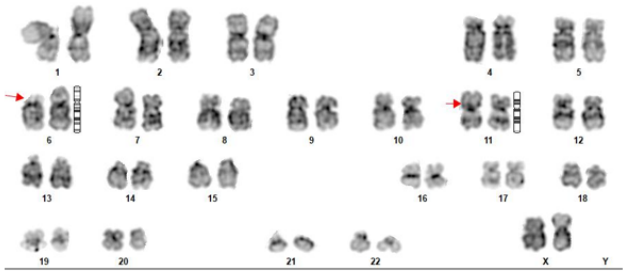

Figure 2: Conventional cytogenetics of Case 2 with 46,XX,t(6;11)(p22;p15)

3. Discussion

Acute myeloid leukemias (AMLs) are a group of diseases representing clonal proliferations of hematopoietic precursors which typically involve the bone marrow and peripheral blood. The evolution of the classification of AML has evidenced a significant change over the past few years. The major breakthroughs help us understand disease in relation to molecular alteration.[22] An important mile stone is the separation of AML with defining genetic

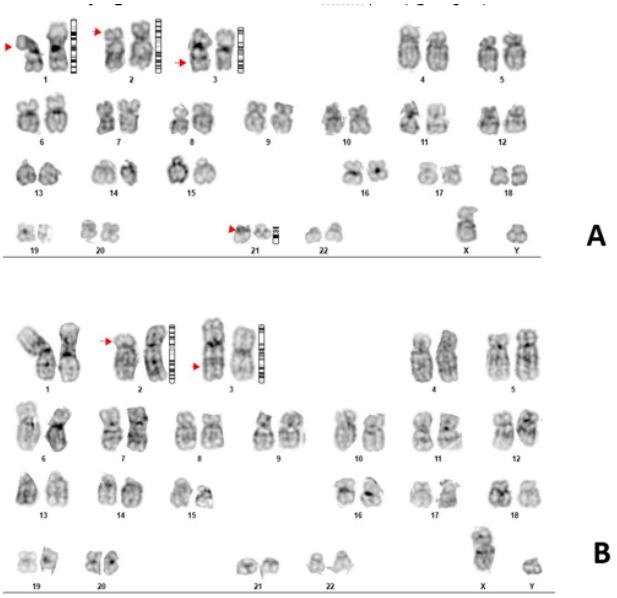

Figure 3: A: Conventional cytogenetics of Case. 3 with (A) showing 46,XY,t(1;21)(p32;q22),t(2;3)(p16;q29) and **B:** Showing 46,XY,t(2;3)(p16;q29)

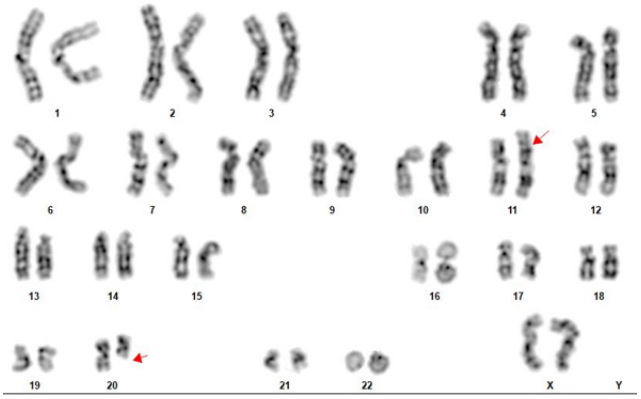

Figure 4: Conventional cytogenetics of Case 6 with46, XX,t(11;20)(p15;q11).

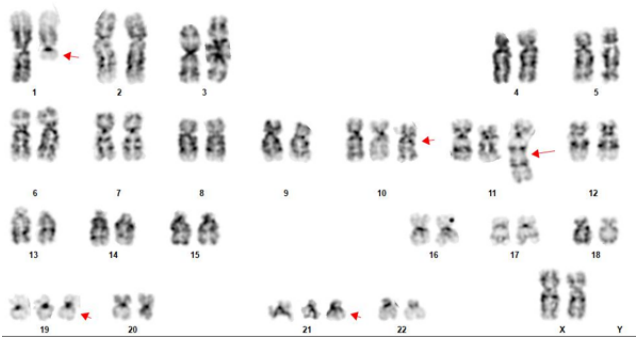

Figure 5: Conventional cytogenetics of Case.7 with 50,XX,t(1,11)(q21;q23),+10+11+19+21[7]

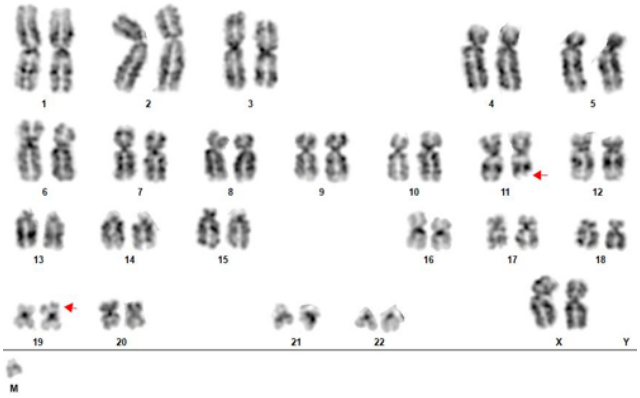

Figure 6: Conventional cytogenetics of Case 8 with 47,XX.t(11;19)(q23;p13.1)+mar

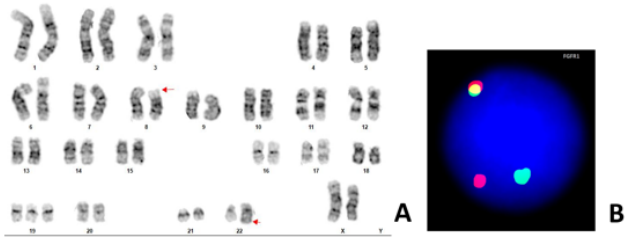

Figure 7: A: Conventional cytogenetics of Case 9 with 47,XX,t(8;22)(p11;q13)+19; **B:** FGFR1 Breakapart probe showing 1 fusion, 1 green and 1 red signal , positive for FGFR1 rearrangement

abnormalities from AML defined by differentiation which was done in the 2017 WHO classification. With a new 2022 WHO update in myeloid neoplasms, a third component AML with other defined genetic alterations has been introduced which could be the home for new and/or uncommon AML subtypes. Few of the entities from this category can be well recognized and defining genetic abnormalities.[23] Conventional cytogenetics can contribute significantly to the identification of uncommon and rare genetic abnormalities and help in risk stratification. Here we described seven such rare cases.

4. Conclusion

We would like to throw light on rare and complex cytogenetic abnormalities encountered in AML. Hence, it is imperative to include cytogenetic analysis as a component of the routine diagnostic work-up of AML not only to provide a framework for risk stratification but also to further predict prognosis in patients who share particular cytogenetic abnormalities.

5. Conflict of Interest

None.

6. Source of Funding

None.

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