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Case Report

Rare cytogenetic abnormalities in MDS evolving from fanconi anemia-A case report

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ABSTRACT

Fanconi anemia (FA) is a genetically heterogenous rare autosomal recessive disorder. Mutations in FANCA gene are the most frequent among FA patients accounting for 60-65%. FA is characterised by congenital malformations, progressive bone marrow failure (BMF) and increased risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). The risk of developing hematological abnormalities in FA patients is around 98% by 40 years of age. The risk of clonal cytogenetic abnormalities during BMF is around 67% by 30 years of age and risk of developing MDS or AML is 52% by 40 years of age. The frequent chromosomal abnormalities are 1q+, monosomy 7 and gains of 3q. Partial duplications/triplications of chromosome 1q are known to represent a nonrandom chromosomal anomaly in myeloid disorders.

1. Introduction

Fanconi anemia (FA) is a genetically heterogenous rare autosomal recessive disorder with an incidence of approximately 1-5 per million. Mutations in FANCA gene are the most frequent among FA patients accounting for 60-65%. FA is characterised by congenital malformations, progressive bone marrow failure and increased risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).[1,2] Approximately 40% of patients with FA develop severe BMF by the age of 20 years, and half of the patients with FA develop BMF by the age of 50 years. The risk of solid tumors and AML by the age of 50 years in FA is estimated to be 30% and 10% respectively.[3] Bone marrow aspiration studies and cytogenetic studies forms an essential investigation for detecting the evolving malignant clone in FA patients. Here we report a case with rare cytogenetic abnormality of 1q triplication and del(5q) in a patient with inherited bone marrow failure syndrome(IBMFS), Fanconi anaemia (FA) evolving to Myelodysplastic syndrome (MDS).

2. Case Report

31 yr old male with short stature and palatal hyperpigmentation was admitted for bicytopenia evaluation. The Bone marrow aspiration studies revealed hypocellular marrow with 3% blasts and significant dyspoiesis in all cell lineages suggesting features of aplastic anaemia evolving into Myelodysplastic syndrome.

2.1. Cytogenetics

2.1.1. Banding

Bone marrow aspirates were incubated in RPMI medium overnight at 37^0C in 5% C02, the cell cycle was arrested by treating with Colcimid. The cells are harvested using hypotonic solution and fixed with carnoy's fixative [methanol: acetic acid::3:l]. Chromosomes were banded

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using trypsin Giemsa staining and analysed as per ISCN 2020 guidelines.

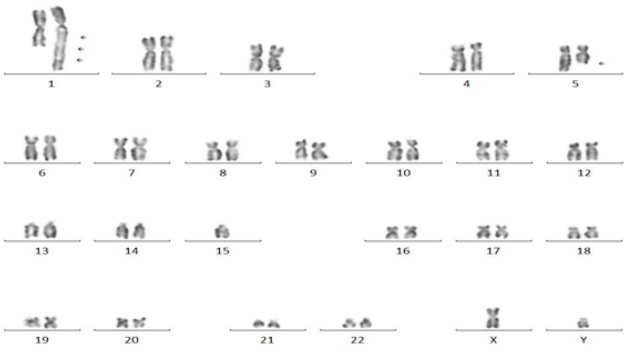

Fig. 1: Karyotype showing 45,XY with trp(1)(q21q32) and del(5)(q22q35)

G banding analysis of BMA revealed tandem triplication of trp(1)(q21q32) in all metaphases and del(5)(q22q35)as secondary abnormality in 50% of metaphases.

FISH analysis was performed on interphase cells and metaphases using metasystem CDKN2C/CKS1B deletion/amplification probe. Cytogenetic preparation of BMA slides, denaturing of probe/chromosomes, hybridization and washing of slides done as per manufacturer guidelines.

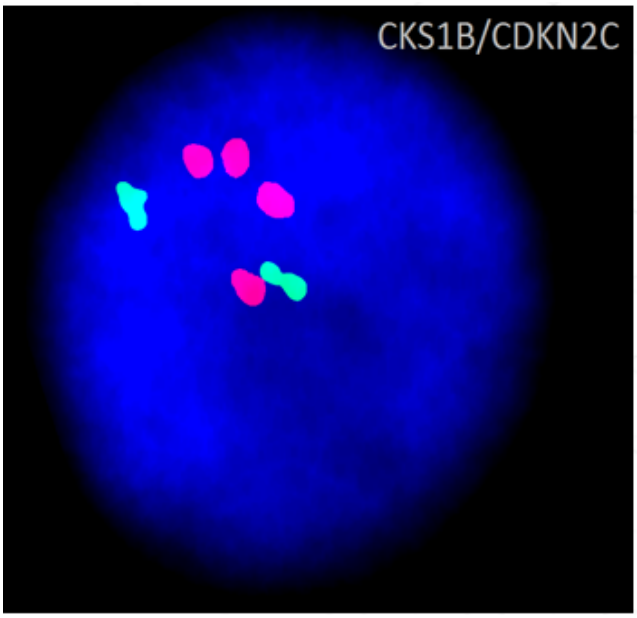

Fig. 2: Fluorescence in situ Hybridization for1p(CDKN2C)[Green]/1q(CKS1B)[Red] showing 4 copies of CKS1B[Red] indicating triplication of 1q

FISH results were analysed using Zeiss microscope equipped with DAPI, Fluorescence Isocyanate (FITC) and Tetramethylrhodamine B Isocyanate (TRITC) fluorescence filters. Metaphase FISH analysis showed 4 copies for CKS1B gene of which 3 signals were located on q arm of abnormal chromosome l, confirming the diagnosis of 1q triplication.

Gene sequencing using exome sequencing showed presence of autosomal recessive inheritance of FANCA gene, confirming the diagnosis of fanconi anemia in our patient.

3. Discussion

FA is a rare autosomal recessive disorder characterised by congenital malformations, progressive pancytopenia, chromosomal aberrations, cellular hypersensitivity to DNA cross linking agents, predisposition to MDS, AML and other malignancies.[4,5]

The advanced molecular testing, clinical exome sequencing specifically analyses the exons of the genes that are involved in the disease. FANCA is the most commonly mutated FA gene and its activity is essential for resolving DNA inter-strand crosslinks during genomic replication.[1,4] The identification of pathogenic variant of autosomal recessive inheritance for Fanconi anemia helps to identify and determine the carriers in the family and the risk of recessive inheritance to offspring.

The common developmental abnormalities observed in FA patients are short stature, upper lib radial ray abnormalities, skin pigmentation changes, renal malformations and central nervous system findings. 80% of FA will have at least one physical feature of developmental abnormalities, short stature and low birth weight are observed in nearly 50% of cases. Short stature and low birth weight is due to the loss of pluripotent stem cells during embryogenesis.[4,6]

Bone marrow failure is a more characteristic feature in FA patients. The incidence of severe BMF reaches 70% by age 50 years. BMF is due to hyperactivation of p53 which hinders the ability of haematopoietic stem cells to deal with replicative stress during prenatal HSC expansion by triggering an apoptotic p53/p21 mediated response that results in a prenatally reduced fraction of CD34+ cells. This compromised HSC pool is further challenged by DNA damage accumulation during extrauterine life.[4]

The Failure of the FA/BRCA pathway in FA causes numerical and structural chromosomal instability in the form of chromosomal breaks, deletions, duplications, fragmentation and translocations. The chromosomal aberrations are the result of initiated but unfinished interstrand crosslink (ICL) repair in FA cells.[4,7] The frequent chromosomal abnormalities are 1q+, monosomy 7 and gains of 3q.[5] Partial duplications/triplications of chromosome 1q are known to represent a nonrandom chromosomal anomaly in myeloid disorders. Tetrasomy of 1q, results from tandem triplication of 1q, frequently involves region in 1q21 which harbors fragile sites and

oncogenes involved in AML. Cells with chromosome triplication are considered to have evolved from a previous duplication.[8,9] The consequence of this is a genomic amplification of a specific chromosomal region. The long arm of chromosome 1 accomodates genes involved in the control of normal myeloid cell kinetics. The imbalance in normal cell cycle leads to more pronounced cell proliferation.[9]

The proteins encoded by FA genes play important role in numerous cellular functions including DNA repair, detoxification of reactive oxygen species and aldehydes, energy metabolism and both proinflammatory and myelosuppressive cytokine homeostasis. The exposure of FA deficient cells to aldehydes result in the accumulation of chromosomal aberrations.[3,4]

The risk of developing hematological abnormalities in FA patients is around 98% by 40 years of age.[10] The common haematologic abnormalities are thrombocytopenia and pancytopenia, often associated with BMF. The risk of clonal cytogenetic abnormalities during BMF is around 67% by 30 years of age and risk of developing MDS or AML is 52% by 40 years of age.[10] The increased risk of cancer in FA is related to defective DNA repair, which makes somatic cells more susceptible to mutations that could initiate the carcinogenic process.[3] The evolving malignant clone can have non specific myeloid chromosomal abberations. Monosomy 7 and 3q gains are commonly reported in FA.[2] Del 5q, which is a known chromosomal abnormality in MDS, accounts for nearly 50% of patients with MDS. Damage to 5q31 and 5q33 regions leads to haploinsufficiency of ribosomal protein S14 gene (RPS14 gene). The loss of RSP14 increases levels of p53 primarily in erythroblasts, promotes their apoptosis, and results in a differentiation defect.[11] Thereby the loss of RPS14 gene in 5q deletion causes clonal evolution in FA patients.

4. Conclusion

FANCA is the most commonly mutated FA gene. Gene sequencing in these patients will help in identification of genetic cause. FA patients with inherited bone marrow failure syndrome (IBMFS) can develop peripheral blood cytopenia, which can ultimately progress to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The increased risk of cancer in FA is related to defective DNA repair, which makes somatic cells more susceptible to mutations that could initiate the carcinogenic process. The evolving malignant clone can have non-specific myeloid chromosomal abberations. Cytogenetic analysis should include karyotyping and FISH for the detection of chromosomal abberations and also to assess clonal evolution in FA patients. The prognosis of evolving malignant clone is based on structural and numerical chromosomal aberrations in FA. Clones with duplication of chromosome 3q (3q+), deletion 7q (7q-), or monosomy 7 (-7) are associated with poor prognosis.

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6. Conflicts of Interest

None to declare.

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