

Heritable RUNX1 and GATA2 Mutation with a Very Rare Gene Variant Associated with AML-MDS: A Case Report and Review of Literature



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Submission: June 19, 2018; Published: July 06, 2018

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Abstract

A 15 years old boy diagnosed as acute myeloid leukemia (AML) with Myelodysplastic syndrome (MDS) related disorder with history of epistaxis since childhood. The only significant family history of epistaxis of his grandmother only. He presented as pancytopenia in ER with prolonged bleeding from his nose. No family history of malignancy. Additional genetic analysis was performed and identified two heterozygous different gene variant, one is *RUNX1* gene for rare germline variant designated c.611G>A, which is predicted to result in the amino acid substitution p. Arg204Gln, another is heterozygous in the *GATA2* gene for a variant designated c.554_628delins 16, which is predicted to result in frameshift and premature protein termination (p.Pro185Leufs*77). To our knowledge this variant has not been reported previously in any patient with autosomal dominant *GATA2*-related disorder but expected to be pathogenic. Germline *GATA2* mutations are involved in a group of complex syndromes with overlapping clinical features of immune deficiency, lymphedema and propensity to acute myeloid leukemia or myelodysplastic syndrome (AML-MDS). This case illustrates the importance of recognizing the clinical features for this rare category of AML-MDS and performing the appropriate molecular testing. The diagnosis of heritable gene mutations associated familial AML-MDS has significant clinical implication for the patients and affected families.

Keywords: *RUNX1*; *GATA2*; Familial acute myeloid leukemia; Myelodysplastic syndrome

Abbreviations: AML: Acute Myeloid Leukemia; MDS: Myelodysplastic Syndrome; NGS: Next Generation Sequence; IDAC: Intermediate Dose Ara-C; CMML: Chronic Myelomonocytic Leukemia; FPAMM: Familial Platelet Disorder with Associated Myeloid Malignancy

Introduction

MDS and AML are mostly sporadic hematopoietic malignancies typically affecting older patients. Familial occurrence of MDS or AML is rare, and most of these cases arise in the setting of genetic syndromes associated with increased risks of developing AML or MDS, including several inherited bone marrow failure syndromes. Rare familial cases of MDS and AML have been reported in families without congenital syndromes who carry germ line predisposing mutations. Examination of families with MDS and AML has led to the detection of several inherited mutations in *RUNX1* or *CEBPA*, and more recently *GATA2*. Here, we report a case of young boy with MDS-AML who carry heterozygous in the *RUNX1* and *GATA2* genes for a rare variant which is never been published before.

Case Report

A 15-year-old Saudi boy not known to have any previous medical illness presented to the emergency department in local

hospital with history of on/off vomiting and prolonged epistaxis for almost 40 minutes' not preceded by any trauma. He did not have bleeding from other sites, no fever or chills, no rash, weight loss or easy fatigability. On presentation he has also revealed history of productive cough for two weeks but no shortness of breath. He had a history of epistaxis since childhood which was never investigated. There was significant family history epistaxis of his grandmother only, no history of bleeding in his siblings or parents or any cousin.

On examination Vital were stable, looking well. No skin rash, pallor, jaundice, no lymphadenopathy or hepatosplenomegaly.

On investigation he had pancytopenia WBCs: 3500/ul, Hb: 93g/l, Platelet: 60,000/ul, Neutrophil 4%, Monocyte 35%, atypical cells 10%. Bone marrow in local hospital revealed hypercellular marrow with trilineage dysplasia, prominent basophilia and Myeloblast 6%. Patient was referred to our

tertiary care center with pancytopenia and peripheral blast of 6%. BM was repeated which revealed atypical monocytosis and significant trilineage dysplasia and 22% blast.

Flow cytometry immunophenotyping performed on the bone marrow aspirate revealed a myeloid blast population that was CD34+partial, CD117+, HL-DR+, CD11b+ CD15 partial+, c-MPO+, CD13+ and CD33+. The flow cytometry supported the diagnosis of acute myeloid leukemia. Cytogenetic analysis performed on fresh bone marrow aspirate revealed 45, XY, -7[20]. FISH was positive for monosomy 7 in 30/100. Based on the morphologic and cytogenetic findings, the patient was diagnosed with acute myeloid leukemia with myelodysplasia related changes. Molecular tests for *FLT3 ITD*, *NPM1*, *CEBPA* and *KIT genes* were negative performed on DNA extracted from fresh bone marrow aspirates. BCR-ABL1 and JAK-2 was also negative. Chromosomal breakage analysis was also negative.

A sample (whole blood) was sent for molecular analysis of MDS/AML Sequencing panel for Next Generation sequence (NGS) to Mayo clinic USA. The result revealed that patient is heterozygous in the *RUNX1* gene for rare variant designated c.611G>A, which is predicted to result in the amino acid substitution p. Arg204Gln. This variant was likely to be primary cause of disease.

This patient is also heterozygous in the *GATA2* gene for a variant designated c.554_628delins 16, which is predicted to result in frameshift and premature protein termination (p.Pro185Leufs*77). To our knowledge this variant has not been reported previously in any patient with autosomal dominant *GATA2*-related disorder but expected to be pathogenic.

The patient was labelled as high risk AML with MDS related changes along with genetic abnormality of *GATA2/RUNX1* variant with monosomy 7. The patient underwent induction with 3+7 (Idarubicin 12mg/m² x 3 days and Cytarabine 100mg/m² x 7 days). Day 14 BM was hypocellular and no residual blast. D+34 bone marrow for remission status confirmed morphological remission without cytogenetic or molecular remission as FISH was positive for monosomy 7. Patient was offered IDAC (Intermediate dose Ara-C) for consolidation to bridge for MUD Allo-SCT. Although it was recommended to confirm the germ line nature of the *GATA2* mutation by submitting additional material such as a skin biopsy or a buccal swab for germline *GATA2* testing, it was not performed due to the patient's poor condition from persistent chronic infection. Other family members declined testing for *GATA2* mutations.

Discussion

Familial syndromes in which MDS/AML is a primary feature include familial platelet disorder with predisposition to myeloid malignancy (FPDMM) associated with germline *RUNX1* mutations characterized by mild to moderate bleeding tendencies and impaired platelet aggregation[1].The incidence of MDS/AML

in patients with *RUNX1* variants is over 40% with wide ranging age of onset from childhood to adults in their 70s. *RUNX1* point mutations in leukemia were first identified in 1999 [2]. Many subsequent studies documented frequent somatic mutations in *RUNX1* in MDS, AML, ALL, and chronic myelomonocytic leukemia (CMML) [3]. Germline mutations of *RUNX1* are associated with familial platelet disorder with associated myeloid malignancy (FPDMM) [4]. The *RUNX1* gene encodes a transcription factor critical for normal hematopoiesis. Causative variants in *RUNX1* are most often missense, nonsense, or frameshift variants resulting in premature protein truncation with possible dominant negative effects. FPDMM (OMIM #601399) is an autosomal-dominant disorder with variable penetrance genetically defined by the presence of germline *RUNX1* mutation. *RUNX1* encodes one of the α subunits of a core-binding transcription factor and plays a critical role in hematopoiesis, myeloid differentiation and platelet function [5]. FPDMM is characterized by abnormalities in platelet number and/or function, namely defective release of δ granules, and a propensity to develop early-onset MDS/AML or, rarely, T-lymphoblastic leukemia/ lymphoma. Until now, about 50 pedigrees with germline *RUNX1* mutations have been reported [6].

The result of NGS of our patient revealed heterozygous in the *RUNX1* gene for rare variant designated c.611G>A, which is predicted to result in the amino acid substitution p. Arg204Gln. This variant has been reported as a germline variant in two families with history of autosomal dominant familial platelet disorder familial platelet disorder that progressed to acute leukemia in some of the family members (aka p.Arg177Gln in Preudhomme et al.PubMed ID: 19357396; Latger-Cannard et al. PubMed ID: 27112265). This variant is likely to be primary cause of disease.

Expression of *GATA2* is significantly higher in AML compared to normal bone marrow and is an adverse indicator of prognosis [8]. Mutations involving *GATA2* coding sequence are not common in sporadic AML cases, and are frequently associated with a more specific subgroup of AML with normal cytogenetics and biallelic *CEBPA* mutations. In these cases, somatic mutation of *GATA2* is likely a secondary event in the leukemogenesis [7,9-11]. However, germline *GATA2* mutations have a very different oncogenic role. Germline *GATA2* mutations are involved in a group of complex syndromes with overlapping clinical features, including a rare genetic disorder called MonoMAC, Emberger syndrome and familial AML following MDS. These diverse syndromes may reflect different clinical manifestations of the common underlying defect of *GATA2* deficiency. MonoMac is a complex congenital immunodeficiency characterized by persistent and profound peripheral monocytopenia, B- and NK-cell lymphocytopenia, near absence of dendritic cells and increased susceptibility to mycobacterium or papilloma virus infections [12-14]. Emberger syndrome is characterized by primary lymphedema inherited in an autosomal dominant pattern [15,16]. Both syndromes are

associated with a predisposition to acute myeloid leukemia and myelodysplastic syndrome. *GATA2* has recently been recognized as a MDS-AML predisposition gene, in addition to the previously reported *RUNX1* and *CEBPA*. Our patient is also heterozygous in the *GATA2* gene for a variant designated c.554_628delins16, which is predicted to result in frameshift and premature protein termination (p.Pro185Leufs*77). To our knowledge this variant has not been reported previously in any patient with autosomal dominant *GATA2*-related disorder but expected to be pathogenic. Similar variants resulting in premature protein termination and located throughout the *GATA2* gene have been reported in several patients with *GATA2* related disorders and predisposition to acute myeloid leukemia (Osterbaard et al., PubMed ID:21892158; Wlodarski et al., PubMed ID: 26702063). The p. Pro185Leufs*77 variant found in the current patient is consistent with being a primary cause of the disease.

Heritable *GATA2* mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia have only been described recently. There is no clear correlation between the genotype and clinical outcome. Based on limited cases reported in the literature, the affected individuals usually have a poor outcome unless successfully transplanted [11,17]. A recent report of *GATA2* p.Thr354Met mutation was observed in a pedigree in which 2 first-degree cousins developed high-risk myelodysplastic syndrome with monosomy 7. A recent study reported six patients who underwent allogeneic stem cell transplant for *GATA2* deficiency had excellent outcomes except one who died from infection [18]. Other anecdotal reports implied a less ideal outcome [17]. It is likely other secondary genetic event such as *ASXL* mutation and loss of chromosome 7 confer a poorer prognosis.

It is important to identify familial cases of AML-MDS and test the heritable mutations. A complete clinical and family history is a clue to recognizing patients with an inherited predisposition to myeloid neoplasm. Germline testing should be considered in a family with more than one close relatives affected by AML-MDS or in patients with early onset disease. A recent study based on large population-based registry data did not show that relatives of patients with AML-MDS are at increased risk of hematologic tumor, but there is a significant increased risk of AML-MDS and other myeloid malignancies among first degree relatives of patients diagnosed at younger than age 21 years [19]. This suggests that young age at the onset of disease is probably the most useful indicator to look for inherited factors in developing AML-MDS. Germline testing should be performed in specimens containing only the nonleukemic cells such as skin fibroblasts. Buccal swab or saliva samples are acceptable; though these may contain lymphocytes derived from hematopoietic stem cells. The detection of an underlying germ line mutation has significant implications for clinical practice. Due to the poor outcomes in the reported AML cases with *GATA2* mutations, aggressive and early intervention such as allogeneic stem cell transplant

should be considered. Family members with identified germline mutations should be avoided as stem cell donors. Although there is no direct data, family members under consideration for being HSCT donors should be tested to exclude mutations in the same predisposition gene, due to the theoretical risk of developing AML in the future from the graft with the same mutation.

Conclusion

In addition to *RUNX1* and *CEBPA*, *GATA2* gene mutations have only been recently reported involved in familial AML-MDS. Here we reported heterozygous *RUNX1* gene variant and very rare heterozygous *GATA2* gene variant which is never published previously in any patient with autosomal dominant *GATA2* related disorder. Heritable gene mutations as a predisposition gene to AML-MDS are likely under recognized but have significant implication in managing the patients and the affected families. It is important to recognize this rare entity, be familiar with the clinical features, and seek appropriate laboratory testing when there is a clinical concern. This rare entity recognizes that patient should be undergoing Allo-SCT as soon as possible.

Informed Consent

Written informed consent was obtained from the patient's next kin for publication of this case report and any accompanying images.

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DOI: [10.19080/OABTJ.2018.02.555590](https://doi.org/10.19080/OABTJ.2018.02.555590)

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