First Report of Myeloid Malignancies in Patients with Biallelic MYSM1 Variants: A Series of Seven Cases

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Introduction

MYSM1, located on chromosome 1p32.1, encodes histone H2A deubiquitinase, a transcription regulator involved in DNA damage response. Biallelic MYSM1 variants are linked to rare bone marrow failure syndrome. progressing into myeloid malignancies (MM) has not been descried before.We report seven cases of MYSM1 mutations progressing from marrow failure to MM.

Aim

To describe the clinical, genetic, and hematologic spectrum of MYSM1-associated bone marrow failure and highlight its progression to myeloid malignancies, along with treatment outcomes.

Methods

Clinical data was extracted from the KFSH-Riyadh Inherited Marrow Failure Registry. Whole exome sequencing was performed to identify causative mutations.

Summary

This series of seven Arab patients with biallelic MYSM1 mutations demonstrates early-onset marrow failure, immunologic abnormalities, and progression to MDS/AML in adolescence. Genetic heterogeneity and clonal evolution were observed, underscoring the need for surveillance and HSCT for progressive disease or malignancy.

References

1- A histone H2A deubiquitinase complex coordinating histone acetylation and H1 dissociation in transcriptional regulation. *Molecular cell*

2- MYSM1 is mutated in a family with transient transfusion-dependent anemia, mild thrombocytopenia, and low NK-and B-cell counts. *Blood*

Results

Seven consanguineous Arab patients carried biallelic MYSM1 mutations with c.1168G>T (p.Glu390Ter) being the main mutation while two additional novel mutations were c.1219G>C p.Glu407Gln and c.1561C>Tp.Gln521Ter which resulted in anemia and early childhood bone marrow failure. The median age at diagnosis was six months. Non-hematological feature includes, facial dysmorphism and heart issues with atrial septal defect and developed Caffey disease . Immunological abnormalities such as hypogammaglobulinemia and lymphocyte subset deficiencies were also noted

Although myeloid malignancies have not been previously reported ,these patients progress to MDS or AML 10–12 years since initial presentation. These patients manifested different degrees of BMF, transfusion dependency, MM transformation; 4 developed hypoplastic MDS, whereas one evolved into MDS/AML. Initially transfusion-dependent during childhood, the patients showed spontaneous improvement before becoming transfusion-dependent again around ages 9–10, suggesting clonal evolution.

Genetic mutations including TP53 and CALR , monosomy 7, 5q deletion and der(19)t(1;19) were identified, highlighting the heterogeneity of MYSM1-related disorders. These alterations likely modulate the clinical progression, as reflected by the variability in disease severity and treatment outcome. HSCT has been performed for progressive BMF , transfusion dependency and MM with adverse cytogenetics. 3 patients with MDS successfully underwent haploidentical HSCT.

Discussion/Conclusion

This case series underlines the phenotypic and genetic complexity of MYSM1-associated BMF. However, careful follow-up with bone marrow biopsy and cytogenetic should be done to detect any MM transformation . HSCT remains critical to attain durable remission. further research are required for refinement of management strategies and to define long-term outcomes.