A Novel Germline Splice Site DDX41 Mutation Causing MDS/AML

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Introduction

Myelodysplastic syndrome (MDS) is a myeloid neoplasm characterised by cytopenias, morphologic dysplasia and risk of progression to acute myeloid leukaemia (AML).

DDX41 has recently emerged as an important gene in familial myeloid malignancies, causing a late-onset MDS/AML with autosomal dominant inheritance[1]. Here we describe a novel germline DDX41 mutation in a patient with MDS/AML.

Case report

A 56-year-old previously well man presented with fatigue, and was found to be neutropenic and thrombocytopenic (see Table 1). Previous investigations identified mild thrombocytopenia at the age of 52. A strong family history of solid organ malignancy, particularly breast and lung cancers, was noted.

Bone marrow biopsy demonstrated morphologic dysplasia and 7% blasts, and a diagnosis of MDS with excess blasts (MDS-EB1) was made. Five months later, a repeat bone marrow biopsy was performed, and demonstrated an increased blast count of 25%, consistent with progression to AML.

	Age 52	Age 56 (Diagnosis of MDS)	Age 56 (Diagnosis of AML)
Haemoglobin (g/L) [ref 130-180]	154	132	138
MCV (fL) [ref 80-100]	87	91	90
Neutrophils (x10^9/L) [ref 2.5 – 7]	2.6	0.8	0.8
Platelets (x10^9/L) [ref 150 – 400]	143	115	113

Table 1. Full blood count results

The patient received induction chemotherapy and an allogeneic stem cell transplant with a matched unrelated donor, achieving complete morphological remission.

References [1]Richards et al. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med;17(5): 405-424. [2]Sebert et al. (2019) Germline DDX41 mutations define a significant entity within adult MDS/AML patients. Blood 134 (17): 1441-1444 [3]Berger et al. (2017) Re-emergence of acute myeloid leukemia in donor cells following allogeneic transplantation in a family with a germline DDX41 mutation. Leukemia (2017) 31, 520–522

Molecular and cytogenetic testing

Cytogenetics: No cytogenetic abnormality detected.

Molecular: A germline splice site variant (c.27+1G>A) was detected in DDX41 (NM_016222.2) (Fig. 1a). This variant occurs at the splice donor site of the exon 1/intron 1 boundary and is predicted by in silico tools to result in abnormal splicing. This variant has not been previously reported in population databases (gnomAD), relevant disease-specific databases or the literature. This variant was classified according to ACMG guidelines[2] and was assigned a “likely pathogenic” classification.

Additionally, a low level somatic ‘second hit’ mutation (R525H) was identified (Fig. 1b), consistent with previous observations that a second DDX41 mutation is the most frequent somatic alteration identified in this cohort of patients[1].

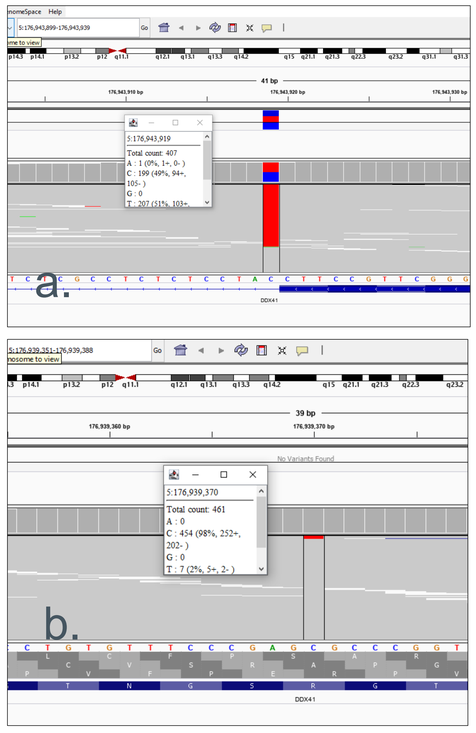

Figure 1a. Next generation sequencing data. Germline DDX41 c.27+1G>A with variant allele frequency (VAF) of 49% 1b. Somatic DDX41 R525H with VAF 2%

Conclusion

We describe a novel germline mutation in DDX41 causing MDS/AML, and demonstrating recently-appreciated typical features of DDX41 disease including late-onset, preceding cytopenias, normal cytogenetics, and a somatic second-hit DDX41 mutation. Due to longer latency, the familial nature of DDX41-associated MDS/AML is likely under-recognised as it presents at similar age to de novo cases. Nonetheless, recognition is critical for optimising management, including;

- genetic counselling/testing of at-risk family members.
- screening of any potential related stem cell donors prior to transplant in order to avoid donor-derived leukaemia, an increasingly appreciated risk in germline haematological disease[3].