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ICUS to ICU: A Case of a Germline DDX41 Mutation in a Patient with Idiopathic Cytopenia of Undetermined Significance (ICUS)

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ABSTRACT

Genetic testing for both somatic and germline mutations is a crucial component of the modern workup of cytopenia, myeloid neoplasms, and bone marrow failure syndromes. However, the specific genes tested in each clinical scenario are continually evolving, making standards for genetic testing a moving target. Germline mutation of the DDX41 gene is associated with familial acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), but its role in idiopathic cytopenia of undetermined significance (ICUS) is less clear. We present the case of a 65-year-old male with a history of rheumatoid arthritis (RA) found to have ICUS with a germline DDX41 mutation. The patient's cytopenia was long-standing, present at least 3 years prior to initiation of immunosuppression for his RA. Two months after his initial hematologic evaluation, the patient was admitted to the ICU for neutropenic enterocolitis. The patient was severely neutropenic and required a right hemicolectomy. Subsequent workup revealed a pathogenic germline DDX41 mutation. A repeat bone marrow biopsy 8 months later was consistent with MDS/AML as defined by the 2022 International Consensus Classification Guidelines. This patient, asymptomatic for years, went through an ICU admission and emergent surgery due to neutropenic enterocolitis before his germline DDX41 mutation was discovered. Expanded guidelines regarding somatic and germline genetic testing will likely prove helpful in delineating the etiology of ICUS and initiating early management in the future.

Keywords: DDX41, idiopathic cytopenia of undetermined significance, genetic testing, germ-line mutation, myelodysplastic syndrome

INTRODUCTION

Hematologic malignancies vary significantly in course, from indolent to rapidly destructive disease. It is estimated that 5-10% of cancers are driven by inherited mutations, and in recent years, there has been a broad effort to stratify the risk of aggressive malignancies in relation to their genetic profile.[1] One gene implicated in the development of neoplasms is the DEAD-box helicase 41 (DDX41), an RNA helicase expressed ubiquitously in human bone marrow.[2] Germline mutations of DDX41 are associated with autosomal dominant familial syndromes of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).[3-8] Currently, there is guidance regarding specific genes for somatic and germline testing in the workup of MDS and AML.[9,10] National Comprehensive Cancer Network (NCCN) Guidelines recommend observation once annually in patients with Idiopathic Cytopenia of Undetermined Significance (ICUS);[9] however, the optimal approach to the genetic workup is unclear.

The diagnostic criteria for ICUS include the presence of peripheral cytopenia, absent or mild dysplasia (<10%), blast cells <5%, and otherwise not meeting MDS criteria.[11,12] The clinical course can involve evolution from an initial cytopenia of one or more cell lines, which is then further defined by genetic analysis to determine clonality. Approximately 40% of ICUS cases are determined to derive from clonal somatic mutations, i.e., representing clonal cytopenia of undetermined significance (CCUS).[11-13] Alternatively, ICUS patients

and their family members may have a germline mutation increasing the risk of neoplasm, i.e., hereditary myeloid malignancy predisposition syndromes (HMMPS).[14] However, only a subset of these patients will progress to MDS or AML.[15] We present a case of ICUS with a germline DDX41 mutation leading to hospitalization in the ICU, with eventual progression to malignancy, and explore the implications of germline testing.

CASE PRESENTATION

A 66-year-old male with seropositive rheumatoid arthritis (RA) and heavy alcohol use was referred to our hematology office with leukopenia. His RA was previously treated with sulfasalazine, but it was discontinued due to leukopenia. He was subsequently started on hydroxychloroquine with persistent leukopenia. On chart review, his leukopenia predated sulfasalazine by at least 3 years. He drank 14 units of alcohol weekly. The patient had no personal history of major infections or hematologic/oncologic disease, but his family history was significant for lymphoma in his father. The physical exam was unremarkable without splenomegaly. Recent labs showed a leukocyte count (WBC) of 1.7k/µL (normal 3.6 – 10.7k/µL) with an absolute neutrophil count (ANC) of 680/µL (normal 2500 – 7000 cells/µL). He was mildly anemic with a hemoglobin of 12.2 g/dL (normal 13.2 – 16.6 g/dL), and his platelet count was normal. The peripheral smear showed severe leukopenia with absolute mature neutropenia and absolute lymphopenia; blasts and dysgranulopoiesis were not identified.

Our initial impression was that his cytopenia was likely related to an autoimmune process, given his history of RA. Other differential diagnoses included Felty syndrome, which was felt to be less likely in the absence of splenomegaly or infectious complications. Large granular lymphocytic (LGL) leukemia was also felt to be unlikely, given the isolated leukopenia without LGL cells on peripheral smear. MDS was also considered; however definitive diagnosis would require a bone marrow biopsy, and there was reluctance to perform testing while clinically asymptomatic. The patient was advised to follow up with hematology if his leukopenia worsened or if he developed infectious complications.

Two months after his hematologic assessment, the patient presented to the emergency department with a fever and abdominal pain. He was admitted to the ICU with neutropenic enterocolitis. His WBC count on admission was 1.2 K/µL with an ANC of 638/µL. Computed tomography of his abdomen showed inflammatory changes of the ascending and proximal transverse colon. The patient underwent an exploratory laparotomy, which revealed impending hepatic rupture, so a right hemicolectomy was performed (Fig. 1). Given his hemodynamic instability and severe neutropenia with nadir ANC of 270/µL, he was treated with a single 480 mcg dose of TBO-Filgrastim. His WBC count gradually improved to 2.4 K/µL with an ANC of 1505/µL. On discharge, the patient was started on pegfilgrastim as needed for ANC <1000/µL.

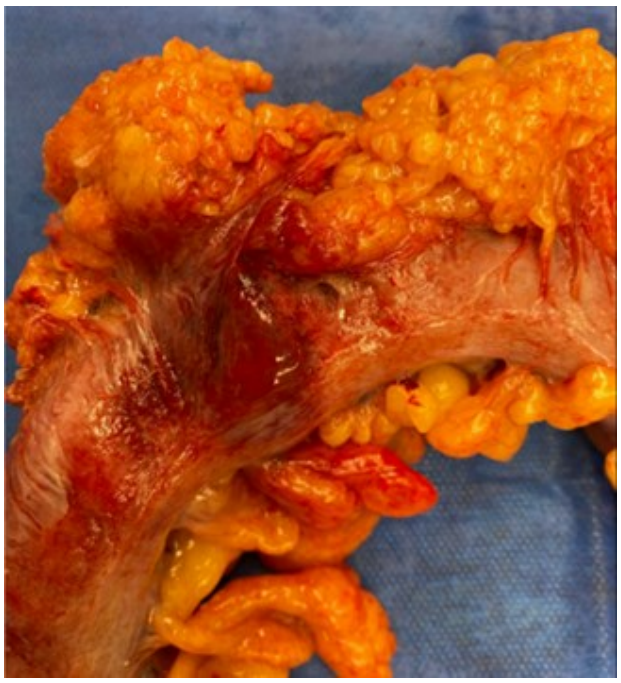

Figure 1. Ischemic Changes of Hepatic Flexure

An outpatient bone marrow biopsy was performed 16 days after his initial TBO-Filgrastim dose, revealing normocellular marrow with increased myeloblasts at 6-8% of total cellularity (Fig. 3). His karyotype and extended panel fluorescence in situ hybridization (FISH) for MDS were normal (Table 1). Next-generation

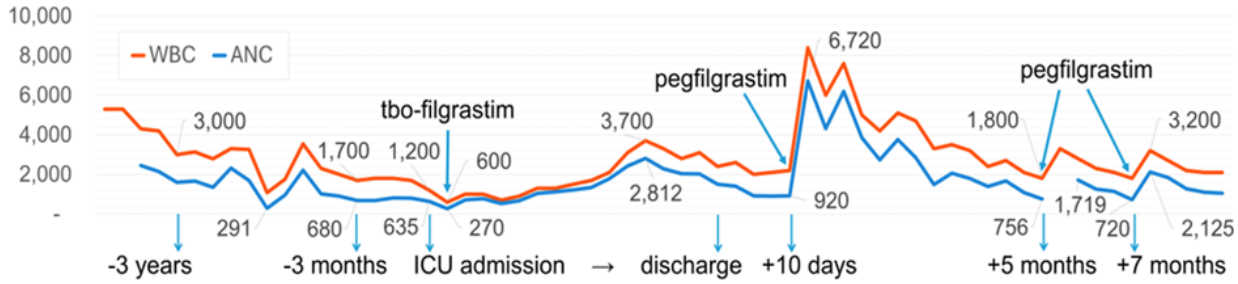

Figure 1. White Blood Cell (WBC) Count and Absolute Neutrophil Count (ANC) Trend.

Genes assessed by NGS DNA	NGS Results	FISH Probes	FISH Results
ASXL1, BCOR, BCORL1, BRAF, CALR, CBL, CEBPA, CUX1, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, HRAS, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NF1, NPM1, NRAS, PDGFRA, PHF6, PPM1D, PTEN, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TET2, TP53, U2AF1, WT1, ZRSR2	DDX41: c.3G>A/ p.M1? VAF: 49%	+19, chromosome 20, 5q-/-5/ +5, 7q-/-7, p53(17p13.1)/NF1 (17q11), ETV6(12p13), KMT2A (MLL) (11q23), RPN/MECOM (3q)	No alterations

Table 1. Initial Bone Marrow Biopsy DNA Next Generation Sequencing + FISH Probe

Genes assessed by NGS DNA	Genes assessed by NGS RNA	NGS Results
ABL1, ASXL1, BCOR, BCORL1, BRAF, CALR, CBL, CDKN2A, CEBPA, CSF3R, CUX1, DDX41, DNMT3A, EED, ETNK1, ETV6, EZH2, FBXW7, FLT3, GATA1, GATA2, GNAS, IDH1, IDH2, IKZF1, JAK2, JAK3, KDM6A, KIT, KMT2A, KRAS, LUC7L2, MPL, MYD88, NF1, NOTCH1, NPM1, NRAS, PAX5, PHF6, PIGA, PPM1D, PRPF8, PTEN, PTPN11, RAD21, RIT1, RUNX1, SETBP1, SF3B1, SH2B3, SMC1A, SMC3, SRSF2, STAG2, STAT3, STAT5B, SUZ12, TET2, TP53, U2AF1, WT1, ZRSR2	ABL1, ABL2, AFDN (MLLT4), ALK, BCL11B, BCL2, BCL3, BCL6, BCR, BIRC3, BLNK, CBFB, CBL, CCND1, CCND2, CCND3, CD274, CD28, CDK6, CDKN2A, CEBPA, CEBPD, CEBPE, CEBPG, CHD1, CHIC2, CIITA, CREBBP, CRLF2, CSF1R, CTLA4, DEK, DGKH, DUSP22, EBF1, EIF4A1, EPOR, ERG, ETV6, FGFR1, FLT3, FOXP1, GLIS2, HLF, ID4, IKZF1, IKZF2, IKZF3, IL2RB, IRF4, IRF8, ITK, JAK2, KAT6A, KLF2, KMT2A, LMO1, LMO2, LYN, MALT1, MECOM, MEF2D, MLF1, MLLT10, MRTFA (MKL1), MUC1, MYC, MYH11, NF1, NFKB2, NOTCH1, NTRK3, NUP214, NUP98, NUTM1, P2RY8, PAG1, PAX5, PBX1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PICALM, PML, PRDM16, PTK2B, RARA, RBM15, ROS1, RUNX1, RUNX1T1, SEMA6A, SETD2, STIL, SYK, TAL1, TCF3, TFG, TLX1, TLX3, TP63, TSLP, TYK2, VAV1, ZCCHC7, ZNF384	CUX1: c.2093_2094delCT/ p.T698Sfs*16 VAF: 4.9% DDX41: c.3G>A/p.M1? VAF: 18.7%

Table 2. Second Bone Marrow Biopsy DNA and RNA Next Generation Sequencing

sequencing (NGS) revealed a pathologic DDX41 mutation ((c.3G>A (pM1?)) eliminating the protein start site. The variant allele frequency (VAF) was 49.3%, suggestive of a germline mutation, which was later confirmed with germline testing. The second copy of DDX41 remained intact. Importantly, the germline DDX41 mutation did not define clonality in his cytopenia.

This DDX41 germline mutation was consistent with a familial MDS/AML predisposition syndrome. A repeat bone marrow biopsy 8 months later revealed an increase in myeloblasts to 12% with immunostain for CD34 immature cells representing 10-15% of cellularity. These results were interpreted as consistent with MDS/AML, as defined by the 2022 International Consensus Classification Guidelines.[16] Repeat NGS also identified a CUX1 mutation (c.2093_2094delCT/p.T698Sfs*16), which was not observed in the patient's original BMB (Table 2). The patient was placed on danazol for treatment and continues to follow up with his hematologist/oncologist.

DISCUSSION

Longitudinal data focusing on the evolution of ICUS to MDS or AML in patients with germline DDX41 mutations is limited, in part because separate somatic mutations are often identified after progression has occurred and, therefore, are no longer categorized as ICUS. Presumably, in such scenarios, a CCUS state of unclear duration occurred prior to progression to MDS or AML. In this case, the patient met the criteria for classification as MDS/AML, which is an overlap disorder defined as displaying one or more cytopenias with 10-19% blasts on BMB with myelodysplasia-related gene mutations.[16] It is also possible that this ICUS patient with a DDX41 germline mutation, notably

without clonal changes identified on workup, could have an unidentified somatic mutation driving disease progression. Patients with hematologic malignancy and germline DDX41 mutations frequently have accompanying somatic mutations, including a second somatic DDX41 mutation, TET2, SRSF2, DNMT3A, ASXL1, or CUX1.[17,18] This patient was discovered to have a presumably somatic CUX1 mutation with VAF of 4.9% on his second BMB that was not present on initial BMB. Of note, a recent prospective study found that patients with CCUS with negative initial NGS were found to have DDX41 mutations on extended sequencing, implying this may be an under-identified driver of disease.[17]

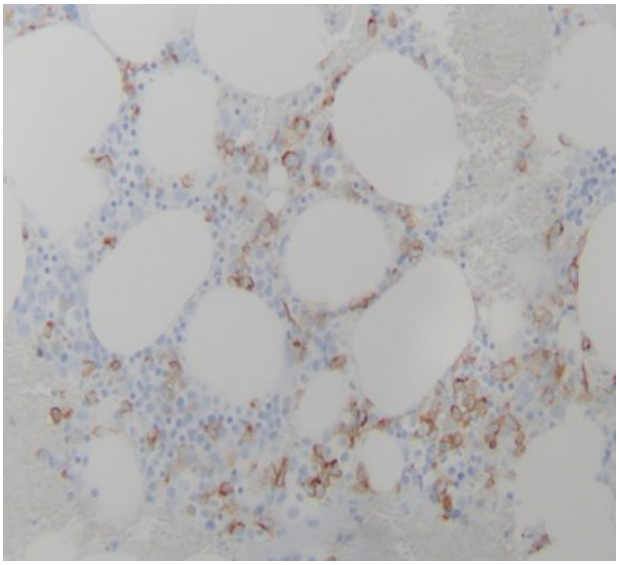

Figure 3. CD34 Immunostain of bone marrow displaying blast cells

In this case of ICUS, a germline DDX41 mutation was confirmed, but only one mutated allele was identified. It is likely that this patient's lifelong haploinsufficiency was sufficient to predispose this patient to developing MDS. Another possibility is that the intact allele's transcription or function could have been altered, resulting in altered activity. Noting the patient's CUX1 mutation identified on the second NGS, which was not present originally, it is also possible this could have been the driver of malignant evolution. Unlike the classic progression from ICUS to CCUS and then MDS or AML, this patient was not identified to have CCUS and instead progressed directly from ICUS to MDS/AML.

In patients with hematologic congenital syndrome/ disorder, including DDX41 mutations, the odds ratio of malignant transformation compared to those without the genetic abnormalities was 5.58.[5] Another recent study found that 60% of ICUS patients with a germline DDX41 mutation progressed to MDS, suggesting a HMMPS.[4] DDX41 germline mutated myeloid neoplasms are associated with more severe bone marrow failure, higher risk disease, and increased risk of progression to AML compared to those with purely somatic mutations,[5] although there is no significant change in overall survival.[4,5] While there appears to be a more severe risk profile associated with germline mutated DDX41 myeloid neoplasm, it has also displayed an improved response to treatment and prolonged relapse-free survival compared to wild-type DDX41 in AML.[6,19]

While guidelines for the workup of MDS and AML increasingly call for both germline and somatic mutation analysis,[7-10] guidelines are lacking when it comes to the workup of patients with ICUS. The efficacy of next-generation sequencing in the assessment of myeloid neoplasms has been well established.[20] With the risk of severe disease progression and the efficacy of NGS assessment, ICUS and CCUS present strong opportunities for establishing more advanced testing guidelines. One expansion to aid clinical decision-making supported by this case and recent literature[15] would be the inclusion of DDX41 as a standard in NGS for ICUS and CCUS, as it is already included in MDS and AML workup. When identifying contributing germline mutations in ICUS, patients and their families would receive a diagnosis earlier, which would improve monitoring and registry enrollment.

CONCLUSION

ICUS presents a diagnostic challenge given the paucity of guidelines for genetic analysis and the possibility of an underlying HMMPS. Germline DDX41 mutations are associated with higher risk of progression to MDS and more severe disease such as AML, however systemic therapy improves the clinical course. DDX41 is an optimal candidate to be included in standard NGS panels for ICUS to accelerate diagnosis of HMMPS. Future studies should focus on the optimal timeline for genetic testing and further define criteria for risk stratification in ICUS germline DDX41 mutations.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.