Synchronous Cancers: Acute Myeloid Leukemia and Pancreatic Ductal Adenocarcinoma with Germline Heterozygous DDX41 and MUTYH Mutations in a Patient from Appalachia, United States

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Abstract

A diagnosis of synchronous cancers within the same individual poses a multitude of diagnostic and treatment-related challenges. Many of these challenges pertain to the vast heterogeneity in cancers and presentations, patient ineligibility for clinical trials, lack of standardized guidelines to direct management and an incomplete understanding of the molecular mechanisms that contribute to the development of these cancers. We present a case of concurrent diagnoses of Pancreatic Ductal Adenocarcinoma (PDAC) and Acute Myeloid Leukemia (AML) with a comprehensive mutational analysis of the pancreatic tumor, AML blasts, and germline DNA collected from cultured skin fibroblast samples. In addition to some commonly detected mutations (e.g. KRAS Gly12Asp in PDAC and TP53 Met237Ile in AML), the genetic testing revealed the presence of DDX41 and MUTYH gene mutations in both germline DNA and tumor tissue specimens. This case underscores the importance of addressing the interplay of genetic, lifestyle and environmental factors in the development of synchronous cancers in an individual, and only by doing so, evidence-based guidelines for early detection and management may be developed.

Keywords: Synchronous cancers • Acute myeloid leukemia • Pancreatic cancer • Hereditary • Genetic• Molecular • DDX41• MUTYH • DDX41 mutated AML

Introduction

Synchronous cancers, also referred to as multiple primary malignancies, are defined as two or more separate cancers that are diagnosed in the same individual within a relatively short period of time, typically within 6 months of each other; however, the precise time frame remains controversial, ranging between 1 month-6 months [1-4]. Synchronous cancers were reported to be rare, occurring in 1.1%-10% of patients with cancer [5-7]. However, as a result of improved techniques for early cancer detection, synchronous cancers are being diagnosed more often, raising concern that they be more common than previously thought [8]. In addition, a diagnosis of synchronous cancers poses significant diagnostic and treatment-relatedchallenges as clinicians contend with the most optimal approach to managing each cancer. Given the marked disease heterogeneity and patterns of synchronous cancer presentations, there are no guidelines or established standards of care for such patients [2,7]. Furthermore, the presence of concurrent malignancies is a universal exclusion criterion for clinical trials, thereby rendering it even more challenging to offer these patients specific therapies. The overall prognosis for such patients varies based on the types of cancers present, molecular features, and stage [3,5,6].

The molecular and genetic underpinnings of synchronous cancers are not well understood [9,10]. Nevertheless, in the era of routine next-generation sequencing on tumor tissue for nearly all cancers, the biology and mutational profiles of many malignancies has become more elucidated, allowing for refined prognostication and staging as well as for the development of more targeted treatments across a broad range of cancer types [11]. Additionally, increased awareness and recognition of hereditary cancer syndromes has led to advances and increased uptake of germline DNA testing in search of hereditary genetic alterations [12-16].

Herein, we report a rare presentation of a patient with synchronous Acute Myeloid Leukemia (AML) and pancreatic adenocarcinoma showing genetic alterations involving DDX41 and MUTYH genes in tumor tissues and from cultured skin fibroblasts.

Case Presentation

A 68-year-old man with hypertension, type 2 diabetes mellitus, gout and a remote history of secondary polycythemia that resolved after smoking cessation presented to his primary care provider with symptoms of a 40-lb unintentional weight loss over three months, persistent belching, worsening gastroesophageal reflux, nausea with vomiting, and abdominal pain. His complete blood count showed pancytopenia with a white blood cell (WBC) count of 2.6 x 10^9/L, hemoglobin 12.7 g/dL, and platelet 109 x 10^9/L. A diagnostic Computed tomography (CT) scan of the abdomen and pelvis showed a 3.4 cm mass involving the head and uncinate process of the pancreas obstructing the pancreatic duct. Adjacent borderline enlarged superior retroperitoneal lymph nodes were also observed. The patient was admitted to hospital after developing symptoms of biliary obstruction.

He underwent Endoscopic Retrograde Cholangiopancreatography (ERCP) and common bile duct stent placement with resolution of obstruction. Pathology from the ERCP confirmed invasive Pancreatic Ductal Adenocarcinoma (PDAC). Staging scans determined no evidence of distant

metastatic disease. His baseline CA19-9 was 170.8 U/mL (upper limit of normal, 37 U/mL). His clinical stage based on radiologic findings was clinical stage IIB, cT2 cN1 M0. Viral serologies for hepatitis B and C and HIV were negative. Of note, his family history was significant for early onset colon cancer in his mother and maternal uncle (Figure 1).

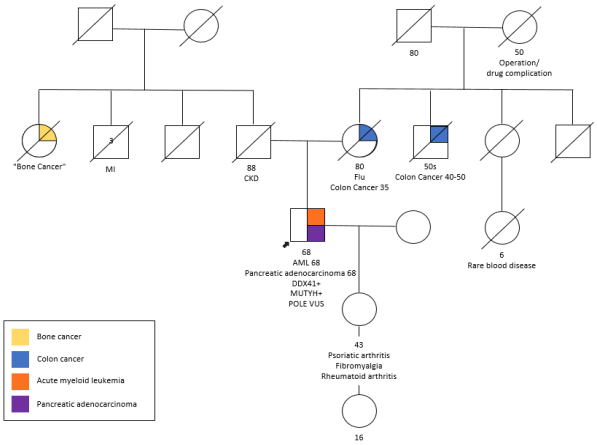

Figure 1. Patient pedigree.

Due to persistent pancytopenia, he underwent a bone marrow aspiration and biopsy and was found to have AML with 40% marrow cellularity and 25%-30% myeloid blasts that, by flow cytometric analysis, expressed CD34, CD117, CD33, CD13, and HLA-DR (Figures 2-5).

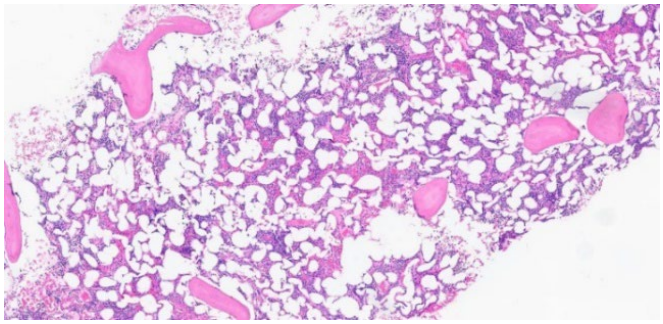

Figure 2. Bone marrow core biopsy, Hematoxylin and Eosin (H&E) stain, 5X magnification.

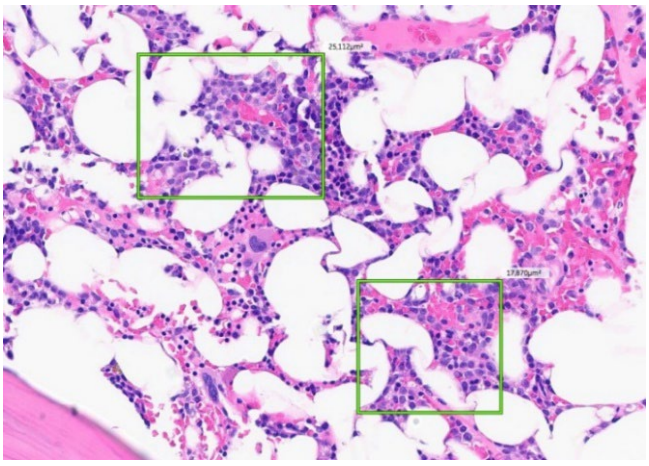

Figure 3. Bone marrow core biopsy, H&E, 20X magnification, highlighting clusters of immature-appearing cells.

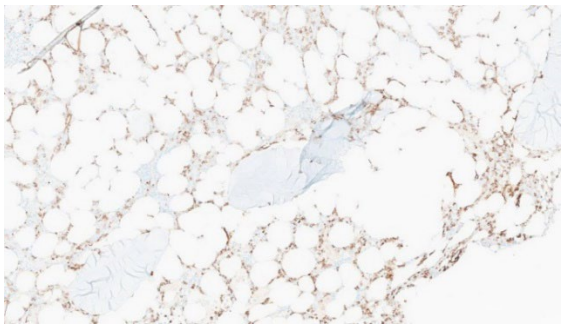

Figure 4. Bone marrow core biopsy, CD34 immunohistochemical stain, 10X magnification, highlighting increased CD34-positive blasts.

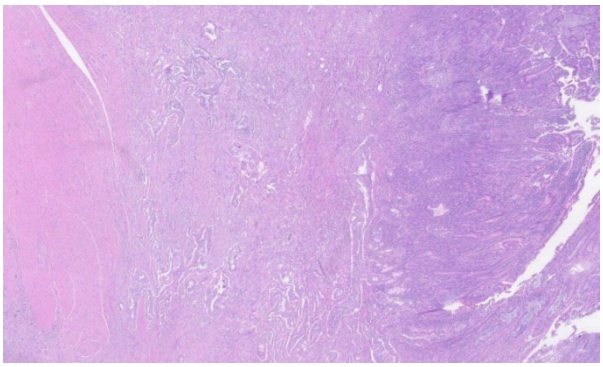

Figure 5. Representative pancreatic adenocarcinoma, H&E stain, 2X magnification, highlighting duodenal invasion.

Fluorescence In Situ Hybridization (FISH) showed monosomy 5. Chromosome analysis revealed an abnormal male karyotype (45, XY, der (5;18) (p10; q10) [17] /46, XY [4]) resulting in 5q and 18p deletions. His marrow was also notable for genomic alterations involving three pathogenic variants identified by Next Generation Sequencing (NGS) analysis, including DDX41 c.3G>A p. Met1? with a Variant Allele Frequency (VAF) of 29%, DDX41 c.1589G>A p. Gly530Asp with a VAF of 9%, and TP53 c.711G>T p. Met237Ile with a VAF of 19% (Table 1). The panel included analysis of the following genes: ABL1, ANKRD26, ASXL1, ATRX, BCOR, BCORL1, BRAF, CALR, CBL, CCND2, CDKN2A, CEBPA, CSF3R, CUX1, DNMT3A, ETNK1, ETV6, EZH2, FBXW7, FLT3, GATA2, HRAS, IDH1, IDH2, JAK2, KDM6A, KIT, KMT2A, KRAS, MAP2K1, MPL, MYD88, NF1, NPM1, NRAS, PDGFRA, PHF6, PTEN, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, TET2, U2AF1, WT1, and ZRSR2.

Table 1. Detected genetic alterations in cultured skin fibroblasts, pancreas, and AML samples.

Gene Alteration	Fibroblasts	PDAC	AML
DDX41 c.3G>A p.Met1?	+	+	+
MUTYH *c.1187G>A p.Gly396Asp/ c.1178G>A p.Gly393Asp (Exon 13)	+	+	
DDX41 c.1589G>A p.Gly530Asp			+
TP53c.711G>T p.Met237Ile			+
KRAS c.35G>A p.Gly12Asp (Exon 2)		+	
MUTYH c.1178G>A p.Gly393Asp (Exon 13)		+	
Abbreviations: AML, Acute Myeloid Leukemia; PDAC, Pancreatic Ductal Adeno Carcinoma			

*This is the same variant but denoted differently due to nomenclature differences between the germline and pancreatic tumor variants and different reference protein-coding transcripts (NM_001128425.1 and NM_0122222, respectively).

Germline genetic sequencing performed on fibroblasts showed DDX41 c.3G>A p. Met1. Pathogenic variant (heterozygous), MUTYH c.1187G>A p.Gly396Asp pathogenic variant (heterozygous), and POLE c.2182C>T p.Arg728Trp variant of Uncertain Significance (VUS) (heterozygous).

Since the patient's PDAC was deemed resectable, and his blood counts, particularly platelets, remained stable for safe surgical intervention, immediate treatment for AML was not warranted and he subsequently underwent pancreatic oduodenectomy with lymph node dissection. Pathology revealed moderately to poorly differentiated adenocarcinoma, 2.3cm in size, arising in the pancreas and invading the duodenum and peripancreatic tissues, with negative margins, but positive for lymphovascular and perineural protein-coding invasion (Figure 2D). Twelve lymph nodes were negative for involvement with PDAC. His final pathological stage was IB, pT2 pN0 M0. Genetic testing on pancreatic tissue did not show microsatellite instability-high or mismatch repair-deficient PDAC. Additionally, several mutations were detected on molecular genomic tumor testing including, KRAS p. Gly12Asp (Exon 2) with a VAF of 11%, MUTYH p. Gly393Asp (Exon 13) with a VAF of 48%, CAPZA2: MET fusion, DDX41 p. Met1? And several variants of Uncertain Significance (VUS) including CKD12 p. P1409R, IL10 p.R177Q, KDR p.R347H, POLE p.R728W, SRC p.Y232C, and YES1 p.S65F. No pathogenic alterations were found in the remaining disease-relevant genes, including ALK, BRAF, BRCA1, BRCA2, ERBB2, FGFR2, MLH1, MSH2, MSH6, NRG1, NTRK1, NTRK2, NTRK3, PALB2, PMS2, RET, and ROS1.

The patient is planning to start palliative treatment for his poor-risk AML with a DNA-methyl transferase inhibitor with or without Bcl-2 inhibitor therapy following his post-surgical recovery. His daughter and granddaughter were recommended for genetics counseling given his germline DNA mutation analysis.

Discussion

The patient described above illustrates a case of synchronous cancers with one being hematologic and the other involving a solid organ, which in and of itself is uncommon as most patients with synchronous cancers are reported to have two solid organ malignancies, often involving the same anatomical region [2,4,5]. Rarely, a few articles reported on "blood-solid tumor" or "blood-blood" synchronous cancers [17-19]. Here, we present a unique management challenge since AML and PDAC are both aggressive cancers, and each, independently, associates with a poor prognosis [16,20-22]. Based on short prospective longitudinal monitoring of the WBC, hemoglobin, platelet as well as blast counts, we elected not to treat his AML and focus on surgical intervention as the initial management approach. We discussed neoadjuvant therapy for PDAC; however, we thought administration of conventional cytotoxic chemotherapy would result in severe myelosuppression causing hemorrhagic and infectious complications that would ultimately preclude him from receiving potentially curative surgery for PDAC. Fortunately, this patient was able to undergo a successful surgical resection and experienced no AML-associated complications in the peri- or post-operative setting.

The major novelty of this case relies on the information from the NGS studies of three different tissue types; two synchronous cancers including a bone marrow sample for AML and pancreatic tissue for PDAC, and one non-malignant tissue (skin fibroblast culture) [9,23,24]. Guidelines for identifying individuals who are at risk for hereditary hematologic genetic syndromes remain unclear whereas such guidelines for identifying at-risk individuals with PDAC are better defined and multiple associated hereditary susceptibility syndromes are described [25,26]. Genetic testing strategies for PDAC can be carried out with accuracy through traditional blood or saliva testing modalities. In contrast, genetic testing in AML patients can prove logistically challenging as a skin punch fibroblast sample is warranted for confirming the diagnosis of a germline mutation. Multiple susceptibility genes in hereditary hematologic cancers, including ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1, and TP53, and several genes associated with dyskeratosis congenita and telomere disorders have been reported. The patient reported here was found to have three germline genetic variants on all tissues, the most striking being DDX41 p. Met1? and MUTYH p. Gly393Asp as well as several somatic mutations on neoplastic tissues [27].

While the exact incidence of hereditary cancer syndromes in hematologic malignancies remains unclear, recent reports suggest that germline pathogenic mutations in DDX41 account for up to 3% of all myeloid neoplasms. DDX41-related familial hematologic cancer susceptibility syndrome is associated with an increased risk for myeloid neoplasms typically Myelodysplastic Syndrome (MDS) and AML [28,29]. Clinical characteristics of patients with DDX41-mutated MDS/AML include a mean age at presentation of 66 years, male predominance (ratio of 3:1), hypo cellular bone marrow with erythroid dysplasia, a normal karyotype, and a better prognosis in patients who harbor no additional poor risk genomic anomalies [24,28-33]. Only 27%-39% of those with a DDX41-related myeloid neoplasm have a documented family history of a hematologic malignancy [24,28,31]. Suggesting a wide variation in penetrance. Haploinsufficient DDX41 expression has also been described as having a key role in those with germline DDX41 mutation-associated myeloid neoplasms [33].

The DDX41 gene is located on chromosome 5q35 and is a putative tumor suppressor gene [33]. DDX41 germline mutations have an autosomal dominant pattern of inheritance and have not been reported as de novo in origin. Co-occurring somatic mutations are identified in more than half of the cases of germline DDX41-mutated MDS/AML, with the most common concomitant somatic DDX41 variant, detected in 80% of cases, being p. Arg525His [24,28,29,33]. The truncating DDX41 c.3G>A, pMet1? start-loss allele has been reported only as a germline pathogenic variant, and as was detected (VAF 29%) in the patient reported here, this specific variant is often reported at a VAF of approximately 30% due to a common population polymorphism in the PCR primer binding region which decreases primer binding. Of note, the DDX41 c.3G>A, p. Met1? variant is more common among those of Northern European descent [29].

The patient's concomitant somatic mutation involving DDX41 c.1589G>A, p. Gly530Asp in his bone marrow genomic profile is consistent with what we would expect to see in a DDX41-mutated myeloid neoplasm, supporting Knudson's "two-hit" hypothesis, whereby the second allele is inactivated due to acquired changes/epigenetic silencing [34]. A germline DDX41 variant was observed, as anticipated, in the tumor tissue from pancreatic cancer as well. However, whether or not the DDX41 mutation played a role as a driver mutation in the development of his pancreatic cancer cannot be ascertained. There are reports of solid tumors in those with DDX41 germline mutations who also have hematologic malignancies; however, it is not certain if these cases confer a risk higher than what one would expect to see in the average population [24,28,31,32]. Nevertheless, if DDX41 is observed, it should always prompt confirmation with fibroblast culture germline testing [29].

In addition to the DDX41 mutations observed in this patient's germline DNA and tumor tissue samples, the patient was also found to have a germline MUTYH c.1187G>A p.G396D heterozygous pathogenic variant on fibroblast genetic sequencing. This same variant described as MUTYH p.G393D was detected in his molecular pancreatic tumor genomic testing with a variant allele frequency of 48% as anticipated. The nomenclature difference between the germline and pancreatic tumor variants is secondary to the use of different reference protein-coding transcripts (NM_001128425.1 and NM_0122222, respectively). The MUTYH gene is located on chromosome 1p34.3-p32.1 [35]. Approximately 1%-2% of the general population is monoallelic MUTYH carriers [36]. MUTYH mutations have been reported in <1% of PDAC samples analyzed in COSMIC (May 2024) and <1% of PDAC samples analyzed in cBioPortal for Cancer Genomics, (May 2024). This observation, coupled with recent data, indicates no elevated risk of cancer in those who are monoallelic heterozygotes. As such, the above patient's MUTYH mutation is not believed to have contributed to the development of his PDAC. However, population-based studies and ongoing research, including analysis of epigenetic factors and the impact of single nucleotide polymorphisms as they relate to cancer susceptibility mutations are

necessary to confirm this. Of note, as was detected in this patient, KRAS Gly12Asp mutation has been reported to in >40% of PDAC [37].

While this patient was also discovered to have a germline POLE gene mutational Variant of Uncertain Significance (VUS), the relevance of this finding is unknown and did not impact his management. The POLE gene is located on chromosome 12q24.33 and is associated with Polymerase Proofreading-Associated Polyposis Syndrome (PPAP), an autosomal dominant genetic disorder associated with colonic polyposis (30-100 adenomatous polyps) and an elevated lifetime risk of colorectal cancer of >20% [38].

Conclusion

We have identified a patient with pathogenic DDX41 and MUTYH mutations who was diagnosed with synchronous PDAC and AML within a few days of each other. Interestingly, both of these genetic alterations were present in germline DNA and within the patient's tumor tissue, perhaps providing greater insights into the pathogenesis of his concurrent malignancies. However, the interplay between germline and tumor genetics in the development of his synchronous cancers remains nebulous and highlights the need for dedicated research focusing on the interplay of these genetic characteristics with lifestyle and environmental factors.

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