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Therapy-related acute myeloid leukemia in a patient with *BRCA1*-positive breast cancer and a *DDX41* possibly germline variant

CAP TODAY *and the Association for Molecular Pathology have teamed up to bring molecular case reports to* CAP TODAY *readers. AMP members write the reports using clinical cases from their own practices that show molecular testing's important role in diagnosis, prognosis, and treatment. The following report comes from Washington University School of Medicine in St. Louis. If you would like to submit a case report, please send an email to the AMP at* amp@amp.org. *For more information about the AMP and all previously published case reports, visit* www.amp.org.

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The 2022 World Health Organization and International Consensus Classification frameworks recognize several well-defined myeloid neoplasm categories that arise in the setting of inherited genetic predisposition. These entities are grouped according to associated clinical features and include myeloid neoplasms with germline predisposition in the absence of antecedent platelet abnormalities or organ dysfunction (e.g. *CEBPA*, *DDX41*, and *TP53*), those associated with inherited platelet disorders (e.g. *RUNX1*, *ANKRD26*, and *ETV6*), and disorders linked to underlying or potential organ dysfunction. The latter category encompasses a broad range of conditions, including *GATA2* deficiency, *SAMD9/SAMD9L*–related disorders, telomere biology disorders, bone marrow failure syndromes, and Fanconi anemia.[1,2] Additionally, rare pathogenic variants in homologous recombination repair pathway genes (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*), mismatch repair (MMR) pathway genes (*MLH1*, *MSH2*, *MSH6*), as well as other tumor suppressors (*CDKN2A*, *NF1*) predispose an individual to multiple solid cancers. Furthermore, cancer predisposition genes are strongly linked with multiple cancer diagnoses rather than a single cancer diagnosis over the lifetime of an affected individual.[3]

Importantly, multiple hereditary cancer syndromes characterized by defects in DNA damage response and repair pathways are associated with an increased risk of both solid malignancies and myeloid neoplasms. These syndromes involve genes such as *CHEK2*, *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[4-6] Germline variants in these broad cancer predisposition genes may be overrepresented among patients with myeloid neoplasms who have a personal history of solid tumors, including those who develop therapy-related myeloid neoplasms.[6,7] In a study by Hein K, et al., germline pathogenic or likely pathogenic variants in cancer predisposition genes were seen in nearly one-fifth of patients with both a solid tumor and a myeloid neoplasm, including those with therapy-related myeloid neoplasms or myeloid neoplasms after prior cytotoxic therapy, supporting a low threshold to pursue germline testing in this population.[8]

Herein, we present an interesting case of therapy-related acute myeloid leukemia (t-AML) in a patient with a history of germline *BRCA1*-positive breast cancer and a *DDX41* p.Q41* variant suspected to be of germline origin.

Case. A 65-year-old female with history of *BRCA1* (NM_007294.4: c.68_69del, p.E23Vfs*17) germline pathogenic variant-positive right breast cancer diagnosed 12 years prior (invasive ductal carcinoma, estrogen receptor positive, progesterone receptor positive, HER2 negative, stage T1 N0) who is post-bilateral mastectomy, chemotherapy (cyclophosphamide, methotrexate, fluorouracil), and adjuvant anastrazole presented at an outside hospital with progressive pancytopenia (WBCs = 1.56 K/mcL; hemoglobin = 7.6 g/dL; platelets = 41 K/mcL). A bone marrow biopsy showed t-AML, with 26 percent blasts (**Fig. 1A–B**). The *BRCA1* variant was confirmed germline in the outside hospital.

Molecular analysis was done using

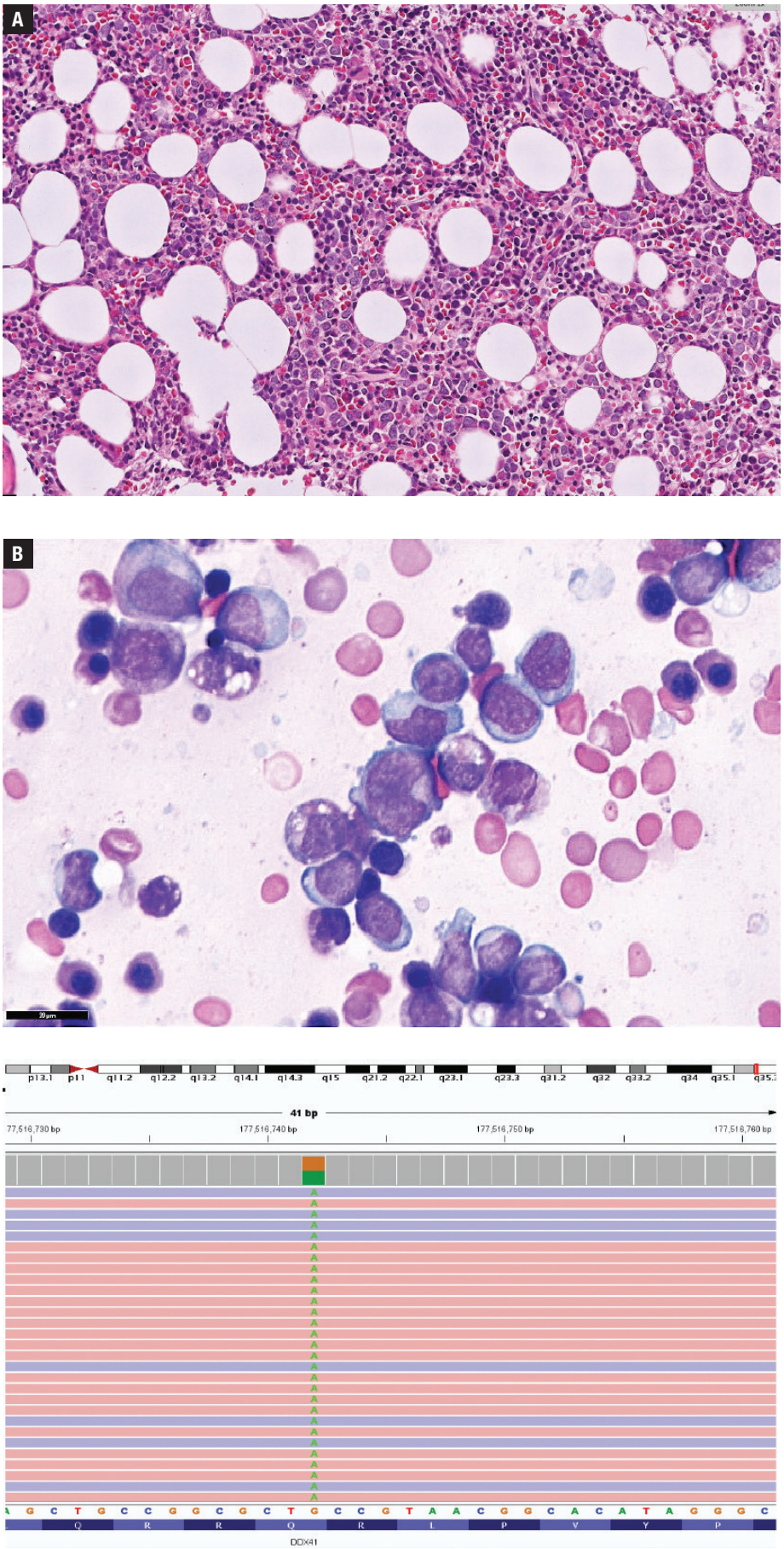

Fig. 1(A-C). A) Bone marrow biopsy (200× magnification) and **B)** bone marrow aspirate (800× magnification) showing myeloblasts in AML. **C)** Integrative Genomics Viewer (IGV) demonstrates the *DDX41* p.Q41* variant.

the MyeloSeq next-generation sequencing assay, a high-depth, tumor-only targeted sequencing panel designed to identify recurrent genetic variants in patients with myeloid neoplasms.[9] MyeloSeq analysis was performed on bone marrow and showed variants in *DDX41* NM_016222.4:c.121C>T, p.Q41* (VAF=50 percent); *DDX41* NM_016222.4:c.1574G>A, p.R525H (VAF=18 percent); *ASXL1* NM_015338.6:c.2385del, p.W796Gfs*22 (VAF=18 percent); and *KRAS* NM_004985.5:c.57G>C, p.L19F (VAF=16 percent) (**Table 1**). *DDX41* p.R525H is the most frequent somatic variant observed in patients with germline pathogenic *DDX41* variants. The *DDX41* c.121C>T, p.Q41* variant (**Fig. 1C**), if germline, would be pathogenic. Due to the positions of the two *DDX41* variants, this assay is unable to determine whether they are in cis (on the same chromosome) or in trans (on opposite chromosomes). Corresponding cytogenetics studies showed a 46,XX[20] karyotype with no aberrations detected by myelodysplastic syndrome or AML FISH panels. The immunohistochemistry stain for CD34 showed an increase in blasts (20 percent) in the bone marrow. Flow cytometry of the bone marrow specimen showed myeloid progenitor population with abnormal surface antigen expression consisting of CD45, CD34, HLA-DR (slightly decreased), CD38 (decreased), CD117, CD13, CD33, and CD123 (dim), without expression of CD11b, CD5, CD19, CD10, CD16, CD14, CD36, CD64, CD56, or CD7. Total non-erythroid cells expressing CD34 were present at 23 percent, representing increased myeloblast population (23 percent of total events).

This case was best classified as AML with myelodysplasia-related gene mutations, therapy-related by International Consensus Classification criteria, or AML, myelodysplasia-related, post-cytotoxic therapy based on the WHO-HAEM5. The overall constellation of variants was consistent with adverse risk AML by National Com-

Gene	*DDX41* (ENST00000330503)	*ASXL1* (ENST00000375687)	*KRAS* (ENST00000311936)
NGS before treatment	c.121C>T, p.Q41* (VAF=50%), pathogenic; c.1574G>A, p.R525H (VAF=18%), pathogenic	c.2385del, p.W796Gfs*22 (VAF=18%), pathogenic	c.57G>C, p.L19F (VAF=16%), pathogenic
NGS after treatment	c.121C>T, p.Q41* (VAF=49%), pathogenic	Absent	Absent

Table 1. MyeloSeq NGS results from bone marrow specimens before and after treatment showing persistent *DDX41* p.Q41*, possibly germline variant.

prehensive Cancer Network guidelines. The patient was started on chemotherapy with daunorubicin and cytarabine induction.

After one and a half months, subsequent bone marrow biopsy showed markedly hypocellular bone marrow with pan-hypoplasia and no morphologic evidence of AML. Repeat MyeloSeq performed on the post-induction bone marrow specimen showed that previously identified variants in *ASXL1*, *DDX41* p.R525H, and *KRAS* were not seen, consistent with variant clearance and measurable residual disease negative status at a sensitivity of at least 0.1 percent. The *DDX41* p.Q41* variant was again detected (VAF=49 percent) at near heterozygous allelic fraction, in the absence of morphological evidence of leukemia, and is also seen in the global population at low levels, which suggest it likely represents a germline variant (Table 1). The germline *BRCA1* variant was again found in a heterozygous state on NGS testing of bone marrow specimen done by Tempus xT in the current encounter when the bone marrow was negative for measurable residual disease.

The proposed diagnosis was t-AML, with possibly germline *DDX41* p.Q41* variant and history of germline *BRCA1*-positive breast cancer. The patient is being evaluated for bone marrow transplantation.

Discussion. This patient with t-AML likely has multiple cancer predisposition syndromes with established *BRCA1* and putative *DDX41* p.Q41* pathogenic germline variants. Longitudinal MyeloSeq molecular data shows that the persistent *DDX41* p.Q41* variant likely represents a germline variant, which predisposes to myeloid neoplasms. In a study by Bannon SA, et al., 94 percent of patients with suspected *DDX41* germline variant had confirmed germline *DDX41* variant on germline testing on DNA extracted from cultured skin fibroblasts obtained from skin punch biopsy.[10] The patient was referred for genetics counseling for further workup.

The *DDX41* p.R525H is one of the most frequently acquired somatic variants affecting the second *DDX41* allele in this setting, as in this case, and may be associated with more rapid progression to myelodysplastic syndrome/AML.[11] In patients with therapy-related myeloid neoplasms, germline variants coexist in 10 to 30 percent of cases, mainly in genes related to *BRCA1/2*, *TP53*, *CHEK2*, and Fanconi anemia.[12] In a study of breast cancer patients who developed t-AML, germline variants were present in 21 percent of cases, mainly in *BRCA1* (six percent), *TP53* (six percent), *BRCA2* (four percent), *PALB2* (two percent), and *CHEK2* (two percent). These findings support a contribution of inherited cancer susceptibility to the development of t-AML following breast cancer.[6] This was observed as well in our patient, who presented with t-AML with a history of *BRCA1*-positive breast cancer. These variants may predispose to clonal hematopoiesis of indeterminate potential (CHIP), which is then naturally selected under cytotoxic pressure leading to t-AML. The association of t-AML with germline pathogenic variants and CHIP represents an emerging and promising field for developing preventive and monitoring strategies.[13] Intriguingly, in a recent study by Korotev SC, et al., one family with another *DDX41* germline pathogenic variant (c. 490 C>T [p.Arg164Trp]) had a coexisting *BRCA1* germline pathogenic variant. The family members developed hematopoietic malignancies as well as solid tumors (colon, ovarian, prostate, spinal).[7]

There are many implications for this patient of having a *DDX41* germline variant. Approximately half of *DDX41* carriers develop myeloid malignancies in their lifetimes, underscoring the need for genetic counseling of the individual with consideration for cascade testing of family members.[14] Moreover, germline pathogenic variants in *DDX41* are relatively prevalent in the general population (approximately one in 429 individuals), a factor that may warrant consideration when developing guidelines for the selection of unrelated adult donors for hematopoietic stem cell transplantation (HSCT).[11] The unrecognized use of related transplant donors with the same germline variant has led to donor-derived myeloid neoplasms, emphasizing the need for increased awareness and recognition of germline predispositions to myeloid neoplasms. Furthermore, patients with pathogenic *DDX41* germline variants frequently develop acute graft-versus-host disease after allogeneic HSCT unless they receive post-transplant cyclophosphamide.[14] Although our testing cannot definitively differentiate between somatic and germline variants, the persistent near-heterozygous allele frac-

tion and disease clearance strongly warranted recommendations for follow-up genetic counseling and germline testing for our patient and any potential related donor. Germline testing of the patient for *DDX41* should be prioritized, and hence the patient has been given a kit for germline testing for *DDX41*. If confirmed that the *DDX41* variant is germline, then cascade testing for family members is relevant to further address cancer predisposition risk in the family.

We note that *DDX41* p.Q41* is a reasonably common germline variant and has not been previously reported as somatic.[11] Genetic counseling and consideration for germline testing is recommended for potential carriers of the *BRCA1* variant in family members. Through tailored management and regular surveillance, individuals with *BRCA* variants can reduce cancer risk or identify malignancies at earlier, more treatable stages.[15]

Here, we present an intriguing patient with t-AML, as well as a history of germline *BRCA1*-positive breast cancer and a *DDX41* p.Q41* possibly germline variant. This case contributes to the emerging understanding of the relationship between t-AML with a history of solid tumor and predisposing germline variant(s), as well as CHIP, offering insight into potential preventive and monitoring strategies for these patients. Our observations may further support the findings of previous studies, to follow up patients with solid tumor with germline predisposition for development of t-AML, as well as to offer germline genetic testing to all patients who develop therapy-related leukemia after breast cancer, to enable primary prevention for at-risk relatives and guide care for survivors of therapy-related leukemia.[6,12]

This case report helps to create awareness of the benefits of germline testing for *DDX41* in suspected cases as well as its implications for bone marrow transplantation in order to address the barriers to germline testing. □

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Test yourself

Here are three questions taken from the case report. Answers are online now at www.amp.org/casereports *and will be published next month in* CAP TODAY.

1. Germline variants in which of the following genes may be associated with increased risk of both myeloid and solid malignancies?

a. *BRCA1/2.*
b. *CHEK2.*
c. *MLH1.*
d. All of the above.

2. Which of the following statements is false?

a. *DDX41* p.R525H is one of the most frequently acquired somatic variants affecting the second *DDX41* allele.
b. *DDX41* p.R525H may be associated with less rapid progression to myelodysplastic syndrome/acute myeloid leukemia.
c. In patients with therapy-related myeloid neoplasms, germline variants coexisted in 10 to 30 percent of cases.
d. Germline variants in *BRCA1/2* are seen in many breast cancer patients who developed therapy-related acute leukemia.

3. Which of the following statements is false?

a. All *DDX41* carriers develop myeloid malignancies in their lifetimes.
b. Germline pathogenic variants in *DDX41* are relatively prevalent in the general population.
c. Patients with pathogenic *DDX41* germline variants frequently develop acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation.
d. Inherited cancer susceptibility contributes to the development of therapy-related AML following breast cancer.