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Letter to the Editor

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Concomitant *ATM* Mutations Identified by Next Generation Sequencing in a Patient With New-Onset Acute Myeloid Leukemia Following Imatinib Treatment for Chronic Myeloid Leukemia

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To the Editor

ATM mutations have been described in breast, lung, hematologic, gastrointestinal and genitourinary malignancies [1, 2]. Pritchard et al report an 11.8% incidence of pathogenic germline mutations in DNA-repair genes among metastatic prostate cancer patients [2]. Of 20 genes surveyed, all associated with hereditary cancer predisposition syndromes, *ATM* variants comprised 13% (11/84). Further, a "second "hit" somatic aberration" was found in 36/61 (59%) with available tumor sequencing data.

We report a 70-year-old man diagnosed with new-onset acute myeloid leukemia (AML) following 14-year maintenance with imatinib for chronic-phase chronic myeloid leukemia (CML) with complete molecular remission and undetectable *BCR/ABL* transcripts. Cytogenetic analysis from initial bone marrow biopsy demonstrated karyotype 46,XY,del(7)(q22) with fluorescence *in situ* hybridization negative for *BCR/ABL,* t(8;21) and t(15;17). Next generation sequencing (NGS) (FoundationOne Heme panel, Foundation Medicine) described four pathogenic mutations: *ATM* (W579*), *DNMT3A* (R882H), *IDH1* (R132C) and *NPM1* (W288fs*10+). Variants of unknown significance (VUS) were found in six genes including *ATM* (G2863V), which *in silico* analysis utilizing PolyPhen-2 software (http://genetics.bwh.harvard.edu/pph2/) predicted as probably damaging (Table 1) [3]. Bone marrow biopsy following induction and salvage chemotherapy with cytarabine and idarubicin showed residual disease. During induction, gallbladder adenocarcinoma was diagnosed by biopsy. The patient subsequently elected for hospice care. During treatment, his family declined genetic counseling.

One reality of NGS is the prospect of identifying pathogenic germline variants in cancer susceptibility genes [4]. Determining the significance of these mutations is difficult when NGS does not utilize matched-normal comparison DNA. Additionally, the clinical significance of VUSs identified by NGS remains elusive [5].

Following NGS, our CML patient was diagnosed with *BCR/ABL*-negative AML with concomitant single nucleotide variants in *ATM*: a pathogenic, non-sense mutation disrupting the protein kinase domain (W579*) and VUS point mutation (G2863V). Public databases including ClinVar and dbSNP supported the pathogenicity of W579*. A search for both variants on ExAc returned no results. Coupled with *in silico* analysis predicting G2863V as likely pathogenic, his AML harbored two presumed pathogenic mutations in *ATM*, although germline status was never established.

This case illustrates both the tremendous value and unique challenge of interpreting genomic information supplied by NGS. Although rare, *BCR/ABL*-negative AML has been previously reported in CML patients following imatinib therapy [6-8], with one CML cohort identifying 3/1,701 patients with development of AML or high-risk myelodysplastic syndrome (MDS) with eventual AML transformation [6]. In our patient, we postulate the *ATM* lesions as contributing to susceptibility to AML following imatinib treatment. Additionally, the identification of coexistent mutations in *ATM* underscores a need for access to genetic counseling and clinical germline testing. Utilized in genetic counseling, we also propose *in silico* analysis as a clinical tool for oncologists to better characterize VUS supplied by NGS.

Author Contributions

MM and MS designed the research. MS analyzed data. MS, MM, MC and EV wrote the paper.

Conflict of Interest

The authors have no conflict of interest to disclose.

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Table 1. *In Silico* Analysis of VUS Identified by NGS of Bone-Marrow Cells in a CML Patient with *BCR*/ABL-negative AML

Gene	VUS	Polyphen-2 score	Prediction
ARID1A	R1593W	0.893 (sensitivity, 0.70; specificity, 0.90)	Possibly damaging
ARID2	T749I	0.001 (sensitivity, 0.99; specificity, 0.09)	Benign
ATM	G2863V	1.000 (sensitivity, 0.00; specificity, 1.00)	Probably damaging
MKI67	Q689R	0.004 (sensitivity, 0.98; specificity, 0.35)	Benign
MYO18A	I1723V	0.011 (sensitivity, 0.96; specificity, 0.51)	Benign
NCSTN	P322S	0.018 (sensitivity, 0.95; specificity, 0.55)	Benign

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