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Case Presentation
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BRAF K601E Mutation Lost in Transformation: Insight from a Case of Splenic Marginal Zone Lymphoma

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Context

The differentiation of splenic marginal zone lymphoma (SMZL) from hairy cell leukemia (HCL) and its variants can be difficult given their overlapping clinical presentations, morphologic features and immuno phenotype. The nearly 100% association of HCL with BRAF V600E mutation and the occurrence of the uncommon BRAF K601E mutation in some cases of SMZL highlights the importance of molecular diagnostics for this differential diagnosis.

Design

The histologic features and immuno profile of a co-occurring SMZL and DLBCL were compared with molecular findings, including *BRAF* mutation analysis performed both by Sanger sequencing and by an amplicon-based Ion Torrent next gene sequencing assay on extracted DNA.

Results

A 73-year-old woman presented with splenomegaly, leukocytosis (12.8 K/uL) with absolute lymphocytosis (9.1 K/uL), anemia (8.9 g/dL) and thrombocytopenia (95 K/uL). The lymphocytes were small to medium-sized with moderate amounts of cytoplasm with polar cytoplasmic projections. The bone marrow biopsy was 95% cellular with diffuse lymphomatous infiltration (Figure 1A). Flow cytometric analysis demonstrated a kappa light chain-restricted population of CD19+/CD20+ lymphocytes that were negative for CD5, CD10, and CD103. The karyo type was complex with del (17p)/TP53 deletion but no evidence of IGH/CCND1 and IGH/BCL2 rearrangements with rare extra signals for 18q/BCL2 by FISH. BRAF mutation analysis was performed on blood and revealed a high level of BRAF K601E mutation consistent with heterozygous mutation in all of the lymphoma cells. A diagnosis of marginal zone lymphoma was rendered.

The patient was found simultaneously to have a lump in her right breast. This biopsy showed uniformly large cells with numerous mitoses consistent with DLBCL (Figure 1B). The lymphoma was positive for CD20, BCL-6, MUM1, Ki67 (>80%) and MYC but no showed no evidence of MYC, IGH/CCND1 or BCL2 rearrangements by FISH. PCR-based IGH gene rearrangement analysis showed identically-sized clonal peaks in the FR1, FR2 and FR3 reactions comparing blood and the breast biopsy (with a minor extra band in FR3) indicating a large cell transformation of the lymphoma seen in blood and bone marrow within the breast (Figure 2). However, next-generation sequencing showed only very low levels of the BRAF K601E (variant allele frequency of 2.8%) in the breast biopsy, possibly related to admixed smaller lymphoma cells.

Conclusion

Here, we present a patient with SMZL with *BRAF* K601E mutation that largely or completely lost this mutation upon transformation to DLBCL. It is speculated that the allele may have been lost due to gene instability resulting from *TP53* dysregulation. Regardless of the cause, this case suggests that *BRAF* mutations are not always essential for oncogenesis and may be lost in some B-cell neoplasms with transformation, complicating use of this marker for diagnosis. Additionally, we have also seen this mutation in a case of chronic lymphocytic leukemia, suggesting that this may be a sub clonal mutation in some lympho proliferative diseases.

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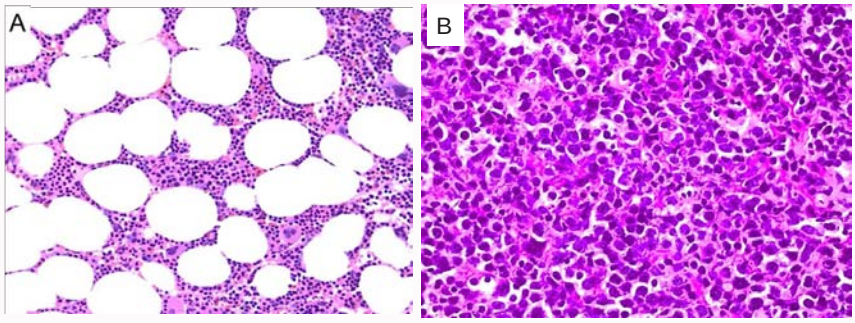

Figure 1: A) Marginal zone lymphoma of the bone marrow, showing a proliferation of small mature appearing lymphocytes and inconspicuous mitoses. **B):** DLBL of the breast. The specimen consists of a diffuse proliferation of atypical lymphoid cells with large nuclei, open chromatin and prominent nucleoli. The mitotic and apoptotic figures are abundant. (Hematoxylin and Eosin, 20x magnification).

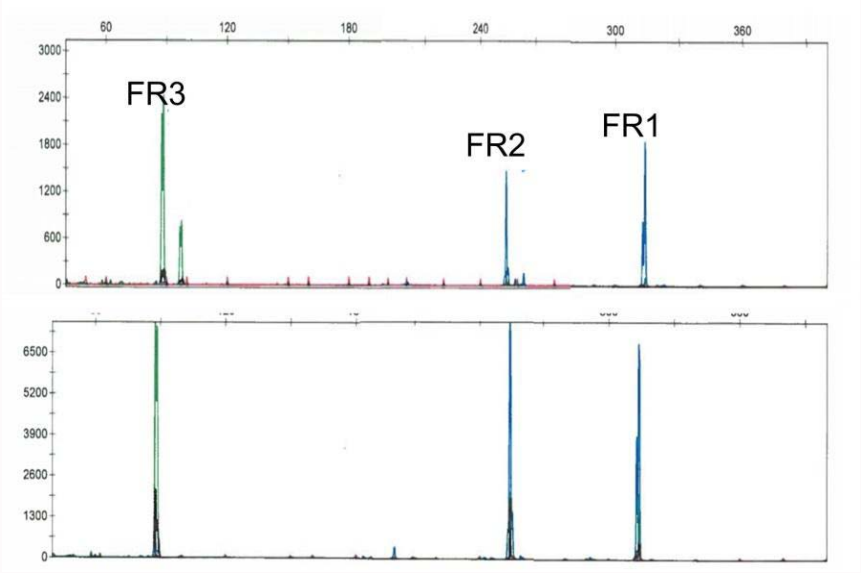

Figure 2: PCR-based IGH gene rearrangement analysis showing identically-sized clonal peaks in the FR1, FR2 and FR3 reactions comparing blood (bottom) and the breast biopsy (top), with a minor extra band in FR3, indicating a large cell transformation of the lymphoma seen in blood and bone marrow within the breast.

Table 1: Features of four cases of B-cell lymphoma (BCL) with exon 15 BRAF mutations.

Case	Sex	Age	Diagnosis on 1st bx	Diagnosis on 2nd bx	% Ly 1st BX (%)	BRAF in1st bx (type, VAF)		% Ly on 2nd BX (%)	BRAF in 2nd bx (type, VAF)		Years Btw bx
KE-L01	F	73	MZL	DLBCL	95	K601E	25.5	90	K601E	2.8	0.2
KE-L02	M	83	CLL	CLL	90	K601E	0	90	K601E	7	6
KE-L03	F	69	CLL	DLBCL	90	K601E	0	90	K601E	9.3	7
VE-L01	M	55	CLL	CLL	90	V600E	50	90	K601E	20.3	7

Extended Study on BRAF Mutations in B-LPD

Our case report prompted us to investigate the stability of BRAF mutations in low-grade B-cell lympho proliferative disorders (B-LPD), in a wider series of cases: Excluding hairy cell leukemia, we studied 112 CLL samples and 29 other B-LPD cases, using next generation sequencing (NGS) for exon 15 of BRAF. For BRAF-mutated cases, retrospective mutation analysis was performed on early or later specimens to assess mutation stability (Table 1).

We identified 1 CLL with BRAF V600E, 2 CLL with K601E and an extra nodal marginal zone lymphoma with K601E mutation (4/141, 2.8%). One CLL underwent large cell transformation between the two biopsies. All cases showed significant variations between the two biopsies in lymphocyte-normalized mutant/variant allele fractions (VAF). As with the index case, this suggests that BRAF mutation in B-LPD may not be a stable, driver or transformation-associated mutation, but instead represent a relatively uncommon sub clonal event with weak selective features.

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