An extremely rare case of concurrent BRAF V600E mutation driven hairy cell leukemia and melanoma

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Abstract

BRAF protein is a serine/threonine kinase with 766 amino acids. Approximately 15% of human cancers harbor BRAF mutations as well as other BRAF anomalies (amplifications, fusions). Somatic mutations mainly occur in the catalytic kinase domain (CR3) and the predominant mutation is V600E which is the substitution of glutamic acid (E) for valine (V) as result of a mutation at codon 600 of the kinase domain. To our knowledge, the vast majority of the cancers have non-germline BRAF mutations. Here we describe a case of a 60 year old female with history of hairy cell leukemia who presented with aphasia and forgetfulness. A follow up Brain CT scan showed 3 distinct brain lesions which were found to be diagnostic of melanoma (confirmed by immunohistochemistry) with no evidence of a concurrent brain involvement by a B-Cell neoplasm. Molecular studies confirmed the same BRAF V600E mutation in both malignancies (Hairy cell leukemia and melanoma). Thereafter the patient was started on BRAF inhibitor treatment and is now symptom-free after one year of follow up. Having two concurrent malignancies with a shared BRAF mutation is extremely rare and makes this an excellent example of a genomic marker-driven treatment in two histologically and immunophenotypically distinct tumors.

Background

BRAF mutation first described in 1992[1] and was soon after found to be one of the most frequently mutated protein kinase genes in human tumors. It showed to be an effective target for cancer treatment, but a key question is whether or not targeted drugs that has been approved for one type of histology could be used for other histology types harboring the same aberration. In 2015, James S. Blachly et al. presented the first case of the co-occurrence of malignant melanoma and HCL, both harboring the BRAF mutation, and its successful treatment with the BRAF inhibitor dabrafenib[2]. Here we present another rare case of a concurrent BRAF V600E positive melanoma and HCL which were successfully treated with targeted therapy.

Case report

HISTORY: A 62 year old female presented in 1993 with marked cytopenias and splenomegaly which were subsequently found to be secondary to Hairy cell Leukemia (HCL) and treated with cladribine. Thereafter she experienced multiple disease relapses while on cladribine and rituximab. Most recently she presented in 2015 with a progressively worsening headaches and expressive aphasia. Follow up brain imaging revealed new brain metastases which were shown to be consistent with metastatic melanoma (Fig. A-F). The follow up bone marrow showed involvement by the patient's known hairy cell leukemia with no evidence of melanoma.

HISTOLOGY: The H&E slides of the brain mass showed sheets of abnormal tumor cells with round nuclei and prominent red nucleoli. (Fig. C) with an immunophenotype (PAX5 negative, CD20 negative, S100 positive, HMB45 positive, and MelanA positive) which is consistent with melanoma (Fig. D-F). Flow cytometry of the bone marrow demonstrated a monotypic B-cell population with an immunophenotype (CD19+/CD20++/CD11c+/ dimCD103+ /dimCD25+) consistent with Hairy cell leukemia (Fig. G-H). The bone marrow biopsy showed a hypocellular marrow (20-30% of cellularity) with an atypical B-cell interstitial infiltrate. By immunohistochemistry, these B-cells were positive for DBA44 and equivocal for Annexin A1 (Fig. I-L). Peripheral Blood Smear showed pancytopenia with rare atypical lymphocytes with few cytoplasmic projections. Overall, given the immunophenotype and morphology, the findings were consistent with relapsed Hairy Cell Leukemia.

MOLECULAR STUDY: BRAF V600E mutation was detected by the Real-Time PCR in both the Hairy Cell Leukemia and the melanoma.

TREATMENT: She underwent CNS radiation therapy in July 2015 and initiated systemic therapy with Mekinist (trametinib) 2 mg tablet (a BRAF inhibitor) in combination with Tafinlar (dabrafenib) 75 mg capsule (a MEK1/2 inhibitor). She tolerated treatment well and enjoyed a significant response. As of June 2016, she remains clinically stable and reveals no overt evidence of significant clinical disease progression.

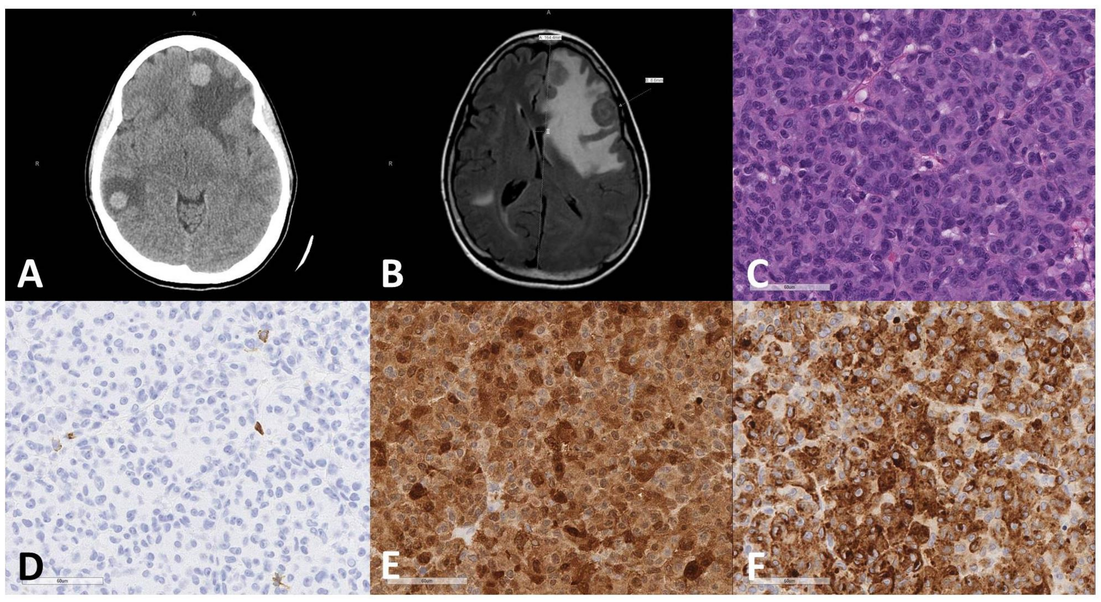
Discussion

The BRAF gene is located at 7q34 and has 22 exons. BRAF protein is a serine-threonine kinase with 766 amino acids composed of 3 conserved regions (CR); CR1 and CR2 are regulatory domains and CR3 contains a catalytic protein kinase domain (Residues 457–717). BRAF somatic missense mutations most commonly occur in CR3 region especially at codon 600 which results in increase BRAF protein kinase activity. V600E (GTG > GAG) accounts for almost 90% of all V600 mutations. In addition to mutations, other types of BRAF aberrations are found in malignancies, including amplification and BRAF fusions. BRAF germline mutations have also been reported in associated with developmental disorders including Noonan syndrome (NS), Cardio-facio-cutaneous syndrome and LEOPARD syndrome. These germline BRAF mutations are different from those found in cancers.

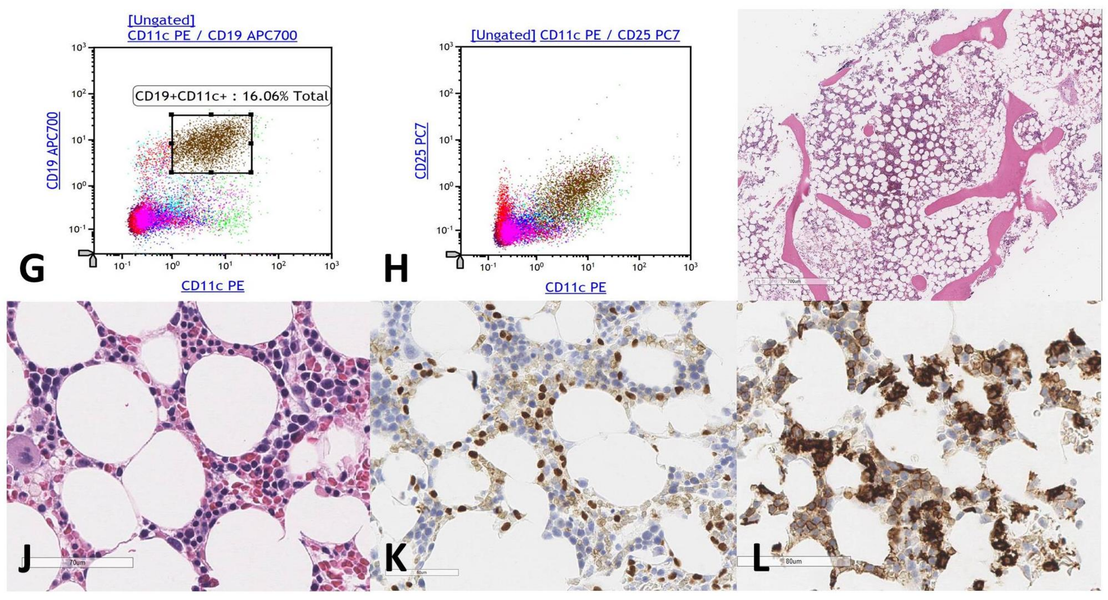
BRAF is under the RAF (Rapidly Accelerated Fibrosarcoma) protein kinase family. The proto-oncogenes of the RAF family include ARAF, BRAF, and CRAF. BRAF (serine/threonine-protein kinase B-Raf) was first isolated in 1993 from a rodent retrovirus and its malignant potential was discovered when inoculated normal mouse fibroblasts transformed into neoplastic fibrosarcoma cells. In 2002, BRAF was first found in human tumors[3] which was found to lead into activation of a family of gene products that stimulate cell growth (RET). Activated RET binds to RAF by a GTP-dependent mechanism. Subsequent phosphorylation of serine and threonine residues by RAF present on the proteins of the mitogen activated protein (MAP) kinase pathway (MEK/ERK) send signals to the nucleus. Mutated RAF leads to constitutive activation of the downstream signaling pathways. This allows the cell to by-pass the G1 restriction point of the cell cycle with upregulation of cyclin D1, resulting in unchecked cellular proliferation and survival. The MAPK pathway is frequently dysregulated in cancer, often via mutations of its intracellular components or activation of growth factor receptor tyrosine kinases. Among the three forms of RAF kinases, (B)RAF is the most potent.

BRAF gene mutations are reportedly associated with papillary thyroid carcinoma (30-70%), malignant melanoma (50%), HCL, adenocarcinoma of the lung and colon (5-20%) and ovarian cancer (15-30%)[2]. The discovery of mutations in BRAF heralded a new era of targeted therapy. HCL and melanoma of particular are noted to have had a dramatic response to such BRAF inhibitory molecules[4].

Vemurafenib and dabrafenib are two FDA-approved BRAF inhibitors that have proven to be effective in treatment of BRAF V600E-mutated melanoma patients[5]. However, Resistance can occur, and possible mechanisms are due to decreased negative feedback of the EGFR pathway, mutations other than V600E codon or CRAF activation. Emerging data suggest that BRAF inhibitors may sometimes be better used in combination therapies rather than sole treatment (e.g., a BRAF inhibitor together with a EGFR or MEK inhibitor) to impact the relevant co-activated pathways. Trametinib is currently the only FDA approved MEK1/2 inhibitor which is also approved in combination use with dabrafenib for melanoma. According to the current studies on the HCL treatment, vemurafenib is on phase II clinical trial and dabrafenib showed effective responses in the case reports[6].



MELANOMA: A. CT scan shows brain masses with significant vasogenic edema. B. MRI-T2 shows brain mass with a targetoid appearance and a central nonenhancing lesion, suggestive of necrosis, surrounded by vasogenic edema. C. H&E sections of the excisional biopsy show sheets of neoplastic epithelioid cells with round nuclei and variably prominent red nucleoli. D-F. By immunohistochemistry, the tumor cells are negative for CD43 (D) and diffusely positive for S100 (E) and Melan-A (F).



HAIRY CELL LEUKEMIA: G-H. Flow cytometry of the bone marrow shows an abnormal CD19+/CD20++ /CD11c+ /dimCD25+ monotypic B-cell population, consistent with relapsed Hairy Cell Leukemia. I-J. H&E sections of Bone marrow shows mildly hypocellular (~30% cellularity) bone marrow with decreased trilineage hematopoiesis and increased abnormal interstitial lymphocytes. K. IHC staining for PAX5 shows positive staining in the abnormal B-cells. L. DBA-44 immunostains highlights the abnormal cells of the HCL.

Conclusion:

The discovery of BRAF mutations in a wide range of cancers shows a great deal of promise in personalized medicine and is a major driver for the rapid drug development of such targeted therapies across a variety of malignancies. However, the approach may ultimately lead to genomic marker-driven treatments independent of their histology and immunophenotype. Our case report was a very rare incidence of two histologically different malignancies with the same BRAF mutation in a patient that clearly showed the effectiveness of such targeted therapy involving different organ systems.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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