Case Report

rare tumors

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BRAF p.V600E associated poly-neoplastic syndrome

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Abstract

We report a male patient who developed eight different cancers between ages 57 and 64. BRAF p.V600E mutation was detected in Langerhans cell histiocytosis, chronic lymphocytic leukemia, histiocytic sarcoma, melanoma, and adenocarcinoma of the lung. It was not detected in multiple myeloma, basal cell carcinoma, and papillary thyroid cancer. BRAF p.V600E was not detected in normal skin tissue biopsy indicating that BRAF V600E was a somatic mutation affecting cancer cells. The presence of eight different cancers with five of them positive for BRAF p.V600E in a single patient is unprecedented. This type of BRAF p.V600E-associated poly-neoplastic syndrome has never been reported in the medical literature.

Keywords

BRAF p.V600E mutation, poly-neoplastic Syndrome, lung Cancer, histiocytosis, chronic lymphocytic leukemia, melanoma

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Introduction

BRAF is a member of the rapidly accelerated fibrosarcoma (RAF) family of cytosolic serine/threonine kinases and is a signal transducer downstream of RAS in RAS-RAF-MEK-ERK signaling cascade, which is one of the most frequently mutated pathways in human cancer.[1–3] BRAF p.V600E mutation, located in the activation segment of the kinase domain, is a common oncogenic mutation which has been found in multiple disparate cancers including melanoma,[4] non-small cell lung cancer,[5] colorectal cancer,[6] histiocytic neoplasms,[7] thyroid cancer,[8] gastrointestinal neuroendocrine tumors,[9] hairy cell leukemia,[10] and chronic lymphocytic leukemia (CLL) among others.[11] It represents an activating mutation which results in high kinase activity leading to cell proliferation and survival via constitutive activation of mitogen-activated protein kinase (MAPK) signaling.[12]

We report a patient who developed five BRAF p.V600E (+) cancers; Langerhans cell histiocytosis (LCH), CLL, histiocytic sarcoma (HS), melanoma, and adenocarcinoma of the lung as well as three BRAF p.V600E (−) cancers; multiple myeloma (MM), basal cell carcinoma of the skin (BCC), and papillary thyroid cancer. This type of somatic BRAF p.V600E mutation associated poly-neoplastic syndrome has never been reported in the medical literature.

Case

The patient was a Caucasian male who developed eight different cancers between ages 57 and 64 years (Figure 1). The

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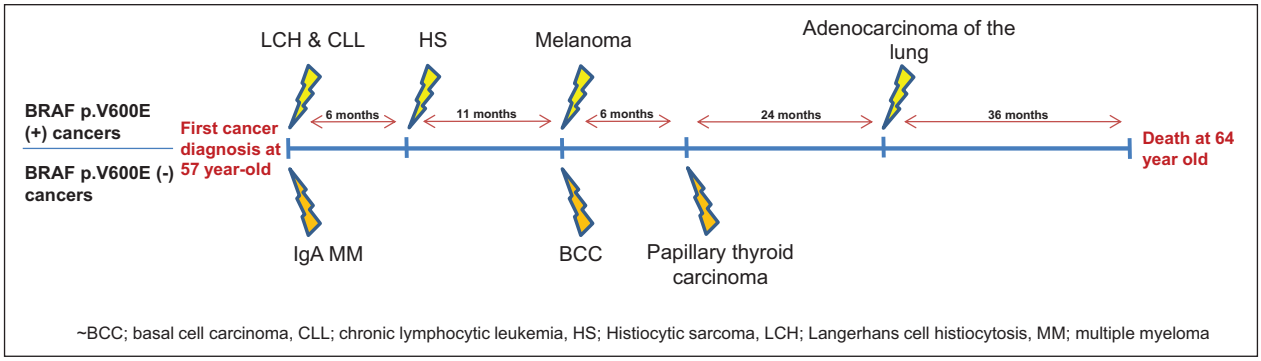

Figure 1. Timeline of cancer diagnoses and BRAF p.V600E mutation status.

family history was significant for melanoma in his sister who died at the age of 27 years; non-Hodgkin lymphoma in his mother who died at the age of 56 years; gastric cancer in his maternal grandmother; and hepatocellular carcinoma in his uncle.

At the age of 57 years, he presented with significant weight loss, severe pancytopenia requiring transfusions, lymphadenopathy, and splenomegaly. Splenectomy specimen showed three different cancers including predominant diffuse involvement with LCH, CLL, and plasmacytomas. Histiocytic cells in LCH were positive for S-100, CD1a, and langerin by immunohistochemistry (IHC). Peripheral blood flow-cytometry showed CD5+ and CD23+ lambda-restricted B cell clone consistent with CLL. Fluorescence in situ hybridization (FISH) for CLL in the blood did not show any cytogenetic abnormality. Monoclonal protein study in the blood demonstrated IgA lambda monoclonal protein. A bone marrow biopsy showed infiltration by B-cell CLL and 15% bone marrow involvement with MM with trisomies 9 and 15 on FISH. The patient was treated with lenalidomide and dexamethasone.

Six months into the treatment, he had persistently elevated liver enzymes with imaging scans showing lesions in the liver. Biopsy of a liver lesion showed findings consistent with HS with IHC showing histiocytic cells positive for CD68, LCA, CD45 RO, CD4, lysozyme and negative for langerin and CD35 (Figure 2(a)). EBV in situ hybridization was negative. The patient was switched to treatment with modified HLH-94 protocol with dexamethasone and etoposide for 6 months leading to resolution of liver lesions and normalization of liver function tests. Five months later he was noted to have a suspicious 1 cm pigmented skin lesion on the left side of his neck. Pathological finding of the resected specimen confirmed stage IIB (T4aN0M0) cutaneous melanoma. The lesion was 4.4 mm in depth with no ulceration and 4 mitoses per mm^2 (Figure 2(b)). At the same time the patient had resection of BCC on the neck.

Six months later, he was found to have a thyroid nodule and had a needle biopsy showing papillary thyroid cancer. He underwent total thyroidectomy followed by Iodine-131 treatment. Three years after the original diagnosis, MM progressed with new L2 lytic lesions and the patient received six cycles of cyclophosphamide, bortezomib, and dexamethasone. At the end of the treatment, recurrence of HS was confirmed in mass on the right kidney. This was monitored without treatment. A year later, he was diagnosed with stage IB invasive mucinous adenocarcinoma of the left lower lobe of the lung and underwent stereotactic radiation therapy. Four months later, the patient developed multiple scattered lesions in the brain stem with left trigeminal involvement associated with diffuse neck lymphadenopathy. Excisional lymph node biopsy of the left neck confirmed LCH (Figure 2(c)). Central nervous system involvement by LCH was suspected. The patient received radiation therapy to the brain stem lesions and left trigeminal nerve followed by high-dose cytarabine (HiDAC) of 1 g/m^2 every 12 hours for four doses every 4 weeks. Unfortunately, after the second cycle of HiDAC, he developed a metastatic recurrence of the lung adenocarcinoma with pleural effusions and possible adrenal involvement. The adenocarcinoma tissue from the lung biopsy was tested with FoundationOne®CDx test, a qualitative next generation sequencing, showing BRAF p.V600E mutation. IHC stain for BRAF p.V600E was positive (Figure 2(d)). FoundationOne®CDx test was also positive for EZH2 R690H, KRAS Q61H, and TNFRSF14 K236fs*15. The patient was started on combination therapy with Dabrafenib 150 mg PO twice daily and Trametinib 2 mg PO daily. The treatment was discontinued after three cycles due to drug intolerance with severe thrombocytopenia, fatigue, decreased appetite, and weight loss. The patient had persistent severe thrombocytopenia requiring frequent platelet transfusions. He underwent a bone marrow biopsy which showed 20% involvement by MM and CLL with significantly reduced megakaryocytes. Thrombocytopenia did not respond to steroids, IVIG, or Rituximab. The patient was not able to receive any further anti-neoplastic therapy due to severe thrombocytopenia and poor performance status and died at the age of 64 years.

We retrospectively tested all the cancer tissue specimens for BRAF p.V600E by Real-Time polymerase chain reaction (PCR) and IHC. The findings are outlined in Table 1. BRAF

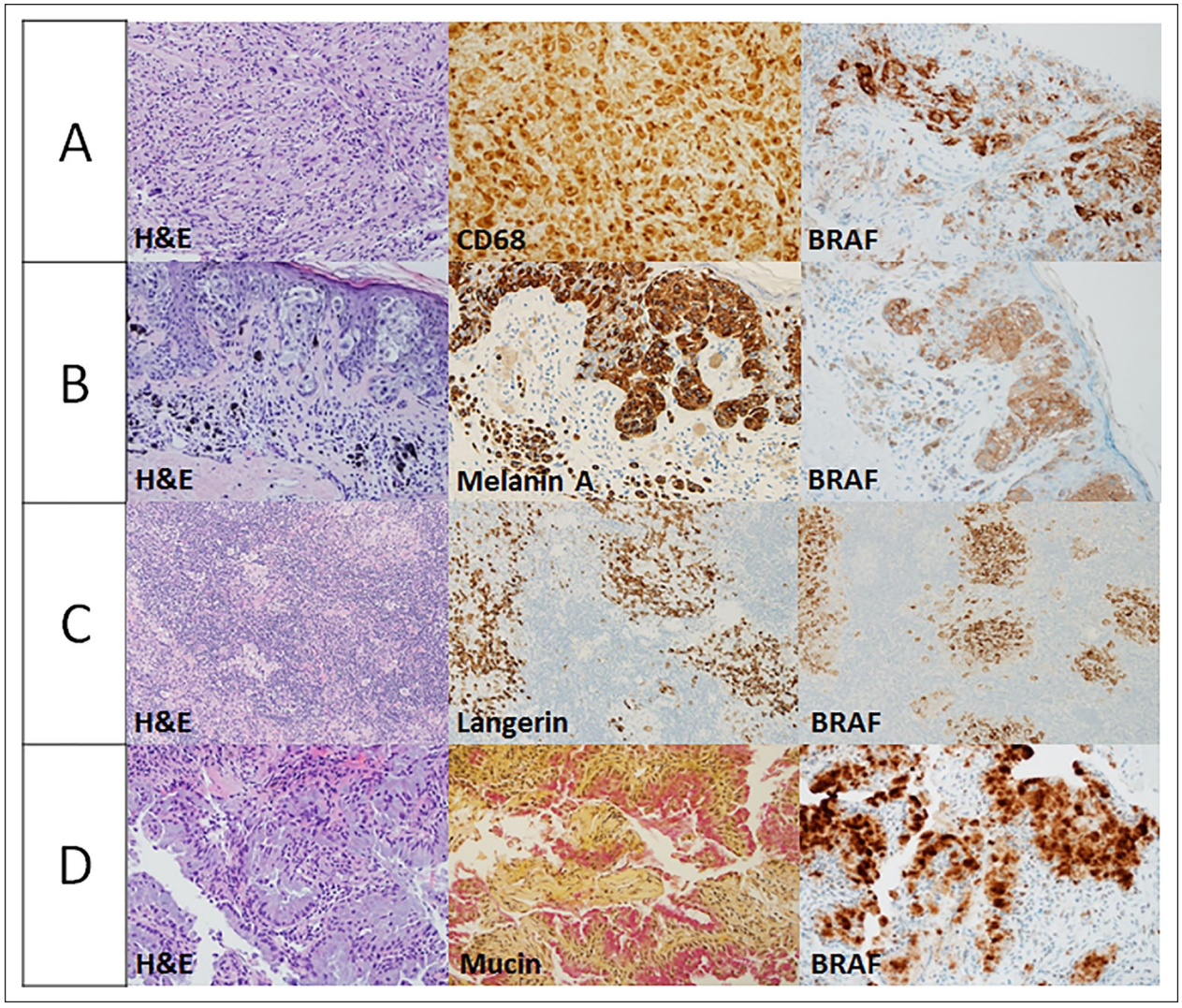

Figure 2. Cancers with BRAF p.V600E positive immunohistochemistry. **(A)**; liver biopsy showing effacement of the liver tissue architecture by histiocytes ([H&E], 100×) that are staining positively for CD68 and BRAF. **(B)**; skin biopsy showing infiltrative melanoma cells in the epidermis and dermis ([H&E], 100×), Melanoma cells stained positively for melanin A and BRAF. **(C)**; left neck lymph node biopsy. Low magnification shows effacement of lymph node architecture by lymphoid infiltrate along with Langerhans histiocytic cells ([H&E], 100×) that are positive for Langerin and BRAF. **(D)**; lung biopsy showing moderately differentiated adenocarcinoma ([H&E], 100×), these cells are positively stained for mucin and BRAF.

Table 1. Cancer diagnosis and location with BRAF Status.

Organ	Diagnosis	BRAF by IHC	BRAF molecular study by PCR or NGS
Skin	Melanoma	+	+
Kidney and Liver	HS	+	+
Lung	Mucinous adenocarcinoma	+	+
Lymph node	LCH	+	+
Bone marrow	CLL	−	+
Thyroid gland	Papillary thyroid carcinoma	−	−
Bone marrow	Plasmacytoma/MM	−	−
Skin	BCC	−	−
Skin	Normal tissue	−	−

BCC: basal cell carcinoma; CLL: chronic lymphocytic leukemia; HS: histiocytic sarcoma; IHC: immunohistochemistry; LCH: Langerhans cell histiocytosis; MM: multiple myeloma; NGS: next generation sequencing; PCR: real-time polymerase chain reaction.

p.V600E mutation was detected in LCH, CLL, HS, melanoma, and adenocarcinoma of the lung. It was not detected in MM, BCC, or papillary thyroid cancer. Germline testing on a normal skin biopsy for the BRAF p.V600E mutation by PCR as well as IHC were negative indicating that BRAF p.V600E was a somatic mutation affecting cancer cells.

Discussion

Our case is quite unique and is characterized by successive development and progression of eight different cancers within the span of 7 years between the ages of 57 and 64 years. This type of somatic BRAF mutation associated poly-neoplastic syndrome has never been reported in the medical literature.

BRAF p.V600E mutation represents over 90% of all BRAF mutations in human cancers.[13] It has been reported in about 50% of melanoma cases,[4] 62.5% of HS,[7] 25%–57% of LCH,[7,14] 1%–5% of non-small cell lung cancer with highest frequency in adenocarcinoma,[5] and 2.8% of CLL.[11] Although it has been reported in 45.7% of papillary thyroid cancer[8,15] and 5.3% of MM,[16] we were not able to detect it in these cancers in our patient. BRAF p.V600E has not been reported in BCC and was negative in our case.[17]

BRAF mutations have never been reported in hereditary cancer syndromes. A study done by Wish et al.[18] showed an increased risk of colorectal cancer (CRC) in first-degree relatives of patients with BRAF mutated CRC. This may be explained by a genetic predisposition in these individuals to develop somatic BRAF mutations.

Germline BRAF mutations are associated with congenital syndromes such as cardio-facio-cutaneous (CFC), Noonan, and Leopard syndromes.[19,20] Pathogenic BRAF variants associated with congenital syndromes are more widely distributed within the gene. Those variants have rarely been identified in cancer-associated BRAF mutations. A germline mutation affecting BRAF p.V600 is extremely rare and was only described in one case of CFC syndrome with BRAF p.V600G mutation.[20,21] Since we established the absence of BRAF p.V600E in normal skin tissue in our patient, the mutation was confirmed to be somatically acquired by cancer cells. Thus, our case does not represent a BRAF p.V600E hereditary cancer syndrome. We suspect that there might be a form of germline predisposition to developing BRAF mutant tumors that is not known to us.

Our case is the first described case of novel BRAF p.V600E associated poly-neoplastic syndrome with more than two primary cancers. The reported cases of multiple primary malignancies with BRAF p.V600E mutation in the literature described two primary cancers in four individuals. The reported cancers include hairy cell leukemia, melanoma, and adenocarcinoma of the lung.[22–25]

In conclusion, we report a novel poly-neoplastic syndrome associated with BRAF p.V600E mutation. As next generation sequencing is becoming more available in cancer diagnosis, more cases with this syndrome may be discovered. From a therapeutic standpoint, we suggest testing for BRAF p.V600E in patients presenting with cancers known to be associated with this mutation as the mutation is targetable with drugs such as BRAF and MEK inhibitors. Further research is necessary to elucidate the underlying genetic and molecular mechanisms responsible for BRAF p.V600E mediated oncogenesis of multiple primary cancers.

Author contributions

MA wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of conflicting interests

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Ethical approval

Mayo Clinic does not require ethical approval for reporting individual cases.

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Informed consent

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