


Exacerbation of Multiple Sclerosis by BRAF/MEK Treatment for Malignant Melanoma: The Central Vein Sign to Distinguish Demyelinating Lesions From Metastases

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Abstract

The emergence of immunomodulators as effective cancer treatments has been an important advance in cancer therapy. The combination therapy of BRAF/MEK inhibition with or without anti-CTLA-4 treatment causes an immunostimulatory effect that has greatly reduced death from melanoma. In this article, we present the case of a patient with prior multiple sclerosis (MS) and who later developed metastatic malignant melanoma, had a marked increase of magnetic resonance imaging (MRI) findings after treatment with the combination of trametinib (MEK) and dabrafenib (BRAF), diagnostic question of metastatic disease versus new MS lesions without brain biopsy is discussed. A healthy 49-year-old man was diagnosed with MS in October 2012. He was stable with an oral disease modifying drug until March of 2016 when the patient discovered a lump in his right groin. Biopsy was positive for S100 and BRAF V600 mutation. Combination MEK/BRAF was given and after immunotherapy an MRI showed 25 new gadolinium-enhancing lesions thought to be metastases. A brain biopsy was recommended but neurology and neuroimaging consultation showed that the MRI was consistent with demyelination (oval/ovoid, homogeneous and open-ring enhancement, and predominance of the central vein sign within lesions) rather than metastasis. Treatment for MS has been successful and there has been no return of his melanoma in 4 years. New immunotherapies are lifesaving but the modulation of the immune system can cause unpredictable events such as markedly increased MS activity. The awareness of the diagnostic value of the central vein sign provided a better outcome for this patient and could be a model in the future for others.

Keywords

hematology oncology, radiology/imaging, multiple sclerosis, diagnostic testing

Introduction

Multiple sclerosis (MS) is a chronic immune complex disease and neurodegenerative disorder of the central nervous system (CNS) that is characterized by inflammation, demyelination, axonal, and neuronal loss.^{1,2} While the mechanisms underlying disease progression in MS remain unclear, evidence suggests that the pathogenesis of all forms of MS involves inflammation-driven oxidative injury in the CNS resulting in mitochondrial dysfunction with subsequent demyelination and neurodegeneration.³

The emergence of immunomodulators as effective cancer treatments has been an important advance in cancer therapy, especially for melanoma. The combination therapy of BRAF/MEK inhibition with or without anti-CTLA-4 treatment causes an immunostimulatory effect that has greatly reduced death

from melanoma.⁴ In some cases, CNS demyelination may occur⁵; here we present a case characterized by significant exacerbation of MS in the context of BRAF/MEK inhibitors. The magnetic resonance imaging (MRI) presence of central

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Table 1. Timeline of Events.

Dates	Historical data	MRI date	EDSS	Disease modifying therapy
October 2012	Initial MS diagnosis (CDMS). Symptoms: numbness, weakness at the T6 thoracic level. Contrast-enhancing lesions in cord and brain with other T2-hyperintense lesions. CSF: 7 OCBs	October 2012	1.5	IVMP, fingolimod 0.5 mg QD
August 2015	MRI, clinical status and labs stable every 6 months	August 2015	1.0	
November 2015	Change in DMT due to low absolute CD4 count of 52 and ALC of 700. Clinically stable.		1.0	Dimethyl fumarate 240 mg BID
March 2016	CD4+ count returns to normal of 728 cells/ μ L and ALC of 1900 cells/ μ L but patient notices a lump in right shin diagnosed as metastatic melanoma—BRAF V600 mutation		1.0	
July 2016	2 new brain enhancing lesions	July 2016	1.0	
September 2016	MEK/BRAF therapy started for 5 months (August 2016 to February 2017) MRI showed 25 new Gd+ enhancing lesions Patient having headaches but no change in EDSS (Figures 1 and 2)	September 2016	1.0	
November 2016	LP done: 11/7/2016 CSF negative for cryptococcus Ab and Lyme 5 OCBs reported, monoclonal protein not apparent. Brain biopsy cancelled after central vein sign lesions noted and 3 days of IVMP improves clinical and MRI status.	November 2016		
January 2017	MRI—a few new lesions observed, patient having headaches; additional IVMP given and then oral steroids	January 2017	1.0	
February 2017	MEK/BRAF treatment stopped		1.5	
May 2017	Most lesions resolved but 3 new enhancing lesions in the left supratentorial regions and one in the left cerebellum Still having headaches, some cognitive slowing		1.5	
July 2017	Started on B-cell depletion therapy on July 26, 2017—returns to work part time one month later		1.0	Ocrelizumab 600 mg
January 2018	No new MS lesions compared with 1/2017 (Figure 3)	January 2018	1.0	
September 2020	No MS symptoms; interval MRIs obtained every 6 months remain stable		1.0	Continuing ocrelizumab

Abbreviations: ALC, absolute lymphocyte count; BID, twice a day; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; QD, once a day; LP, lumbar puncture; MRI, magnetic resonance imaging; MS, multiple sclerosis; CDMS, clinical definite MS; IVMP, intravenous methylprednisolone; OCBs, oligoclonal bands.

veins within the new lesions helped solidify the diagnosis of MS disease exacerbation rather than metastatic disease.

Case Report

A 49-year-old man with no significant prior medical history was initially diagnosed with MS in October 2012 when he presented with bilateral lower extremity hypoesthesia and mild weakness. MRI then revealed a gadolinium-enhancing (Gd+) lesion of the thoracic spinal cord at T9 and also at C5 with typical MS lesions throughout his brain MRI. There were periventricular and pericallosal lesions compatible with Dawson's fingers fulfilling the 2010 McDonald Criteria for clinically definite MS. Cerebrospinal fluid (CSF) revealed 7 unique oligoclonal bands. He was given intravenous methylprednisolone and begun on oral fingolimod 0.5 mg, which he tolerated well with full recovery of function and resolution of enhancing lesions (Table 1).

In September 2015, the patient's white blood cell count was 5000 cells/ μ L, absolute lymphocyte count was 700 cells/ μ L, with an absolute CD4 count of 52 cells/ μ L and a CD4/CD8 ratio of 0.27. MRI assessment of his brain and spine revealed several small new interval (asymptomatic) T2-hyperintense lesions of his cervical cord. Fingolimod was stopped and he began dimethyl fumarate (DMF) within 2 weeks of his last fingolimod dose. His clinical status was stable and his complete blood count returned to normal by March 2016 with white blood cell count of 6000 cells/ μ L, absolute lymphocyte count of 1900 cells/ μ L, and CD4 of 728 cells/ μ L and a CD4/CD8 ratio of 1.08.

Also in March of 2016, the patient discovered a lump in his right groin. A biopsy revealed metastatic melanoma from an unknown primary source. The biopsy was positive for S100 and BRAF V600 mutations. FDG-PET (fluorodeoxyglucose-positron emission tomography) for his melanoma showed only disease localized to the groin/pelvic region. He

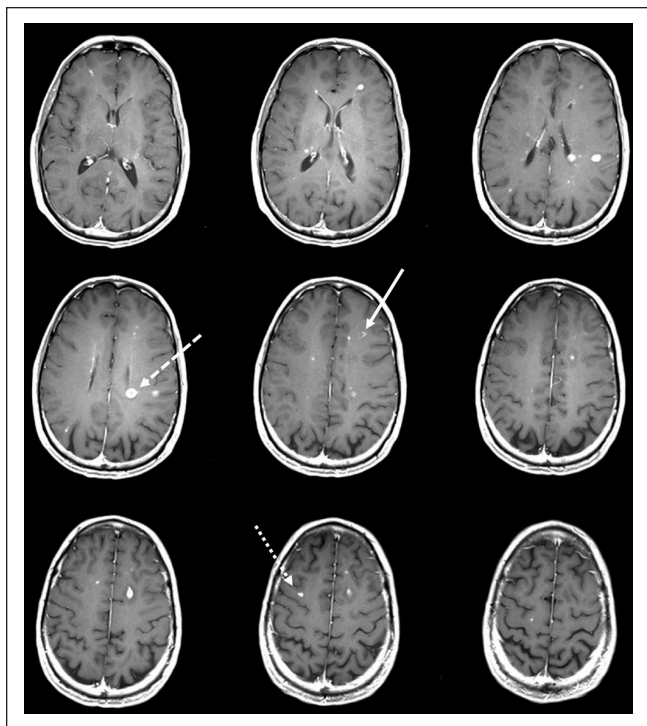


Figure 1. Numerous gadolinium-enhancing lesions following initiation of BRAF/MEK inhibitors in a patient with multiple sclerosis. Key: Images are axial T1-weighted magnetic resonance imaging acquisitions from a 3T Siemens Verio scanner, following the administration of intravenous gadolinium contrast. At least 25 lesions in total demonstrated enhancement with nodular (dotted arrow), open-ring (solid arrow), and close-ring (dashed arrow) characteristics.

therefore underwent a local surgical resection. His neurologic status remained stable with the Expanded Disability Status Scale (EDSS) of 1.0. In September 2016, after approximately 6 months of observation, he began combination trametinib (MEK 1/2 inhibitor, 2 mg daily) and dabrafenib (BRAF inhibitor, 75 mg twice daily) for a duration of 5 months. He remained on DMF 240 mg twice daily. EDSS of 1.0. A baseline MRI prior to starting immunomodulatory anti-neoplastic therapy demonstrated several small gadolinium-enhancing lesions in the brain. One month later, an MRI was repeated and showed at least 25 new gadolinium-enhancing lesions with patterns consistent with demyelination (oval/ovoid, homogeneous and open-ring enhancement, and the central vein sign) rather than metastasis (Figures 1 and 2). Repeat CSF was again unrevealing for malignancy with negative cytology, and he received 3 days of intravenous methylprednisolone. However, subsequent MRIs continued to demonstrate gadolinium enhancement at 4 months post-BRAF/MEK therapy, and only abated following treatment with B-cell depletion 5 months after BRAF/MEK treatment ended. Figure 3 shows the evolution of FLAIR lesions from baseline, to 1 month following BRAF/MEK therapy, followed by lesion recovery after B-cell therapy. On his most recent visit, 4 years since the last treatment of melanoma, the patient

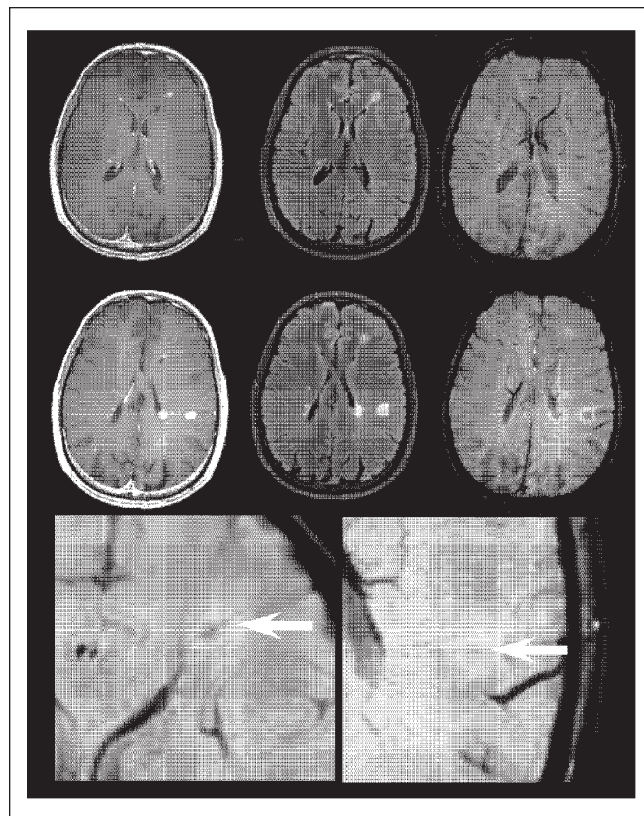


Figure 2. Characterization of lesions using susceptibility weighted imaging. Key: Left to right: axial T1-weighted post-gadolinium, FLAIR, and susceptibility-weighted images (SWIs) of the acute demyelination event following initiation of BRAF/MEK inhibitors in a patient with multiple sclerosis. The SWI was a single echo 3-dimensional sequence with a voxel size of $0.89 \times 0.89 \times 2.6$ mm and scan time of ~ 3 minutes. Several of the enhancing lesions demonstrate susceptibility (darkening) on the SWIs, as well as enlargement of single or multiple central veins both characteristic of demyelination pathology. Eighty-three percent of T2 hyperintense lesions with a size of at least 3 mm in diameter (10/12) showed a hypointense central vein sign. The top and middle rows represent 2 anatomic slice levels. The bottom row shows zoomed high-resolution SWIs, optimized for brightness/contrast, to illustrate typical examples (arrows) of the hypointense central vein sign with hyperintense lesions.

showed a nearly full recovery and remains free of cancer. He has had some minor residual effects of his MS such as fatigue and minor incoordination but has returned to work part time with an EDSS of 1.0.

Discussion

The successful use of immunotherapy for metastatic melanoma by BRAF/MEK inhibitor combination trametinib and dabrafenib allowed resolution of the melanoma, but was associated with a significant clinical and radiologic exacerbation of the patient's MS. The marked brain inflammatory reaction was dramatic with many enhancing lesions with acute edematous appearance (see Figures 1 and 2).

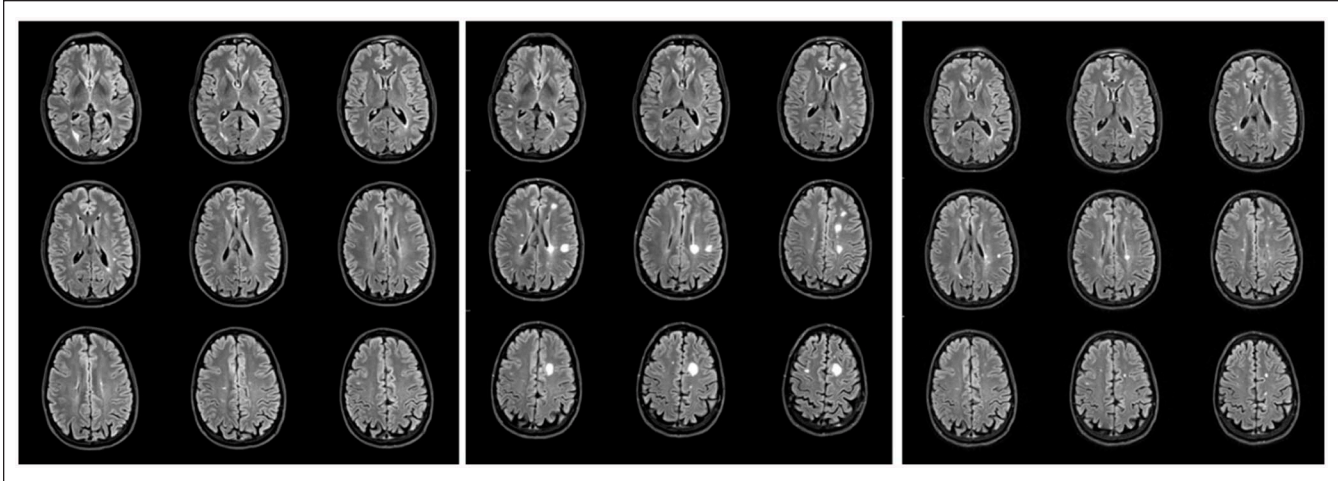


Figure 3. Evolution of lesions. Key: Comparison axial FLAIR images at different time points; baseline magnetic resonance imaging (left), 1 month following BRAF/MEK inhibitors (center), and following B-cell depletion therapy (right). Note the acceleration of lesion load following BRAF/MEK therapy followed by marked improvement.

Since he had known metastatic melanoma and his brain MRI appearance was alarming, potentially so for metastatic disease, a neurosurgical consultant did recommend a brain biopsy. His clinical status was not extreme and his brain MRI appearance greatly favored MS with the majority of lesions (83%) showing the central vein sign (a new finding further supporting MS rather than malignancy, especially when >40% of lesions show central veins).⁶ CSF analysis did not show any evidence of melanoma. A 3-day course of 1000 mg intravenous MP improved his clinical status and nearly all of the contrast-enhancing lesions resolved.

The occurrence of a malignant melanoma following a 33-month treatment course of fingolimod may be relevant. Several previous case reports⁷⁻¹⁰ and one case series¹¹ demonstrate a higher-than-expected incidence of melanoma while on fingolimod, the latter of which showed statistical significance compared with the expected incidence. Although we attribute the melanoma in part to fingolimod treatment, this rationale is based purely on prior published associations. There is a possibility of a coincidental occurrence due to excess ultraviolet exposure (long distance runner) and positive family history of melanoma, or, less likely, a potential relationship with DMF which the patient was on for 4 months prior to the melanoma presentation and DMF. Additionally, there are no reports of melanoma occurring during the DMF phase III clinical trials DEFINE¹² or CONFIRM.¹³ This stands in contrast to 3 melanomas occurring in the fingolimod phase III TRANSFORMS trial¹⁴ with none in the placebo arm (0.4%, relative risk = 3.6, $P > .05$). The phase III FREEDOMS I and II trials^{15,16} show similar or no melanoma incidence in both the treatment and control arms. Of note, both fingolimod and DMF show antineoplastic properties in both murine and in vitro melanoma models

(DMF^{17,18}; fingolimod¹⁹). Although increased vigilance and regular skin checks for patients taking fingolimod treatment for MS may be recommended in this case, a superficial primary melanoma was not observed.

The combination of BRAF/MEK inhibitory treatment has been life saving for many people. But the activation of prior MS is also a significant adverse event and represents a risk which should be accounted for in risk/benefit medical decision making. In this case, DMF was insufficient to control disease activity; whereas B-cell depletion therapy has been successful in preventing further MS relapses. In over 3 years of clinical follow-up, there has been no recurrence of melanoma or MS inflammatory disease activity.

Conclusions

We recommend vigilance prior to starting kinase inhibitor therapy for melanoma in patients with relapsing MS, as it was associated here with a significant inflammatory exacerbation. The clinical appearance and careful analysis of MRI, including the use of the central vein sign, may be informative to differentiate MS exacerbation from metastatic melanoma.

Authors' Note

The datasets and images used and analyzed for the case report are included in this published article. The datasets generated and/or analyzed during the current study are not publicly available due to institutional privacy regulations of patients' medical records data but are available from the corresponding author on reasonable request.

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Author Contributions

CCH, RH, ST, JT, and KRE contributed to the conception, design, analysis and interpretation of findings, and writing of the case report. RS, MR, and VK were responsible for literature search and data collection.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Written informed consent was obtained from the patient for his anonymized information and/or clinical images to be published in this article.

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