Ref: Ro J Neurol. 2017;XVI(4)
DOI: 10.37897/RJN.2017.4.9

Multiple cerebral melanoma metastases with unknown primary tumor location: A case report

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ABSTRACT

Introduction. Diagnostic and therapeutic approach of multiple cerebral lesions is often challenging.
Case report. A 66-year-old man with unremarkable medical history was admitted to our hospital for recent inability and stereotyped movements of the left upper limb. Brain MRI identified eight tumoral masses with contrast enhancement and marked SWI signal loss that displayed increased metabolic activity on 18F-FDG PET/CT scan. Cerebral biopsy led to the diagnosis of melanoma with BRAF V600E mutation. Stereotactic radiosurgery and molecular therapy were planned afterwards.
Conclusion. Brain MRI is a useful tool in guiding diagnosis of cerebral metastases of unknown origin.

Keywords: cerebral metastases, unknown primary tumor, melanoma, BRAF mutation, SWI hypointensity, fluid-blood level

INTRODUCTION

Mutiple cerebral lesions without identified primary tumor often raise diagnostic and therapeutic dilemmas. In this report, we present a mild symptomatic case of multiple melanoma brain metastases and discuss the importance of brain MRI in distinguishing different neoplasms, as well as the therapeutic strategies for melanoma brain metastases.

CASE REPORT

A 66-year-old man was admitted to our hospital for persistent left hand inability with sudden onset two weeks earlier. He had recently experienced two episodes of stereotyped movements of the left upper limb. Apart from a right shoulder melonocytic nevus of unknown significance that had been excised 5 years prior, the patient reported irrelevant medical history.

Clinical examination identified global hypoprosexia and left upper limb motor deficit (4/5 MRC scale). Blood tests were within normal range, including serology for parasitoses (Echinococcus, Taenia, Toxocara and Toxoplasma) and HIV infection. Cerebral MRI was performed, showing eight lesions with contrast enhancement, marked SWI signal loss and peri or intratumoral bleeding (details in Table 1 and Figures 1, 2 and 3). On ^{18}F-FDG PET/CT scan increased metabolic activity of brain lesions was noticed, indicating metastases with unknown primary site. Cerebral biopsy from the right frontal lesion was performed, histopathological examination identifying a poorly differentiated carcinoma. Furthermore, immunohistochemistry tests and molecular testing by PCR were applied, diagnosing melanoma with BRAF V600E mutation.

Remission of neurologic deficit was achieved with symptomatic treatment (i.e. intravenous dexa-

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Article History:
Received: 9 November 2017
Accepted: 22 November 2017

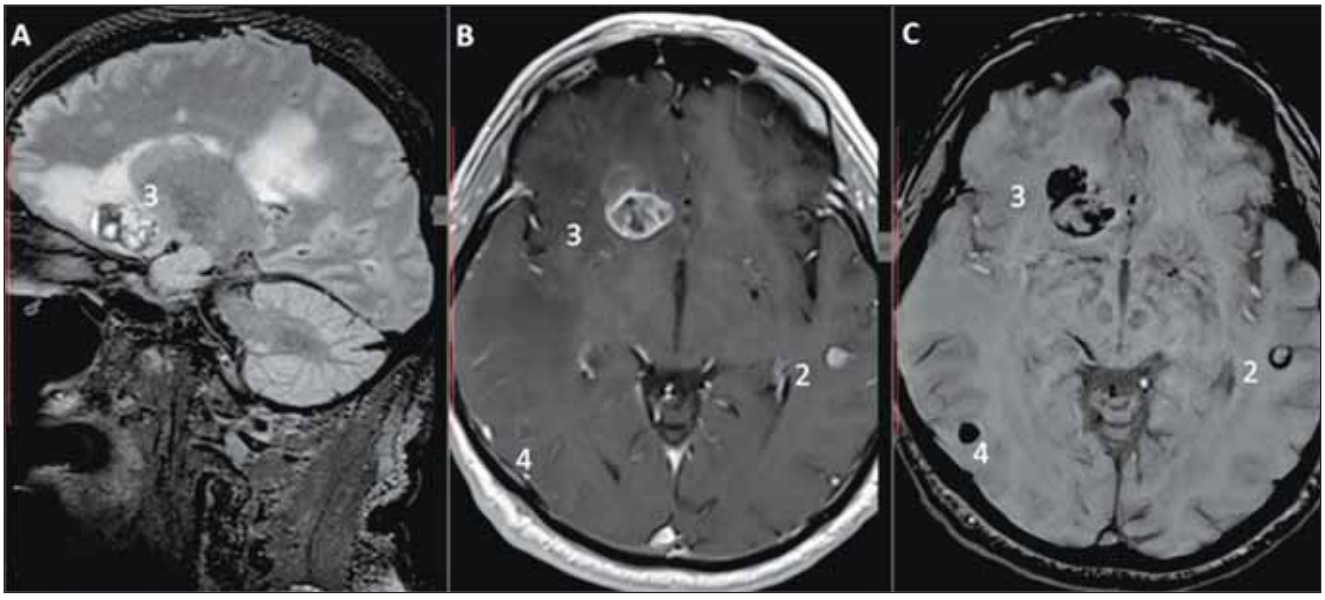

FIGURE 1. *A – FLAIR, B – T1 + contrast, C – SWI.* **Lesion no. 3** *located in the right frontal lobe shows high FLAIR, low SWI signal and ring CE and contiguous hematoma with a fluid-blood level on FLAIR sequence.*
Lesion no. 4 *is seen in the right temporal lobe and shows marked SWI signal loss, T1 hypointensity with small ring CE.*
Lesion no. 2 *is seen in the left temporal lobe with normal central SWI signal and peripheral rim signal loss and marked CE.*

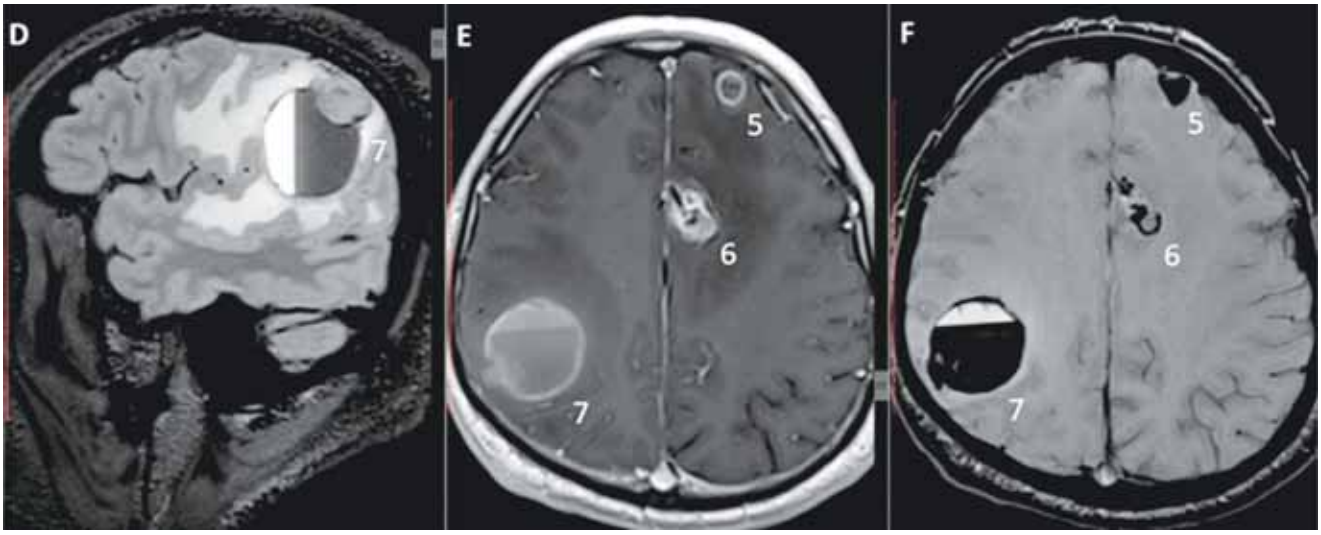

FIGURE 2. *D – FLAIR, E – T1 + contrast, F – SWI.* **Lesion no. 7** *displays an iso/hyperintense signal on FLAIR and T1/SWI signal loss in the right parietal lobe and an adjacent large hematoma with a fluid-blood level.*
Lesion no. 6 *is in the medial region of the left frontal lobe and shows heterogeneous CE and SWI hypointensity.*
Lesion no. 5 *is located in the anterior part of the frontal lobe and has both marked SWI signal loss and ring CE.*

methasone 16 mg daily) and epileptic seizures emerged no longer following levetiracetam use. The patient was afterwards guided towards an oncology department where stereotactic radiosurgery and targeted inhibition of BRAF kinase (molecular therapy) were planned. Periodic reevaluation would be provided in order to identify the primary tumor and treatment complications.

DISCUSSION

A cerebral lesion with malignant features requires differentiation between primary brain tumor and brain metastasis in order to apply the appropriate management strategy. In our case, the large number of brain lesions and ^{18}F-FDG PET/CT appearance facilitated the diagnosis of multiple brain metastases from an undetected primary site. The

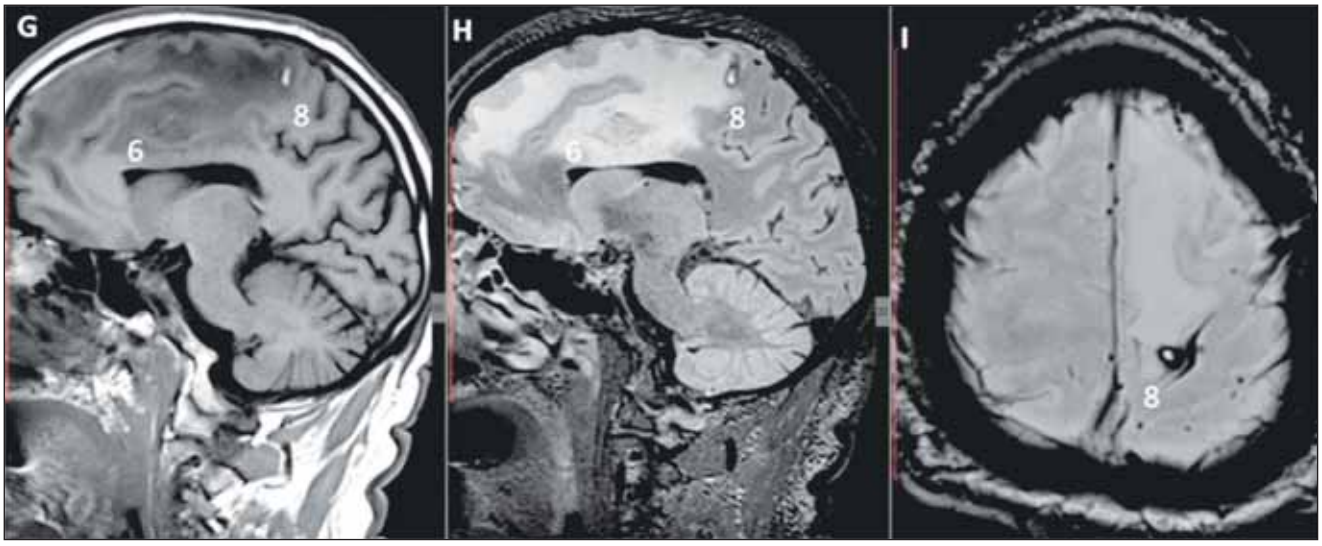

FIGURE 3. *G – T1, H – FLAIR, I – SWI.* **Lesion no. 8** *is noticed in the left parietal lobe as a hyperintense T1/FLAIR/SWI lesion with a hypointense T1/FLAIR/SWI rim.* **Lesion no. 6** *appears in heterogeneous signal on T1/FLAIR.*

most common causes of brain metastases are lung and breast cancers followed by melanoma (1); moreover, when the clinical presentation is not metachronous, lung cancer is still most frequently diagnosed during follow-up period (2).

Cerebral MRI could provide useful information regarding tumor's origin. Radbruch et al. emphasized the importance of SWI sequence, namely the percentage of low SWI signal in the tumoral mass to distinguish between melanoma and other neoplasms (3). A cut-off value of 3% SWI signal loss was found to be suitable to differentiate melanoma from breast cancer (values above 3% indicating melanoma), whereas values of SWI signal loss above 20% suggest melanoma instead of lung cancer (3). The marked SWI signal loss of melanoma metastases is believed to be the consequence of either melanin that chelates metal ions or blood products resulting from microbleeds (3). Nevertheless, higher melanin content was proved to correlate with T1 hyperintensity as opposed to SWI signal loss, arguing for the theory that microbleeds are the ones responsible for the SWI features of melanoma (4,5). In our case, all lesions appeared hypointense on SWI sequences, five of them showing obvious signs of peri or intratumoral bleeding. Three lesions had adjacent fluid-blood level suggestive of acute hemorrhage, an unusual finding in intracerebral hemorrhage that has been described in melanoma metastases (6). Another particular feature was the presence of two hyperintense lesions on T1, T2 and SWI sequences evocative for late subacute bleeding (due to extracellular methemoglobin), as opposed to common knowledge that all blood products appear SWI hypointense (7).

Although brain MRI is highly indicative of melanoma metastases, cerebral biopsy is mandatory in order to confirm the neoplastic origin of the cells. Furthermore, as histopathological examination failed to identify the specific lineage of the carcinoma displayed, immunohistochemical panels were required to enable an accurate classification of the tumor (8).

Brain metastases from an unknown primary tumor require local brain tumor control and repeatedly monitoring for systemic disease. Traditional management strategies include surgery (usually in solitary metastases/very large symptomatic lesions) and radiotherapy (either as whole brain radiation therapy or stereotactic radiosurgery); the observation that despite local control the majority of patients still developed intracranial progression has led to efforts conceiving novel therapies (1). As up to 50% of melanomas display BRAF mutation responsible of significant cellular proliferation, survival and differentiation (tumorigenicity), molecular therapies targeting BRAF inhibition improve the outcome; moreover, they seem to act synergically with radiotherapy by inducing radiosensitivity (1). However, as enhancement of toxicity has also been reported, further large clinical trials are required to prove the efficiency and safety of this therapeutic combination (1).

TABLE 1

Lesion No.	Location	Dimensions (mm)	T1	T2/FLAIR	CE	SWI
1	Right frontal	14.5/22/18.3	↓	↑	ring	↓
Other features: fluid-blood level hematoma (11.1/12.9/12.4 mm) + ring CE + ↑ T1/T2/SWI						
2	Le temporal	4.84/5.36/4.3	↓	↑ + ↓ rim	↑↑	↔ + ↓ rim
3	Right frontal	3.14/6.39/2.65	↓	↑	ring	↔ + ↓ rim
Other features: hematoma (5.19/5.78/5.07 mm) with ring CE						
4	Right temporal	8.17/8.64/3.22	↓	↓	↓	↓
5	Le frontal	10.5/10.1/9.85	↓	↑/↓	ring	↑/↓ + ↓ rim
Other features: fluid-blood level hematoma						
6	Le frontal	22.7/16.9/18.5	↓	H	↑ / H	↓ / H
7	Right parietal	16/16.5/14.3	↓	↑	ring	↔ + ↓
Other features: fluid-blood level hematoma (33.1/33/34.6 mm) with ring CE and ↓ rim on SWI						
8	Le parietal	3.47/3.15/10.3	↑	↑ / ↓ rim	↑↑	↑ + ↓ rim
Other features: intratumoral bleeding						

CE = contrast enhancement, ↓ = low signal, ↑ = high signal, ↑↑ = marked CE, ↔ = normal signal, H = heterogeneous signal

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Conflict of interest: none declared
Financial support: none declared