Absent Response of Intracranial Melanoma Metastases Harboring BRAF V600E Sequence Variation to Vemurafenib

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A 75-year-old man with metastatic malignant melanoma had been treated with the selective BRAF inhibitor vemurafenib at 960 mg twice daily after detection of the BRAF V600E sequence variation by molecular analysis in a cutaneous metastasis. The patient’s clinical symptoms improved promptly within 5 weeks. After 4 months of treatment, no progression of initially hypermetabolic lymph nodes could be detected on computed

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**FIGURE 1.** Macroscopic findings. Note innumerable pigmented melanoma metastases in the ileum (A) and brain (B).

**FIGURE 2.** Microscopic findings. A, Ileal metastasis consisting predominantly of pigment-laden macrophages and scattered viable tumor cells (hematoxylin-eosin, original magnification ×200). B, Viable brain metastasis in the frontal cortex with single interspersed melanophages (hematoxylin-eosin, original magnification ×200). C, On immunohistochemical analysis, tumor cells of the brain metastasis stained positive for the BRAF V600E sequence variation—specific antibody. Note strong staining of melanophages, BRAF V600E, VE1. (Ultrared, original magnification ×200).
tomography. Hepatic and splenic metastases had regressed. Three weeks before death, miliary brain metastases were detected on a magnetic resonance imaging scan of the head. The patient, who also had long-standing Parkinson disease, died of aspiration pneumonia 5 months after initiation of vemurafenib treatment.

Autopsy revealed innumerable pigmented extracranial and intracranial metastatic lesions (Figure 1, A and B). On histologic examination, pigmented lesions in the thyroid, pleura, pancreas, spleen, adrenal glands, testis, mediastinum, and lymph nodes consisted exclusively of pigment-laden macrophages with no viable tumor cells. The remaining extracranial lesions contained a mixture of melanophages and a few viable tumor cells scattered throughout the metastatic lesions (Figure 2, A). In contrast, metastatic brain lesions lacked any signs of a therapeutic response (Figure 2, B) despite the presence of \( \text{BRAF V600E} \) sequence variation on immunohistochemical (Figure 2, C) and molecular analysis.

Inefficiency of vemurafenib in brain metastases has been described before. Patients with untreated metastases to the central nervous system were excluded from most vemurafenib clinical studies. For these patients, drugs with greater brain penetration such as dabrafenib might be more effective than vemurafenib.\(^1,2,3\)