

# Diffuse Hemorrhagic Brain Metastases in an ALK Fusion Positive Patient on Crizotinib

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A 52-year-old woman and lifetime nonsmoker was presented initially with pleuritic chest pain. Investigations revealed a small lower left lobe nodule, extensive intrathoracic lymphadenopathy, and a large adnexal lesion. Her initial brain magnetic resonance imaging was negative. Biopsies revealed an adenocarcinoma, TTF-1 positive compatible with a primary lung carcinoma. Molecular testing was negative for *epidermal growth factor receptor* mutations, but immunohistochemical staining revealed positivity for *ELM4-ALK* fusion, which was confirmed by FISH. After failing standard chemotherapy, crizotinib was initiated as second-line therapy with rapid symptomatic and radiological response. She remained on crizotinib for 2 years when she developed a vague and nonspecific feeling of bruising over her right temporal area. She denied any other neurological symptoms and was otherwise clinically asymptomatic. Despite the unusual symptoms a brain magnetic resonance imaging was ordered. Surprisingly, imaging revealed innumerable metastatic foci distributed throughout the brain (Fig. 1). The lesions ranged from 5 to 10 mm with the largest lesion measuring 1.7 cm. Almost all the lesions showed evidence of iron deposition indicating hemorrhagic metastases. Restaging computed tomography scans of the chest and abdomen continued to show a sustained partial response to crizotinib. The patient was referred to radiation oncology where she benefited from whole brain radiotherapy and crizotinib therapy was continued.

The systemic efficacy of crizotinib in *ALK*-positive patients has been well described.<sup>1,2</sup> However, isolated brain metastases, as defined as central nervous system (CNS) relapse without evidence of extracranial progression, is becoming an increasingly common pattern of progression in this patient population.<sup>3,4</sup> Isolated relapse could be explained by reduced concentrations of crizotinib in cerebrospinal fluid suggesting that the CNS represents a sanctuary site.<sup>5</sup> This mirrors the situation seen in patients treated with epidermal growth factor receptor tyrosine kinase

inhibitors.<sup>6</sup> Interestingly, our patient presented with diffuse hemorrhagic metastases. The incidence of spontaneous intracranial hemorrhage in patients with non-small-cell lung cancer (NSCLC) with brain metastasis is estimated at 1.2%.<sup>7</sup> There are no published reports of intracranial hemorrhage in patients with *ALK*-positive NSCLC treated with crizotinib. A recent Children's Oncology Group trial evaluated single agent crizotinib in pediatric oncology patients with refractory solid tumors.<sup>8</sup> Two patients with primary CNS tumors developed intratumoral hemorrhages which were deemed possibly related to crizotinib. Subsequently, the trial was amended to exclude future patients with CNS tumors. There are also several reports of patients with NSCLC presenting with intracranial hemorrhage (both subdural and intratumoral) while on gefitinib, although it could not be confirmed whether bleeding was spontaneous or treatment related.<sup>9,10</sup> Whereas there is no definitive evidence to suggest that patients on tyrosine kinase inhibitors are at higher risk of intracranial bleeding, physicians must remain vigilant as the use of targeted therapies and incidence of isolated CNS relapse increases.

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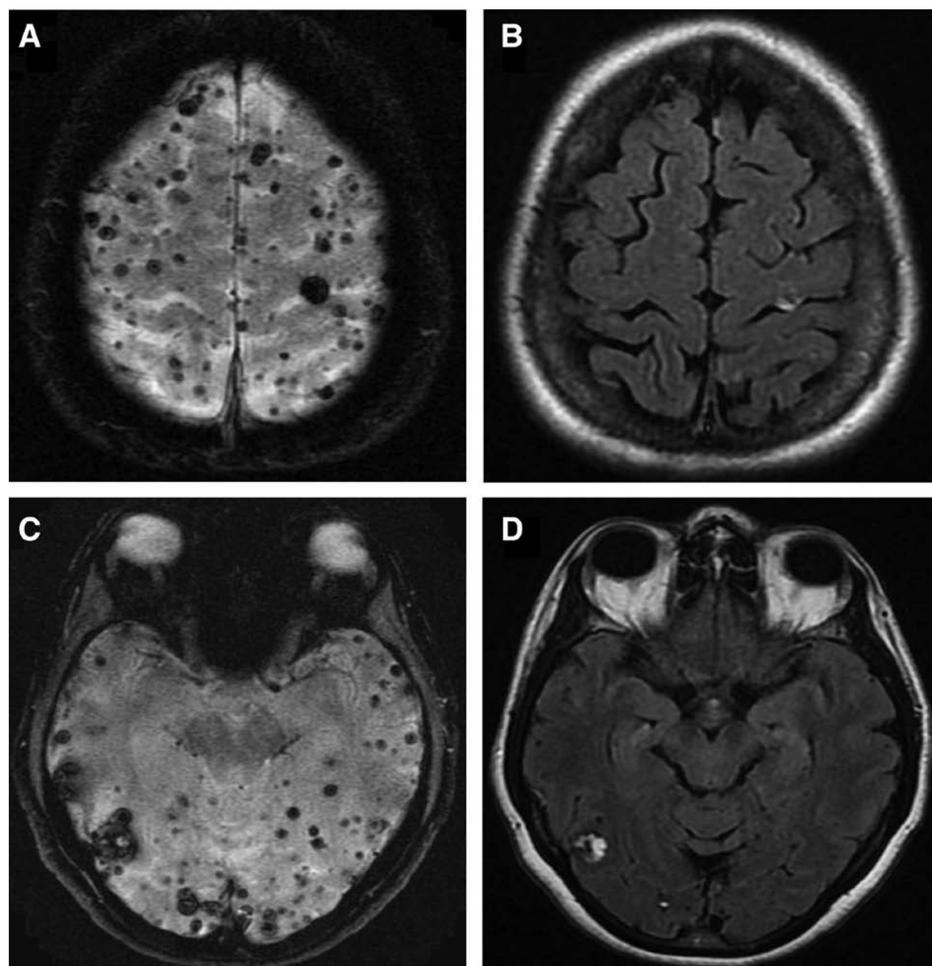
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**FIGURE 1.** A–D, Diffuse hemorrhagic metastatic foci in the brain after 2 years of crizotinib therapy. The presence of iron deposition indicating hemorrhagic nature better seen with GRE with gadolinium contrast MRI sequences (A, C), than with FLAIR sequences (B, D). GRE, gradient echo; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.

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