Pathol. Oncol. Res. (2012) 18:539–543
DOI 10.1007/s12253-011-9464-x

COMMUNICATION

Relapsing Tumefactive Lesion in an Adult with Medulloblastoma Previously Treated with Chemoradiotherapy and Stem Cell Transplant

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Received: 30 July 2011 / Accepted: 19 September 2011 / Published online: 28 September 2011

Abstract Herein, we present an adult case of medulloblastoma who received chemotherapy, radiation therapy and stem cell transplantation, and underwent multiple surgical resections for what were thought to be recurrences; however pathology confirmed a diagnosis of relapsing tumefactive lesions. This phenomenon seems to be a consequence of stem cell transplantation rather than a simple radiation treatment effect.

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Keywords Medulloblastoma · Tumefactive · Stem cell transplant · Radiation necrosis

Case Report

A previously healthy 41-year-old man, presented with persistent headache, vomiting, diplopia and unsteady gait. MRI of the brain showed hydrocephalus with a 3.3×2.8 cm enhancing left posterior fossa mass that appeared to infiltrate the leptomeninges (Fig. 1a–b). Intraoperatively the mass appeared adherent to the meninges and a subtotal resection was performed based on post-op MRI (Fig. 1c–d). The pathology showed a malignant neoplasm made up of small, round neuroblastic cells embedded in a fine synaptophysin-positive neuropil matrix (Fig. 2a–b). The mitotic index was focally brisk and there were single necrotic and karyorrhectic cells. Reticulin and trichrome stains demonstrated a vaguely lobular architecture, consistent with the growth pattern of desmoplastic medulloblastoma. Focally, stroma composed of dense connective tissue was also found, supporting the radiographic suspicion of leptomeningeal involvement (Fig. 2c). A subset of the tumor cells demonstrated low-level copy number increases of the EGFR locus consistent with aneuploidy but high-level amplification was absent (Fig. 2d). Overall, the pathology supported the diagnosis of medulloblastoma. Subsequent MRIs of the entire spine showed no abnormal enhancing lesions. Cytology examination of CSF revealed no evidence of leptomeningeal seeding. A systemic work-up, including computed tomography of abdomen, pelvis, chest were negative for metastatic disease. The baseline

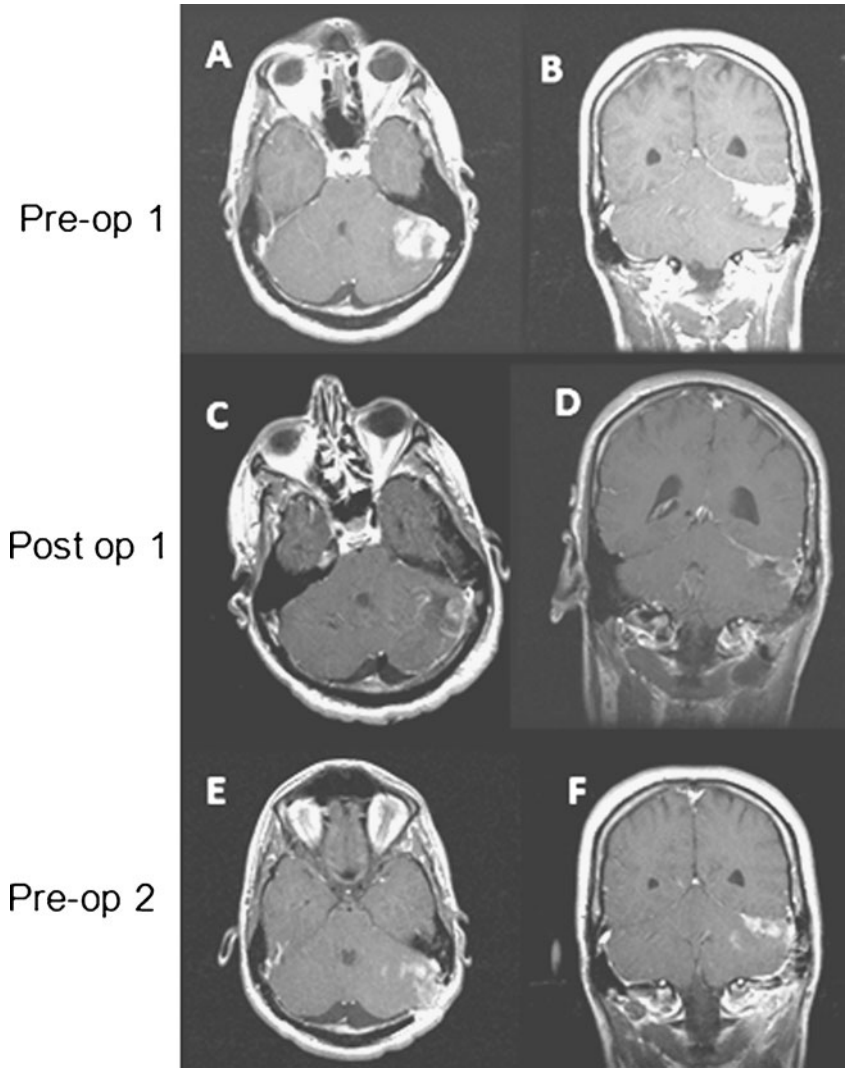

Fig. 1 Brain MRI images. Pre-operative (**a**,**b**) and postoperative (**c**–**f**) at various clinical stages. **a**, **c**, **e** are axial post-gadolinium T1 images and **b**, **d**, f are coronal post-gadolinium T1 images

MRI of the brain prior to starting radiation therapy, however, showed progression of the lesion (Fig. 1e–f). Craniospinal irradiation was given with a total dose of 5,940 cGy administered to the tumor bed and 3,600 cGy to the spine, delivered concurrently with oral etoposide over 2 months. A repeat brain MRI showed persisting nodular enhancement in the left cerebellar hemisphere (Fig. 3a–b), which was hypermetabolic on FDG-PET scan, so the patient underwent stereotactic radiotherapy boost to the residual disease, to the total dose of 2,800 cGy in 7 fractions. Subsequent MRIs showed increase in enhancing lesion (Fig. 3c–d) which was positive on FDG-PET scan, so the patient underwent a second surgical resection, and the pathology was again suggestive of cerebellar medulloblastoma (Fig. 4a–b). The patient had brain MRI a month after surgery, which demonstrated postoperative changes with minimal blood products without any clear evidence of residual or recurrent tumor. Symptom relieve was also noted. The patient was started on high-dose chemotherapy with cytoxan and carboplatin, followed by autologous stem-cell transplantation. Follow-up MRI, PET scan and MRI spectroscopy showed no significant changes and the patient was clinically stable. However, 1 month later, a spine MRI showed enhancement along the anterior conus and cauda equina at the L1–L2 level, suggesting a possible leptomeningeal involvement. Brain MRI showed only a subtle enhancement around the surgical resection (Fig. 3c–d) and a spinal tap was negative for malignant cells. Seven months post-stem cell transplantation, a brain MRI showed an increase in enhancement (Fig. 3e–f) and a PET scan demonstrated an interval

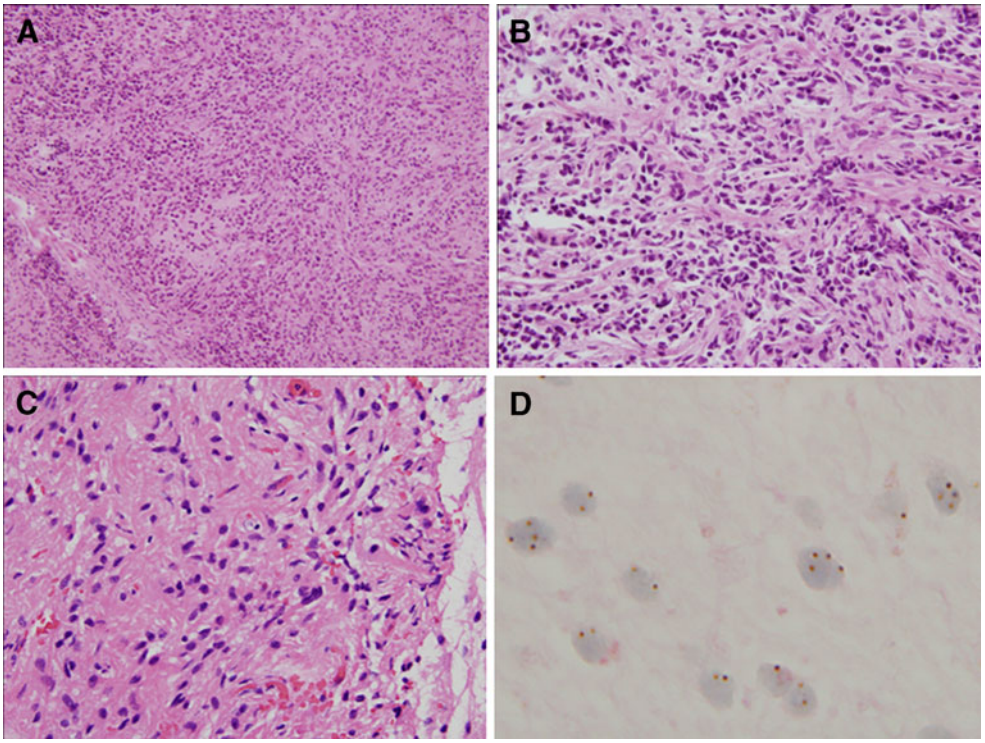

Fig. 2 Histopathologic features of the tumor after initial resection. (**a**–**c**). (**d**). Low-level Copies of EGFR locus within a subset of tumoral cells

increase in FDG uptake focally, yet again raising suspicion for tumor recurrence. The patient was closely monitored. Several MRI and PET scans over a 3 month period revealed continued enhancement and hypermetabolism. Concerns remained about tumor recurrence but changes related to prior radiation, surgery or transplantation were also considered. Due to uncertain nature of lesion, the patient underwent a third surgical resection. The pathology showed a few atypical cells and a low MIB-1 count (Fig. 4c). Mitoses, vascular proliferation and necrosis were not seen. Overall, the findings were most consistent with non-specific gliosis although a recurring neoplasm could not be entirely excluded (Fig. 4d). The patient ultimately underwent two additional surgeries over the next year when MRI and PET scans indicated increased growth of the lesion. The MRI images prior to the final surgery (Fig. 3g–h) in fact demonstrated infiltrative features and meningeal involvement. It was surprising that the pathology of each of these lesions continued to demonstrate reactive gliosis and treatment associated changes despite the MRI and PET scans that were highly concerning for tumor recurrence. The radiographic changes were therefore indicative of reactive changes to radiation and/or transplantation. Despite mild cognitive difficulties due to cerebellar damage and radiation, the patient has been clinically stable and he continues to do well without any new symptoms 7 years after his final surgery.

Discussion

This case is very instructive clinically. The patient was treated with both aggressive chemotherapy causing bone marrow suppression and subsequently autologous stem cell transplantation. He was for the most part clinically stable during the growth and regrowth of his lesion. In general, recurring tumors do produce symptoms but this is not true universally. Cranial irradiation induced effects such as atrophy, radiation necrosis and vasculopathy have previously been well described [1, 2]. The immense diagnostic challenge lies in differentiating these radiation induced effects from recurrent or residual intracranial tumor [3]. Despite the fact that the neuroimaging techniques available today are relatively accurate in the distinction between radiation effects and recurring tumor [4–6], the risk of misdiagnosing, and therefore mistreating a patient, still remains a problem. Correctly differentiating between the two is crucial as it influences treatment and prognosis. The distinction can be particularly challenging in the setting of medulloblastoma. Fouladi et al. reported that out of 134 pediatric patients with medullobastoma or supratentorial PNET

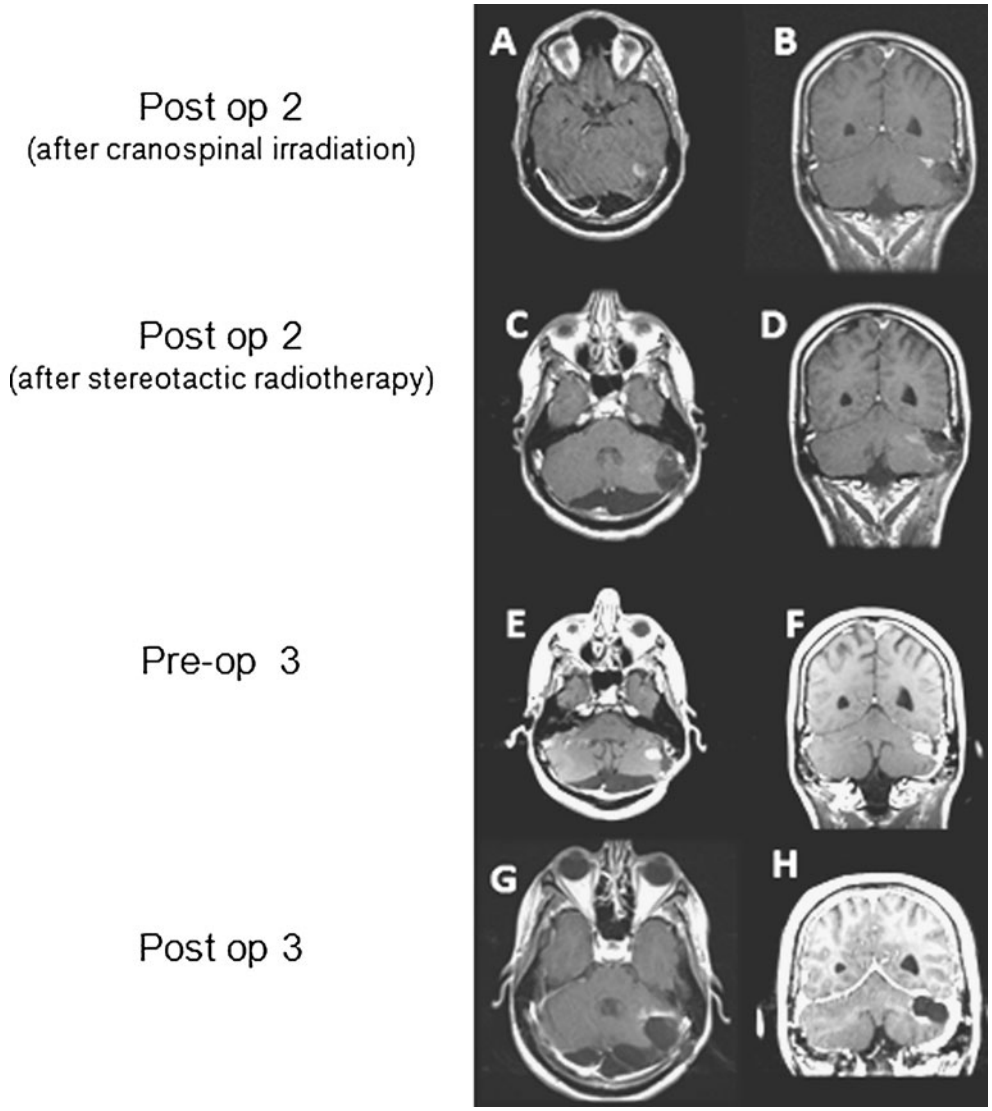

Fig. 3 Axial and coronal images of Brain MRI at various stages. **a**,**b**: nodular enhancement in left cerebellar region. **c**, **d**: status post resection. **e**,**f**: persistent nodular enhancement in left cerebellar lobe. **g**,**h**: status post resection. **a**, **c**, **e**, **g** are axial post-gadolinium T1 images and **b**, **d**, **f**, **h** are coronal post-gadolinium T1 images

(primary neuroectodermal tumor), 22 showed signs of white matter lesions on T1 and/or T2 weighted MR images. 16 out of the 22 patients (73%) had resolution of their lesion relatively quickly, with a median time of resolution being 6.2 months. These white matter lesions were asymptomatic in the majority of patients (only 3 out of 22 experienced symptoms) [7]. They conclude that despite the appearance of recurring lesions on MR images, patients may best be served by careful monitoring of the lesion. To reduce the risk of misdiagnosis and mistreatment a careful clinical, radiological and behavioral observation of the patient may be critical. In the case of our patient, the third to fifth surgeries showed no clear evidence of tumor recurrence even though the MRI and PET studies were concerning. As the patient in this report demonstrates, a similar phenomenom may occur in adult medulloblastoma patients after chemoradiation and stem cell transplant. As far as we know, this is the first report of such a case in an adult with medulloblastoma, although several cases have been presented in the pediatric literature [8–10]. Khong PL, et al. showed that diffusion tensor (DT) imaging with use of fractional anisotropy (FA) index could be a helpful procedure when detecting treatment induced white matter injuries [11]. From this, we can conclude that this phenomenon can be seen most likely as a consequence of stem cell transplantation in medulloblastoma patients rather than a simple radiation treatment effect. A combination of many different imaging methods may help to understand the nature of the lesion and lead to more optimal management of such recurring lesions.

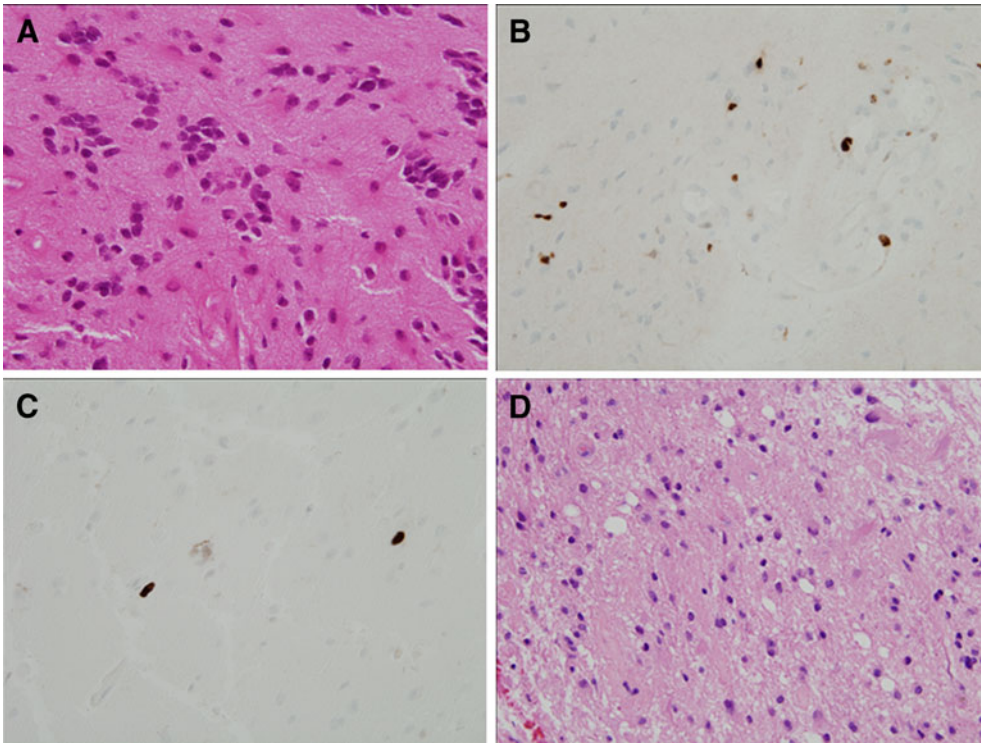

Fig. 4 Histopathologic (**a**,**d**) and Ki67 (**b**,**c**) immunohistochemical features of the tissue after second (**a**,**b**) and third (**c**,**d**) surgical resections

Acknowledgements This work was supported in part by grants from NIH 3P30CA023100-25S8 to S. Kesari

Financial Disclosures The authors report no disclosures.

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