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Brain radionecrosis after radiation therapy for atypical meningioma. An unexpected treatment outcome. Case report

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ABSTRACT

Introduction. Atypical Meningioma (AM) is at high risk of local failure. The role of radiation therapy (XRT) as an adjuvant to surgical resection is incompletely defined. The most deleterious consequence of brain-directed XRT is radiation necrosis. Brain radionecrosis (BRN) after AM has been rarely reported. The relevant literature is reviewed, highlighting its diagnostic challenges.

Case presentation. We report a 25-year-old male with a BRN after adjuvant XRT for AM, which has been misdiagnosed as a recurrent neoplastic lesion upon magnetic resonance spectroscopy (MRS) examination. Surgery and histopathological description were made and yielded a definitive diagnosis of BRN. The patient was treated by dexamethasone with concomitant hyperbaric oxygen therapy (HBO2). The patient showed a further progression of the disease. Therefore, he was elected to receive bevacizumab. However, the patient finally died for refractory brain edema.

Conclusion. BRN is a relatively rare instance after XRT for AM. There is no single modality that can reliably distinguish BRN from tumour recurrence. Therefore, reaching an early prompt treatment decision is challenging.

INTRODUCTION

Meningiomas are extra-axial tumors that represent 30% of all primary brain tumors (1). The most common locations are along the cerebral falx and over the cerebral convexity, such in the case reported here (2). AM falls under the World health organization (WHO) Grade II tumors, accounting for 20% of all meningiomas (1-3). The distinction of AM is given to the meningeal tumor that exhibits high mitotic rate and brain invasion (1, 3). The median age for AM patients at diagnosis is 56 years (3). AM has a female predominance and a high predilection for recurrence (1-3).

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Currently, AM's treatment guideline entails the combination of maximum safe surgical resection and XRT (1-3). Despite the absence of solid evidence to support XRT for AM, several studies have reported encouraging results (1, 2). XRT has been shown to improve AM prognosis with a median 5-year progression-free survival of 54.2% ranging from 38% to 100% after XRT (1). Nevertheless, XRT carries a risk of radiation necrosis (1, 4-16).

Herein, we report a case of BRN after adjuvant XRT for AM, which has been misdiagnosed as a recurrent neoplastic lesion upon the MRS examination.

Case presentation

A 25-year-old male presented with a nine-month history of intermittent headache, described as 'generalized pressure' and dizziness. The symptoms had become more severe, and weakness on the left side extremities started to progress over the last week. The vital signs were stable, and the patient was fully conscious. Neurological examination showed no abnormality aside from mild left hemiparesis (Grade 4/5 Medical Research Council).

Cranial computed tomography (CT) scan revealed an enhancing extra-axial mass in the right frontal region, which contained multiple foci of calcification. There was significant peritumoral edema. Cranial magnetic resonance imaging (MRI) showed an iso-intense mass, with an area of low-intensity corresponding to the calcification observed on the CT scan (**Fig. 1**). Magnetic resonance arteriogram and magnetic resonance venogram showed multiple feeding arteries mainly from the anterior cerebral arteries and, to a lesser extent, from the distal right middle cerebral arteries with multiple, prominent draining veins. Based on the radiographic appearance, a diagnosis of right frontal convexity meningioma was made.

The patient underwent a craniotomy with total resection of the mass. The postoperative Cranial CT scan reported no residual tumor with a regression of brain edema (**Fig. 2**). The histopathology was AM (WHO grade II) (**Fig. 3**). This case discussed in the multidisciplinary tumor board. Accordingly, the patient was referred for XRT for a total dose of 60-Gy (30 fractions of 2-Gy) over six weeks duration, all delivered with intensity-modulated technique.

The patient reported new-onset of generalized seizures and worsening of left hemiparesis (Grade 3/5 Medical Research Council) three months after completion of XRT. An electroencephalogram revealed epileptic discharges over the right frontal derivations. Cranial MRI reported an iso-signal poorly defined lesion in T1 and T2 sequences compromising the right frontal lobe with extensive central necrosis and peri-lesional edema (**Fig. 4**). Additionally, a ring, cut green-paper enhancement, was seen involving the genu of the corpus callosum (**Fig. 4**). A confirmatory MRS study was used. The metabolites studied were choline (Cho), which appeared at 1.4ppm, N-acetyl aspartate (NAA) at 0.65ppm, creatine (Cr) at 0.6ppm, and lipid at 1.3ppm (**Fig. 5**). Using multi-voxel MRS, the Cho/NAA ratio > 2.15 and Cho/lipid>1 were favoring a recurrent neoplastic lesion.

Nonetheless, surgery and histopathological description were made and yielded a definitive diagnosis of pure BRN (**Fig. 6**). The lesion was non-vascular and intra-axial involving the right frontal lobe parenchyma and deep, abutting the frontal horn of the lateral ventricle. The patient had improvement of neurologic function after surgical resection.

However, the patient was readmitted due to breakthrough seizures and worsening of left hemiparesis. A high dose of dexamethasone was initiated with concomitant HBO2. The patient showed a further progression of the disease. Thus, he was elected to receive four cycles of 5mg/kg Bevacizumab intravenously every two weeks. However, the patient finally died for refractory brain edema.

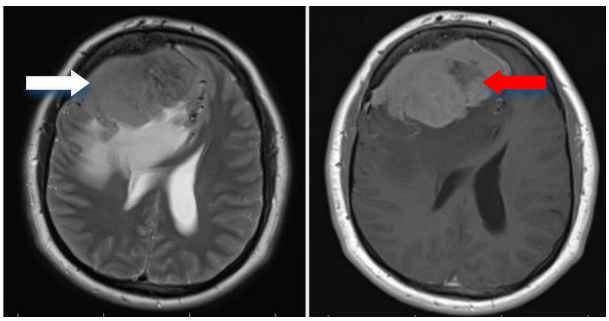


Figure 1. Preoperative, MRI brain of the lesion showing iso-intense signal (White arrow) in the T2-weighted sequence. The tumor homogeneously enhanced with areas of central hypo-intensity (Red arrow) in post-contrast, T1-weighted images.

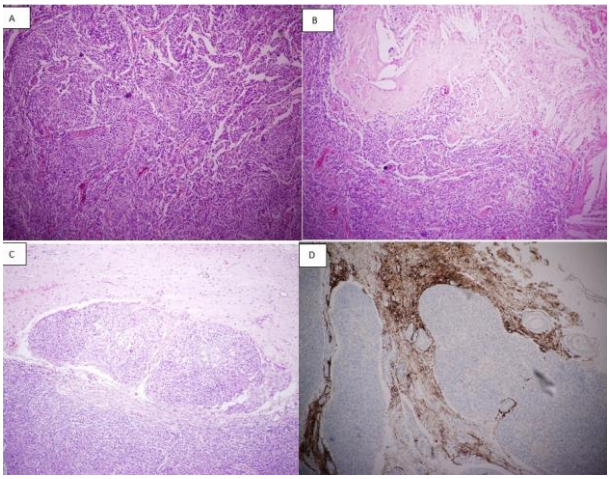


Figure 2. Sections from atypical meningioma show syncytial pattern along with areas of necrosis,10X(A&B). Brain invasion noted in H&; E stain and highlighted by GFAP immunostain,10X(C&D).

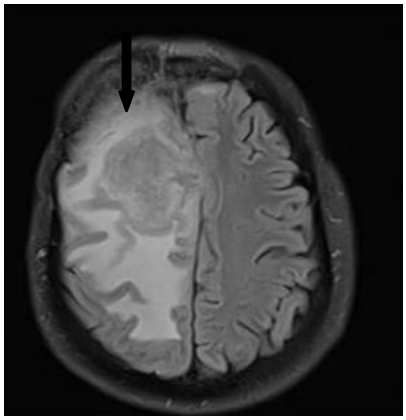


Figure 4. MRI brain of the lesion showing an ill-defined, peripheral enhancing lesion (White arrow) with central necrosis in post-contrast, T1-weighted sequence. The genu of the corpus callosum was also enhanced (Red arrow)—the lesion iso-intense (Black arrow) in the T2-weighted sequence, surrounded by extensive, vasogenic edema.

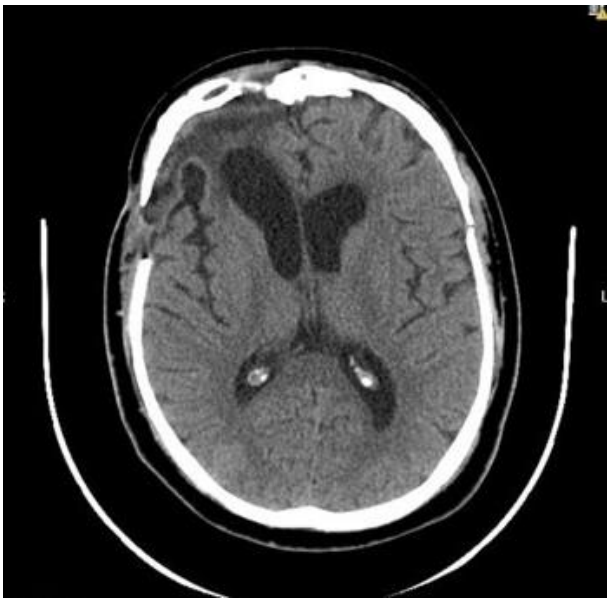


Figure 3. A Postoperative CT scan of the brain showing total excision of the tumor with regression of brain edema.

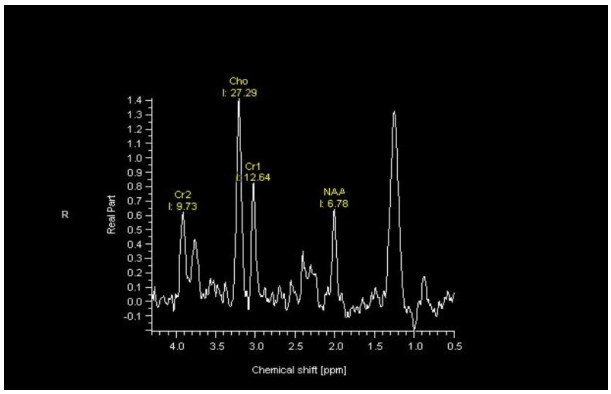
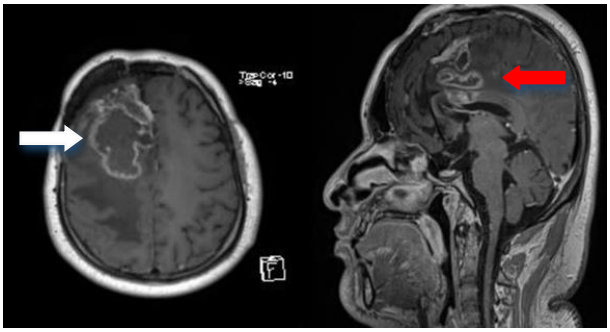


Figure 5. Magnetic resonant spectroscopy showed a high elevation of Cho and depression of NAA.



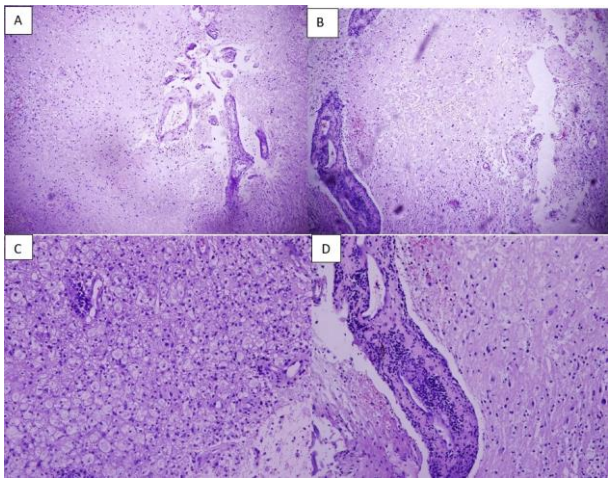


Figure 6. Post RT resection specimen is entirely submitted, and sections show areas of necrosis, mixed inflammation,10x(A&B).

Infiltration by foamy histiocytes,20x(C) and vasculitis, 20x(D). No neoplastic pathology noted.

Discussion

The incidence of BRN ranged from 3.4% to 16.7% for AM after XRT (1). It peaks at two years after XRT and pursues a regressive course in most cases (5, 6). It regresses 40% at six months and 76% at 18 months from the onset of BRN's radiological changes (6). There is a myriad of reasons for this, including total radiation dose, dose per fraction, treatment duration, irradiated volume, and concurrent use of chemotherapy (4-6). Wang TM et al. implicated a radiation injury susceptibility gene (Cep128) as an underlying mechanism of BRN, as it tightly interacts with multiple radiation-resistant genes (7) .

The pathophysiology of BRN is not well understood. However, two main theories suggested. The first theory postulates that irradiation damages endothelial cells by upregulating ceramide. Thus, results in vascular insufficiency and infarction (4, 6, 8, 9). Hypoxia caused by endothelial cell damage leads to the liberation of hypoxia-inducible factor 1α and vascular endothelial growth factor (VEGF) (4, 6, 8, 9). VEGFs induce new vessel formation, but these tend to be leaky capillaries, resulting in perilesional edema (6, 8, 9). The second theory postulates that necrosis arises due to direct injury of the brain parenchyma, especially glial cells. The glial injury causes demyelination and white matter necrosis (4, 6).

The clinical features of BRN vary depending upon the location and size, including features of increased intracranial pressure. The characteristic findings are seizures, hemiparesis, headache, vomiting, poor concentration, and altered level of consciousness (4-6, 10). The literature also reported neurocognitive impairment (hippocampus), especially in children, which includes poor academic performance, distorted self-image, and psychological distress (6, 11).

MRI of the brain will demonstrate some degree of contrast enhancement surrounded by edema (4-6, 9, 10). Although, the patterns of enhancement described in the literature as swiss cheese, cut green-paper or soup bubble, are believed to favor BRN, these patterns posse a 88% negative predictive value (12). MRS is used to assess the metabolite composition of the lesion (6, 13, 14). On MRS, the peak of Cho and the depression of NAA and Cr correlated with a neoplastic lesion than BRN. Anbarloui et al. demonstrated that Cho/NAA > 1.8 or Cho/lipid ratio >1 had increased odds of being a pure neoplastic lesion rather than pure necrosis, with sensitivity and specificity of 73% and 75%, respectively, for Cho/NAA ratio, and 87% for Cho/lipid ratio (13).

Our patient's MRS failed to differentiate BRN from tumor recurrence. The study revealed a neoplastic lesion, and the histopathology was purely BRN. Why there was such a non-concordant finding, it is not clear. Hellstrom J et al. found 51/208 cases of clinically indicated MRS to have false-positive MRS findings (14). As demonstrated by this study, MRS findings are not accurate when compared to the histopathology findings.

Positron emission tomography (PET) scan uses 18F-fluorodeoxyglucose (FDG) to assess the tissue activity (4, 6, 10). Necrotic tissue will demonstrate low FDG uptake (4, 6, 10). However, a PET scan may not distinguish BRN when epileptic activity coexists. Sasaki M et al. reported the case of 37 years old female with ependymoma treated by surgery and XRT, complicated later by BRN, presented with seizures, and the PET scan was showing abnormally high FDG uptake (10).

As the viable tumor has an intact vasculature, perfusion MRI can predict tumor recurrence (4, 6, 12, 14). Sugahara et al. suggested that a relative cerebral blood volume (rCBV) >2.1 favors tumor recurrence, while an rCBV value <0.6 favors radiation necrosis (15). However, we could not be able to spare time for this advanced imaging method. We applied surgical intervention to relieve the mass effects and to obtain a histopathology specimen.

BRN responds well to conservative management if diagnosed early (4, 6, 9, 12). Corticotherpay is the first option to treat these cases (6, 9, 12). Other supportive treatments include antiplatelet, anticoagulant, and a high dose of vitamins (6, 9). HBOT utilized to improve tissue oxygenation and neovascularization (4, 6). Several studies found that Bevacizumab, an anti-VEGF monoclonal antibody is effective in treating radiation-induced brain edema (4, 6, 8, 9). However, the safety of Bevacizumab warrants further validation as the only randomized control trial published by Levin VA et al. in 2011 involved a limited number of 14 patients (9). If the conservative management fails or significant mass effects exist, then surgical extirpation is mandatory

(4, 6, 9, 12). Recently, laser interstitial thermal therapy (LITT) has become a treatment option for lesions that are difficult to access or for patients who are not candidates for surgery (16). A review study by Katherine G et al. documented a favorable clinical response after LITT for BRN (16). Unfortunately, none of the mentioned treatment approaches utilized halted the progression of BRN in this patient.

Conclusion

This case highlights the fact that BRN is a potential complication of XRT for AM. There is no shadow of a doubt that a diagnosis of BRN is a matter of high importance in all settings since misinterpretation can result in delays in treatment and thus noticeable morbidity and mortality. There is no single modality that can reliably distinguish BRN from tumor recurrence. Thus, multimodality approach is highly recommended.

Abbreviations

AM: Atypical meningioma; XRT: Radiation therapy; BRN: Brain radionecrosis; MRS: Magnetic resonance spectrometry; HBO2: Hyperbaric oxygen therapy; WHO: World Health Organization; CT: Computed tomography; MRI: Magnetic resonance imaging; Cho: Choline; NAA: N-acetyl aspartate; Cr: Creatine; VEGF: Vascular endothelial growth factor; PET: Positron emission tomography; FDG: 18F-fluoro-deoxyglucose; rCBV: relative cerebral blood volume; LITT: laser interstitial thermal therapy.

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