RECURRENT OLIGODENDROGLIOMA IDENTIFIED AFTER AN INTRATUMORAL HEMORRHAGE 10 YEARS POST-DIAGNOSIS

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ABSTRACT:
Oligodendrogliomas are slow-growing brain tumors arising from the glial cells. The initial treatment consists of debulking surgery, chemotherapy, and/or radiation therapy. Recurrence of the tumor is often diagnosed within the first few years post-treatment and it is usually diagnosed on follow-up MRI. We report an unusual case of recurrent large oligodendroglioma identified after an intratumoral hemorrhage that occurred 8 years post initial treatment. Serial annual MRI studies in the post-treatment period were compared, suggesting no tumor recurrence. However, when all the MRI studies are reviewed in a sequential manner, there were very subtle abnormalities consistent with earlier recurrence. This article discusses the role of clinical and imaging evaluations in the diagnosis of oligodendroglioma recurrence.

INTRODUCTION:
Gliarial cells are non-neuronal brain cells that have multiple roles in the nervous system, including participating in homeostasis, synapse transmission, neuronal support and protection. Gliomas are central nervous system (CNS) tumors arising from the glial cells. They are classified by the World Health Organization (WHO) based on grade and prognosis. Gliomas range from grade I tumors (pilocytic astrocytoma) that are non-progressive and hence have better prognosis, to grade IV tumors (glioblastoma multiforme) with the greatest aggressiveness and poorest prognosis1. Low grade gliomas (WHO grade II) encompass mostly oligodendrogliomas and oligoastrocytomas and represent about 11% of the primary CNS tumors that are diagnosed in Canada and USA every year.2 Oligodendrogliomas constitute approximately 5-18% of all grade II gliomas.3

The typical patient with oligodendroglioma is male, Caucasian, median age 35 years.3 The typical initial presentation includes new onset of seizures.2 Neurological function on physical examination may be normal, or alternatively there may be motor and/or sensory deficits (e.g., contralateral motor weakness if primary motor cortex or
CASE REPORT:

A 33 year-old man without any prior history of seizures presented to a community hospital in December 2001 with a grand mal seizure. CT scan of his brain demonstrated a left frontal lobe mass with surrounding edema. In April 2002, he underwent craniotomy and partial-to-subtotal excision of the tumor. The pathologist reported an infiltrating glial neoplasm with satellitosis, but without cellular atypia, necrosis or endovascular proliferation. Subsequently, the patient underwent 2 cycles of PCV chemotherapy (procarbazine, lomustine and vincristine) followed by 24 cycles of temozolomide (total treatment time was 2 years). The patient declined an extra 6 cycles of temozolomide recommended due to fatigue. The patient also declined the radiation therapy, as he was concerned about radiation-related cognitive impairment. In the post surgical period, he experienced intermittent simple partial seizures involving the right upper extremity. The seizures were successfully treated with phenytoin (100 mg TID).

Following surgery, the patient completed annual clinical assessments, which included brain MRI studies with gadolinium. The MRI studies reported similar findings: encephalomalacia, wedge-shaped surgical bed defect at left frontal lobe with surrounding gliosis, ipsilateral left lateral ventricle ex vacuo dilation, and no evidence of enhancement after gadolinium administration. None of the scans raised any suspicion of recurrence. Of note, the radiologist was given the information at one point that the patient had received radiation therapy when in fact he did not. At the time of the 2011 follow-up visit (done in February), the patient was advised that there were no clinical or radiological features to suggest tumor recurrence.

In 2005, after a 4 year period of being free of seizures, he experienced worsening headaches and recurrent seizure activity. The phenytoin level was determined to be in the subtherapeutic range and his dose was increased accordingly (from 100 mg PO TID to 200 mg PO BID). He remained seizure-free until September 2011 when he experienced another seizure. At that time, CT scan of the head revealed no evidence of a recurrent tumor (figure 1). In October 2011, the patient fell while going down the stairs. He lost his consciousness and was later admitted to the hospital. CT scan of the head revealed a new intra-axial left frontal lobe hemorrhage. This appeared to be located within the surgical bed of previously resected oligodendroglioma (figure 1). Since an MRI completed 8 months prior was reported as tumor free, the treating physicians concluded that the hemorrhage was unlikely related to recurrence of the tumor. The hemorrhage was attributed to bleeding into the tumor-free surgical bed.

At this time, the primary impairments of the patient were related to higher-level cognitive dysfunction (more specifically, poor judgement and insight). There were no language deficits noted. In this context, the patient was admitted to our rehabilitation unit. The primary goal for this admission was to evaluate if the patient’s cognitive and functional status was sufficient to return to living independently in the community.

An MRI was performed after admission to our rehabilitation unit. Given the history of partial resection of the tumor and an incomplete adjuvant regimen, it was crucial to clearly establish if the hemorrhage was into the surgical bed versus into a recurrent tumoral bed.

The MRI completed in November 2011 demonstrated that there was recurrence of the tumor. First, although the hemorrhage appeared to...
be located in the surgical bed in the axial views, the sagittal images confirmed that it was clearly separated from and inferior to the surgical bed (figure 2). Second, there were new subtle rim enhancements around the hematoma and new foci of enhancement posterior to the hematoma in the left frontal and temporal lobes (see solid arrows in figure 2). Third, there was a large area of increased T2 signal around the surgical bed (see axial images in figure 2), extending into the adjacent left temporal lobe. These T2 signal changes appeared similar to the changes in February 2011, but they were more clearly evident and obviously spreading over time when the yearly MR images were compared to the ones from 2005. This suggested that the tumor was likely present in 2005 and enlarging over time (we were not able to locate the scans prior to 2005 for comparison). Overall, it was apparent that there was a large tumor recurrence located within the left frontal lobe extending into the left temporal lobe, with an intratumoral hemorrhage.

In the context of the newly diagnosed recurrence, the tumor location and its large size, chemotherapy was started for this patient.

**DISCUSSION**

In clinical practice, the most challenging cases allow clinicians to reflect on clinical successes, as well as identify opportunities for quality improvement. Our team would like to highlight the following learning points related to this case.

Oligodendrogliomas may present as non-enhancing lesions with T2 hyperintensity and possible calcifications. The sensitivity and specificity of the MRI in detecting a low-grade glioma are reported in the literature as 80-85% and 60-64% respectively compared to gold standard (histology). Gliosis (glial scarring after CNS injury) may present similarly to primary tumor or recurrence on MRI, and radiation therapy in itself is known to lead to scarring as well. The combination of surgical scarring and radiation therapy has an additive effect on brain scarring, but the usual MRI appearance of the above combination is stable (not enlarging) over time. In retrospect, there were radiological abnormalities consistent with tumor recurrence as early as 2005 in our patient. Given that the patient did not have radiation therapy, the high T2 signal noted in 2005 around the surgical site was less likely to represent gliosis. Moreover, this high T2 signal area (slowly) increased in size over time, which is again not consistent with gliosis (see figure 3). Of note, we identified that the radiologists interpreting the MRI scans were informed that the patient had radiation therapy in the past, (when in fact he did not) and this may have been another factor that influenced the interpretation. If the later MRI studies had been compared to the baseline MRI from 2005, the tumor recurrence might have been recognized earlier. From a quality improvement perspective, clinicians should review all the imaging studies, when making determinations about brain tumor recurrence. Clinically significant abnormalities that would not be apparent on comparison with the previous most recent study may be more evident when all the available images are reviewed on a sequential basis.

Clinicians should note that a brain hemorrhage that occurs many years after a brain tumor resection is more likely to be located within a recurrent tumor bed than in a tumor-free surgical bed (within the brain area where surgical removal took place). This is even more likely when the tumor is partially resected, and with an incomplete adjuvant treatment regimen. Intratumoral hemorrhage is a known relatively late complication of brain tumors and it is due to a more
friable neovascularization that develops over time around and within
the tumor. As a general construct, radiation therapy increases the
fragility of the brain vasculature and therefore increases the risk of
relatively late hemorrhage. On the other hand, a hemorrhage that
occurs relative early after the tumor resection is more likely related
to bleeding into the surgical bed. The vasculature of the tumor-free
surgical bed is usually less stable in the immediate post-operative
period due to the surgical manipulation, and it becomes more stable
as time progresses. In our patient, the new onset (late) hemorrhage
pointed the treating team to revisit the scans and contributed to
identifying the recurrent brain tumor.

It is important to recognize that most oligodendrogliomas, even if
described as low grade tumor, will ultimately lead to the patient’s death
because of their location as well as their infiltrative pattern within the
brain matter. The median survival period after the oligodendroglioma
diagnosis is 8-10 years. About 70% of the WHO grade II tumors will
progress into grade III in a median time of 72 months, which carries a
poorer prognosis. This anaplastic transformation is usually correlated
with a faster rate of tumor growth. It is also associated with typical
radiographic features, such as new areas of contrast enhancement in
a previously non-enhanced tumor bed on an MRI. In our patient,
a transformation was likely to have occurred and this was supported
by the new foci of gadolinium enhancement, given that these were
not present in prior scans. This transformation could only have been
confirmed with a tissue diagnosis (brain biopsy), but this would not
have changed the management.

The hemorrhage in this case may have been caused by the fall,
either mechanical or related to one of his simple partial seizures.
The patient’s seizure activity began with movement of the right arm,
which is consistent with a seizure focus in the left frontal lobe. In
2005, the patient had recurrence of seizures after a 4 year seizure-
free interval, on a background of low phenytoin levels. Perhaps, the
seizure activity at that time was due to tumor recurrence and not due
to patient noncompliance.

Possible differential diagnoses for a non-enhancing T2 hyperintense
MRI lesion are intracerebral edema, lymphoma or cerebral metastases.
The fact that the patient was known with an oligodendroglioma in
the past, with an incomplete resection and incomplete follow-up
oncological treatment, as well as the infiltrative pattern and the
location of the tumor strongly suggests that this is indeed a recurrent
oligodendroglioma. The gold standard for this diagnosis would
have been a biopsy, which was not deemed necessary by the neuro-
oncological team at that point.

The survival for patients with low grade gliomas has increased over
the last decades. Reports from the 1980s give a 5 year survival rate
between 17 and 32%, whereas recent data indicates a 5 year survival
rate of up to 66%. This may likely be the result of better detection
with MRI and MR spectroscopy, as well as more aggressive and newer
therapy regimens. Of note, the literature supports the use of the more
advanced MRI techniques (such as dynamic susceptibility-weighted
contrast enhanced (DSC) perfusion MRI and arterial spin labeling
(ASL) MRI) in the regular follow-up of these patients, as they seem
to be more sensitive at detecting tumor recurrence and malignant
transformation compared to the routine gadolinium enhanced MRI
protocols.

In conclusion, any changes in the clinical presentation after
oligodendroglioma treatment (e.g., recurrent seizures after a
prolonged seizure-free interval, worsening headache, new findings
on physical exam (e.g., focal signs) and/or new findings on imaging
scans (e.g., new brain hemorrhage on a CT head) should raise a
very high suspicion for tumor recurrence. A gadolinium enhanced
brain MRI with DSC PWI and ASL protocols should be ordered.
Because the MRI changes are usually very subtle, especially between 2
consecutive closely apart scans, the opinion of a neuroradiologist with
expertise in brain tumors is invaluable in interpreting the MRI scans.

Figure 3. There is an obvious increase in size of the high T2 signal area from 2005 through to 2011. Of note, an MR spectroscopy may be able
to identify pathologic spectra outside of the regular MRI signal for high grade gliomas, suggesting the infiltrative tumor pattern,
therefore differentiating these types of tumors from well circumscribed ones (such as meningiomas or metastases).
Abbreviations:

References:
10. Weber MA, Giesel FL, Stieltjes B. MRI for identification of progression in brain tumors: from morphology to function. Expert Rev Neurother 2008;8:1507-25. Surgical defect (pointed by arrows) is easily identified in the September 2011 scans as low intensity (black) signal located in the left frontal lobe, outside (lateral) of the lateral ventricle. In the October 2011 scans, the new high intensity signal in the left hemisphere represents hemorrhage, and this appears to be located within the surgical bed in both axial and coronal images. There is nothing to suggest tumor recurrence and there is no identifiable cause of the hemorrhage in these scans.