Late post-treatment radiographic changes 3 years following chemoradiation for glioma: the importance of histopathology

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Treatment-related changes can mimic brain tumor progression both clinically and radiographically. Distinguishing these two entities represents a major challenge in neuro-oncology. No single imaging modality is capable of reliably achieving such distinction. While histopathology remains the gold standard, definitive pathological criteria are also lacking which can further complicate such cases. We report a patient with high-grade glioma who, after initially presenting with histopathologically confirmed pseudoprogression 10 months following treatment, re-presented 3 years following concurrent chemoradiation with clinical and radiographic changes that were most consistent with progressive disease but for which histopathology revealed treatment effects without active glioma. This case highlights the potential late onset of treatment-related changes and underscores the importance of histopathologic assessment even years following initial therapy.

First draft submitted: 9 October 2016; Accepted for publication: 18 January 2017; Published online: 18 July 2017

High-grade gliomas are the most common malignant primary brain tumors, with an incidence of 5 per 100,000, and a dismal prognosis with a median survival of 15 months in patients with newly diagnosed glioblastoma [1]. Standard of care consists of safe, maximal neurosurgical resection followed by radiotherapy with concurrent and adjuvant temozolomide (TMZ) chemotherapy, according to the EORTC 26981/NCIC 22981 protocol [2,3]. Regardless of treatment, high-grade gliomas recur and it is vital to rapidly and accurately identify progressive disease (PD), broadly defined histologically by the presence of active high-grade tumor cells. This can be a major challenge in neuro-oncology as the imaging characteristics of PD cannot be reliably differentiated from radiation treatment effects with conventional MRI. Advanced neuroimaging techniques which can accurately differentiate from PD and post-treatment changes are being explored but, to date, none have proven effective. In clinical practice, timing is often incorporated into therapeutic decision making. Some have even advocated dividing post-treatment neuroimaging changes into early (i.e., those occurring within 12–24 weeks of radiation) and late changes (manifesting several months to years after therapy). However, the challenges of clinical decision making, treatment response assessment,

KEYWORDS

- brain cancer • diagnostic challenge • DWI • high-grade glioma • MRI • MRS • neuro-oncology • PET • post-treatment changes • pseudoprogression • radiation necrosis • radiation therapy

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research candidacy and clinical trial recruitment, design and interpretation remain [4].

Case presentation

• Initial presentation

A 31-year-old man presented to an outside facility in June 2011 after a generalized tonic-clonic seizure. MRI with and without gadolinium revealed a 4 × 2 cm nonenhancing lesion in the left frontal lobe (June 2011, diagnosis, [Figure 1A](#)). Craniotomy with gross total resection revealed a WHO III infiltrating astrocytoma with oligodendroglial features (1p but not 19q deletion present, further molecular classification not reported and tissue unable to be obtained). External beam radiation therapy (6000 cGy) with concomitant TMZ (75 mg/m²) was completed in its entirety in September 2011 and was followed by adjuvant TMZ (150 mg/m², escalating to 200 mg/m² after cycle #1) [3].

• Early post-treatment changes

After eight cycles of adjuvant TMZ, neuroimaging revealed increased contrast enhancement in the left frontal lobe (July 2012, 10 months post radiation, [Figure 1B](#)) with new right hemiparesis and aphasia. A second surgery was performed with resection of enhancing tissue and placement of Gliadel® wafers (Eisai Inc, NJ, USA), though pathology ultimately was read as prominent treatment effect without active tumor. Despite this, the patient received nine subsequent cycles of adjuvant TMZ (17 total cycles) completing therapy in January 2013. MRI continued to demonstrate prominent contrast enhancement and surrounding T2/FLAIR hyperintensity, associated with an insidiously progressive right hemiparesis requiring prolonged glucocorticoid therapy (>2 years total duration). The patient suffered from steroid-induced diabetes mellitus, Cushingoid appearance and proximal myopathy resulting in gait dysfunction and multiple falls. Functional imaging including brain ¹⁸F-fluorodeoxyglucose-PET scan (April 2013, 19 months post diagnosis, [Figure 1C](#)), magnetic resonance (MR) perfusion and MR spectroscopy, were consistent with late post-treatment effects showing lesional hypometabolism.

At that time, care was transferred to our institution wherein bevacizumab was considered for management of radiation necrosis and prolonged glucocorticoid dependence. The patient developed recurrent venous thromboembolism requiring anticoagulation and suffered a

spontaneous lesional intracranial hemorrhage requiring inferior vena cava filter and bevacizumab was not initiated. Pentoxifylline and vitamin E were considered but the patient opted to undergo hyperbaric oxygen therapy (HBO₂) which coincided with gradual improvement in clinical symptoms to full strength, functional independence and only mild residual expressive aphasia. By October 2014, neuroimaging had improved dramatically with only a small region of residual enhancement and T2/FLAIR hyperintensity adjacent to the frontal horn of the left lateral ventricle (October 2014, 38 months post radiation, [Figure 1D](#)).

• Late post-treatment changes

In December 2014, 3 years following initial diagnosis, the patient presented with 1 month of progressively worsening, refractory partial seizures and right hemiparesis. After two hospitalizations for antiepileptic titration and empiric re-initiation of glucocorticoids, neuroimaging revealed a marked increase in expansile T2/FLAIR hyperintense signal involving the left frontal gyri, with associated increase in enhancement and local mass effect highly concerning for disease progression (December 2014, 40 months post radiation, [Figure 1E](#)). Subtle restriction of diffusion and increased blood volume supported PD and a third craniotomy was performed for symptomatic debulking and diagnostic confirmation. Surprisingly, pathology again revealed no evidence of active tumor, portraying hyalinized vessels and macrophage infiltrate consistent with prominent treatment effect ([Figure 2](#)).

Imaging continued to show progressive worsening for 7 months following the third resection (July 2015, 46 months post radiation, [Figure 1F](#)) and the patient opted for corticosteroids despite consideration of bevacizumab. By December 2015 (51 months post radiation, [Figure 1G](#)) the patient was off all corticosteroids with improvement in neurologic exam and neuroimaging back to baseline prior to his decline in November 2014. In August 2016, the patient again developed new radiographic changes (59 months post radiation) and underwent a fourth surgery with pathology showing quiescent glioma with extensive treatment effect. The tumor tested negative for p53 and IDH1 with ATRX retained by immunohistochemistry. Postoperative imaging in November 2016 again showed decreasing regions of enhancement and T2-weighted hyperintensity consistent with recurrent treatment effects.

Figure 1. Radiographic history of a patient with high-grade glioma, from diagnosis to confirmed late post-treatment changes. MRI, FDG-PET and MRP imaging methods were utilized to assess patient's progression throughout time. (A) On diagnosis (month 0), increased hyperintensity in the left frontal lobe was seen, and histopathology diagnosed Grade III infiltrating astrocytoma with oligodendroglial features. (B) A total of 10 months following chemoradiation, surveillance MRI revealed increased contrast enhancement in the left frontal lobe, and craniotomy yielded a histopathologic evaluation consistent with prominent treatment effect and no active tumor cells. (C) Following second surgery, 19 months post-treatment, MRI continued to demonstrate an area of contrast enhancement around the intervention region, in the left frontal lobe, while ^{18}F -FDG PET showed decreased tracer uptake in the same location. (D) The radiographic improvement seen on month 38 indicates that the imaging changes from month 19 were probably treatment related. (E) In December 2014, 40 months after chemoradiation, MRI examination displayed increased contrast enhancement in the left frontal gyri associated with a markedly increased T2/FLAIR hyperintense signal and increased perfusion involving the same region, highly concerning for disease progression. However, histopathological examination was consistent with late post-treatment changes, showing no evidence of active tumor (Figure 2). (F) During the 7 months following the third craniotomy, imaging continued to progressively worsen until, 46 months post RT, MRI demonstrated an increase in the size of the contrast-enhancing area which, in turn, was consistent with a hypermetabolic focus on 18-F-FDG PET. (G) By December 2015, the patient's neurologic exam had significantly improved, and neuroimaging showed a significant decrease in the size of the contrast-enhancing area on MRI, returning to baseline prior to his late decline in November 2014.

FDG: Fluorodeoxyglucose; MRP: Magnetic resonance perfusion; RT: Radiotherapy.

Figure 2. Histological features of treatment effect occurring 40 months post radiation.

In December 2014, 40 months after chemoradiation, although the results of MRI examination were again highly concerning for disease progression, histopathological investigation was consistent with post-treatment changes showing the presence of hyalinized vessels and a macrophage infiltrate in the absence of active tumor cells.

Discussion

Late treatment-related changes do occur and may manifest even years after therapy, without an obvious inciting event or treatment. In this report, we show that in the same patient both early and late treatment-related changes may occur. Histopathologic confirmation was essential and allowed us to appropriately forego initiation of antineoplastic therapy particularly when clinical symptoms and radiographic imaging strongly suggested tumor recurrence.

The pathophysiology of treatment-related changes remains controversial. Vascular injury, glial injury, neuronal injury, enzymatic disturbance and inflammatory response related changes have been suggested [5]. TNF- α is a key cytokine produced after irradiation which contributes to endothelial cell apoptosis, astrocyte activation and blood–brain barrier permeability [1]. Increased VEGF expression has been found in white matter following radiation therapy (in particular in late reactions), correlating to the degree of edema and breakdown of the blood–brain barrier [1,6,7].

Determining factors associated with an increased risk of treatment-related changes is critical. These may include total radiation dose, dose fractionation, volume irradiated, age and re-irradiation. Studies suggest that the risk may

be reduced through adjusting fractionation schedules, conformal radiation or radioprotective agents, or via performing genetic testing or tissue culture en route for assessing radiosensitivity [5]. The treatment-related imaging changes in the patient occurred within the high-dose radiation field.

Postradiation treatment effects have been shown to occur in patients with low- and high-grade gliomas [8,9]. Risk of postradiation treatment changes has been suggested to be higher in patients with methylguanine-DNA methyltransferase promoter methylation, though its reliability has not been established in large prospective studies [10]. Notably, a higher rate of radiation damage has been reported when chemotherapy agents like TMZ are given either concurrent or adjuvant to radiation. This may be explained by the radiosensitization effect of this drug, as well as the higher degree of endothelial damage inflicted when both modalities are used [5,11–13]. Continued TMZ treatment in our patient in the setting of early post-treatment changes may have contributed both to the prolonged course, the difficulties with management, and perhaps the occurrence of this late post-treatment effect, though this is speculative.

Early post-treatment changes tend to resolve with time, though corticosteroids may be used in symptomatic cases [12,14,15]. Late postradiation necrosis can be irreversible, progressive and may, if untreated, lead to permanent neurological deficits or death [16]. Common strategies to offset delayed effects of radiation are the use of corticosteroids, bevacizumab or surgery [1,17]. Alternative strategies such as HBO₂, anticoagulation, laser interstitial thermal therapy or the combination of pentoxifylline and oral vitamin E are under investigation [1].

Not all contrast-enhancing lesions on an MRI scan of a patient with previous brain malignancy represent a tumor, even following a prior event of radiation-induced injury. Regardless of the location and time point at which they present, radiation-derived changes can lead to an increase in T1-weighted postcontrast enhancement and/or edema which makes them very hard to discriminate from PD based on MRI alone [18,19]. At times, postseizure radiographic changes and the stroke-like migraine attacks after radiation therapy syndrome can also mimic tumor progression [20,21].

While noninvasive imaging techniques for distinguishing radiation-induced damage

from true tumor progression are being sought, none are currently available which are clearly proven to be reliable. Several novel amino acid PET radiotracers including ¹¹C-MET, (18)F-fluoroethyltyrosine and (18)F-DOPA PET appear to be superior to glucose PET in differentiating PD from radiation damage [2,22–24]. Clinical trials utilizing these and various MR-based techniques are underway and will require validation and regulatory approval [25–27].

While histopathological assessment remains the gold standard, no clearly defined pathologic criteria for tumor recurrence exist. Histologic analyses of early changes tend to demonstrate hyalinized vessels and areas of eosinophilic coagulation necrosis [4]. Late reactions tend to occur in the white matter and are associated with calcification, fibrinoid deposition, vascular hyalinization and endothelial thickening, resulting in chronic inflammation and oxidative stress, as well as inhibition of neurogenesis [1,28,29].

The importance of tissue diagnosis, even when evaluating very late occurring imaging changes, is highlighted in this report. While both imaging and clinical symptoms supported tumor recurrence 10 months following chemoradiation, histopathology revealed treatment-related changes. The improvement that followed was consistent with the reported reversibility of early radiation-induced changes. Whether if in our patient this reversibility was inherent to the natural disease process or, instead, brought

about by the different modalities exploited (specifically HBO₂ and glucocorticoids) can only be theorized. A total of 3 years after chemoradiation, the timeline of our patient's symptoms and radiographic worsening was acute and dramatic. We considered enrolling this patient into a clinical trial underscoring the importance of histopathologic evaluation prior to protocol enrollment for these patients.

Conclusion

Treatment-related changes and tumor progression are common occurrences following radiation therapy in patients with high-grade glioma. At present, no imaging modality is able to reliably distinguish between these entities, presenting a major diagnostic challenge in neuro-oncology. While novel diagnostic techniques, both structural and metabolic, have recently shown promising results, none of them have been validated through prospective studies. This case highlights the significance of histological examination in patients with suspected tumor progression on imaging, while reminding of the need for established pathologic criteria to consistently differentiate between tumor recurrence and post-treatment effects in order to accurately guide further clinical decision making. In addition, it raises awareness to the fact that treatment-induced changes should always be considered in the differential diagnosis of a patient where tumor progression is suspected, regardless of the time they occur, and even if treatment-related changes have manifested previously.

EXECUTIVE SUMMARY

- Late treatment-related changes occur, and may manifest even years after therapy.
- In the same patient, both early and late reactions may occur, separated by radiologic and clinical improvement.
- The exact pathophysiology of post-treatment changes remains unknown.
- Not all contrast-enhancing lesions on an MRI scan of a patient with previous brain malignancy represent a tumor, even in a patient with a prior event of radiation-induced injury.
- Radiation-derived changes lead to an increase in T1-weighted post-contrast enhancement and/or edema, which makes them appear indistinguishable from progressive disease on structural MRI.
- No imaging modality can, alone or in combination, reliably distinguish tumor progression from post-treatment changes. Time can be a guide, but not replace clinical judgment and histopathologic assessment.
- Histological examination should be included in suspected cases of post-treatment changes, even when occurring years after diagnosis and chemoradiation. While histopathology is the most reliable investigation at present, the lack of clearly defined pathologic criteria for distinguishing progressive disease from treatment effects renders further studies imperative.
- Accurate methods to diagnose and manage treatment-related damage in neuro-oncology are still to be determined.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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• of interest; •• of considerable interest

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