Unfavorable radionecrosis in low-grade astrocytoma: a case report

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Abstract

We describes a unique case of life threatening radionecrosis in a female affected by left parieto-temporal IDH-wildtype, WHO grade II astrocytoma treated by partial resection, radiotherapy and chemotherapy. Steroid, oral pentoxifylline, vitamin E, surgery and bevacizumab (2 + 9 cycles) were given, obtaining a partial clinical response, while signifiant radiologic reduction was documented. An individual radiation hyper-sensivity was suggested in this patient and data on this topic are higtly needed with increasing interest in personalized medicine worldwide. Radionecrosis should be considered after radiotherapy in low-grade astrocytoma, because its course may be devastating and exacerbated by anti-tumoral therapies.

Keywords: Low-grade Glioma Radionecrosis, Radionecrosis Case Report, Radiation Sensitivity

Introduction

Extent of resection with minimal neurologic dysfunction is the most important therapy-dependent prognostic factor in low-grade glioma. Surgical removal may be incomplete, especially in eloquent cortical areas and subcortical white matter fibers, thus adjuvant therapies, as radiotherapy and/or chemotherapy, are required based on age, performace status and molecular markers such as IDH mutation and 1p/19q codeletion [1].

Here we describe a case of a left parieto-temporal low-grade glioma treated by surgery, adjuvant radiotherapy and chemotherapy. Progression disease with malignant trasformation was suggested but steroid–resistant radionecrosis (RN) was documented by histology. The RN course in this patients was very aggressive, with recurrence despite surgery and bevacizumab treatment, and never described as severe as in this case after radiotherapy in low grade glioma.

Case Presentation

A 69-year-old female was admitted to our Institute for expressive aphasia and mild right hemiparesis; a subsequent MRI demonstrated a left parieto-temporal non-enhanced glioma (Fig.1). The patient had no significant medically history or familial disease; she was treated for hypertension and previous intervention were cholecystectomy and hysterectomy for fibroma. She refused an awake craniotomy with functional language mapping, so we performed a microsurgical maximal safe resection guided by fMRI and DTI navigation in addition to intraoperative ultrasound (October 2017). At that time, the histological examination revealed a gemistocytic astrocytoma (grade II, WHO 2016) and molecular pattern was IDH-1 and IDH-2 WT, nuclear ATRX retained and 1p19q non-codeleted. Postoperative KPS was 90 with mild deficiency in reading and writing. Based on molecular markers, age, KPS and extent of resection, on December 2017 she underwent adjuvant radiotherapy on residual tumor (IMRT, 54 Gy in 27 fractions) and then chemotherapy with temozolomide [2].

Over the following months, after the third temozolomide cycle, the patient became aphasic and drug-resistant seizures occurred; perilesional edema with contrast agent enhancement of resdidual tumor was detected on follow-up MRI. The challenge issue of differential diagnosis between disease progression versus radionecrosis was advanced but the multidisciplinary

discussion supported the first hypothesis. Patient received benefit after steroid therapy and antiepileptic drugs thus a II-line chemotherapy was initiated (PCV regimen), but progressively neurological worsening occurred (KPS 60 and then 40). On November 2018 patient presented right hemiplegia, global aphasia and finally impaired alertness (KPS 20); the MRI study shown features of mass effect, increasing edema and enhanced tissue (Figures. 1 and 2). New surgeries, 11 and 12 months after RT, were then scheduled: the first for removing the contrast-enhanced nodular area and the subsequent to treat hydrocephalus and CFS fistula by ventriculo-peritoneal shunt. Histological diagnosis was concomitant radionecrosis and astrocytoma, without tumor malignant transformation (grade II). Clinical improvement was observed as the patient became responsive again, speech was dysphasic but gradually improved as right hemiparesis did (KPS 60).

Few months later the patient showed drowsiness, aphasia and right hemiplegia (KPS 20), despite combination of oral pentoxifylline, vitamin E and steroid. MRI imaging demonstrated increased RN alterations (Figures. 1 and 2). After a multidisciplinary discussion and a new biopsy, confirming the diagnosis of radionecrosis and excluding super-infection, bevacizumab therapy was indicated. The patient underwent 2 cycles of bevacizumab therapy (10 mg/kg) administered once every 3 weeks with clinical and radiological improvement. Progressive steroid therapy decalage was started and the patient was discharged, but aphasia and hemiparesis did not resolve (KPS 50). Three months later, clinical and radiological follow-up demonstrated a new downhill (KPS 20). Bevacizumab therapy was re-administered since September 2019 for 9 cycles. MRI showed a marked decrease in perilesional edema and contrast enhancement and since May 2020 a radiological stability was obtained. Unfortunately, the radiological improvement did not correspond to a clinical improvement, with the exception of alertness (KPS 40). The patient died on July 2020 due to pneumonia during Covid-19 pandemia.

Discussion

Guidelines defined by European Association for Neuro-oncology in 2017 recommend adjuvant radiotherapy and chemotherapy in IDH WT grade II astrocytomas, when age is <70 years and KPS >70, after

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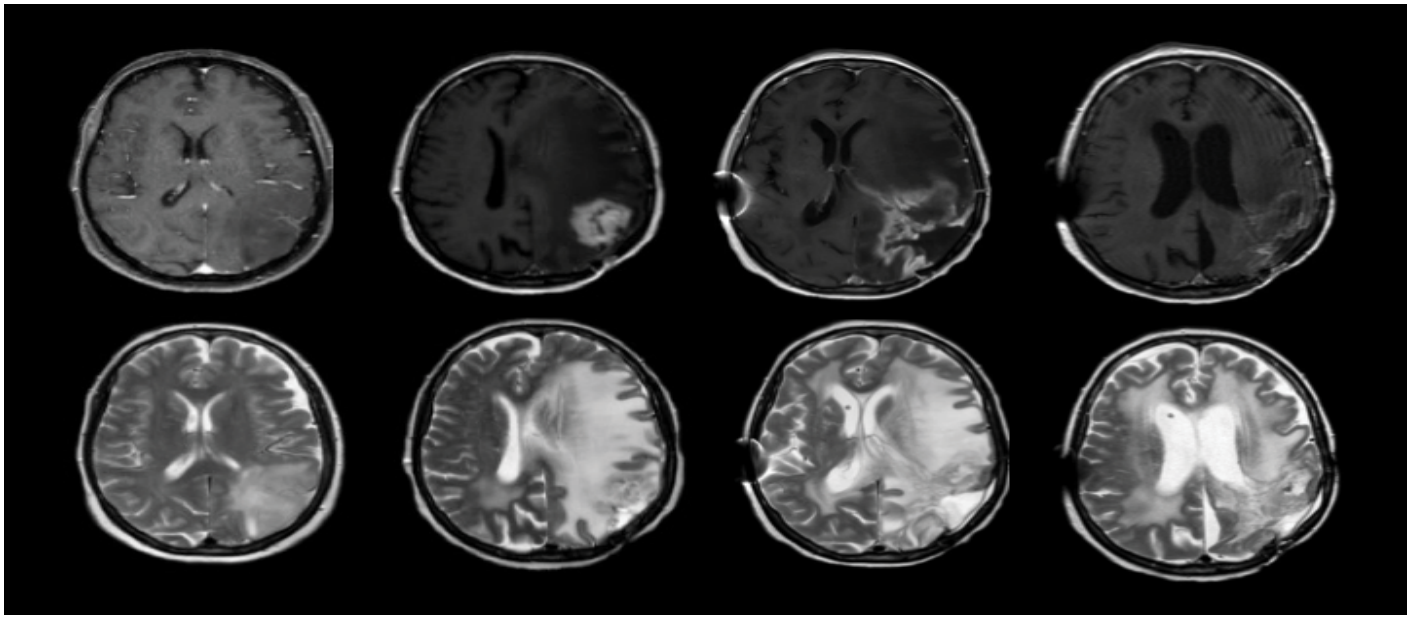

Figure 1: upper row illustrates MRI T1 weighted image (T1WI) contrast-enhanced and lower row T2 weighted image (T2WI). From left to right: a) preoperative studies (October 2017) showing a hypointense infiltrative pattern in T1W1 sequences, without contrast enhancement, and hyperintense in T2WI; b) imaging before second surgery (November 2018) shown increased enhanced area, diffuse edema and mass effect; c) after second surgery and bevacizumab discontinuation imaging on August 2019 shown a market increase of radionecrosis; RN reappears as "soap-bubble" enhancement in T1WI contrast-enhanced sequences around to the surgical cavity; d) after new administrations of bevacizumab the contrast-enhanced area decreased but a diffuse white matter change and atrophy on both hemispheres appeared (May 2020).

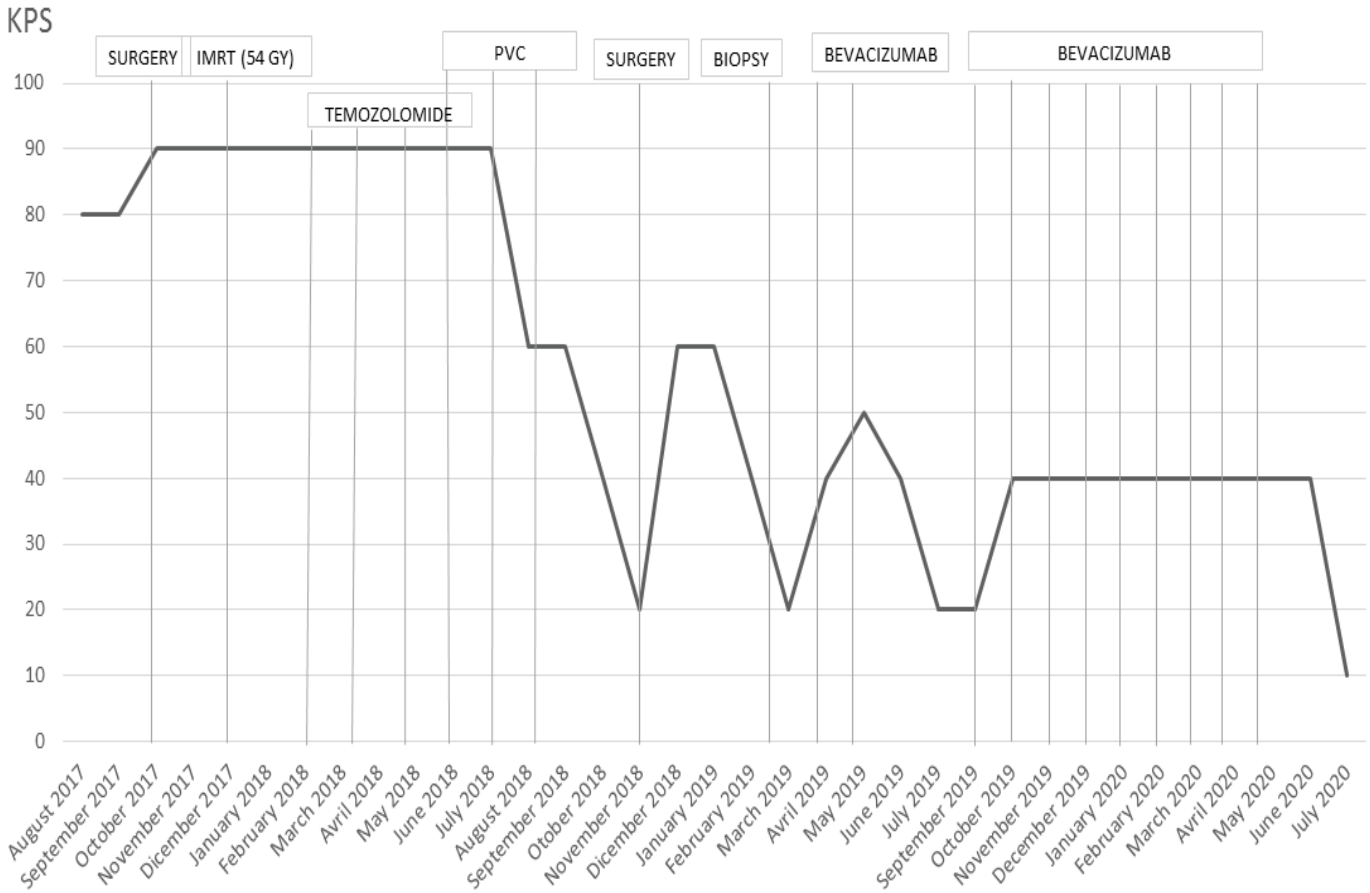

Figure 2: timeline treatment and KPS evaluation.

partial removal.

Radionecrosis (RN) is a late complication of brain radiotherapy and stereotactic radiosurgery, occurring in mean 11-12 months after. It is characterized by degenerative changes in vasculature with telangiectasias, hyaline thickening and fibrinoid necrosis leading to blood-brain barrier disruption, white matter necrosis and

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demyelination. In cerebral gliomas, RN was described in 4.9% of 426 patients irradiated and followed for at least 3 years, with an actuarial rate plateau of 13.3% at 3 years after radiotherapy; in all RN cases reported the grade of glioma was III or IV (high grade glioma, HHG) [2]. In this contest, RN needs to be differentiated from progression and pseudoprogression, which is an increase enhancement around recently treated brain tumor, considered as the effect of local inflammation and transient permeability of the blood-brain barrier caused by chemotherapy and radiotherapy, usually occurring within 2 months from treatment [1]. In low-grade gliomas (LGG) the late adverse effect mainly described is neurocognitive impairment whereas incidence of grade 3 radiotherapy late toxicity, which includes RN, was 1-2% and no grade 4 and 5 were reported [3]. For this reason, in LLG surveillance the appearance of enhanced tissue is usually due to malignant transformation and tumor progression. No case of so aggressive, resistant and recurrent RN after surgery, radiotherapy and chemotherapy has been previously reported in LLG.

Most RN cases are actually diagnosed based on brain Magnetic Resonance Imaging (MRI), using a combination of studies (diffusion, perfusion, spectroscopy), or positron emission tomography (PET) so, currently, biopsy is not required, although the histopatological examination still remain the gold standard [4]. In this case, surgery or biopsy would have been, probably, necessary when contrast-enhanced area appeared, anticipating thus the radionecrosis treatment and stopping chemotherapy. Indeed even if radiation parameters, as total radiation dose, BED and fraction size, are the main predictive factors of RN, chemotherapy after radiation significantly increases the risk [1]. The limitation of our case report is the abcence of PET studies due to severe patient condition.

If on one side the misdiagnosis of malignant transformation and consequent treatments could have aggravated the condition, on the other side the course of RS in this patient was very impressive. Why this patient developed a malignant and life threatening radionecrosis is not completely known and, certainly, the atypical condition here described suggests an individual predisposition to radiation injury of normal brain tissue, which we actually can not predict based on current knowledge. A genetic predisposition could be a possible explanation, as suggested by several Authors and by the evidence of rare hyper-radiosensitive syndromes [5,6]. The identification of radiation sensitive and susceptiblily individuals using a screening tool would allow to change the management in specific conditions.

Historically, RN has been treated with corticosteroids with poor results and many side effects. Surgical decompression of necrotic areas is an option but other therapeutic options include hyperbaric oxygen, laser interstitial thermal therapy, high-dose vitamin E or the combination of oral pentoxifylline and vitamin E. Recently, bevacizumab (a humanized murine monoclonal antibody against VEGF) has been suggested as a new treatment modality for RN. The rationale of bevacizumab use relies on vascular mechanism underlying radiation necrosis development. Despite only one randomized double-blind placebo-controlled clinical trial was published, bevacizumab treatment appears to be beneficial for patients affected by RN and shows good efficacy in improving KPS score, symptoms and MRI imaging [7]. In the present case, the administration of bevacizumab was at first associated with marked radiological and good clinical improvement but a new worsening occurred after bevacizumab discontinuation; in spite of brain edema and contrast enhancement decreased after numerous subsequent cycles, only little clinical improvement was observed: right hemiplegia and language disturbances were finally permanent.

Conclusion

The first lesson learned by this case was that RN should be considered after radiotherapy in low-grade glioma even if very uncommon, because it may be devastating and exasperated by antitumoral therapies. Predisposing factors to individual radiosensivity are probably determinant and further studies looking for potential risk factors are needed. The second consideration is that Bevacizumab is effective in interrupting angiogenesis and radionecrosis self-maintenance but failed in this patient in establishing the resolution of brain damage probably because it was interrupted too early and readministered after RN recurrence.

Statement of Ethics:

The munuscript was conducted ethically in accodance with the World Medical Association Declaration of Helsinki and both the subject and her kin have given their written informed consent to any treatment and to publish this case with images.

Authorship statement:

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Declarations of interest:

None.

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Abbreviation:

RN = radionecrosis

MRI = Magnetic Resonance Imaging

FLAIR = Fluid Attenuated Inversion Recovery

PET = Positron Emission Tomography

fMRI = Functional Magneti Resonance Imaging

DTI = Diffusion Tensor Imaging

T1WI = T1 weighted image

T2WI = T2 weighted image

WHO = World Health Organization

IDH1-WT = Isocitrate Dehydrogenase 1 - wildtype

IDH2-WT = Isocitrate Dehydrogenase 2 – wildtype

IMRT = Intensity Modulated Radiation Therapy

PVC = Procarbazine, Lomustine, and Vincristine

BED = Biolocically Effective Dose

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