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Occipital radionecrosis and neuroplasticity in astrocytoma

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Abstract: *Background: Late-delayed complications after radiotherapy (RT) results from an imbalance between cell lesions and the protective capacities of the CNS. Temozolomide (TMZ) after RT may represent a potent radiosensitizing regimen. Although radionecrosis (RN) of the anterior visual pathway has been documented, in our opinion this is the first report of reversible visual field loss associated with occipital lobe radionecrosis.*

Case observation: We report a patient who suffered a left lateral homonymous hemianopia one year after radiochemotherapy (RCT) for an infiltrative low grade fibrillary astrocytoma. The visual field deficit was completely reversible after one month. Visual field defects have been described after the use of conventional external beam therapy for lesions near the anterior visual pathway. The cortex is relatively spared after RT.

Conclusions: Given the new scientific data, we suppose that neuroplasticity may play a role in the reversibility of visual field deficit. At this time there is no proven treatment of radionecrosis. Homonymous hemianopia caused by occipital lesions are attributable to vascular disease and tumors, but take into account radiation effects. The risk of neurogenic visual loss must be factored into the decision to irradiate the whole brain.

Keywords: *fibrillary astrocytoma, temozolomide, radiation necrosis, visual recovery, neuroplasticity*

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INTRODUCTION

Radiation therapy is an integral part of modern therapy in gliomas. Early or delayed side effects are taken into account in determination of the therapeutic algorithm of each patient. The combination of radiotherapy and chemotherapy further increases the vulnerability to side effects. In this context, we present the case of a young woman diagnosed with fibrillary astrocytoma. One year after combined radiotherapy and chemotherapy with Temozolomide, right occipital lobe radionecrosis with impaired vision appeared.

Although such cases cited in literature are irreversible, in this case, both visually campimetric deficit and occipital brain lesion were fully reversible.

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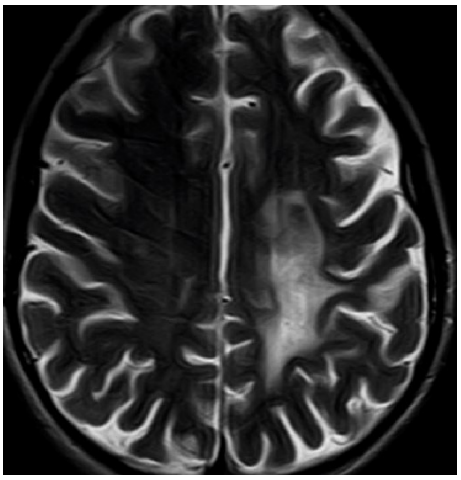
MATERIAL AND METHODS

A 21 years old, right-handed Caucasian female with mild idiopathic thrombocytopenia presented to the hospital with right sensory-motor hemiparesis. MRI revealed a subcortical low grade glioma in left rolandic region, extended to basal frontal and ascending parietal white matter regions, invading the dominant arcuate fasciculus, confirmed by brain biopsy.

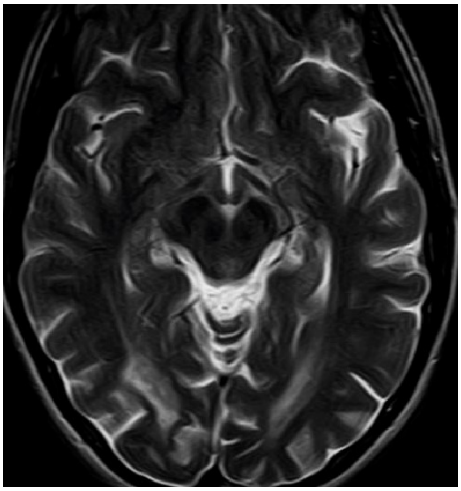
Given the infiltrative character of the tumor and its deep location, a surgical intervention is considered risky (the tumor invades left pyramidal fibers, thalamocortical fibers and superior longitudinal fascicle), especially without perioperative functional cortico-subcortical cartography procedures. Our patient undergoes 64Gy (photon teleradiation) radiotherapy for 6 weeks, followed by chemotherapy with Temozolomide (TMZ), 250 mg/day, 5 days/month for 6 months. Conventional MRI control reveals stationary aspect of the tumor (figure 1).

Figure 1



One year after chemotherapy, the patient insidiously develops left lateral homonymous hemianopia. A new conventional brain MRI shows a new 26/10 mm, irregular, non-homogenous, imprecisely defined right occipital lesion with hyperintense T2/Flair and isointense T1 signals, without contrast media enhancement. Fluorodeoxiglucose (FDG) PET-CT scan allows the differential diagnosis between tumor growth or radionecrosis and it reveals significantly decreased FDG uptake in the right occipital region, including the visual cortex (figure 2).

Figure 2

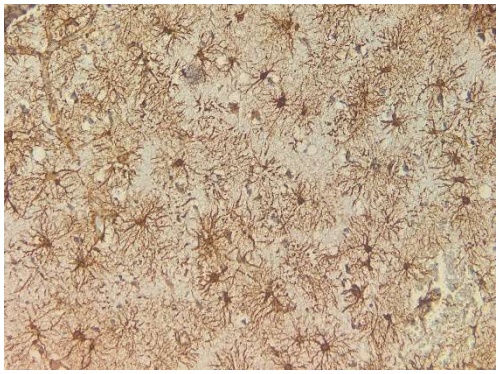


RESULTS

We conclude that the visual field deficit is the result of cerebral radionecrosis. The patient started a short period of corticoid treatment, with no improvements. One month from the first appearance of the hemianopia, it completely remitted and occipital right lesion were not visible.

Worsening deficit in patients with cerebral tumors may suggest either tumor progression or its recurrence [1]. Imagistic methods reveal edema and enhanced lesions near the tumor area. On the other hand, radiotherapy may determine effects after months or years and these are called late-delayed reactions [2].

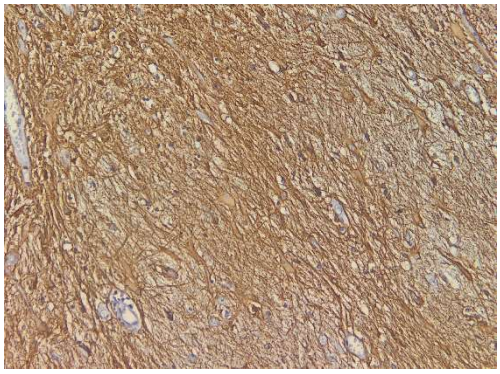
Figure 3



One of them is radionecrosis that occurs by vascular changes and ischemia, increase of capillary permeability and cerebral edema. Due to capillary permeability disturbances, adverse reactions of

chemotherapy appear earlier and are more severe (figures 3, 4). Necrosis can be a result of radio and chemotherapy combination [3].

Figure 4



Temozolomide (TMZ) amplify the answer to radiations through DNA modifications and apoptosis [4]. TMZ combined with radiotherapy, enhances blood-brain barrier damage, leading to increased concentrations of therapeutic agents [5].

DISCUSSIONS

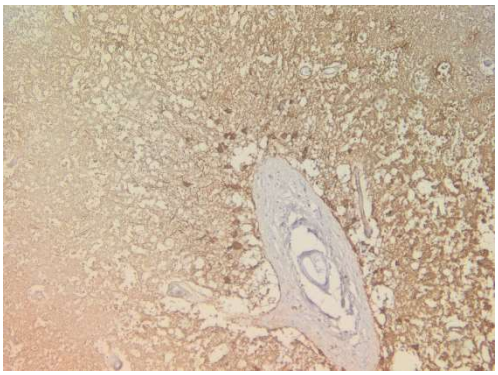
Few things are known about radionecrosis because it is difficult to differentiate from the tumor relapse with imaging techniques [6] and because the rate of surgical secondary interventions and brain autopsies are low in these patients [7].

In a study of 426 patients presenting glioma, Ruben and co. prove that the average time for the first appearance of necrosis is 11.6 months [8]. Also, adjuvant chemotherapy rises to over 4 times the cerebral necrosis risk. Peterson and co. reported a 2.5% incidence of radionecrosis, 8-31 months post-radiation, in a study including 200 patients with radiated and chemo-treated cerebral tumors [9]. So, as many have already demonstrated, chemotherapy has an amplifying effect in cerebral radionecrosis development. The incidence of radionecrosis is slightly raised in anaplastic oligodendroglial tumors than anaplastic astrocytomas and this is an argument for glial theory and its role in radionecrosis occurrence.

Things are even more complicated because the edema associated to this pseudoprogression is as symptomatic as the tumor actually progresses [10]. Conventional MRI (T2 and T1 with contrast) is limited in differentiating between tumor relapse and RT induced necrosis. Unfortunately, in many Gad positive lesions that occur after combined treatment, there are necrosis lesions and viable tumor cells and molecular magnetic resonance imaging of endogenous proteins and peptides are not for current use [11]. Diffusion MRI measures the mobility of water from tissues into the cells. After treatment, tumor cells are dehydrated and have a high apparent diffusion coefficient (ADC). Decreases of ADC indicate high cellularity [12]. Magnetic Resonance Spectroscopy detects tumor metabolites from tissues (choline, creatinine, lactate, lipids, N-acetyl aspartate) and is more sensible [13]. Dimensional spectroscopy has superior sensitivity indicating a relapse based on raised choline/NAA and choline/creatinine ratios [14].

18-Fluorodeoxyglucose PET scan is useful for differentiating between radionecrosis and recurrence and is 81-86% sensitive and 40-94% specific [15]. Still, false positive results have been encountered in non-malignant inflammatory processes, electric epileptic seizures and healing processes up to 3 months post-surgery. Even though, radionecrosis activates healing mechanisms and raises the glucose metabolism. This is why MRS is superior. There are some mechanisms that can explain postradiation necrosis: DNA modifications, coagulation factors imbalance with thrombosis facilitation [16]. The main mechanism of radionecrosis is associated with oligodendroglia injury or vascular endothelial damage (figures 5, 6).

Figure 5

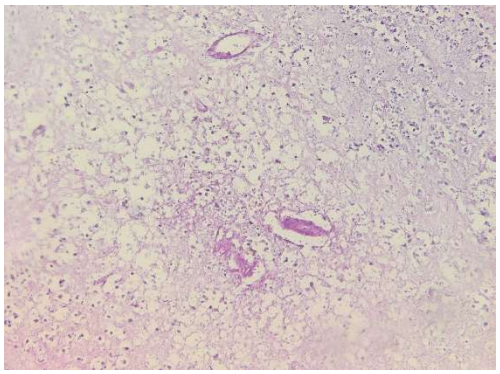


As a result, white matter tissue is often affected than gray matter tissue. Cytotoxic edema and tissue necrosis are the consequence of imbalance between

tissue plasminogen activator and urokinase plasminogen activator.

But an autoimmune mechanism may be also involved.

Figure 6



Anterior visual pathways necrosis was well documented, especially in pituitary tumors, craniopharyngioma, parasellar meningiomas or optic nerve tumors [17]. In generally, visual field defects occur after one or more years after the radiotherapy stopped. Corticosteroids, surgery, bevacizumab and Hyperbaric Oxygen Therapy (HBO) are all possible good treatment options for symptomatic RN. The treatment goal is to provide the patient with resolution of neurologic symptoms, with the least toxicity and invasiveness [18]. Corticosteroid therapy was used to diminish the cerebral edema and cytokine release after radiation. Hyperbaric oxygen is considered to be useful in raising the tissular oxygen supply and for initiating tissue healing.

Diffuse, infiltrative, low grade gliomas (LGG) represent a clinical, histopathological and molecular distinct group with a very controversial management [19]. LLG patients may survive up to 20 years from the moment they were diagnosed, but there is the risk of tumor evolution into higher grades, eventually leading to neurological deficits and death [20]. Diffuse astrocytomas include the fibrillary, gemistocytic and protoplasmic types [21]. The fibrillary one is the most widespread and it presents a homogenous cellular population and moderate uncharacteristic nuclear modifications. Mitosis rate in grade II OMS astrocytomas is very small [22]. Clinically, the patient presents epileptic seizures, focal deficits occurred after many years and intracranial high pressure, especially in the subtentorial and intraventricular location. Conventional MRI is useful for guiding the biopsy and the resection, for radiotherapy and treatment monitoring. The usual method is MRI without contrast media, but when we add contrast it reveals changes in tumor grade transformation, better. In LGG spectroscopy shows high choline (high turn-over) and low NAA, reflecting neuronal loss [23]. Even though, similar results can be seen in non-tumor lesions. MRI is used rather for guiding the biopsy in an intense active area than for monitoring the evolution. 18 Fluorodeoxyglucose PET scan has a limited value as long as LGG indicates a low caption comparative to normal cortex [24]. The role of PET-FDG is, however, demonstrated in differentiating radionecrosis from tumor recurrence. More frequently used are [11C] methionine-PET scans given the fact that methionine is captured by tumor cells showing their proliferation process, thus giving a better contrast. PET-MET is also used for differentiating LGG from non-tumor lesions [25].

Neuroplasticity defines the ability to regain function after a neuronal lesion due to neuronal structures that take over the function of the damaged area and to nervous tissue reorganization (that is based on formation of new connections between neurons and/or new cell synthesis). The theory imposed in 1920 by S. Ramon y Cajal (which stated that once the development stopped, growth and regeneration of the axon and dendrites irrevocably stop) is torn down discredited by present scientific data [26]. Altman and co. showed the ability of some brain areas (such as hippocampus and olfactory bulb) to generate new neurons and they called this process neurogenesis [27]. Later, proves appeared that shown this process is influenced by factors like age, stress, physical condition [28].

Multipotent stem cells divide periodically in our brain giving birth to other stem cells or to adult cells. The newly formed stem cells move into areas that allow maturation. Approximatively 50% of them will die without reaching maturity. The others will become glial cells or neurons depending on the necessities of the brain area where they migrated. Fred H. Gage, emphasized in his review, that the necessary time for a stem cell to become functional and adapted to brain

is about a month [29]. In this way we could explain full recover of the patient with left lateral homonymous hemianopia a month after the debut. A series of growth neuronal factors play an important role in keeping stem cells alive, mature and functional. Regaining cortical functions can be somehow explained by reorganization of cortical areas [30]. This process takes also place in the areas near the lesion or near the contralateral homologous cortex. Visual cortex reorganization after focal lesions implies plasticity mechanisms accompanied by excitation/ inhibition imbalances and changes in dendritic and axonal divisions [31]. Studies demonstrated a decrease in GABA inhibition and a growth of glutamate answer mediated by NMDA receptors in adjacent areas with the afflicted visual cortex [32].

CONCLUSIONS

Combined radiation and chemotherapy rises many times the cerebral necrosis risk, which may occur months or years later. Patient management should use specific and sensitive diagnostic tests. The differential diagnosis between tumor recurrence and radionecrosis is very important. Based on this differentiation, therapeutic attitude is different. For diagnosis certainty, tumor molecular biology tests are very useful, especially that current imaging techniques still cannot make a clear distinction. Low-grade gliomas should be better supervised by complete excision of the tumor, where the situation allows. Other therapeutic interventions, like chemo and radiotherapy, especially in the early years of evolution, should be used with caution, given their unpleasant effects. Radionecrosis should be treated promptly with corticosteroids, surgery, hyperbaric oxygen or bevacizumab.

Also, we need a plan for neurorehabilitation that assist in the neuroplasticity. All these compete to increase life expectancy and quality of life.

Conflict of interests

The authors declare that they have no conflict of interests.

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