Advances in Medicine and Engineering Interdisciplinary Research, 2025, Volume 3, Issue 4
DOI: 10.32629/ameir.v3i4.4857
ISSN Online: 2972-3825
ISSN Print: 2972-3833

Cerebral radionecrosis in an adult

Duniel Abreu Casas, Alfredo Daniel Alemán Bacallao *, Mercedes Rita Salinas Olivares

National Institute of Neurology and Neurosurgery, Havana, Cuba
*Corresponding author.
Email address: alemanbacallao25@gmail.com

Abstract: The case report of a 37-year-old patient with history of having received radiotherapy due to a tumor lesion in the right frontal region is presented, who attended to the Institute of Neurology and Neurosurgery in Cuba because of intense headache and left hemiparesis. After carrying out the necessary examinations, the clinical-imaging diagnosis of a radionecrosis lesion in the contralateral hemisphere was established, which was corroborated in the pathological examination once the tumor was removed; then, immunotherapy was indicated. The patient had a favorable clinical course because the control of the disease was achieved as well as the resolution of symptoms.

Key words: cerebral ventricle neoplasm; glioma; central nervous system; radionecrosis; radiotherapy; immunotherapy

1 Introduction

The wide variety of options for treating patients with high-grade gliomas and other brain tumors include surgery, ionizing radiation, antineoplastic chemotherapy, antiangiogenic therapies, and active or passive immunotherapies. In this regard, radiation procedures such as external beam radiation therapy, stereotactic radiosurgery, and brachytherapy, produce short- and long-term effects on brain tissue, including inflammation, vascular injury, and necrosis [1,2].

In this vein, radionecrosis (RN) is defined as tissue death caused by the side effects of radiation, which mainly affects white matter when it occurs in the central nervous system, with a significant impact on the person's quality of life. The first case that occurred after irradiation for intracranial neoplasia was described by Fischer and Holfelder in 1930. The underlying pathophysiological mechanism of this condition is still unclear, making it difficult to indicate effective treatments [3,4].

It generally occurs between 6 and 24 months after radiation, with an incidence ranging from 5% to 40%, varying according to differences in radiation dose and fractionation, the volume of the target lesion, and the time of notification [1,5,6].

In fact, increased contrast enhancement and non-progressive lesions on T1-weighted magnetic resonance imaging sequences are associated with a higher incidence of RN. According to several authors [7], surgical resection and histopathological evaluation, provided that the patient's condition allows it, is the diagnostic and therapeutic method of choice.

Controlling the effects of brain irradiation (such as severe symptomatic radionecrosis) in patients with high-grade tumors is a challenge for the medical team due to the manifestations of this entity. In Cuba, both the Institute of Neurology and Neurosurgery and the Institute of Oncology and Radiobiology have experience in treating these patients, but their incidence remains very low. New technological advances and the development of different therapies, based on randomized controlled studies, pose new challenges in terms of devising an effective strategy for each individual patient.

2 Clinical case

We present the clinical case of a 37-year-old right-handed male patient with a history of alcoholism who, four years ago, was diagnosed with a lesion in the right frontal region after presenting with severe, oppressive, holocranial headache accompanied by disorientation, behavioral changes, drowsiness, and loss of appetite.

2.1 Physical examinations

— Neurological physical examination: mild left hemiparesis with crural predominance was observed.

— Neuro-ophthalmological evaluation: normal ocular motility, isocoric and reactive pupils; bilateral incipient papilledema was observed in the fundus.

— Neuropsychological analysis of the frontotemporal circuit: indicated impairment in memory, attention, verbal fluency, and perseverance.

2.2 Imaging studies and therapeutic approach

A brain CT scan revealed a space-occupying lesion in the right frontal region measuring 6.19 by 5.38 cm in the axial slices, which crossed the midline, infiltrated the corpus callosum, and displaced the anterior cerebral and pericallosal arteries. Areas of necrosis were observed in front of the intratumoral cyst, along with glove-finger edema and displacement of the midline structures by 1.94 cm (Fig. 1).

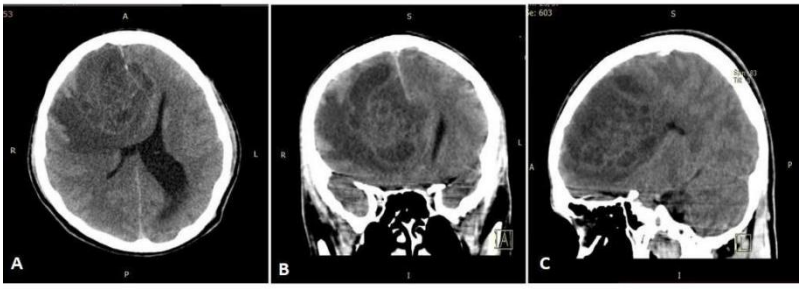

Figure 1. Preoperative non-contrast cranial computed tomography (CT): axial (A), coronal (B), and sagittal (C) views.

It was decided to operate on the patient to remove the lesion. A right frontal lobectomy was performed under microscopic visualization and ultrasonic guidance through a frontotemporal craniotomy, without intraoperative complications.

The postoperative magnetic resonance imaging (Fig. 2) showed total macroscopic resection of the tumor. Anatomopathological analysis yielded a diagnosis of grade 3 anaplastic oligodendroglioma, according to the World Health Organization classification.

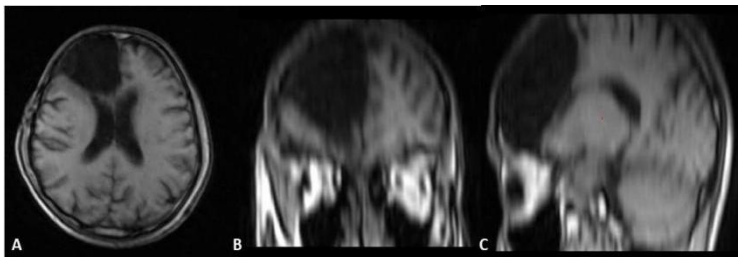

Figure 2. Postoperative cranial magnetic resonance imaging (MRI), T1-weighted, axial (A), coronal (B) and sagittal (C) sections; right frontal lobectomy cavity with no residual tumor lesion.

Adjuvant treatment with radiotherapy was indicated for 6 weeks, 5 days a week, in fractions of 2 Gy per session, for a total of 60 Gy after 30 sessions, in addition to concomitant chemotherapy with temozolomide.

The patient progressed favorably with no neurological abnormalities on physical examination. During the first year, clinical follow-up was performed quarterly and then annually; imaging studies were also performed using MRI at 6 months,

1 year, and 3 years after discharge.

Four years after surgery, the patient came to the clinic with moderate holocranial headache associated with asthenia and weight loss. On physical examination, he was conscious, oriented, but with bradypsychia, bradyphasia, abulia, and apathy; pupils were isocoric and reactive, with no motor or sensory deficits.

Cranial MRI showed an area of postsurgical encephalomalacia in the right frontal region, with no change from previous studies. A diffuse intraxial lesion was found in the left cerebral hemisphere, displacing the ipsilateral lateral ventricle, with little enhancement after administration of iodinated contrast. Midline shift, infiltration of the corpus callosum, effacement of the subarachnoid space, and infiltration of the basal ganglia were also found (Fig. 3A-C).

Given the new clinical and imaging findings, it was decided to perform surgical treatment consisting of complete resection of the lesion area, with microscopic support and neuronavigation, through a 6 x 6 cm left frontal craniotomy, without complications. The postoperative MRI study at 48 hours (Fig. 3D-F) confirmed total resection of the lesion.

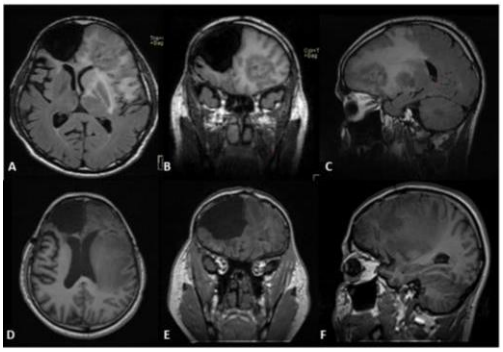

Figure 3. Cranial magnetic resonance imaging, FLAIR-weighted images: axial (A), coronal (B), and sagittal (C) views, showing a radionecrosis lesion in the left frontal region. Postoperative MRI study: (D) axial, (E) coronal, and (F) sagittal views, revealing resection of the radionecrosis area.

The anatomopathological study analyzed fragments consisting of cerebral cortex and cortical white matter stained with hematoxylin/eosin, where the following alterations predominated: cavitation of the white matter, atypical gliosis around small blood vessels with collagenized walls, multinucleated astrocytes with bizarre nuclei, vascular hyalinization with vascular endothelial proliferation, areas of necrosis with ghost vessels and numerous macrophages. No residual or recurrent neoplasia was observed. It was concluded that this was a late adverse effect of distant radiotherapy (contralateral hemisphere): a radionecrosis lesion.

The patient had a 14-day hospital stay and progressed favorably, with a negative neurological examination at discharge. Four weeks after surgery, immunotherapy with nimotuzumab (200 mg/dose) was started once a week for six periods. The outcome was satisfactory, as the disease was controlled.

3 Comments

Radiotherapy is established for patients with different types of brain tumors, making it a possible therapeutic option in addition to surgical intervention and chemotherapy.

It should be noted that radiation causes disruption of the blood-brain barrier and damage to endothelial cells, followed by edema and tissue hypoxia; it triggers increased expression of hypoxia-inducible factor 1 α (HIF-1 α), which stimulates the production of vascular endothelial growth factor. The latter has been identified as the most potent proangiogenic factor; its high levels of expression result in neovascularization with abnormal and fragile vessels that promote cerebral edema, neuronal demyelination, and vascular fibrinoid necrosis [8].

RN is a generally delayed complication of radiation toxicity; in this patient, it was diagnosed 4 years after receiving radiation. It usually occurs within 1-2 years after the start of treatment; although cases of early onset within the first 6 months after exposure have been reported, mainly related to radiosurgery, these are milder and transient. The literature consulted [1,5,9,10] reports severe cases of very late-onset cerebral radionecrosis. Decades after the patient has been treated for this lesion, these conditions are usually progressive and irreversible, for which there are no effective treatments.

Among the risk factors for developing radionecrosis, which are related to the time of onset, the total radiation dose, the volume of irradiated tissue, male sex, history of previous irradiation, and the combination of radiation and chemotherapy are noteworthy [5]. Doses below 60 Gy in daily fractions of 2 Gy are considered safe, with an incidence of RN of 5%, which is considered the standard protocol for the treatment of patients with high-grade gliomas (Stupp protocol) [9].

However, diagnosing cerebral radionecrosis and differentiating it from actual tumor progression is challenging, as both conditions have similar clinical and imaging characteristics, such as neurological focality, edema, and contrast uptake in the tumor bed. Advances in neuroimaging have aided diagnosis, despite the high rate of false negatives/false positives. In conventional MRI, they are usually described as "Swiss cheese" or "soap bubble" lesions.

Perfusion and MR spectroscopy, fluorodeoxyglucose positron emission tomography, and intraoperative contrast-enhanced ultrasound are also among the studies that offer the best diagnostic advantages. Biopsy of the suspected lesion is the gold standard for diagnosis, but this is not always feasible and its interpretation can sometimes be confusing; therefore, serial follow-up imaging is of utmost importance [6,7,9].

Cerebral radionecrosis generally appears in or near the tumor bed. Although neurons do not appear to suffer significant direct damage after radiation, they are nevertheless involved in the processes responsible for the late effects of radiotherapy through changes in synapses and axonal dysfunction processes. Microglial cells also play a role in the production of the toxic effects of radiotherapy through the generation of free radicals and oxidative stress processes. This could explain the appearance of radionecrosis lesions in sites distant from the irradiated area, even in the contralateral hemisphere, as presented in this case, which are rare and difficult to diagnose [10].

It is important to note that most patients with radionecrosis are asymptomatic and resolve spontaneously. Symptoms include seizures, cognitive impairments, and nausea, depending on the irradiated area; those affected may require medical and/or surgical treatment [3,4]. In the case presented, a severe lesion was found in the contralateral cerebral hemisphere that appeared 4 years after irradiation, which was diagnosed based on a clinical picture of left frontal neurological focal deficits.

The management of these patients is complex and therapeutic options are limited, including steroids, surgery, bevacizumab, and hyperbaric oxygen therapy. Several authors [4,7,9] conducted a review of interventions for the treatment of patients with cerebral radionecrosis after radiotherapy or radiosurgery, using systematic review databases: The Cochrane Register of Controlled Trials, MEDLINE, Embase, and The Cumulative Index to Nursing and Allied Health Literature, which included randomized controlled trials, prospective comparative interventions, and quasi-randomized trials, provided that these studies included a comparison group (placebo or corticosteroids) [3]. The findings demonstrated a lack of evidence to quantify the risks and benefits of interventions for treating patients with cerebral radionecrosis after radiotherapy or radiosurgery.

Similarly, in a randomized clinical trial involving 14 patients, bevacizumab showed a radiological response that was associated with minimal improvement in cognition or symptom severity. Although the trial was randomized in design, the small sample size limited the quality of the data. In a trial using edaravone (a potent antioxidant) plus corticosteroids

versus corticosteroids alone, a greater reduction in surrounding edema was reported with the combination treatment, but no effect on the radionecrosis lesion uptake. There was no evidence to support any non-pharmacological intervention for the treatment of patients with this condition, which is why more prospective randomized studies of pharmacological and non-pharmacological interventions are needed to generate more robust evidence [3]. The use of angiotensin-converting enzyme (ACE) inhibitors has resulted in the mitigation of such radiation-induced injury in various organs, such as the optic pathway, brain, and kidney. Ramipril, one of the ACE inhibitors, reduces the expression of vascular endothelial growth factor, which correlates with better paralysis outcomes in irradiated rats. Erpolat et al, [8] in an experimental study, evaluated the effect of this inhibitor in the prevention and treatment of radiation-induced brain injury and compared its efficacy with that of bevacizumab in reducing RN in rat brain tissue. They concluded that ramipril could be a promising agent for patients with radionecrosis, but clinical studies are needed to investigate the effective and safe doses of the compound, despite it being an inexpensive and well-tolerated drug that can cross the blood-brain barrier. The prophylactic use of bevacizumab and ramipril appeared to be more effective than therapeutic administration.

The most effective way to treat patients with radionecrosis causing mass effect and neurological deficits is surgical resection, as it improves the clinical condition of these patients [9]. This strategy was used in this case with the support of corticosteroid therapy and post-surgical immunotherapy with nimotuzumab, achieving clinical and radiological control of the disease to date (two years after the surgery).

It is difficult to predict the onset of adverse effects of radiotherapy in the short and long term, even when doses within safe therapeutic margins are used. The diagnosis of cerebral radionecrosis and its differentiation from actual tumor progression is complex despite new technological advances. Management must be individualized for each patient according to the severity of the disease and implemented by a multidisciplinary team. Surgical intervention is an effective diagnostic and therapeutic method in severe disease, which can be combined with immunotherapy for better clinical and radiological control.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Ellingson BM, Chung C, Pope WB, Boxerman JL, Kaufmann TJ. Pseudoprogression, radionecrosis, inflammation or true tumor progression? Challenges associated with glioblastoma response assessment in an evolving therapeutic landscape. J Neurooncol. 2017 [citado 12/05/2023];134(3):495–504. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7893814/.

[2] Wernicke AG, Taube S, Smith AW, Herskovic A, Parashar B, Schwartz TH. Cs-131 brachytherapy for patients with recurrent glioblastoma combined with bevacizumab avoids radiation necrosis while maintaining local control. Brachytherapy. 2020 [citado 12/05/2023];19(5):705-12. Disponible en https://www.sciencedirect.com/science/article/abs/pii/S1538472120301318?via%3D ihub.

[3] Chung C, Bryant A, Brown PD. Interventions for the treatment of brain radionecrosis after radiotherapy or radiosurgery. Cochrane Database of Systematic Reviews. 2018 [citado 12/05/2023];7(7):CD011492. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513335/.

[4] Raggabi A, Bourazza A, Lalya I. Prise en charge de la radionécrose cérébrale: expérience du Service de Neurologie de l'Hôpital Militaire d'Instruction Mohammed V. Pan Afr Med J. 2019 [citado 12/05/2023];33. Disponible en: https://www.panafrican- med-journal.com/content/article/33/188/full/.

[5] Donovan EK, Parpia S, Greenspoon JN. Incidence of radionecrosis in single-fraction radiosurgery compared with

fractionated radiotherapy in the treatment of brain metastasis. Curr Oncol. 2019 [citado 12/05/2023];26(3):e328-e33. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6588068/.

[6] Lupattelli M, Alì E, Ingrosso G, Saldi S, Fulcheri C, Borghesi S, et al. Stereotactic Radiotherapy for Brain Metastases: Imaging Tools and Dosimetric Predictive Factors for Radionecrosis. J Pers Med. 2020 [citado 12/05/2023];10(3):59. Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7565332/pdf/jpm-10-00059.pdf.

[7] Rascón Ramírez FJ, Sallabanda Díaz K, Salazar Ascencio OA, Trondin A, Avecillas Chasín JM. Radionecrosis gigante recurrente imitando un glioma de alto grado: el uso de ácido 5-aminolevulínico como técnica para su diferenciación. Gliomat. 2015 [citado 12/05/2023];1(3):51-3. Disponible en: https://www.researchgate.net/publication/297038197_Radionecrosis_recurrente_imit ando_glioma_de_alto_el_uso_de_5-aminolevulinico_como_tecnica_para_su_diferenciacion.

[8] Erpolat OP, Demircan NV, Sarıbas GS, Kuzucu P, Senturk E, Elmas C, et al. A Comparison of Ramipril and Bevacizumab to Mitigate Radiation-Induced Brain Necrosis: An Experimental Study. World Neurosurg. 2020 [citado 12/05/2023];144:e210-e20. Disponible en:https://www.sciencedirect.com/science/article/abs/pii/S1878875020318489.

[9] Rascón Ramírez FJ, Salazar Asencio OA, Trondin A. Recurrent Agressive Brain Radionecrosis or High-Grade Glioma: How to Treat? Int J Brain Disord Treat. 2019 [citado 12/05/2023];5(1):1-4. Disponible en: https://clinmedjournals.org/articles/ijbdt/international-journal-of-brain-disorders- and-treatment-ijbdt-5-027.php?jid=ijbdt.

[10] Sayan M, Şahin B, Zoto Mustafayev T, Sare Kefelioğlu ES, Vergalasova I, Gupta A, et al. Risk of symptomatic radiation necrosis in patients treated with stereotactic radiosurgery for brain metastases. Neurocirugía. 2021 [citado 12/05/2023];32(6):261-7. Disponible en: https://www.revistaneurocirugia.com/es-risk-symptomatic-radiation- necrosis-in-articulo-S1130147320301111.