

**BRAIN RADIONECROSIS IN PATIENTS IRRADIATED FOR NASOPHARYNGEAL CARCINOMA: ABOUT ONE CASE AND REVIEW OF LITARATURE**

Taghzout Hasnae\*, Chbihi Hassani Ghita, Hafidi Khaoula, Alami Zineb, Bouhafa Touria and Hassouni Khalid

Departement of Radiotherapy and Oncology University Hospital Center Fes Morocco.

\*Corresponding Author: Dr. Taghzout Hasnae

Departement of radiotherapy and oncology University Hospital Center Fes Morocco.

Article Received on 13/02/2019

Article Revised on 06/03/2019

Article Accepted on 27/03/2019

**ABSTRACT**

Cerebral radionecrosis is a rare, late iatrogenic complication that occurs after more than six months from the start of treatment in irradiated patients for undifferentiated nasopharyngeal carcinoma. This could be explained by the conjunction of vascular, glial and immunological lesions. This may involve the patient's functional and vital prognosis. Conventional MRI (Magnetic resonance imaging), coupled with spectroscopic sequences, greatly contributed to the follow-up of irradiated patients to refine the differential diagnosis between tumor recurrence and radionecrosis. Getting histological evidence by surgical excision or stereotactic biopsy remains to be discussed. given the lack of potentially effective treatment prevention through better dosimetric planning is fundamental. We report a case in a patient treated with induction chemotherapy followed by concomitant radiochemotherapy for locally advanced nasopharyngeal cancers. The diagnosis was guided by spectroscopic MRI and the evolution was favorable under steroids.

**KEYWORDS:** Cerebral radionecrosis, Nasopharyngeal cancers, radiotherapy, Spectroscopic MRI**1. INTRODUCTION**

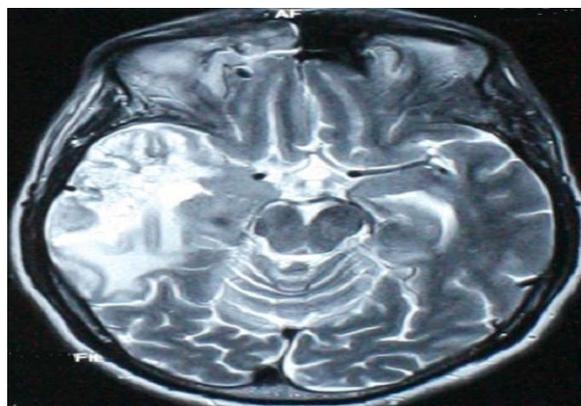
Radiation therapy is the essential treatment for nasopharyngeal carcinomas.<sup>[1]</sup> In order to sterilize a nasopharyngeal tumor, it is necessary to deliver doses at the limit of the tolerance of the neighboring cerebral parenchyma. In addition, the dose of radiation is usually 65 to 70 Gy, which exceeds the tolerance of brain tissue.<sup>[2]</sup> The first case of cerebral radionecrosis was described by Fischer and Holfelder in 1930.<sup>[3]</sup> Cases of cerebral radionecrosis reported are still rare in Morocco. The diagnosis of cerebral radionecrosis is based on clinical and neurological imaging (CT and MRI) but above all on the clinical and radiological evolution.<sup>[3]</sup> Through our case and a review of the literature, we will proceed to a clinical, radiological, therapeutic and evolutionary description of cerebral necrosis after irradiation for nasopharyngeal carcinoma.

**2. CASE RAPPORT**

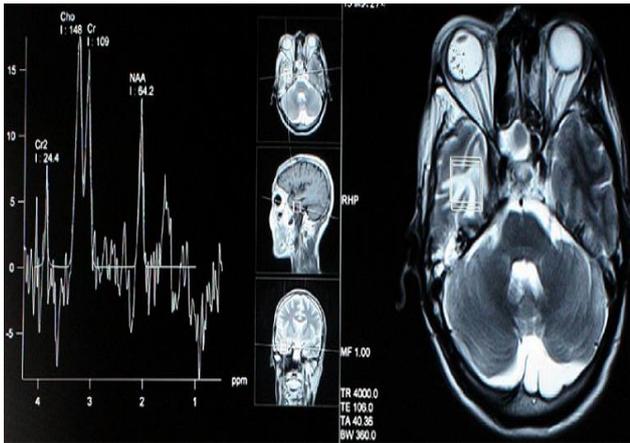
a 45 year old patient, followed since 2011 for undifferentiated carcinoma type UCNT nasopharynx, initially classified: T4N1M0 with extension to the left infra-temporal fossa and presence of centimetric lymphadenopathy under maxillary fist, he benefited from a induction chemotherapy followed by concomitant radiochemotherapy at a total dose of 70 Gy : 2Gy per fraction in 35 Fractions; 5 days out of 7, over 7 weeks, combined with weekly chemotherapy with cisplatin at a

dose of 30 mg / m<sup>2</sup>, with good clinical and radiological response.

At 30 months of follow-up, he presented with headache resistant to analgesic treatment, with vertigo, and memory disorders, a control CT showed secondary locations, but MRI brain (Figure.1) especially spectro-MRI (Figure.2) straightened the diagnosis in favor of radionecrosis (decrease of N-acetyl-Aspartase (NAA) increase in choline, presence of traces of lactates). The evolution was favorable with corticotherapy, the patient is still alive with good locoregional control.



**Fig. 1: MRI of a brain radionecrosis: right temporal image, contrast enhancement and peri-lesional oedema.**



**Fig. 2: MRI coupled to spectroscopy showing an injury process of the right infra-temporal fossa and a slight decrease in NAA with increased choline in favor of radionecrosis.**

### 3. DISCUSSION

The late and rare neurological complications of radiotherapy of nasopharyngeal cancers are postradiation myelopathy and cerebral radionecrosis.<sup>[4]</sup> which occurs after more than six months after the start of treatment<sup>[5]</sup>, 30 months in our case. Irradiation for nasopharyngeal carcinoma is the main etiology, the treatment of nasopharyngeal cancers is indeed difficult because of its highly invasive nature and proximity to critical structures such as the brain. Cerebral radionecrosis, mainly temporal, is a well-known complication and one of the most important dose-limiting factors in nasopharyngeal cancer. Its incidence rate varies between 0.95 and 14% depending on the series.<sup>[2,6]</sup> It could be explained by the conjunction of vascular, glial and immunological lesions.

The most important lesions occur on small and medium-sized vessels, with endothelial proliferation and thickening of the intima, resulting in ischemic necrosis. Achieving the blood-brain barrier, due to enlargement of the glial endothelial junctions, results in plasma exudation in the parenchyma. In addition, oligodendroglial cell involvement has been observed and may explain the vulnerability of the white matter.<sup>[6,7,8]</sup> Finally, inflammatory phenomena and local antibody production could be triggered by antigenic substances represented by glial cells lysed by irradiation. These different phenomena could associate and explain the signs observed at different stages of the lesion process.<sup>[7,9]</sup> The risk factors that play a key role in the development of cerebral radionecrosis are the age of the patient with a higher risk in children and the elderly, the total dose, the duration of the irradiation and especially the dose by fraction with a protective role of split schemes.<sup>[2,10]</sup>

The majority of clinical (and experimental) studies have highlighted the major role of fractional dose in the determinism of brain radionecrosis.<sup>[11,12,13]</sup> Most authors described a large number of radionecrosis after hypofractionated radiotherapy. In contrast,

complementary brachytherapy and sequential chemotherapy did not significantly influence the risk of temporal radionecrosis. However, combining concomitant platinum-salt chemotherapy with radiotherapy appears to increase the risk of cerebral radionecrosis, but this has not been demonstrated.<sup>[9,13,14]</sup> Cerebral radionecrosis after interstitial curie-therapy is mainly described in the treatment of brain tumors.<sup>[14]</sup> In the case of nasopharyngeal carcinoma, it is mainly radionecrosis of the nasopharyngeal wall that has been reported after brachytherapy.<sup>[15,16]</sup> The dose rate seems to play a major role in the risk of radiation necrosis after brachytherapy, as well as the geometric distribution of sources in the tumor and the proximity and functional importance of surrounding healthy tissues.<sup>[13]</sup> A comparative study conducted by Teo *et al.*<sup>[16]</sup> Showed no statistically significant difference in late neurologic complications between the brachytherapy boost group and the treatment group treated with external irradiation alone.

This complication occurs after a latency period whose duration is very variable, ranging from six months to 24 years. However, nearly 90% of lesions become symptomatic within five years of irradiation.<sup>[11]</sup> This latency interval reflects the ability of the cerebral parenchyma to tolerate chronic alterations without potentially elevating intracranial pressure.<sup>[17]</sup> The clinical symptoms are variable. It can be manifested by major symptoms, such as unconsciousness and convulsions or minor complaints, such as dizziness or memory impairment, or incidental discovery during follow-up imaging examinations in asymptomatic patients.<sup>[1,10]</sup>

A study conducted by Cheung *et al.*<sup>[18]</sup>, evaluating the impact of cerebral radionecrosis on the severity of cognitive disorders in 50 patients irradiated for nasopharyngeal carcinoma, demonstrated a significant association between the volume of radionecrosis and the degree of cognitive disorders but also between the seat of brain injury and the type of symptoms. The temporal location, which is the most common, is associated with disorders of language, behavior and memory. vertigo, and memory disorders in our case.

Cerebral CT shows a hypodensity with mass effect that may or may not take the contrast. However, MRI in this context is more sensitive than CT.<sup>[11,19]</sup> As reported by Gaucher *et al.*, MRI can detect non-visible white matter lesions on CT scan<sup>[20]</sup>, which remains the test of choice for monitoring patients after radiotherapy. However, in the presence of suspicious enhancement, the differential diagnosis between recurrence in the form of very exceptional cerebral metastases and radionecrosis is often difficult. The diagnostic decision is important because it results in radically different therapeutic attitudes (surveillance, systemic treatment, surgery). Multimodal MRI techniques with perfusion sequences and spectrometry greatly improve the sensitivity and specificity of the examination.<sup>[10,21]</sup>

Our patient had magnetic resonance imaging coupled with spectrometry and that was in favor of radionecrosis. The distinction between radionecrosis and tumor recurrence remains difficult<sup>[19,22,23]</sup>, this distinction is facilitated by the dynamic study to study the perfusion of the cerebral parenchyma.

The contribution of FDG PET was evaluated in the follow-up of irradiated brain metastases. If it is less sensitive and less specific than the latest MRI techniques, it allows, coupled with MRI, to provide an additional argument in favor of tumor recurrence if the lesion is hypermetabolic. Its main limitation is physiological glucose hypermetabolism.<sup>[21]</sup> 18F-DOPA PET, a labeled amino acid, provides a relevant complement to multimodality MRI in the differential diagnosis between radionecrosis and cerebral tumor recurrence.<sup>[24]</sup> However, the diagnosis of certainty can only be histological. The evocative lesion is white matter coagulation necrosis associated with demyelination and vascular lesions (fibrinoid necrosis).<sup>[8,9,11,13]</sup> In the absence of anatomopathological evidence, the diagnosis is based on the clinical and radiological evolution that supports the diagnosis.<sup>[19,25]</sup>

The main goal of cerebral radionecrosis treatment is clinical cure with minimal risk of morbidity. Few therapeutic means are available. Surgical resection of the necrosis is risky and especially carried out in case of syndrome of intracranial hypertension or rapid progression of the clinical signs under symptomatic treatment.<sup>[15]</sup> It is associated with a high risk of morbidity.<sup>[7,12]</sup> As a result, the use of corticosteroids and symptomatic treatments is often the only remedy. The favorable response to corticosteroid therapy is explained by the vasogenic edema often associated with radionecrosis. However, the possibility and risks of side effects and, above all, prolonged corticoid dependence must be emphasized<sup>[13]</sup>, in our case the evolution was favorable with corticotherapy.

Hyperbaric oxygen therapy is an alternative that has been used.<sup>[2,10]</sup> Bevacizumab is a monoclonal antibody allowing a reduction in neoangiogenesis and a decrease in the permeability of the blood-brain barrier that has recently been proposed in the treatment of brain radionecrosis that is refractory to drug treatment and hyperbaric oxygen therapy.<sup>[26]</sup> Further experiments will be needed to confirm the effect of hyperbaric oxygen in the treatment of cerebral radionecrosis. For the prognosis, Lee found a 5-year survival rate for cerebral radionecrosis of 59%, with or without treatment.<sup>[27]</sup>

#### 4. CONCLUSION

The diagnosis of cerebral radionecrosis is difficult, it relies on a clinical, radiological, dosimetric and evolutionary correlation. The new means of metabolic imaging (PET) will facilitate diagnosis. A better understanding of the pathophysiology of cerebral radionecrosis would help improve the prevention and

treatment of cerebral radionecrosis. The fractionation dose is a major factor for the determinism of late neurological complications. Advances in radiotherapy techniques (conformational, with or without intensity modulation) should reduce the risk of cerebral radionecrosis by improving the protection of risky tissues. In the absence of effective treatment, prevention through better dosimetric planning is fundamental.

#### REFERENCES

1. Leber KA, Eder HG, Kovac H, Anegg U, Pendl G. Treatment of cerebral radionecrosis by hyperbaric oxygen therapy. *Stereotact Funct Neurosurg* 1998; 70(Suppl1): 229–36.
2. Hsu YC, Wang LF, Lee KW, Ho KY, Huang CJ, Kuo WR. Cerebral radionecrosis in patients with nasopharyngeal carcinoma. *Kaohsiung J Med Sci*. 2005; 21(10): 452–459. [PubMed]
3. Fischer AW, Holfelder H. Lokales amyloid in Gehirn. *Dtsch Z Chir* 1930; 227: 475–83.
4. Mrabet A, Maalej M, Mrad Ben Hammouda I, Gouider KHouja N, Bes- bes M, Ben Hamioda M. Les myélopathies post-radiques : à propos de six observations. *Tunis Med.*, 1992; 70(1): (in press).
5. Lartigau E, Dubray B, Mornex F. Mécanismes biologiques des effets tardifs des radiations ionisantes. *Cancer Radiother*, 1997; 1: 669–76.
6. Lee AWM, Kwong DLW, Leung S-F, Tung SYT, Sze W-M, Sham JST. Factors affecting risk of symptomatic temporal necrosis: significance of fractional dose and treatment time. *Int J Radiation Oncology Biol Phys*, 2002; 53(1): 75–85. [PubMed]
7. Lee AWM, Ho JHC, Tse VKC, Poon YF, Tse CCH, Au GKH, et al. Clinical diagnosis of late temporal lobe necrosis following radiation therapy for nasopharyngeal carcinoma. *Cancer*, 1988; 61: 1535–42.
8. Schultheiss TE, Kun LE, Ang KK, Stephens LC. Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys*, 1995; 31: 1093– 112.
9. Mornex F, Beauvois S, Van Houtte P. Effets tardifs des radiations ionisantes sur le système nerveux central, la moelle épinière, les nerfs périphériques. *Cancer Radiother*, 1997; 1: 25–8.
10. Nasr Ben Ammar C, Chaari N, Kochbati L, Attia I, Ben Hamadi D, Chebbi A, Saadi A, Besbes M, Maalej M. Brain radionecrosis in patients irradiated for nasopharyngeal carcinoma: about nine cases. *Cancer Radiother*, 2007; 11(5): 234–240. [PubMed]
11. Delattre J-Y, Poisson M. Complications neurologiques de la radiothérapie cérébrale : apport des études expérimentales. *Bull Cancer*, 1990; 77: 715–24.
12. Lee AWM, Foo WF, Chappell RC, Fowler JF, Sze WM, Poon YF, et al. Effect of time, dose, and fractionation on temporal lobe necrosis following radiotherapy for nasopharyngeal carcinoma. *Int J Radiation Oncology Biol Phys*, 1998; 40: 35–42.

13. Delattre J-Y, Ameri A, Albuquerque L, Poisson M. Complications cérébrales tardives de la radiothérapie. *Ann Med Interne (Paris)*, 1994; 145: 125–32.
14. Ruben JD, Dally M, Baily M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. *Int J Radiat Oncol Biol Phys*, 2006; 65: 499–508.
15. Law SCK, Lam W-K, Ng M-F, Au S-K, Mak W-T, Lau W-H. Reirradiation of nasopharyngeal carcinoma intracavitary mold brachytherapy: an effective means of local salvage. *Int J Radiat Oncol Biol Phys*, 2002; 54: 1095–113.
16. Teo PML, Leung SF, Lee WY, Zee B. Intracavitary brachytherapy significantly enhances local control of early T-stage nasopharyngeal carcinoma: the existence of a dose-tumor-control relationship above conventional tumoricidal dose. *Int J Radiat Oncol Biol Phys*, 2000; 46: 445–58.
17. Woo E, Lam K, YU YL, Lee PWH, Huang CY. Cerebral radionecrosis: is surgery necessary? *J Neurol Neurosurg Psychiatry*, 1987; 50: 1407–14.
18. Cheung M-C, Chan AS, Law SC, Chan JH, Tse VK. Impact of radionecrosis on cognitive dysfunction in patients after radiotherapy for nasopharyngeal carcinoma. *Cancer*, 2003; 97: 2019–26.
19. Tsui EYK, Chan JHM, Leung TW, Yuen MK, Cheung YK, Luk SH, et al. Radionecrosis of the temporal lobe: dynamic susceptibility contrast MRI. *Neuroradiology*, 2000; 42 :149–52.
20. Jen Y-M, Hsu W-L, Chen C-Y, Hwang J-M, Chang L-P, Lin Y-S, et al. Different risks of symptomatic brain necrosis in NPC patients treated.
21. Patsouris A, Augereau P, Tanguy JY, Morel O, Menei P, Rousseau A, Paumier A. Differential diagnosis of local tumor recurrence or radionecrosis after stereotactic radiosurgery for treatment of brain metastasis. *Cancer Radiother*, 2014; 18(2): 142–146. [PubMed]
22. Gaucher S, Viala J, Lusinchi A, Vanel D, Sigal R. CT and MRI aspects of 28 patients with cerebral radiation necrosis irradiated for ORL tumors: correlation with the radiation technique. *J Radiol*, 2002; 83: 1749–57.
23. Tsui EYK, Chan JHM, Ramsey RG, Leung TW, Cheung YK, Luk SH, et al. Late temporal lobe necrosis in patients with nasopharyngeal carcinoma: evaluation with combined multi-section diffusion weighted and perfusion weighted MR imaging. *Eur J Radiol*, 2001; 39: 133–8.
24. Dufour MA, Papin-Michaud C, Vandenbos F, Bourg V, Bondiau PY, Chanalet S, Fauchon F, Fontaine D, Saada E, Darcourt J. Impact de la TEP à la 18F-DOPA sur la décision thérapeutique en RCP lors du diagnostic différentiel entre radionécrose et récurrence de néoplasie cérébrale. *Médecine Nucléaire*, 2014; 38(3): 132–134.
25. Wang CT, Young YH. Potential usefulness of T1-201 SPECT for differentiating radionecrosis in an irradiated nasopharyngeal carcinoma patient. *Eur Arch Otorhinolaryngol*, 2006; 263: 135–8.
26. Gronier S, Bourg V, Frenay M, Cohen M, Mondot L, Thomas P, Lebrun C. Bevacizumab for the treatment of cerebral radionecrosis. *Rev Neurol*, 2011; 167(4): 331–336. [PubMed].
27. Lee AW, Foo W, Chappell R, et al. Effect of time, dose, and fractionation on temporal lobe necrosis following radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*, 1998; 40(1): 35–42. [PubMed].