Brain Radionecrosis in Patients Irradiated for Nasopharyngeal Carcinoma: About Four Cases


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ABSTRACT

Purpose: to study the clinical, radiological, therapeutic and progressive aspects of brain radionecrosis after treatment for nasopharyngeal carcinoma.

Patients and methods: four patients (two men and two women) of mean age 53.5 years were treated for UCNT (undifferentiated carcinoma of the nasopharynx), between 2009 and 2014, and developed cerebral radionecrosis. All patients were treated with radical radiotherapy. The mean dose was 70 Gy. Dose per fraction was 2 Gy, one fraction daily. All patients received chemotherapy. Result: patients presented non-specific neurological signs, and one case was discovered fortuitously. The mean latent period was 46 months, brain radionecrosis was authenticated by brain imaging. The localisation was temporal in two patients and bulbomedullar in two patients. After a mean follow-up period of 14 months, clinical outcomes were favorable in one case, stabilisation in two cases and one patient died. Conclusion: brain radionecrosis is a rare iatrogenic complication for patients irradiated for UCNT. Imaging techniques play a major role in the diagnosis. Corticotherapy is the main treatment.

Keywords: Brain Radionecrosis, Irradiation, Nasopharyngeal Carcinoma

1. INTRODUCTION

Radiotherapy is the standard treatment of nasopharyngeal carcinoma (NPC). However, it is not without morbidity, the irradiation field may include brain tissue, which may result in cerebral radionecrosis (CRN). It’s a rare but severe iatrogenic complication.

We present four cases diagnosed as cerebral CRN among NPC patients in our institute.

2. METHODS

The charts of four patients (two women and two men) treated for UCNT, from 2009 to 2014 at National Institute of Oncology, Rabat, Morocco, and affected with cerebral radionecrosis were studied (Table 1).
The diagnosis of UCNT was proved with histology and the classification was based on the 2010 AJCC staging classification: 2 patients stage III (T3N2M0), 2 patients stage II (T2N1M0 and T2N0M0).

All patients received complete radiotherapy with 6 and 18 MV photons using the same technique of two lateral opposed field supplemented by an anterior field. The radiation dose was 70 GY, delivered in 2 GY fraction once daily for 5 days per week. All patients had concurrent chemotherapy with cisplatin based regimen.

### Table 1. Patients data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at diagnosis of RNC (yr)</th>
<th>TNM</th>
<th>Total dose (Gy)</th>
<th>CCT</th>
<th>Latency (Mo)</th>
<th>Lesion site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>44</td>
<td>T3N2M0</td>
<td>70</td>
<td>Yes</td>
<td>34</td>
<td>Bil T</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>54</td>
<td>T2N1M0</td>
<td>70</td>
<td>Yes</td>
<td>70</td>
<td>bulbar</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>72</td>
<td>T2N0M0</td>
<td>70</td>
<td>Yes</td>
<td>45</td>
<td>bulbar</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>44</td>
<td>T3N0M0</td>
<td>70</td>
<td>yes</td>
<td>36</td>
<td>Bil T</td>
</tr>
</tbody>
</table>

CCT: concurrent chemotherapy; bil T: bilateral temporal

The mean age at diagnosis of CRN was 53.3 years (range, 44 and 71 years). Clinical symptoms and signs included hemiparesis for 2 patients, memory impairment and headache for one patient, one patient was asymptomatic. The radionecrosis was found by follow up imaging studies. The mean latent period from the end of the last radiation to the diagnosis of CRN was 46 months (range 34 to 70 months). CRN was clinically diagnosed based on brain imaging (computed tomography magnetic resonance imaging), which was performed in all patients and MR spectroscopy in one patient. CRN was in the bilateral temporal lobe of the brain for two patients and bulbar for two patients.

### 3. RESULTS

All patients were treated with corticotherapy, one patient received hyperbaric oxygen therapy. The follow up period lasted for a mean of 14 months (range 5 to 31 months). Outcome was favorable after corticotherapy in one case and stationary in two cases, while patient n°2 died 8 months after diagnosis.

### 4. DISCUSSION

The first case of extracranial neoplasm with cerebral radionecrosis was described by Fischer et Holfilder in 1930(1). It’s a late complication of radiotherapy, occurring after more than six months following the onset of treatment(2). The most common primary site of malignancy is the nasopharynx(3). The reported

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![Fig.1. MRI of bitemporal radionecrosis, contrast enhancement and perilesional oedema](image-url)
incidence of CRN in NPC patients ranges from 0.40% to 18.6% (3,4,5).

The mechanism could be explained by vascular, glial and immunological lesions. The most important lesions occur on small and medium-sized vessels, with endothelial proliferation and intimal thickening, leading to ischemic necrosis. The attainment of the blood - brain barrier, due to enlargement of the glial endothelial junctions, results in a plasma exudation in the parenchyma. In addition, oligodendrogial cell damage was observed (4,6,7).

The most significant risk factors of developing CRN are: total dose, treatment time and fractional dose (6,8). Lee et al analyzed their irradiation regimen for 1008 patients and observed that the percentage of CRN in 10 years was 18.6% for patients treated with 4.2Gy/fraction (total dose was 50Gy) and 4.6% for patients treated with 2.5Gy/fraction (with a total dose 60Gy). Prolonging the treatment time offered little protective effect (8,9). other factors also appeared to affect the occurrence of CRN like age, hypertension, diabetes.

Latency has been reported at 6 months to 24 years, with approximately 90% occurring within 5 years after radiotherapy completion (4,10). The clinical symptoms of CRN are variable, including major symptoms, such as changes in consciousness, and minor complaints, such as dizziness, vertigo, headache or memory impairment. Asymptomatic patients are sometimes found by follow-up imaging studies (3). The volume and location of radionecrosis had an influential impact on the pattern of cognitive impairment found in patients with NPC (11).

Differentiating radionecrosis from recurrent tumor is difficult with computed tomography (CT) and magnetic resonance imagine (MRI) finding alone. MRI has a high sensitivity but a low specificity (10,12,13). Recent MRI techniques, such as perfusion- and diffusion- weighted scans or MR spectroscopy may help distinguish the lesion (3). 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been proposed as a diagnostic alternative, particularly when co-registered with MRI which appears to improve the sensitivity of FDG PET from 65 to 86%, with the same specificity (14,15). The general characteristics of CRN and tumors are summarized in table 2.

<table>
<thead>
<tr>
<th>Diagnostic tool</th>
<th>Recurrent NPC</th>
<th>Cerebral radionecrosis</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Low-density, post-contrast enhancement</td>
<td>Digitiform or round hypodense lesion Post-contrast enhancement</td>
<td>Reported detection rate:50% Detection rate &lt; MRI</td>
</tr>
<tr>
<td>MRI</td>
<td>Low signal in T1W, high signal in T2W Heterogeneous contrast enhancement</td>
<td>Low signal in T1W, High signal in T2W Heterogeneous contrast enhancement</td>
<td>Poorly differentiated from tumor with only T1W, T2W Superior sensitivity to CT scan</td>
</tr>
<tr>
<td>MRI perfusion-weighted scan (rCBV map)</td>
<td>High signal</td>
<td>Low signal</td>
<td></td>
</tr>
<tr>
<td>MRI diffusion-weighted scan (ADC map)</td>
<td>Low signal</td>
<td>High signal</td>
<td></td>
</tr>
<tr>
<td>MR spectroscopy</td>
<td>↑NAA/Cr ratio</td>
<td>↑ Choline peak and ↓NAA/Cr ratio</td>
<td>Expensive and limited availability</td>
</tr>
<tr>
<td>PET-18 FDG</td>
<td>↑ uptake</td>
<td>↓ uptake</td>
<td>No significant differences in sensitivity or specificity for FDG-PET and 201Tl SPECT</td>
</tr>
<tr>
<td>SPECT</td>
<td>↑ uptake</td>
<td>↓ uptake</td>
<td></td>
</tr>
</tbody>
</table>

NPC= nasopharyngeal carcinoma ; CT = computed tomography; MRI = magnetic resonance imaging; PET-18 FDG = 18F-fluorodeoxyglucose positron emission tomography; SPECT = single photon emission computed tomography; T1W = T1 weighted; T2W = T2 weighted; rCBV = relative regional blood volume; ADC = apparent diffusion coefficient; NAA/Cr = N-acetylaspartate/choline ratio.

Until now there is no potentially effective treatment of CRN (12). Therapeutique options include conservative management or invasive procedures. Craniotomy or brain lobectomy which are associated with a high risk of morbidity. Corticotherapy, hyperbaric oxygen has also been reported. Bevacizumab (monoclonal
antibody neutralizing the effect of vascular endothelium growth factor (VEGF)) has been recently used as treatment of CRN resisting conventional drug treatment and hyperbaric oxygen\textsuperscript{(16)}.

5. CONCLUSION

The cerebral radionecrosis is a rare iatrogenic complication of radiotherapy, compromising the functional and vital prognosis. Prevention is fundamental considering the absence of effective treatment.

REFERENCES
