

**RADIO INDUCED OSTEOSARCOMA: A PEDIATRIC CASE REPORT**

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**ABSTRACT**

Radiotherapy is one of the major components of curative management of cancer. This is not without side effects, especially the development of radiation-induced tumors. Due to improved treatments and an overall increase in the lifespan after cancer, osteosarcoma is considered to be one of the most commonly found tumours in this context. We report the case of a patient treated with radiotherapy for orbital rhabdomyosarcoma, who subsequently developed radio-induced osteosarcoma, which had a localisation hard to manage by surgery.

**KEYWORD:** Radio-induced, osteosarcoma, tumor.**INTRODUCTION**

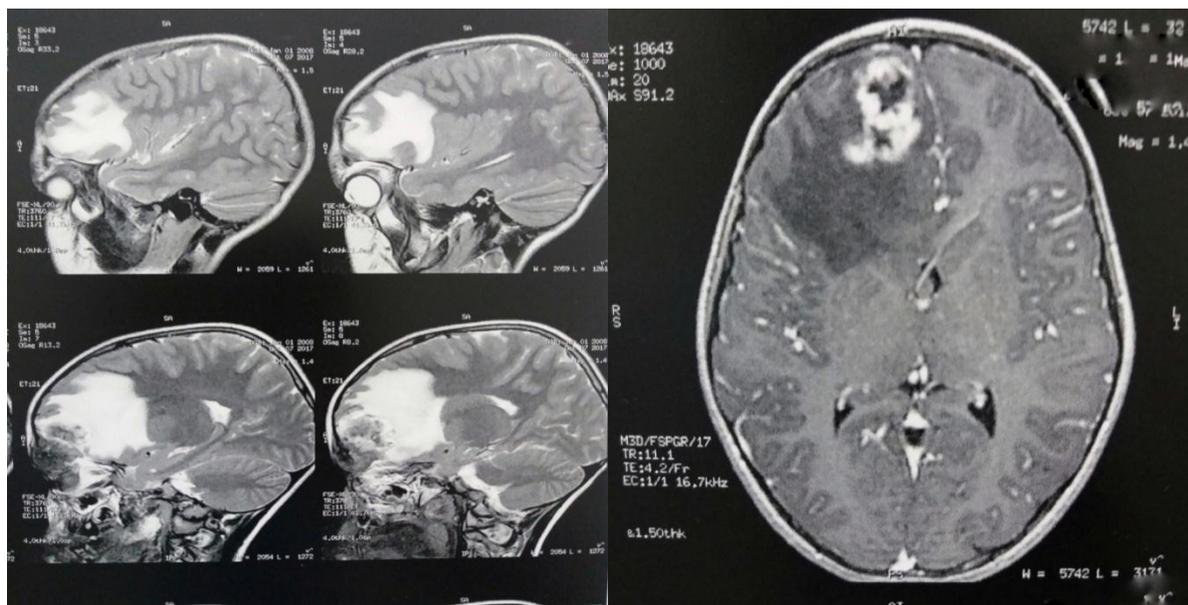
Radiotherapy is one of the major components of curative management of cancer. This is not without side effects, especially the development of radiation-induced tumors. Due to improved treatments and an overall increase in the lifespan after cancer, osteosarcoma is considered to be one of the most commonly found tumours in this context.

We report the case of a patient treated with radiotherapy for orbital rhabdomyosarcoma, who subsequently developed radio-induced osteosarcoma.

**OBSERVATION**

B.Safaa, 9 years old, 5th of a sibling of 5, born of a twin pregnancy, of second degree inbred parents, having as family history a cousin who died of osteosarcoma of the forearm.

The history of the disease dates back to the age of 02, when a swelling of the right nasal wing appeared, increasing in volume, painless, with inflammatory signs. A cerebro-orbital CT was performed, showing an extra conical internal orbital lesion process, with pre-orbito-nasal and pre-frontal development, well limited of 35x22 mm in diameter, with outward and backward discharge of the globe, without cerebral abnormalities.



**Fig. 1: Cerebro- orbital CTScan.**

The exegesis biopsy was performed, and the anatomopathological study showed embryonal rhabdomyosarcoma.

The extension assessment was normal. The diagnosis was therefore a right orbit rhabdomyosarcoma not metastatic classified T2N0M0. The patient was put under protocol MMT 95 group 3: IVA-CEV-IVE (ifosfamide, vincristine, adriamycin, etoposide, cisplatin), then an evaluation by CT was made after 03 cures which showed a partial response to 50%. The patient received 03 other IVA-CEV-IVE cures according to the protocol. The control orbital cerebro CT showed a discreet reduction in tumor size and that it was inoperable.

Radiotherapy was therefore indicated according to the protocol. The patient received a total of 50.4 Gy during the first 02 months. After radiotherapy, a control cerebro-orbital CT showed a 12 mm long-axis lateral-internal and supra-right orbital tissue lesion. Since then, the patient has been seen in consultation every 03 months for 06 months and then every 06 months for 03 years. The evolution was favorable with a complete remission.

Three years later she shows post-radic cataracts with implant placement and good evolution.

On 15/09/2017, after 7 years of regression, the patient presents with a conscience disorder. A cerebral CT scan made objective a right frontal hypodense bone lesion surrounded by a range of edema. A cerebral MRI showed a right frontal expansive bone-starting process consistent with tumor localization. The biopsy was performed and the anatomopathological (morphological and immunohistochemical) study was performed: conventional osteosarcoma.

Molecular biology could not be performed.

The extension assessment was normal.

The patient received chemotherapy for osteosarcoma. The tumor was inoperable, and the decease occurred secondary to severe sepsis on severe febrile neutropenia.



**Figure 2: clinical examination of the patient having osteosarcoma.**

## DISCUSSION

In 1948, Cahan et al. defined the diagnostic criteria for radiotherapy induced osteosarcomas.

The tumour in question must meet these 4 criteria to be considered radiation-induced:

Osteosarcoma must occur in a previously irradiated area.

The histological nature of the new tumour should be histologically different from that of the originally irradiated tumour.

The absence of tumor at the bone currently reached at the time of irradiation.

The latency period between irradiation and tumour development must be beyond 05 years.

These criteria, considered too limiting, were expanded by Arlen in 1971.<sup>[1,2]</sup> They shorten the period of accountability to 03 years. Some authors retain even shorter deadlines. For example, in a Swedish study, the deadline is 1 year.<sup>[3]</sup>

At present little is known about the cytogenetic changes involved in the tumorigenesis of radio-induced sarcomas. In a study published by Mertens *et al.*<sup>[4]</sup> these tumours had a complex karyotype, with chromosomal loss of 3p21 being more common than in sporadic sarcomas. They also described polyclonal tumors with many quasi-diploid chromosomes.

Today there are several explanatory models:

1. Polyclonal karyotypes, with simple and balanced translocations (rearrangements between ends of non-homologous chromosomes), preferably observed after long culture.
2. Chromosomal alterations observed in very complex aneuploid karyotypes (chromosomes greater than or less than that of a normal cell) and usually detected in short-lived cultures or xenografts.<sup>[5]</sup> Alterations of the RB1 and TP53 genes, tumor suppressor genes (also called anti-oncogenes, are genes whose function is to limit cell proliferation and loss of this function promotes tumour transformation and growth) are common.<sup>[6,7]</sup>

According to a study by Nakanishi *et al.*<sup>[6]</sup> the frequency of TP53 mutations is higher in radio-induced sarcomas than in sporadic sarcomas. Gains of 7q or 8q are associated with poor prognosis or large tumours.<sup>[8]</sup>

In all studies, the youngest of patients with radioinduced osteosarcoma was a 9-year-old boy with mandibular localized rhabdomyosarcoma who received high-dose radiotherapy (50.4 Gy), who had presented five years after irradiation with temporally localized bone osteosarcoma. Its evolution is identical to that of our patient, both in terms of post-radiotherapy evolution, as well as in terms of irradiation age and the onset of osteosarcoma.

Indeed, a study had shown that the irradiation age of less than 10 years was associated with a shorter latency period preceding the occurrence of radio-induced sarcomas.<sup>[9]</sup> Compared to adults, Huvos *et al.* found shorter latency in the pediatric population (8.7 years versus 13.5 years;  $p = 0.02$ ).<sup>[10]</sup>

The paediatric population is more at risk than the adult population of developing a second cancer.<sup>[11]</sup> and in particular a sarcoma in irradiated territory.<sup>[12,13]</sup> In a study of long-term survivors of irradiated cancers in childhood, 15 of 414 patients had a second cancer compared to 0.7 expected in the general population of the tumour registry, a significantly higher risk in children ( $p < 0.001$ ).

Among radiation-induced tumours, sarcomas have an estimated incidence between 0.03% and 0.3% in all patients who have been irradiated. Osteosarcoma is the most frequently found secondary tumour in 20 years following cancer treatment in children,<sup>[14]</sup> and radio-induced osteosarcoma makes up 3.1% to 5.5% of all osteosarcomas. In more recent series such as that of Buis and Spiro which analysed the records of 42 patients, malignant fibrous histiocytoma was the most common followed by osteosarcoma.<sup>[16]</sup> Huvos *et al.*, whose study on radio-induced osteosarcomas has been the widest to date, found that cranial involvement was in 4th position (13.5%).

In the study of Koshy *et al.* reporting 109 cases, of the primary treated tumours, Ewing's tumours are the most represented, followed by rhabdomyosarcomas, retinoblastomas and Hodgkin's disease.<sup>[17]</sup>

The relationship between radiation-induced tumour and irradiation modalities was studied by Cantini *et al.*, who, through their study, deduced that certain tumours such as meningioma are more likely to occur following low-dose irradiations, less than 15 Gy, and that other malignant tumors such as glioma or sarcoma may occur as a result of higher doses of radiation, between 15 and 56 Gy.

Cantini *et al.* concluded that there was an absolute risk of developing sarcoma after irradiation of 48 to 59.99 Gy was 24.9/10000, and for doses of 60 Gy the risk was 131/1000.<sup>[18]</sup>

It should also be noted that chemotherapy increases this risk, especially if it is alkylating drugs (relative risk: 4.7; 95% confidence interval: 1-22.3).<sup>[19]</sup> This increased risk was also found by Vathaire *et al.* The risk of secondary sarcomas is 21.4 after a combination of radiochemotherapy versus 4.4 and 2 after radiotherapy or chemotherapy alone.<sup>[20]</sup>

Our patient had received chemotherapy prior to radiotherapy, and some of the drugs administered included alkylating agents (Ifosfamide). The administration of chemotherapy, concomitant or sequential with irradiation, increases the risk of second cancers. Some chemotherapy is more at risk. In children, alkylating drugs were particularly related to the occurrence of bone sarcomas with a relative risk of 4.7 increasing with the irradiation dose.<sup>[19]</sup>

Osteosarcomas are known to be radio-resistant. Thus, the gold standard treatment of these radiation-induced tumors is complete surgical resection.<sup>[21]</sup> However, if surgery is difficult in certain situations such as our context given the location, adjuvant chemotherapy and radiation therapy may be discussed eventually. These therapeutic methods are nevertheless inadequate. A protocol for surgically resectable tumours has not yet been established, but it has been reported in some studies that proton and carbon beam radiotherapy has been effective on these tumours.<sup>[22,23]</sup>

Radio induced osteosarcoma with cranial localization is a complication with a very pejorative prognosis.<sup>[24]</sup> It is rare, but very aggressive and can be recurrent. The average reported survival is 29 months.<sup>[25]</sup>

## CONCLUSION

Radiotherapy needs to be administered in some cases, but its acute and subacute side effects need to be widely discussed.

The prognosis of radio-induced osteosarcomas is more pejorative than that of primitive osteosarcomas because of the high rate of rapid local recurrences and possible pulmonary metastasis and the complexity of management.

This should lead to more studies on proton and modulated intensity radiotherapy, to better discussions of the indication, and better targeting of doses and the site to be irradiated to reduce the occurrence of radio induced tumours.

## ACKNOWLEDGEMENT

Conflict of interests: None

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