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Case Report: Secondary Osteosarcoma In A Retinoblastoma Patient

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***Abstract**:*
Retinoblastoma (Rb) is the most common intraocular malignant tumour in infants and young children. The tumour is bilateral in 40% of cases, and unilateral in 60% of cases. The hereditary form is due to a germ mutation in the RBl tumor suppressor gene. Patients followed for retinoblastoma have excellent survival, but face an increased risk of bone and soft tissue sarcomas. This predisposition to sarcomas was attributed to genetic susceptibility due to inactivation of the RBl gene as well as previous radiotherapy. Sarcomas are more common in hereditary Rb survivors but are very rare in patients treated for non-hereditary Rb.Sarcomas in hereditary retinoblastoma ***[1].***
Although rare the secondary development of osteosarcoma is a serious event in these patients because it is a tumor that has a strong metastatic power thus engaging the vital prognosis.
***Keywords**: Retinoblastoma, bone tumors, osteosarcoma.*

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I. INTRODUCTION

Retinoblastoma is the most common intraocular malignancy in infants and young children. The tumor is bilateral in 40% of cases. Patients treated for retinoblastoma, especially those treated with radiotherapy, have a higher risk of developing the disease.

Patients treated with retinoblastoma and especially those treated with radiation therapy have a higher risk of developing secondary tumors such as bone sarcoma.

Although rare, the secondary development of osteosarcoma is a serious event in these patients because it is a tumor with a high metastatic potential power, thus engaging the vital prognosis.

Interest: We report the medical observation of an osteosarcoma of the right knee of a patient followed for retinoblastoma. We will discuss this case in the light of data from the literature.

II. MEDICAL OBSERVATION

We report the medical observation of a child treated for retinoblastoma at the age of 8 months who presented after 7 years of follow-up with an osteosarcoma of the right knee. We will discuss this case in the light of the data in the literature.

This is the case of the child Z.M. of 8 years old, from a non-consanguineous marriage who presented since the age of 2 months (October 2013) a leucocoria of the right eye noticed by the mother, motivating the consultation to the ophthalmological emergencies. The child was taken in charge at the pediatric ophthalmology department of Casablanca. He underwent an ophthalmologic examination under general anesthesia which revealed:

Right eye: corneal edema with tumor lumps in the anterior chamber and intra ocular pressure at 12 mmHg. Pupillary secclusion with no passage to the fundus. The retinoblastoma was classified as Group E in the right eye.

Left eye: The anterior segment was normal and the fundus showed a multifocal retinoblastoma classified as Group D on the left eye : a main T1 tumor measuring 6 to 8 papillary diameters located nasally and totally hiding the papilla with 3 calcifications within it. A second T2 tumor of about 3 papillary diameters located in the extreme periphery at 6 o'clock. A third T3 tumor at the level of the superior temporal arch measuring two papillary diameters. A fourth T4 tumor under the superior temporal arch measuring 1.5 papillary diameters.

The patient underwent a cranio-orbital CT scan which did not reveal any optic nerve involvement or loco regional extension.

Therapeutically: The patient underwent chemoreduction and enucleation of the right eye. Pathological examination revealed infiltration of the retina and ciliary process without choroidal or scleral involvement. The optic nerve and its resection limit were healthy.
In view of the infiltration of the ciliary processes and the involvement of the anterior segment, the patient received a further 4 sessions of postoperative chemotherapy.
In the left eye, he was put under conservative treatment with 7 sessions of transpupillary thermotherapy and two sessions of cryotherapy. It is useful to note here that our patient did not benefit from radiotherapy sessions

Course:
Ophthalmologically:
The evolution was favorable and marked by an atrophic and sequelae regression of the 4 tumors with a stationary non evolving aspect after 11 months of treatment since 11/11/2014, i.e. a 6 year recoil (Figure 1, 2).

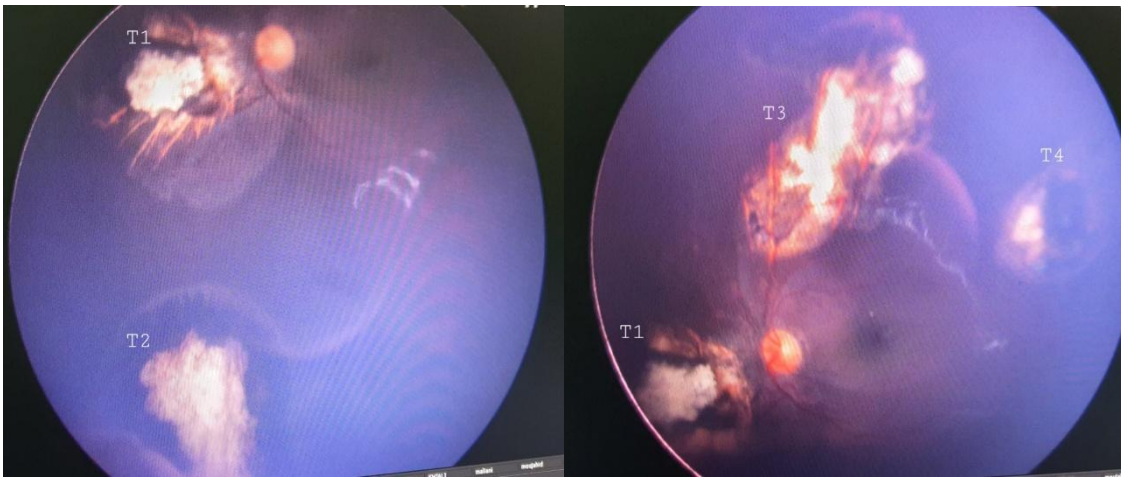

Figure 1,2: Left eye: Aspect of the 4 tumors after conservative treatment:
T1: cicatricial and calcified paranasal tumor and atrophic in the periphery with an unobstructed papilla
T2: calcified atrophic tumor at 5 o'clock in the extreme periphery
T3: atrophic tumor following the superior temporal vascular arcade
T4: cicatricial atrophic tumor located in the extreme periphery at 2 o'clock

● Current History:
The child presented in August 2020 (7 years after the diagnosis of retinoblastoma) with right gonalgia intensifying at night, partially relieved by paracetamol, associated with bone pain and swelling of the leg with the onset of a limp when walking, after 1 month the family therefore decided to consult in hospital; a radiological and biological workup was requested:
* A standard X-ray of the right knee: found an osteolytic image with cortical effraction of the upper third of the tibia
MRI of the right knee: in favour of a neoplastic process of the upper end of the tibia, invading the soft tissues opposite, suggesting Ewing's sarcoma. Figure (3, 4, 5)

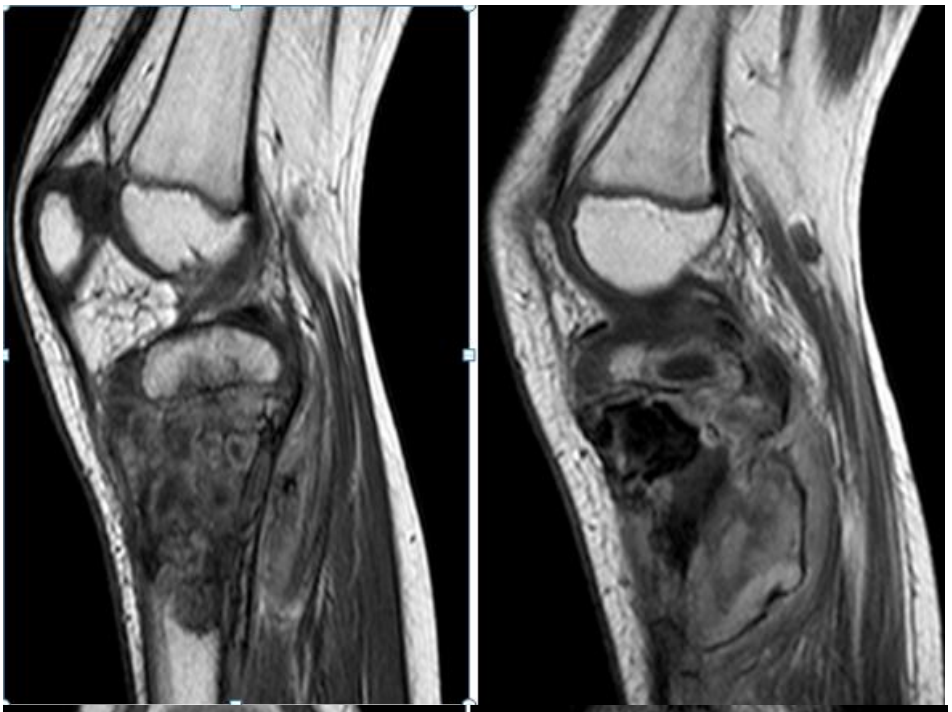

Figure 3: Sagittal section, T1-weighted sequence: metaphyseal process of the upper end of the right tibia with heterogeneous signal, pushing back the soft parts of the posterior muscle compartment of the leg.

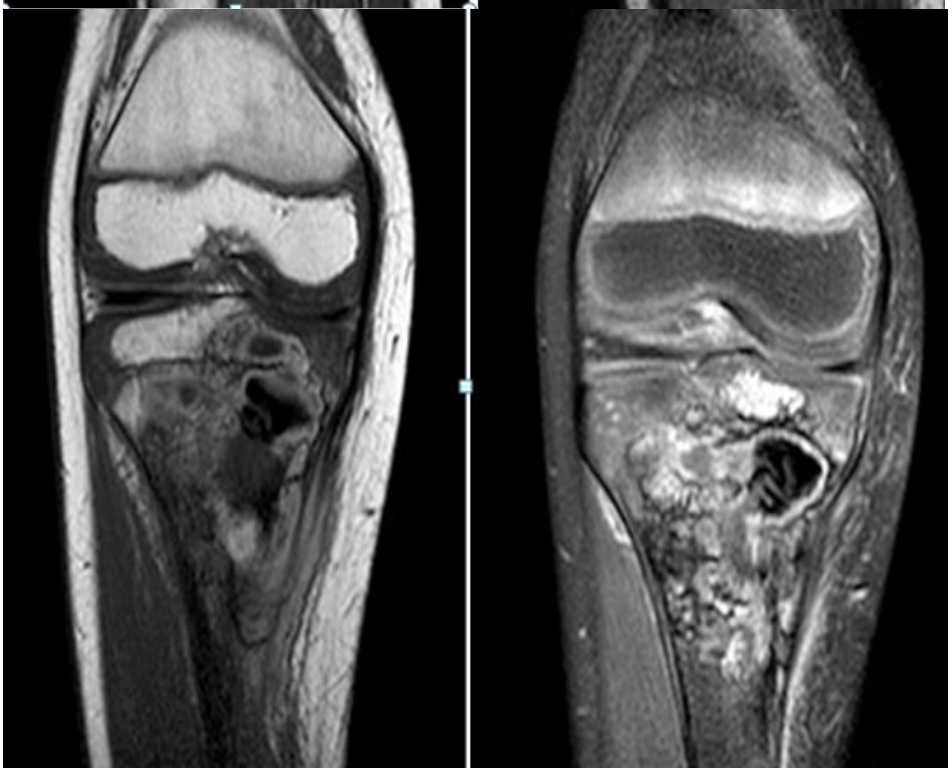

Figure 4 : Coronal section, T1-weighted sequence (a: without injection / b after injection of Gadolinium): this lesion process is heterogeneously enhanced after injection of Gadolinium, it crosses the conjugation cartilage, extends towards the epiphysis; absence of skip metastasis or intra-articular extension

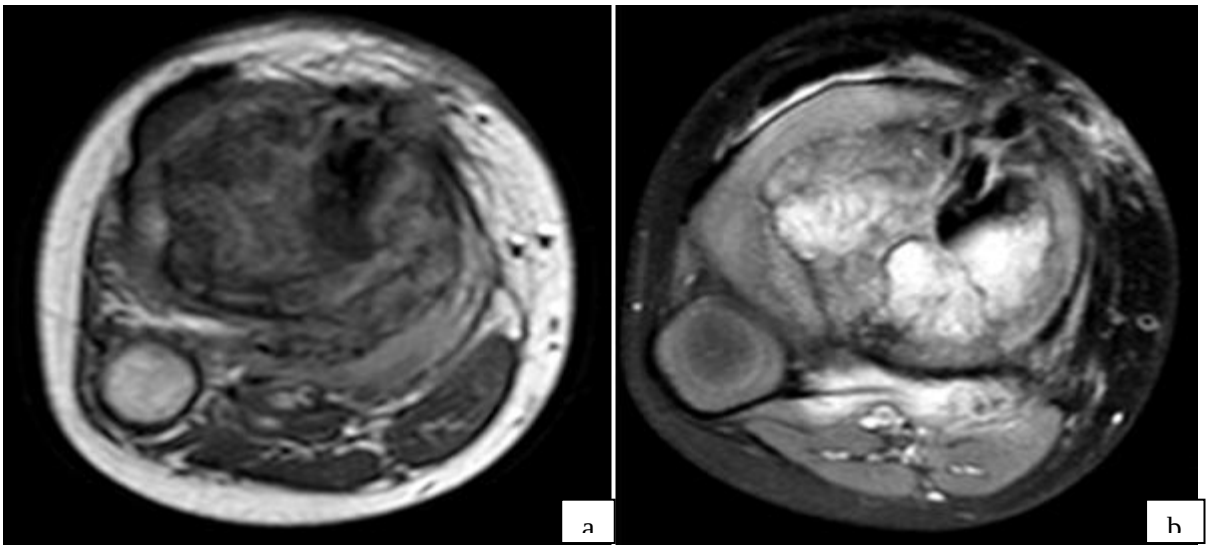

Figure 5: Axial section in T1-weighted sequence (a: without injection / b: after injection of Gadolinium): this process is responsible for lysis of the bone cortex, infiltrating the soft tissues and pushing back the popliteal pedicle without invading it.

● A bone biopsy was therefore indicated for histological study:
It was performed under general anesthesia the approach on the swelling revealed a tumor of friable hemorrhagic appearance with pearly white spots; the histological study was in favor of a conventional high-grade osteosarcoma of fibroblastic type.
● Extension workup was performed:
* Thoracoabdomino-pelvic CT: found a dense sub pleural nodule in the right Fowler's to be monitored.
* Bone scan: finds moderate hyperfixation of the right knee at the distal end of the femur and intense at the proximal end of the tibia with the presence of lytic foci and rupture of the cortex. In addition, the scintigraphy did not find any bone signs in favor of a secondary localization.
● Therapeutic:
The patient benefited from 3 courses of neoadjuvant chemotherapy (Cisplatin, Adriamycin) and then a monobloc resection of the upper end of the tibia, with cement placement and additional chemotherapy postoperatively. A prosthesis is planned.

III. Discussion

Retinoblastoma can be hereditary or non-hereditary [2]. The hereditary form of the disease involves a mutation in the germ cells of the Rb gene and the non-hereditary form involves a mutation in a cell of the retina. The frequency of occurrence of malignant secondary tumors is significantly higher in patients with bilateral retinoblastoma [3].Advances in the early diagnosis of retinoblastoma and in the improvement of treatment have improved the survival of patients. This survival requires close monitoring due to the risk of development of secondary tumors [4]. 98% of malignant secondary tumors occur in patients treated for bilateral retinoblastoma [5]. Patients with unilateral uni-focal retinoblastoma without a family history are not considered to be at high risk of developing a secondary malignancy.

The most common secondary malignancy is osteosarcoma [6]. The second most common group is the soft tissue sarcoma group [7]. In patients followed for retinoblastoma who were treated with radiation therapy, 70% of secondary tumors occur within the radiation field and 30% outside the radiation field [2]. Abramsom and colleagues identified 2302 retinoblastoma survivors. 71.3% of the secondary malignancies developed in the radiation field after a latency period of approximately 11.4 years.

These results suggest that carriers of the retinoblastoma gene have a higher risk of developing secondary tumors and that the incidence rate is even higher in patients who have been treated with radiation therapy [8]. The parcularity of our observation is that our patient was not treated with radiotherapy. Long-term survivors of hereditary retinoblastoma have a 20 times higher risk of developing and dying from subsequent non ocular cancers, primarily bone and soft tissue sarcomas, melanomas, and brain tumors [9]. Bone sarcomas are usually diagnosed in retinoblastoma survivors aged 10 to 20 years, similar to the general population [10].

Osteosarcoma is the most common type of bone sarcoma during retinoblastoma follow-up, but chondrosarcoma and Ewing's sarcoma are also possible [11].

Osteosarcoma is the most common secondary malignancy [12]. There is an association between retinoblastoma and the development of secondary osteosarcoma. The Rb gene mutation, which is involved in the genesis of retinoblastoma, is also strongly implicated in the oncogenesis of osteosarcoma. Patients with a family history of retinoblastoma or those with a bilateral tumor have a germinal defect in Rb1 and a higher risk of developing osteosarcoma than the general population [13]. Indeed, this gene encodes the retinoblastoma protein (pRb), a cell cycle regulatory protein and its mutation causes the inactivation of pRb leading to the loss of osteoblast cell cycle control and thus favoring the initial tumor growth [13] . For some authors, the inactivation of pRb also leads to a loss of cell adhesion while promoting metastasis of the osteosarcoma. For many authors, the prognosis of primary osteosarcomas would be better than that of secondary osteosarcomas that develop after bilateral retinoblastoma [14].

Osteosarcoma is a primary malignant skeletal tumor characterized by the production of immature bone or osteoid tissue by the tumor cells. It affects mainly long bones and rarely in soft tissues. The age at diagnosis varies from 10 to 25 years. It classically reveals itself by bone pain sometimes associated with swelling. The diagnosis, the assessment of extension as well as the decision of the type of surgical intervention and if necessary of the type of reconstruction require the use of radiography, CT scan, magnetic resonance imaging and dynamic bone scintigraphy.

Our patient has a non-metastatic osteosarcoma treated with initial chemotherapy which has many advantages. It allows for early general preventive treatment of metastases, decreases the size of the initial tumor, which facilitates conservative surgical resection. Chemotherapy also allows the evaluation of the histological response of the tumor to chemotherapy. This response has been shown to be one of the most important prognostic factors in children with non metastatic osteosarcoma. Treatments combine high-dose methotrexate, doxorubicin, cyclophosphamide, cisplatin, ifosfamide and etoposide. This initial chemotherapy is followed by surgery. This surgery avoids amputation: the tumor and adjacent tissues are removed by moving away from the tumor into healthy tissue and including the biopsy path. With this strategy, there is no greater risk of local recurrence than with amputation. However, amputation may be necessary when the local invasion is such that it is impossible to preserve healthy tissue around the lesion. During the surgical procedure, the tumor may rupture.

Surgery must be followed by chemotherapy. The 5-year event-free survival of localized forms is between 50 and 80%. Localized osteosarcomas that cannot be removed receive palliative treatment consisting of intensive chemotherapy and localized radiation.

IV. Conclusion

Our clinical case highlights the fact that patients followed for retinoblastoma are at increased risk of developing a second malignant neoplasm, the latency period of which is highly variable. Unilateral retinoblastoma, which accounts for the majority of cases, is not immune to the development of second malignant neoplasms, as germinal mutation can never be excluded. Careful monitoring of all patients followed for retinoblastoma is the key to early diagnosis and management of secondary bone sarcomas, which requires multidisciplinary collaboration.

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