Retinoblastoma and Second Bone Sarcomas: A Pediatric Case Report

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Abstract
The occurrence of secondary malignant neoplasia remains the most important long-term risk but rare of retinoblastoma. Osteosarcoma represents the most frequent second malignant tumor. We report here a case of a right femur osteosarcoma in a 7 years and half old-boy after being treated for retinoblastoma at two years of age. The treatment consisted of chemotherapy and conservative surgery with intercalary tumor resection and reconstruction by two autologous fibulas. Three years after, the child died from pleural metastasis.

The purpose of this report is to review the genetic relationship between retinoblastoma and osteosarcoma and to discuss treatment protocol for the latter.

Keywords: Retinoblastoma; Second sarcoma; Osteosarcoma; Rbgene

Introduction
Retinoblastoma is the most common ocular primitive tumors [1]. The appearance of Secondary Malignant Neoplasia (SMN) remains the most important long-term risk but rare of retinoblastoma [1-3]. Generally, sarcomas are the most frequent of SMN, especially osteosarcoma, with uncertain prognosis [4-8]. We present here a pediatric observation of osteosarcoma associated to retinoblastoma and osteosarcoma and we propose to discuss relation between these two malignant tumors.

Case Presentation
A 7-year-old boy presented to the consultation of one of the authors (MS) with a distal right femur tumor (Figure 1 and 2). Previously, at two years of age, he was diagnosed to have unilateral retinoblastoma of the right eye. Enucleation of right eye followed by chemotherapy and radiotherapy were performed. There were no other cases of retinoblastoma noted in the family medical history.

Osteosarcoma was confirmed by histological study after biopsy and treatment consisted of neoadjuvant and adjuvant chemotherapy based on high dose of methotrexate as well as conservative limb surgery. After trans-epiphyseal tumor resection, reconstruction was made by means of autologous both fibulas (one fibula was vascularized and the other fibula was non-vascularized) (Figure 3). Histological examination showed a very limited effect of chemotherapy and good resection margins (Figure 4). Pseudarthrosis of the grafts occurred later and a cancellous graft was necessary in order for consolidation to be completed (Figure 5). At three years of follow-up, a pleural metastasis appeared causing death.

Discussion
Retinoblastoma may be hereditary or not [1]. The hereditary form of the disease involves a germ cells mutation of the Rb gene and the not hereditary form involves a mutation in a cell in the retina. It is well established that there is an increased risk of second cancers occurring after retinoblastoma and the cumulative risk of SMN in retinoblastoma survivors is 32% [9]. This risk is more important in the hereditary form and tends to decrease with age. Occurrence of SMN is significantly high in patients with bilateral retinoblastoma [1,5,7,10].

A recent analysis of SMN in retinoblastoma survivors revealed that 76% of the second tumors occurred in the head and neck region with a median age at diagnosis of 16 years [11]. Cumulative occurrence of SMN, fifty years after the diagnosis, is believed to be 36% in retinoblastoma survivors [6].

A wide variety of soft tissue and bone second malignant tumors had been reported but the
most common is for osteosarcoma [10,12]. Fujiwara et al. [13] retrospectively reviewed a database of patients with retinoblastoma and osteosarcoma occurring as a second malignancy between 1964 and 2010 at the National Cancer Center Hospital of Japan. Among 857 patients with retinoblastoma registered in the database, the authors found 10 cases (1.1%) that developed secondarily osteosarcoma.

The nature of the association between retinoblastoma and second osteosarcoma had been studied extensively. The mutation of the Rb (retinoblastoma) gene is strongly implicated in oncogenesis of osteosarcoma. Patients with family history of retinoblastoma or those having bilateral tumor, have an Rb1 germ-line defect and a higher risk of developing an osteosarcoma than that of the general population [5,6]. Indeed, this gene code for Retinoblastoma protein (pRb), a regulatory protein of the cell cycle and its mutation causes the pRb inactivation leading to the loss of osteoblasts cell cycle control and promoting there by the initial tumor growth [7]. For some authors, the inactivation of pRb also leads to a loss of cell adhesion while promoting metastasis of osteosarcoma.

The risk of developing SMN in patients with retinoblastoma is increased by radiotherapy, an additional treatment to surgery [1]. In a series of patients with bilateral retinoblastoma, Rotary et al. [14] found a cumulative incidence of SMN of 35% for patients who received radiation therapy and only 5.8% for patients who did not receive radiotherapy. SMNs occur frequently on irradiated tissue and rarely outside the field of irradiation [12, 14].

For many authors, the prognosis of primary osteosarcomas is believed to be better than second osteosarcomas that develop after bilateral retinoblastoma. For successful treatment of osteosarcoma, complete surgical resection is necessary [15-17]. However, secondary osteosarcomas developing on irradiated tissue in the craniofacial region are mostly inoperable, making their prognosis very bad. Furthermore, the efficiency of chemotherapy in secondary osteosarcomas is contested in retinoblastoma survivors [10]. This might be due to the absence of the retinoblastoma protein in the human sarcoma, causing the cells to be resistant to antimetabolites [16]. The losses of heterozygosis at the Rb locus have been also implicated in the poor prognosis of osteosarcomas [1]. However, in the series of
Fujiwara et al. [13], four patients with tumors on an extremity were treated by wide resection with neo adjuvant and adjuvant high-dose methotrexate-based multi-agent chemotherapy and three of these four patients (75%) were good responders to chemotherapy and survived with no evidence of disease (median follow-up period, 17.3 years). The authors concluded that the clinical outcomes of second osteosarcoma in an extremity occurring in retinoblastoma survivors may be more favorable than those of conventional osteosarcoma. In addition, the German-Austrian-Swiss cooperative study group of osteosarcoma (COSS) had found that secondary osteosarcoma treated by a combined approach could have a similar prognosis to that of primary osteosarcoma [10].

**Conclusion**

Faced with the risk of second sarcomas in patients treated for retinoblastoma, regular monitoring and screening are required for adequate management. Achieving a consensus on protocols of chemotherapy seems to be necessary in order to standardize patient care. A revision of irradiation techniques and radiation doses may decrease the occurrence of SMN in the irradiated sites in patients with retinoblastoma.

Finally, faced to the rarity of these cases, scientists have to develop an international database for all these case reports in order to build large series that will enable us to make more reliable guidelines and conclusions.

**References**


