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Case Report Open Access

Ewing's Sarcoma as Second Malignancy after Bilateral Retinoblastoma: A Case Report and Literature Review

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Abstract

Background: Children diagnosed with the hereditary form of retinoblastoma (Rb) have excellent survival, but face an increased risk of bone and soft tissue sarcomas. This predisposition to sarcomas has been attributed to genetic susceptibility due to inactivation of the RB1 gene as well as past radiotherapy for Rb.

Objectives: To report the case of a child with hereditary form of bilateral RB, who developed Ewing's sarcoma of the right femur 10 years after the Enucleation of the both eyes.

Methods: The child was diagnosed as a case of bilateral RB at the age of 3 months. He was fully investigated and found to have locally advanced RB. Enucleation was done. The patient received chemotherapy and radiotherapy. At 14 years, he was investigated for a small swelling in his right lower leg. After extensive investigations, it was reported as Ewing's sarcoma. He is treated with chemotherapy.

Results: This report confirms that patients suffering from RB are at an increased risk of developing Second Malignant Neoplasms (SMNs).

Conclusions: This case confirms the increased risk of a SMN in children with hereditary RB. These children need a very close follow-up for the early diagnosis of SMNs.

Keywords: Retinoblastoma; Ewing's sarcoma; Second malignancy

Abbreviations: AP: Antro-posterior; CT: Computerized Tomography; N/C: Nuclear Cytoplasmic Ratio; TC-MDP: Technetium-Methylene-Diphosphonate

Introduction

Retinoblastoma (RB) is the most common form of malignant eye tumor found among children. It could develop due to hereditary (30-40%) and non-hereditary (60-70%) reasons [1]. Patients who suffer from the hereditary type have a germ line mutation of the RB1 gene, present at an early age and usually have bilateral disease, while children without germ line mutation of the RB1 gene present at a later age and develop unilateral disease. Children with the hereditary form of RB are prone to Second Malignant Neoplasms (SMNs). These second malignancies are usually in the form of bone or soft-tissue sarcomas, which may or may not be related to radiation therapy. Children with a germ line mutation of the RB1 gene and who receive radiation therapy as part of their treatment for RB are at the risk of developing SMNs [2]. We report the case of a child with the hereditary form of bilateral RB, who developed Ewing's sarcoma of the right femur 10 years after the Enucleation of the both eyes. Informed consent was obtained from parents to publish their child photographs.

Materials and Methods

Our patient aged 14 years with history of right side retinoblastoma at the age of 3 months (Figure 1), Enucleation of the right eye was done then patient had received chemotherapy (Cyclophosphamide and Carpoblatin) and radiotherapy for 1.5 years. At the age of 4 years, patient developed left side retinoblastoma then Enucleation of the left eye was done then patient received another course of chemotherapy and radiotherapy till 2005. At October 2012, right swelling in right femur was noticed, not associated with any other swelling in the body (Figure 2). X-ray of right femur (lateral, AP) revealed a medullary lytic area in middle third of the shaft of the right femur with periosteal reaction and cortical interruption at its posteromedial aspect together with soft tissue swelling posteriorly (Figure 3). Non contrast CT of femur revealed mixed osteolytic sclerotic lesion seen involving the distal half of the right femoral shaft with permeative destruction. Lateral cortical erosion, sunray's and condman's triangle periosteal reaction and large extra osseous soft tissue component measuring about 11 cm in height… picture of highly malignant osseous tumor mostly osteosarcoma,

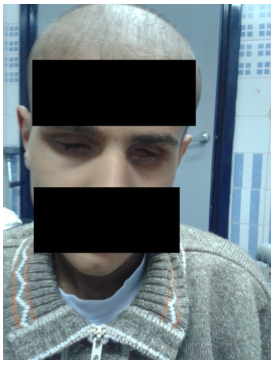

Figure 1: Bilateral Retinoblastoma after bilateral enucleation.

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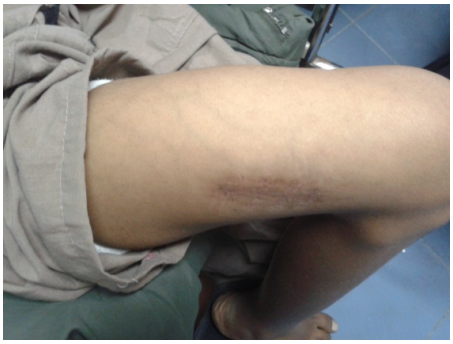

Figure 2: Swelling in the middle third of right femur.

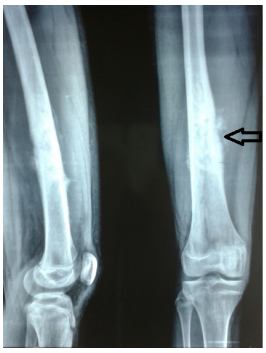

Figure 3: Medullary lytic areas (arrow) in middle third of the shaft of the right femur.

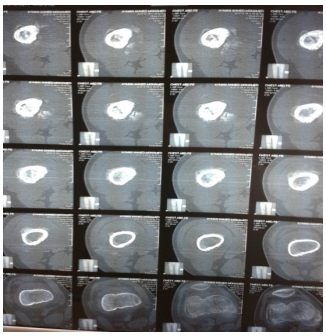

Figure 4: Non-contrast CT of femur.

however possibility of Ewing's sarcoma should be considered (Figure 4). Pre and post contrast MRI of right thigh revealed abnormal bone marrow SI is seen in the distal 2/3 of right femur, it is associated with extra osseous soft tissue component, after IV contrast administration it shows enhancement of bone marrow of extra osseous soft tissue component, possibility of malignant bone tumor (osteosarcoma) should be considered for pathological evaluation (Figure 5). TC-MDP Bone scan was done revealing a large active osteogenic lesion is seen at the distal 2/3 of right femur. No distant osseous deposits detected. Post contrast CT scan chest and abdomen was done to exclude metastasis but multiple pulmonary nodules are seen scattered in both lungs more at the lung bases, mostly metastatic. Few enlarged mesenteric LNs. Biopsy was done from right femur revealing malignant tumor tissue formed of sheets of spheroidal cells with moderate degree of pleomorphism, clear cytoplasm, increased N/C, vesicular nuclei and prominent nucleoli, frequent mitotic figures as well as areas of necrosis are seen. Peritheliomatous pattern is seen. Malignant round cell tumor is highly suggestive of atypical Ewing's sarcoma (Figure 6). The patient started the protocol of Ewing's sarcoma at November 2012 with improvement of size of tumor after 9 weeks of chemotherapy.

Results and Discussion

Retinoblastoma is a rare pediatric cancer of the eye with an autosomal dominant inheritance pattern. It is caused by mutations in the RB1 tumor suppressor gene, located on chromosome 13q14 with very high penetrance and expressivity [3]. Approximately 80-90% of RB1 gene carriers develop ocular tumors. This gene encodes the cell cycle regulatory retinoblastoma gene protein (pRb), controls cellular differentiation during both embryogenesis and in adult tissues, regulates apoptotic cell death, maintains cell cycle arrest and preserves chromosome stability [4].

Retinoblastoma occurs in two forms: hereditary (30-40%) and non-hereditary (60-70%). Hereditary retinoblastoma is caused by a germ line mutation in one allele of the RB1 gene and an acquired somatic mutation in the other allele, whereas the non-hereditary form is caused by somatic mutations in both alleles. The hereditary form

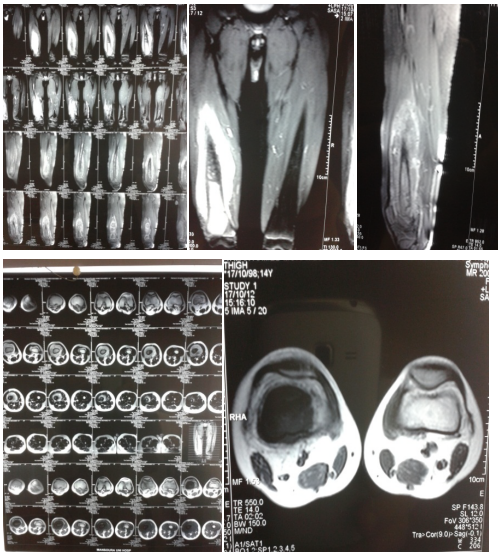

Figure 5: Pre and post-contrast MRI of right thigh.

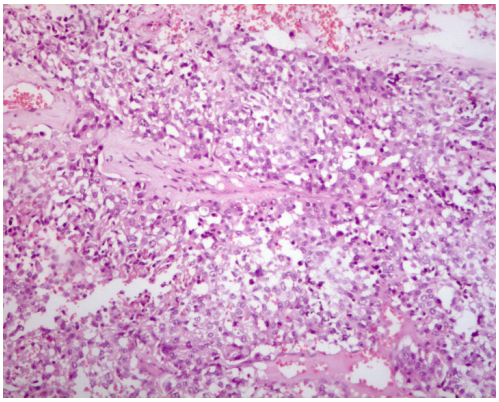

Figure 6: Biopsy from right femur.

is characterized by disease in both eyes (bilateral Rb) and is typically diagnosed before 12 months of age, whereas, the non-hereditary form affects one eye (unilateral Rb) and is diagnosed between 2-5 years of age. About 10-15% of patients with unilateral Rb, however, carries a germ line mutation and is considered hereditary [5]. Treatment for Rb has historically consisted primarily of radiotherapy, Enucleation, chemotherapy, focal therapies such as laser or cryotherapy [6].

Long-term survivors of hereditary retinoblastoma are at an increased 20-fold risk of developing a subsequent non-ocular cancer, primarily bone and soft tissue sarcomas [7]. Survivors of non-hereditary Rb are at much lower risk of a subsequent primary cancer, similar to the risk in the general population [8]. The risk for sarcomas in hereditary patients has been attributed to genetic susceptibility and past treatment with radiation [9].

Bone sarcomas are one of the most common second primary cancers occurring after hereditary retinoblastoma accounting for 25-30% of all second primary cancers [10]. The majority of bone sarcomas occurred within the radiation field in the head region, but up to 40% was diagnosed outside the treatment field, primarily in the lower legs [9].

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