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Case Report

An unusual case of late recurrence of bilateral retinoblastoma

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ABSTRACT

Recurrence of retinoblastoma usually occurs within the first few years after treatment. Despite complete tumor regression, delayed relapse of retinoblastoma can occur, predisposing patients to osteosarcoma as second malignancy. Our case was unique regarding the late relapse 13 years after treatment and recurrence at the femur. The initial tumor was treated with chemotherapy, enucleation of the right eye, and plaque radiotherapy. The relapsed tumor was treated with chemotherapy, consolidation, and autologous stem cell transplant. Our patient is currently in complete remission and continues to follow-up with oncology and ophthalmology. This report illustrates the possibility of late recurrence of retinoblastoma.

1. Introduction

Retinoblastoma (RB1) is the most common primary intraocular neoplasm in pediatrics, with most tumors manifesting in children younger than two years old. Retinoblastoma affects only one eye in approximately 70% of cases, involving a spontaneous mutation of the RB1 gene on chromosome 13q14 (Ray et al., 2012). Bilateral disease, which is more rare, is heritable in an autosomal dominant pattern due to a germline mutation of the RB1 gene (Ray et al., 2012). Mutation of RB1, which results in the elimination of restriction of cellular proliferation, is one component of a "two hit" hypothesis causing tumor formation. In heritable retinoblastoma, this mutation is present in germline cells but requires a second mutation of the remaining allele in a retinal cell. Heritable retinoblastoma is commonly associated with another form of cancer, usually osteogenic and soft tissue sarcoma (Wong, 1997). Survivors of hereditary retinoblastoma are also at increased risk of developing second cancers (Abramson, 2005).

Most recurrences of retinoblastoma tumors occur within the first few years after treatment completion. Intraocular retinoblastoma often recurs within the retina, vitreous cavity, and subretinal space (Shields et al., 2002). Extraocular retinoblastoma is less common, with a reported incidence of 2% to 5% in the United States, and is usually confined to the soft tissue around the eye or invades into the optic nerve (Jubran et al., 2004). Even more rare is extraocular spread outside the orbit and dissemination to the central nervous system, bones, bone marrow, and lymph nodes. We report a late-onset relapse of retinoblastoma to bone occurring 13 years after the completion of initial treatment for the tumor.

2. Case

A 6-week-old male was referred for leukocoria in both eyes. Exam under anesthesia (EUA) showed 3 lesions in the left eye and 4 in the right. At initial presentation, the tumor in the right eye measured 9 mm at its base and 1.0 mm in height. Targeted next generation sequencing of the enucleated recurrent tumor specimen revealed a p.Lys319AsnfsTer13 frame shift variant in the RB1 gene at a variant allele fraction of 97.1%. The RB1 p.K391fs variant was predicted to result in a frame shift and subsequent loss of RB1 protein function. FISH testing was negative for EWSR1, BCOR and CIC gene rearrangements. One month later, the patient underwent examination under anesthesia (EUA) every month with cryotherapy and laser therapy. He received intravenous chemotherapy consisting of 6 cycles of vincristine (0.05 mg per kg), carboplatin (18 mg per kg) and etoposide (5 mg per kg) every 28 days. The first course was complicated by an allergic reaction requiring premedication with diphenhydramine and methylprednisolone for subsequent courses of carboplatin, which were tolerated well. However, he developed vitreous relapse in the right eye, so it was enucleated and replaced with a prosthetic eye. At that time, there was no tumor post-laminar and no choroid invasion, but 2 sites of disease were later found in the left eye. One site of recurrence was at supratemporal and inferotemporal arcades of the macula, with the active area measuring 4 × 4 mm. The other site of recurrence was at a chorioretinal lesion with vitreous seeding, which extended 1.3 to 1.4 mm into the vitreous from the base of

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the retina.

To address residual disease in the left eye, the patient then underwent Ruthenium-106 plaque brachytherapy at 36.2 Gy to 5 mm from the sclera, in the area of the superior oblique muscle. Transpupillary thermotherapy (TTT) was applied to the recurrent site along the macular arcades. The area of vitreous relapse regressed after plaque therapy, but residual disease remained in the arcades. Two months later, he was treated with TTT followed by 4 cycles of carboplatin (18 mg per kg) and Vincristine (0.05 mg per kg). The lesion in the inferotemporal arcade still showed recurrent activity, so our patient was treated with Ruthenium-106 plaque therapy at 36 Gy at the apex for a second time. Three years after initial diagnosis, the patient experienced another tumor relapse, for which he received TTT. At that time, the tumor regressed completely, and the patient remained in remission for the next 13 years.

Following 13 years of tumor remission, the patient experienced pain in the right femur. PET scan showed abnormal marrow signal throughout the distal femoral shaft extending to the epiphysis (Fig. 1). Both bone marrow biopsy and spinal fluid analysis were performed as soon as the patient presented with relapsed disease. Both biopsy and spinal fluid analysis were negative, suggesting that the lesion was a relapse rather than metastatic disease. Biopsy of the right femur was performed, exhibiting primitive, small round blue cells with many Flexner-Wintersteiner rosettes, apoptotic cells, and mitotic figures. The tumor cells showed diffuse positivity for synaptophysin and were negative for NKX2.2 and CD99, confirming late relapse of retinoblastoma. The patient was started on 4 cycles of chemotherapy per ARET0321, consisting of Vincristine (1.5 mg/m^2, maximum 2 mg/m^2 IV on day 0), Cisplatin (105 mg/m^2 IV over 6 h on day 0), Cyclophosphamide (1950 mg/m^2 IV over 1 h on days 1 and 2) with Mesna, and Etoposide (120 mg/m^2 IV on days 1 and 2). He tolerated the first 2 cycles well, other than nausea, vomiting, and neutropenia, for which antiemetics and granulocyte colony-stimulating factor (G-CSF) were administered. Before starting the third cycle of chemotherapy, he underwent autologous stem cell collection via a double-lumen apheresis catheter placed at the right side of his neck at the internal jugular vein. Along with nausea and cytopenia, he finished cycles 3 and 4 with an additional side effect of cisplatin-induced sensorineural hearing loss at high frequencies, for which he was followed up by audiology. Following the recovery of neutrophil counts, he proceeded with high-dose chemotherapy consisting of Carboplatin (500 mg/m^2/dose for 3 days), Thiotepa (300 mg/m^2/dose for 3 days), and Etoposide (250 mg/m^2/dose for 3 days). Since he had an allergic reaction to carboplatin as an infant, he also received pre-medications with diphenhydramine.

Four months later, he underwent autologous stem cell transplant. His post-transplant course was complicated by mucositis, transaminitis, fever and neutropenia, and vomiting and diarrhea. After the complications resolved, radiation therapy at 36 Gy was administered in 20 fractions to the right femur. Following radiation therapy, MRI detected abnormal signal and fluorodeoxyglucose uptake in the right distal femur, but biopsy and PET revealed reactive bone with necrosis and fibrosis with no neoplasm identified (Fig. 2). A week after biopsy, he was admitted to intensive care for hypotension and influenza A, from which he recovered after receiving saline boluses and antibiotics. Five months later, 3 left cervical lymph nodes near the angle of the mandible showed increased avidity on PET and MRI scans. However, these nodes were normal in size, and biopsy was negative for neoplasm, showing only reactive nodes. The patient was last seen for bilateral sensorineural hearing loss and tinnitus. Currently, our patient is in remission and continues to follow up with audiology, oncology, and ophthalmology every 6 months.

3. Discussion

Generally, recurrence of retinoblastoma occurs within the first 2–3 years after completion of the initial treatment. Most studies report local intraocular relapse within several months after the initial treatment (Abramson, 2005; Shields et al., 2002; Berry et al., 2017). Since the vast majority of retinoblastoma tumors recur within 3 years after treatment completion, patients undergo rigorous screening for tumor recurrence during the first 3 years (Berry et al., 2017). There have been several reports of late onset recurrent retinoblastomas. Overall, local intraocular recurrence has been more commonly reported; while, there have been

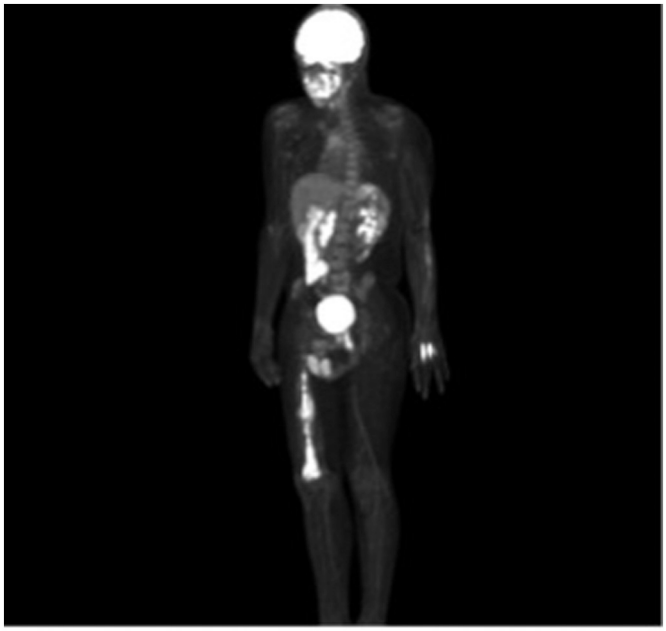

Fig. 1. PET scan shows findings compatible with metabolically active process within the majority of the right femur including some soft tissue alongside the femur. SUV max 8.24 mid femoral shaft. The findings, especially given the PET appearance of the femur and the biopsy results of the femur, are very concerning for femoral and left long and ring finger metacarpal recurrent disease.

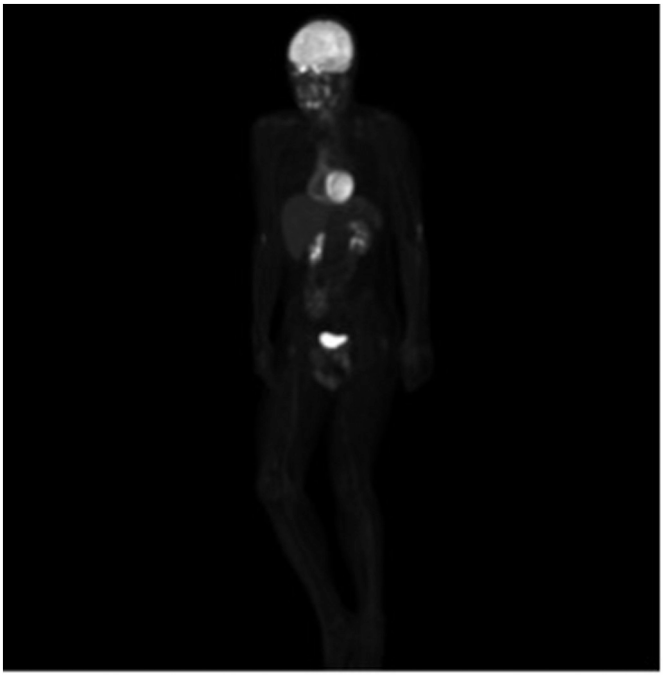

Fig. 2. PET scan shows no metabolic evidence of active neoplasm after chemotherapy and autologous stem cell transplant.

few reports of extraocular recurrences. Choi et al. described a patient with bilateral retinoblastoma that recurred in the nasal cavity 13 years after completion of chemotherapy (Choi et al., 2015). Gu et al. reported retinoblastoma recurrence at the cervical lymph nodes in an adolescent girl after 9 years of remission (Gu et al., 2021). To our knowledge, this is the first report of retinoblastoma relapse at the femur and represents the latest onset of recurrence to bone.

To develop into a retinoblastoma, both alleles in a retinal cell must acquire a mutation of the RB1 gene. In heritable retinoblastoma, the RB1 mutation manifests in all germline cells, but a second mutation of the remaining allele in a retinal cell is required for tumor formation (Ray et al., 2012). Since the patient had heritable retinoblastoma, he can be presumed to have the RB1 mutation in every retinal cell, and any one of those cells has the potential to transform into a new tumor (Shields et al., 2003). His germline RB1 mutation not only predisposed him to develop bilateral retinoblastoma as an infant, but also increased his risk of developing recurrent tumors or secondary cancers after treatment completion, such as osteosarcoma and Ewing sarcoma (Shields et al., 2003).

Multiple reports have demonstrated that patients with recurrent tumor growth are more likely to be younger at diagnosis (median age 2 months), have bilateral disease, and have family history of retinoblastoma (Shields et al., 2003; Wilson et al., 2007). Our patient was 6 weeks old when he was initially diagnosed with bilateral retinoblastoma. In this case, probable risk factors for late tumor recurrence 13 years after remission were young age at diagnosis, bilaterality of tumor, and germline mutation of retinoblastoma. Initial large dimensions of tumor (Reese-Ellsworth staging groups I to III), and tumor-associated subretinal or vitreous seeds are additional risk factors for tumor recurrence (Wilson et al., 2007). For extraocular relapse specifically, risk factors include tumor remnants in the optic nerve posterior to the lamina cribrosa and microscopic invasions of retinoblastoma into the sclera, choroid, or anterior chamber (Berry et al., 2019). In this case, the large initial tumor in the right eye measuring 9 mm at its base, consistent with Reese-Ellsworth group II, and the presence of vitreous seeding in the left eye predisposed him to tumor recurrence. Additionally, the invasion of the initial tumor in the right eye into the optic nerve posterior to the lamina cribrosa increased his risk of developing extraocular relapse. Intraocular relapse confined within the eye has excellent prognosis with survival rates over 90% (Ray et al., 2012). However, for extraocular relapse, when the tumor invades into the optic nerve as in our case, survival rates drastically decrease to approximately 50% (Shields et al., 2002).

Hereditary retinoblastoma has been shown to predispose patients to secondary blue-cell lesions, including osteosarcoma, pineoblastoma, and Ewing sarcoma (Moll et al., 1996). Several studies have demonstrated that radiotherapy further increases the risk of secondary cancers in hereditary retinoblastoma patients. Abramson et al. showed that radiotherapy increases the incidence of secondary cancers that arise in the radiation field, while no increased risk was observed for tumors outside of the field (Abramson and Frank, 1998). It was later reported that increased risk for tumors in the field of radiation is significantly correlated with the age at which radiotherapy is given, with increased incidence of second cancers seen for radiotherapy administered to patients younger than 12 months (Abramson et al., 2001). Kleinerman et al. reported that the risk of second tumors was significantly increased in hereditary retinoblastoma patients compared to nonhereditary patients, and that radiation therapy further increased the risk of another cancer in hereditary patients by more than three-fold (Kleinerman et al., 2005). Our patient received multiple treatments of plaque radiotherapy after intravenous chemotherapy, consisting of vincristine, carboplatin, and etoposide, failed to achieve regression of the initial tumor. The multiple rounds of radiotherapy may have predisposed him to develop tumor recurrence after 13 years of remission.

In conclusion, this case highlights the possibility of late recurrence of retinoblastoma. The patient's germline retinoblastoma mutation and treatment with radiation therapy both increased his risk of developing tumor recurrence and second malignancies such as osteosarcoma. Although complete remission was achieved for the first few years, the tumor can recur after more than 10 years. Since radiotherapy can predispose patients to recurrent disease, the cumulative toxicity of radiotherapy also requires close evaluation (Lee et al., 2003). Continuous follow-up with pediatric oncologists and ophthalmologists may allow for earlier detection of recurrent tumors. Much remains to be learned about tumor biology in order to better understand and recognize the pattern of recurrence for these tumors that typically occur in infancy and early childhood.

Declaration of competing interest

The authors have no conflicts of interest to report.

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