Secondary acute myeloid leukemia in a child treated for retinoblastoma: A case report with review of literature

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ABSTRACT
The most devastating late adverse effect of childhood cancer treatment is development of second malignancies. Retinoblastoma is the most common ocular malignancy of childhood and has a very good cure rate. Children with hereditary retinoblastoma have an increased risk of developing second malignancies due to the genetic cancer predisposition status and the additional risk factors are exposure to chemotherapy (alkylating agents and topoisomerase II inhibitors) and external beam radiotherapy during treatment. The common chemotherapy regimen of retinoblastoma consisting of etoposide, an epipodophyllotoxin is associated with risk of secondary AML (s-AML). We report a case of child with bilateral retinoblastoma who developed secondary AML after being treated for retinoblastoma.

Keywords: Epipodophyllotoxins, retinoblastoma, secondary AML

Introduction
As treatment modalities increase the survival of patients with pediatric malignancies, the sequelae of cancer treatment are of increasing concern. With newer treatment regimens for retinoblastoma, most of them survive and live into adulthood. Patients with hereditary retinoblastoma carry a significant risk of secondary malignancies, which are now the leading cause of death in these patients. [1] A rare but a serious toxicity associated with etoposide component of systemic VEC (Vincristine, Etoposide, Carboplatin) chemotherapy is the development of myelodysplastic syndrome or secondary acute myeloid leukemia.

Case Report
In 2018, a 2-year-old girl child, second born of non-consanguineous marriage was brought with complaints of white eye reflex in both eyes since last 1 month. There was no significant family history of any malignancies. Child was diagnosed as bilateral retinoblastoma with Group D in right eye and Group C in left eye. Child underwent chemoreduction with 6 cycles of chemotherapy with standard dose VEC along with focal consolidation by trans pupillary thermotherapy in both eyes. Three months after completing the therapy she developed a large recurrence in right eye with vitreous seeding and anterior chamber seeding. So, she underwent enucleation of right eye. No high risk pathological factors were observed in the enucleated specimen. The tumor in left eye has regressed completely. Rb1 gene mutation studies were not done due to financial constraints.

One year later, she developed gum hypertrophy and was brought with petechial lesions and ecchymotic patches over upper and...
lower limbs. Blood tests revealed hemoglobin of 8.9 gms/dl, total counts 57000 cells/cumm, platelets 11,000 lakhs/cumm. Peripheral smear showed normocytic normochromic RBCs and many blasts (78%). Blasts are large with moderate amount of cytoplasm, increased nuclear cytoplasmic ratio and large nucleus which is round to indented with fine chromatin and 1-2 nucleoli. Bone marrow aspiration showed 90% blasts with maturation arrest [Figure 1]. Flow cytometry was confirmatory of Acute myeloid leukemia M1 subtype, positive for CD13, CD19, CD 33 and HLA DR. With a previous history of bilateral retinoblastoma and exposure to topoisomerase II inhibitors and developing AML after one year of therapy, she was presumed to have secondary AML (s-AML). Karyotyping revealed translocation t (8:X).

Epipodophyllotoxin mediated s-AML generally develops after 2-3 years of exposure and is of M4/M5 subtype associated with 11q23 or MLL rearrangements. In our case, it was of M1 type and we could not attribute any significance of 8X translocations associated with s-AML from the existing literature. Our case represents a short interval for developing s-AML in a retinoblastoma child.

As the general outcome of s-AML is poor even with allogenic hematopoietic transplants, family opted for palliative treatment. The family opted for alternative therapy and finally succumbed to disease.

**Discussion**

Retinoblastoma is a classical tumor model in which genetics and treatment received have been shown to play a major role in the development of second malignancies. The underlying pathology of retinoblastoma is the defective functioning of retinoblastoma tumor suppressor gene Rb1 on 13q. Among retinoblastoma survivors, the common second malignancies that occur during the first decade are Wilms tumor, midline PNET, leukemia/lymphoma and rhabdomyosarcoma. Osteosarcomas, Soft tissue sarcomas, Ewing sarcoma were noted in the second decade.

Based on the primary cancer and treatment exposure, the incidence of pediatric t-AML/MDS varies between 1 and 6%.[13] Although s-AML after retinoblastoma is rare, there is consensus that treatment with alkylating agents and topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines) increases the risk.[11]

Alkylating agent-related s-AML is often preceded by MDS with loss or deletion of chromosome 5 or 7. This type typically occurs 5-7 years after therapy. French American British (FAB) type M1 or M2 is the commonest.

Epipodophyllotoxin induced s-AML is usually of FAB M4 or M5 subtype. Unlike the alkylating agent related s-AML which occurs relatively late and has a preleukemic phase, this type commonly presents as overt AML, after a brief latency period of 2-3 years and carries a poor prognosis. The leukemic cells have 11q23 abnormalities and or MLL gene involvement. Studies have revealed that it is the schedule of administration of epipodophyllotoxins that is more important than the cumulative dose.[10] Despite the use of epipodophyllotoxins, patients treated for retinoblastoma were found to be less susceptible to s-AML than patients with other solid tumors.[13] The cumulative risk for s-AML after treatment with etoposide varied from 5 to 10% in hematological malignancies in 0.6% in solid tumors.[12]

Gombos et al. has reported 15 cases of s-AML among 1601 patients and Turaka et al. has reported 1 case of AML in 245 retinoblastoma patients who were treated with chemotherapy.[3] In the study by Gombos et al., among the 15 cases with s-AML, 13 occurred in childhood, and mean latent period from retinoblastoma to AML diagnosis was 9.8 years. Nine of the 15 cases had bilateral or multifocal retinoblastoma and 9 cases were of M2 or M5 subtype. According to Turaka et al., 4% of children with germline retinoblastoma developed second malignancies at a mean of 11 years and no second malignancies were identified in non-germline patients.

The prognosis of s-AML is considered to be poor than the denovo AML, due to its refractory nature to chemotherapy and lower rates of remission and frequent relapses. Efforts to improve treatment responses by intensifying induction regimens were largely unsuccessful. Allogenic hematopoietic stem cell transplantation is the treatment of choice. But the outlook still remains poor. Barnard et al. has reported lower rates of remission induction, survival and event-free survival in 24 patients with s-AML who were treated on CCG 2891 study.[8] The 5 year survival rate in children with s-AML was reported as 23.7% by SEER cancer registry.[9] Hypomethylating agents like azacitidine have been tried with minimal success rates with majority of the studies in elderly population.

As most of the cancer survivors are in follow up with primary physicians, the possible complication of secondary AML in children treated for retinoblastoma should be carefully monitored.
Conclusion
The case report highlights the importance of a pediatrician/family physician to be aware of the increased risk of second malignancies in children with retinoblastoma.

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Conflicts of interest
There are no conflicts of interest.

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