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Consolidative Proton Radiotherapy for Pediatric Extramedullary Ocular Acute Myeloid Leukemia

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ABSTRACT

Purpose: Pediatric acute myeloid leukemia (AML) often involves extramedullary sites, which can be resistant to standard induction chemotherapy. Consolidative radiation therapy can be used in select cases to improve local control rates and help bridge patients to curative stem cell transplants. However, there is no previously published data to support the use of proton radiotherapy (PT) in this setting. We present radiographic findings and pathologic outcomes of the first reported patient with extramedullary ocular AML to be treated with PT.

Patients and Methods: Details regarding diagnostic evaluation and treatment were obtained from the electronic medical records at the University of Florida Proton Therapy Institute, Nemours Children's Health, and St. Joseph's Children's Hospital.

Results: This 7-month-old patient presented with biopsy-proven relapsed AML in the bilateral anterior chambers of the eyes, which did not resolve with induction chemotherapy. The patient then received PT to a dose of 24 cobalt gray equivalent to both eyes and was found to have no evidence of disease following treatment.

Conclusion: This case provides further evidence that consolidative radiotherapy may be considered for select patients with extramedullary AML who have limited response to induction chemotherapy. Given the increased prevalence of extramedullary AML in pediatric patients, it is worth considering the utilization of PT to mitigate damage to nearby organs and the risk of secondary malignancies.

Introduction

Leukemias are the most common malignancies in children, accounting for 25% of all childhood cancers before age 20 in the United States.[1] Pediatric acute myeloid leukemia (AML) is a heterogeneous disease composed of hematologic malignancies that originate from myeloid cell lineage precursors. AML represents a minority of childhood leukemias, accounting for 15% to 20% of all acute leukemias. Most remaining leukemias are classified as acute lymphoblastic leukemia.[2] Children with AML present with a variety of nonspecific symptoms, including fever, bone/joint pain, fatigue, easy bleeding, and recurrent infections. Diagnosis involves a complete blood count with differential, bone marrow biopsy, cytogenetic screening for risk stratification, and a cerebrospinal fluid (CSF) analysis to rule out central nervous system (CNS) involvement.[3]

Acute myeloid leukemia presenting outside of the bone marrow is termed "extramedullary disease," which includes soft-tissue infiltration, involvement of other hematopoietic organs (eg, spleen, liver), and CNS disease. Previous nomenclature for isolated extramedullary solid tumors has included myeloid sarcoma, chloroma, and granulocytic sarcoma.[4] CNS-specific disease is classified into 3 categories: no blast cells in the CSF (CNS1), ≤ 5 white blood cells with blasts (CNS2), or > 5 white blood cells with blasts/CNS symptoms (CNS3).

Similar to acute lymphoblastic leukemia, treatment for AML involves multiagent induction chemotherapy with cytarabine and an anthracycline followed by a hematopoietic stem cell transplant.

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Adjuvant radiation therapy is not the standard recommended first-line therapy; however, patients with symptomatic extramedullary disease may be considered for palliation to decrease local disease burden.[5] Outcomes have improved with intensified chemotherapy and enhanced supportive care; however, the 5-year overall survival rate remains at approximately 70%.[6] Therefore, AML has one of the highest relative mortality rates leading to over 30% of deaths in childhood leukemia. Furthermore, CNS leukemia involvement is associated with even greater relapse rates and worse disease-free survival rates despite additional intrathecal therapy.[7] The high mortality associated with pediatric AML is partly due to the heterogeneity of the disease and lack of specific tumor cell antigens, which makes modern targeted therapy less effective.[8]

Case report

A previously healthy 7-month-old female initially presented to an outside emergency department with lethargy and respiratory distress. On further evaluation, she was found to be pancytopenic and underwent a bone marrow biopsy, which revealed 50% marrow involvement by AML. Additional genetic analysis demonstrated a t(10;11) AF10-KMT2a rearrangement and her disease was categorized as high-risk AML. FLT3 was negative. A subsequent lumbar puncture showed no evidence of blast cells in the CSF, classified as CNS1.

She was enrolled in a clinical trial in which she received standard chemotherapy with liposomal daunorubicin and triple intrathecal chemotherapy (methotrexate, hydrocortisone, and cytarabine) with each cycle of therapy. She had 2 cycles of induction chemotherapy, and after each cycle, she had bone marrow and CSF assessments that were negative.

Shortly after the completion of her second cycle of induction chemotherapy, she began to develop “eye cloudiness,” as reported by her parents. Ophthalmology was consulted and identified bilateral corneal clouding associated with diffuse keratoconjunctivitis of unknown etiology (Figure 1). No focal infiltrate, sign of injury, other lesions, hypopyon, hyphemia, ptosis, globe proptosis, or facial asymmetry were seen. Visual acuity showed age-appropriate fixation with central steady and maintained vision. Intraocular pressures were elevated, with a concern for acute glaucoma. The presentation of isolated bilateral corneal clouding was noted to be highly unusual, and the differential diagnosis included a wide range of infectious and inflammatory etiologies. Anti-inflammatory eye drops were subsequently administered; however, her corneal cloudiness did not improve.

She then underwent an magnetic resonance imaging (MRI) of the brain and orbits to investigate further. This revealed a prominent appearance of the bilateral anterior chambers of the eyes (Figure 2). No abnormal enhancement was seen in the orbital regions, and no abnormal intracranial findings were visualized. She then proceeded with a left peripheral iridectomy, and aqueous fluid was sampled from the bilateral anterior chambers. Surgical pathology from the left iris biopsy revealed extensive involvement of AML with KMT2A rearrangement.

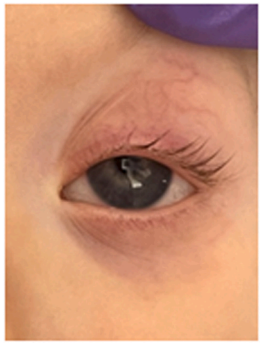

Figure 1. Picture of corneal clouding of the patient.

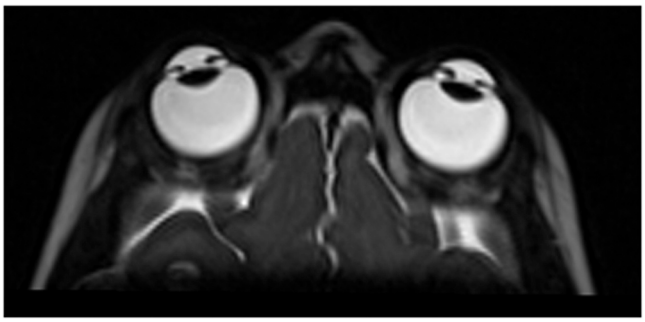

Figure 2. MRI orbits were obtained as part of a diagnostic workup of the patient’s corneal clouding. The image demonstrates a prominent appearance of the bilateral anterior chambers of the eyes.

Due to the presence of relapsed extramedullary disease, she was then removed from experimental protocol and proceeded with standard-of-care high-dose cytarabine and etoposide. She then completed 1 cycle of standard-of-care systemic therapy with weekly intrathecal therapy due to concern for CNS disease. Her bilateral corneal cloudiness minimally improved. She was then referred for proton radiotherapy (PT) to focally treat the extramedullary AML involvement of the bilateral anterior chambers of the eyes. She received 24 cobalt gray equivalent (CGE) at 2 CGE per daily fraction to the entire bilateral globes using a proton pencil beam scanning plan (Figure 3). Her optic nerves and chiasm received a maximum dose of 22 CGE, placing her at low risk of optic neuropathy. The pituitary received a mean dose of 0 CGE. The bilateral lenses, lacrimal glands, and retinas received mean doses of 24.1 CGE, 24.3 CGE, and 25 CGE, respectively, as a result of which she is at risk of future sequelae such as dry eyes, cataracts, and retinopathy. All treatments were performed under anesthesia without any significant acute side effects.

After completing radiotherapy, she began bridging chemotherapy with low-dose cytarabine monotherapy while awaiting a haploidentical hematopoietic stem cell transplant. An additional bone marrow biopsy and CSF analysis again showed no evidence of AML. A repeat MRI of the orbits completed 2 weeks postradiotherapy showed decreased prominence of the globes and anterior chamber without any acute findings. She then underwent bilateral iris biopsies and drainage of the anterior chamber aqueous fluid 1-month postradiotherapy. Pathology demonstrated no morphologic evidence of residual AML, and fluorescence in situ hybridization was negative for KMT2A rearrangement. She was then classified as in remission and discharged for an autologous stem cell transplant at an outside facility.

Discussion

Extramedullary AML is rare in adults (< 5%); however, it is relatively common in pediatric patients, where it is present in up to 40% of cases. It often presents as a myeloid sarcoma involving the skin (leukemia cutis), orbits, lymph nodes, gastrointestinal tract, CNS, testis, or soft tissue.[9] The orbital area is the second most common location of myeloid sarcoma in children and typically presents with unilateral exophthalmos, retinal hemorrhage, or ptosis. Prior literature is limited to case series, which typically include an initial presentation of orbital extramedullary AML and not in the setting of refractory disease.[10-12] To our knowledge, a presentation of corneal clouding in the setting of relapsed or initial onset AML has never been previously described. For this case, the lack of CNS involvement at the initial presentation or any subsequent CSF analysis throughout treatment makes the presentation of bilateral ocular globe infiltration even more unusual.

The standard treatment for relapsed extramedullary AML is repeat induction chemotherapy followed by high-dose cytarabine. Initial radiotherapy or surgical intervention is only indicated for palliative purposes such as pain relief and neurologic symptom improvement.[13]

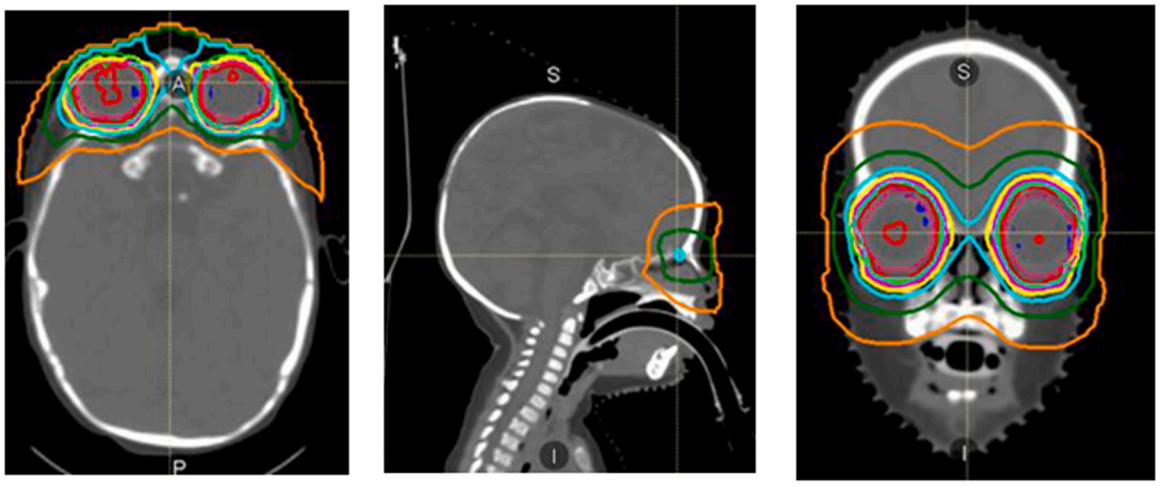

Figure 3. Dosimetric representation of the proton pencil beam scanning plan generated to treat bilateral eyes, visualized in axial, sagittal, and coronal axes. The prescription dose of 24 cobalt gray equivalent is depicted with a red isodose line. In ascending order, isodose lines at 10%, 50%, 80%, 90%, 95%, 98%, and 104% are displayed in orange, green, cyan, yellow, magenta, green, and dark blue, respectively.

Combining radiation therapy with chemotherapy has only been shown to improve symptoms but not survival outcomes.[14-16] However, if a complete response is not obtained with standard chemotherapy, consolidation radiotherapy can be considered on a case-by-case basis for local control.[17]

Extramedullary AML is radiosensitive, and low-dose radiotherapy has previously demonstrated excellent local control outcomes.[18] Complete response rates have been especially favorable with doses > 20 Gy. Specifically, a dose of 24 Gy in 12 fractions has produced a local control rate of > 90% at 1 year in small retrospective studies.[19,20] However, extramedullary sites in these reviews have not included ocular sites, with instead neck, extremity, and vertebral spine comprising most cases. These studies also exclusively used conventional photons, and to our knowledge, there is no prior literature regarding PT for treating relapsed extramedullary AML. Proton radiotherapy was found to be dosimetrically advantageous for this case, given the patient's young age and nearby organs at risk (brain, hypothalamus, and pituitary). Similar to prior literature, our patient also had a favorable local response with no evidence of disease on repeat biopsy. She then proceeded with a stem cell transplant in an attempt for cure.

Conclusion

This is the first reported case of pediatric AML presenting as isolated extramedullary ocular refractory disease, which was then treated with PT. This case provides further evidence that consolidative radiotherapy may be considered for select patients with extramedullary AML who have limited response to induction chemotherapy. Given the increased prevalence of extramedullary AML in pediatric patients, it is also worth considering the utilization of PT to mitigate damage to nearby organs and the risk of secondary malignancies.

Ethics

The study protocol was registered at ClinicalTrials.gov with the number NCT04293562 on July 20, 2020. Informed consent was obtained to participate in this study.

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Author contribution

Aaron Bush: Conceptualization, Methodology, Resources, Writing-Original draft, Visualization. Don Eslin: Writing- Review and editing. Michael Joyce: Writing- Review and editing. Derek Hess: Writing-Review and editing. Diana Leon: Writing- Review and editing. Ralph Ermoian: Writing- Review and editing. Raymond Mailhot Vega: Conceptualization, Methodology, Resources, Writing- Review and editing, Visualization, Supervision.

Data Availability Statement

The authors agree to share anonymized data upon reasonable request by researchers.

Declaration of Conflicts of Interest

All authors report no conflict of interest.

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