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Nuanced Management of a Skull Base Tumor in the Setting of Relapsed Acute Lymphoblastic Leukemia

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Abstract

Introduction Relapsed acute lymphoblastic leukemia (ALL) involving the central nervous system (CNS) is a significant issue that contributes to both morbidity and mortality. Given the poor outcomes in patients with CNS relapse, understanding how ALL involving intracranial relapse presents and is treated is critical. Here, we present a complex case of relapsed recurrent ALL in a pediatric patient.

Case Report An 11-year-old patient presented with double relapse of ALL in the form of an extensive skull base lesion and again with leptomeningeal disease. For the skull base lesion, she was treated nonsurgically with chemotherapy and radiation, which led to a remarkable reduction in the size of the lesion. However, she was found to have early recurrence with leptomeningeal enhancement resulting in hydrocephalus 5 months after completing therapy. A shunt was placed successfully. Currently, she is being managed with monthly intrathecal chemotherapy with cerebrospinal fluid sampling and bone marrow biopsies every 2 months.

Discussion We report the significant effect of chemotherapy and radiotherapy in reducing the size of the extensive skull base lesion, saving the patient from the risks associated with surgery. This patient's initial relapse, with a large skull base lesion that had intracranial involvement, is an unusual presentation of relapsed ALL. The additional early recurrence of leptomeningeal disease further makes this case unique and the management even more nuanced. Here, we demonstrate a multidisciplinary approach for the successful treatment of our patient, which can help guide the management of similar patients in the future.

Keywords
- skull base tumor
- acute lymphocytic leukemia

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Introduction

Acute lymphocytic leukemia (ALL) is a progressive cancer characterized by the proliferation of immature lymphoid cells in the bone marrow, blood, and extramedullary sites. Typically, most cases of ALL are diagnosed in the pediatric population. In fact, ALL is the most common form of childhood cancer, accounting for up to 25% of cancers in children under the age of 15 years.[1] Although childhood ALL is highly curable, relapsed disease is a significant problem that contributes to morbidity and mortality.[2,3] For patients with relapse, the 5-year survival rate is estimated to be between 25 and 50%.[4–8]

The central nervous system (CNS) is one of the most common sites of extramedullary ALL relapse and can occur as isolated recurrence or alongside bone marrow involvement, both of which have devastating consequences.[9,10] Given the poor outcomes in patients with CNS relapse, understanding how ALL recurrence involving intracranial infiltration presents and can be managed is essential.

Here, we describe the case of a patient with late isolated CNS relapse of ALL in the form of an extensive skull base lesion, who was effectively treated nonsurgically with chemotherapy and radiation, which led to a drastic decrease in the size and intensity of the lesion.

Case Presentation

An 11-year-old girl with a history of standard-risk B-cell ALL 7 years prior presented with left facial droop, recurrent mastoiditis/otitis, and right elbow swelling. She was first diagnosed with SR-ALL at 18 months of age and was enrolled on study DFCI 11-001. She went into remission and completed 2 years of therapy with minimal complications.

When she presented presently, physical examination was limited due to agitation. She had a notable left facial droop and swelling of her left ear and mastoid with bony prominence, though the area was not tender or erythematous. A peripheral cranial nerve VII palsy was observed, without evidence of other cranial nerve dysfunction. She was able to move all extremities and demonstrated normal strength and sensation. The remainder of her exam was noncontributory.

Magnetic resonance imaging (MRI) of the brain revealed a large skull base lesion centered on the sphenoid bones and clivus with extensive intracranial, nasopharyngeal, and left neck extension (►**Fig. 1**). The mass encapsulated the left VII and VIII cranial nerves, dorsally displacing the pons and medulla, and filling the left cavernous sinus. The lesion was biopsied, and cerebrospinal fluid (CSF) was obtained for cytologic examination. Pathologic evaluation revealed the tumor was consistent with relapsed pre-B ALL rather than a new second malignancy. Moreover, CSF from the lumbar puncture (LP) showed 15% blast-like cells, with tissue flow from the tumor further being consistent with relapsed pre-B ALL. Notably, the blasts were negative for the B-cell biomarker CD19. The bone marrow biopsy was negative, suggesting late isolated CNS relapse.

She was started on reinduction chemotherapy as per AALL1331, with systemic mitoxantrone, dexamethasone, vincristine, and pegaspargase and weekly intrathecal methotrexate, cytarabine, and hydrocortisone, which she tolerated well (ClinicalTrials.gov identifier: NCT02101853). End of induction LP and bone marrow biopsy showed no residual disease. End of induction MRI brain scans, however, showed that while the intracranial lesion decreased significantly, there remained a residual mass centered on the left skull base, with mass effect upon the brainstem. Prolonged systemic chemotherapy was continued as per AALL1331. Surgery was not considered due to the extensive intracranial component of the lesion and the high risk of the procedure. Given the absence of CD19 positivity on the leukemic cells, the patient was also ineligible for CAR-T cell therapy targeting CD19, and no open clinical trials were available. While allogeneic hematopoietic stem cell transplantation was considered, the patient's parents decided to forego the treatment in favor of a targeted radiotherapy and chemotherapy approach.

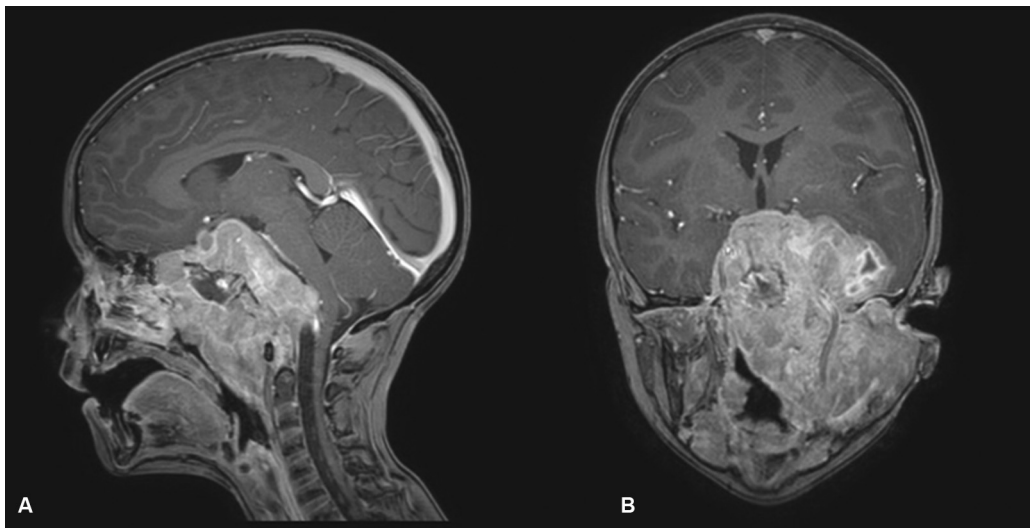

Fig. 1 Sagittal (**A**) and coronal (**B**) T1-weighted magnetic resonance imaging from 2020 of the patient's initial relapse prior to therapy demonstrating a large skull base lesion centered on the sphenoid bones and clivus.

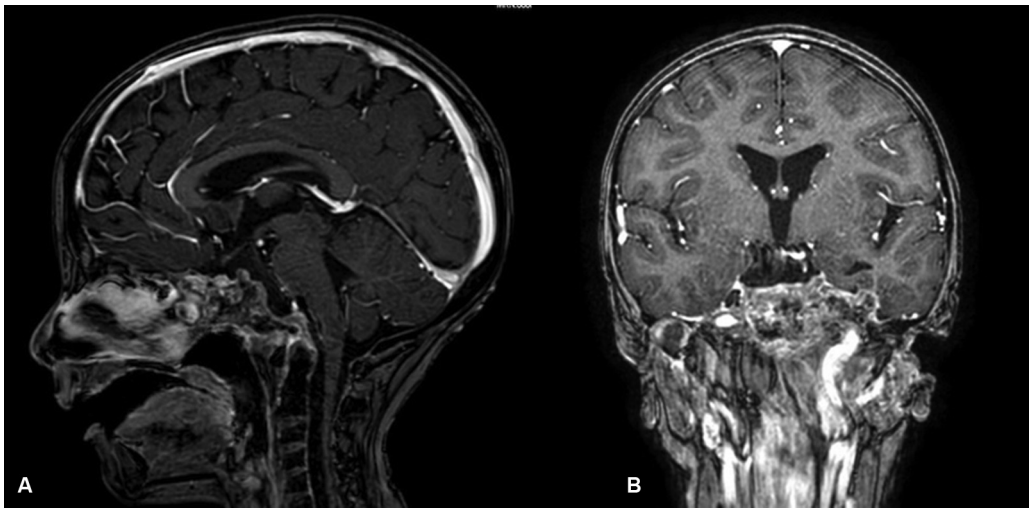

Fig. 2 Sagittal (**A**) and coronal (**B**) T1-weighted magnetic resonance imaging from 2022 following the completion of chemotherapy and radiotherapy demonstrating the reduction in the size of the skull base lesion.

The patient received chemotherapy for approximately 2 years as per AALL1331 and targeted radiation (24Gy) to the lesion. Her treatment was complicated by fungal pneumonia. MRI scans of the brain at the end of therapy showed a remarkable decrease in the size and intensity of the skull base lesion as compared to the MRI scan taken 2 years prior, although her facial droop persisted (►**Fig. 2**). Given the duration of treatment for the chemotherapy was exhausted, a discussion at tumor board yielded a decision to monitor the residual lesion and consider biopsy and excision if the mass started to re-grow.

Unfortunately, 5 months after completing therapy, the patient presented to the hospital with worsening facial droop and neck pain. MRI scans showed the skull base lesion was stable, but there was a new finding of diffuse leptomeningeal enhancement (►**Fig. 3**). She subsequently had an initial LP, which showed no blasts but elevated intracranial pressure (ICP) to 41 and a white blood cell count of 35,000/mm^3. Repeat LP 1 week later revealed 20% blast cells confirming CNS relapse. Bone marrow biopsy was negative for leukemic infiltration and computed tomography scan further revealed communicating hydrocephalus and possible obstruction from crowding cerebellar tonsils at the level of the foramen magnum. The patient had emergent external ventricular drainage placement for increased ICP and eventually underwent ventriculoperitoneal shunt placement. She also received biweekly intrathecal therapy until the CSF was cleared of blasts.

Currently, she is receiving monthly intrathecal therapy consisting of methotrexate, hydrocortisone, and cytarabine, and a bone marrow biopsy every 2 months to evaluate for disease. Given her extensive ALL history and CNS recurrence, bone marrow transplantation was once again recommended. The risks and benefits of transplantation in alignment with the family's wishes have been an ongoing discussion. The patient has been tolerating chemotherapy well and has not

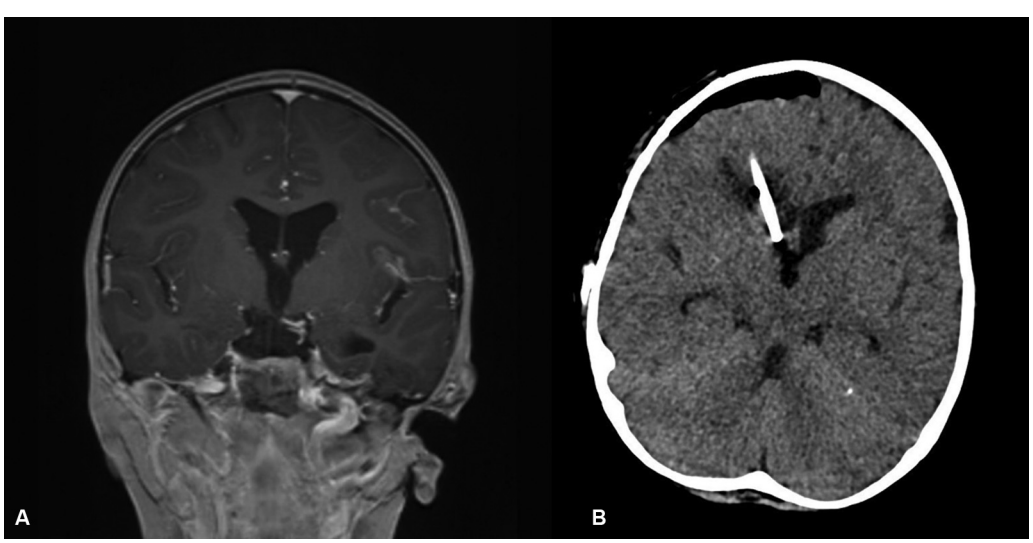

Fig. 3 Coronal magnetic resonance imaging (**A**) and axial computed tomography (**B**) scans 5 months after completing therapy depicting a stable skull base lesion and new leptomeningeal enhancement.

had any headaches or emesis. CSF remains negative for leukemia.

Discussion

Currently, there is no unified treatment plan for CNS relapse in ALL and evaluating the best course of treatment for these patients can be challenging. Depending on the degree of intracranial invasion, strategies typically involve a combination of the following: cranial radiation, conventional chemotherapy, hematopoietic stem cell transplantation, and, more recently, immunotherapies.[11,12] Early isolated CNS relapses, defined by past literature as relapse less than 18 months from diagnosis, are often treated with intensive systemic chemotherapy followed by hematopoietic stem cell transplant if patients are eligible.[13,14] For late isolated CNS relapses, there has been relative success with clinical trials using high-dose chemotherapy and cranial radiation.[11] While the utilization of radiation has improved survival, it is known to have several long-term side effects including cognitive and growth impairments.[15,16]

Here, we report a case of a young patient with relapsed recurrent ALL involving the CNS who was treated with a nonsurgical multidisciplinary approach that drastically reduced the tumor size. The patient's initial relapse with a large skull base lesion and intracranial involvement is an interesting and uncommon presentation of relapsed CNS-ALL. The patient's early recurrence of leptomeningeal disease is another uncommon presentation of relapsed ALL. Lastly, and most importantly, the patient's radiographic response to standard chemotherapy and radiation was unexpected and profound, highlighting how a patient with relapsed CNS-ALL can be managed nonsurgically. Many available treatment options for CNS relapse involve a high risk of toxicity, making such interventions suboptimal in certain patients. Here, however, we demonstrate the profound effect of chemotherapy and radiotherapy in reducing the size of an extensive skull base lesion, saving the patient from the risks associated with surgery.

While our therapeutic approach had a significant impact on the growth of the lesion, complications with this strategy did arise. The early recurrence of the patient's CNS disease, in the form of leptomeningeal enhancement and hydrocephalus, despite intensive chemotherapy, was unfortunate and unexpected. While we believe our course of therapeutic action was the most appropriate given the patient's history of disease and family wishes, it is clear that more effective forms of therapy for CNS-ALL are needed. In order to truly develop an optimal form of therapy, it is crucial to first identify more diagnostic and prognostic biomarkers for relapsed CNS-ALL. Such an endeavor would allow for the identification of patients who are at high risk of CNS relapse as well as the development of more targeted therapies to better manage these patients in the future.

In summary, we report a unique case of an 11-year-old girl with a history of SR-ALL who presented with relapsed CNS-ALL in the form of a large skull base lesion with intracranial involvement. The patient's initial relapse, additional early recurrence of leptomeningeal disease, and response to standard chemotherapy and radiation make our case particularly unusual. We demonstrate the intricate decision-making process behind optimizing a treatment plan for such a nuanced case of CNS-ALL and show how similar patients can be managed without the use of surgical interventions. Moving forward, we believe it is important to be able to identify patients at risk of relapsed CNS-ALL, as this would allow for swift clinical action to be taken before progression of disease. Through early identification as well as the development of more targeted therapies for intracranial disease, we will be able to better manage and treat patients with relapsed ALL involving the CNS.

Ethical Approval and Consent to Participate

Approval for the publication of this work was granted by the Albert Einstein IRB and consent to publish this report was obtained from the patient's family.

Consent for Publication

Consent for publication was obtained from the patient's family.

Authors' Contributions

G.J., E.B.W., R.F., and T.K. were involved in the composition of this manuscript and A.T., G.L., M.B., A.K. were involved in revision and review of this manuscript. G.J. and A.K. developed the concept for this report.

Conflict of Interest

None declared.

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