Hydrocephalus as Clinical Indicator of Central Nervous System Relapse in Acute Lymphoblastic Leukemia

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosis in children. While current treatment has greatly improved survival rates, relapse occurs in 15-20% of patients. Signs and symptoms are similar to those found at initial presentation. However, in some patients, relapse can occur in the central nervous system (CNS), even if they did not have previous CNS involvement. Many cases of CNS relapse are clinically silent and are discovered at the time of bone marrow relapse. These patients can be asymptomatic or show signs of mass effect or increased intracranial pressure. Classic MRI findings include signs of leptomeningeal disease (LMD) in the ventricles along with hydrocephalus. In this case report, we describe a child with pre-B cell ALL in remission who relapsed with CNS involvement. Unique to this case is that imaging revealed hydrocephalus without definitive evidence of LMD. A ventriculoperitoneal (VP) shunt was placed for the treatment of presumed idiopathic hydrocephalus. CSF analysis revealed leukemic cells. There has been no previous reporting in the literature of hydrocephalus being the only finding on MRI, without the highlighting of LMD. In this case, we had to consider general pediatric causes of hydrocephalus and the final diagnosis was made by examining the cerebral spinal fluid (CSF). This case report points out that hydrocephalus can be an initial indicator for CNS relapse.

INTRODUCTION

Leukemia is the most common form of childhood cancer, making up 25% of childhood cancer cases [1]. Seventy-eight percent of cases are acute lymphoblastic leukemia (ALL) [2]. Over the past four decades, improvements in treatment regimens and supportive care have led to improved cure rates. Around 95% of children achieve remission and up to 80-85% of children see long term cure with ALL [1, 3, 4]. Despite the excellent current cure rates, 15-20% of patients will relapse. Most relapses occur during treatment or within 2 years following the end of treatment. Prognosis in relapsed patients depends on several factors, including the length of the first complete remission, immunophenotype of relapsed ALL, and the site of relapse. With intensive combination chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT), 30-50% of all children with relapsed ALL can be cured [1, 5]. Before the advent of CNS prophylaxis, 30-50% of patients would relapse with CNS involvement [6]. With current prophylaxis, less than 10% of ALL patients relapse with CNS disease, but in those identified as ‘good-risk’ this number decreases to 5% [7].
There are several routes by which leukemic cells are thought to penetrate into the CSF. Tumor cells from the bone marrow of the skull can find access via bridging, choroid plexus, brain capillaries, or direct infiltration of the leptomeninges. Alternatively, circulating tumor cells from peripheral blood can enter the CSF via trauma, spinal tap or CNS bleed [1, 8]. Studies in mice show that leukemic cells disrupt the blood brain barrier, allowing leukemia to spread into the CNS [9]. CNS relapses present a challenge to treatment as many chemotherapy agents have limited penetration into the CSF, and the side effects of CNS directed therapy limit dosing options. CNS prophylaxis primarily consists of intrathecal chemotherapy, which allows chemotherapy to penetrate the ‘sanctuary’ space containing CSF. Cranial irradiation has also been used for this purpose, but the use of prophylactic cranial irradiation has decreased due to long-term sequelae such as weight gain and short stature [10-13], without clear additional protection over intrathecal chemotherapy alone in up to 90% of patients [14]. However, chemotherapy has its own adverse side effects and these changes can be seen sometimes on imaging [15].

While patients are often asymptomatic, they can also present with findings such as cranial nerve palsy, hemiparesis, auditory changes, double vision, or signs of CNS hemorrhage such as seizure, vomiting, altered mental status, or headache. Signs of spinal cord compression such as back pain, altered sensorium, conus-medullaris syndrome, extremity weakness, and bladder dysfunction are rare but may also be detected [1, 16]. Less common manifestations that have been reported include hypothalamic obesity syndrome (hyperphagia and uncontrolled weight gain caused by damage to the ventromedial hypothalamus) [17-19] and optic nerve infiltration [20]. However, many cases of CNS relapse are clinically silent and are discovered at the time of bone marrow relapse. In this case report, we describe a child with pre-B cell ALL in remission who is subsequently found to have relapsed disease with the main finding of hydrocephalus on imaging and no conclusive evidence of LMD. This case report points out that hydrocephalus can be an indicator for CNS relapse.

**CASE REPORT**

A previously healthy 2 year old boy was diagnosed with pre-B cell ALL. He presented with no significant clinical symptoms except mild bruising. Labs showed thrombocytopenia and a white blood cell count greater than 200,000 K/ul. His bone marrow showed leukemia cells positive for CD10, TDT, and CD19. T cell and myeloid markers were negative. Cytogenetics showed a modal chromosome number of 53. BCR-ABL, TEL-AML, and MLL rearrangements were negative. He was diagnosed with pre-B cell ALL and classified as high risk based on the initial WBC. He had no symptoms involving the CNS, and his CSF was negative for leukemia cells during that time. He was treated on CCG-1961, which included IT methotrexate but no irradiation. He was treated on CCG-1961, which included IT methotrexate but no irradiation. He completed this course without any complications, and his disease was in complete remission 2 years later at the end of treatment. He did well on follow-up exams for several months.

At his 9 month post-treatment visit, he came into clinic with complaints of new onset double vision and an occasional, mild headache for the last 2 months. He denied any fever, night sweat, weight loss, bone pain, or easy bruising. The parents did note considerable weight gain (9 kg over 2-4 months) despite no changes in activity. The family noted a change in the patient’s mood. He was irritable and also consuming more food. He also had low energy, headaches, intermittent deficit of his right eye, and twitching of his left eyelid. Lab evaluation of his CBC was within normal limits. A brain CT scan done at an outside hospital was read as normal. The patient then had a mild viral upper respiratory infection. During this time, endocrinology was consulted for his previously noted, persistent symptoms. No polydipsia, polyuria, urinary incontinence, numbness, or weakness were found on review of systems. Since the CT scan had been normal, an MRI was ordered. The result was significant for hydrocephalus. No mass was noted. While there was brightening of the cortical sulci, this finding was not definitive of LMD and no other enhancement suggestive of leptomeningeal involvement was present. It was thought, without clear evidence of LMD and no high risk factors for CNS relapse, that the hydrocephalus could be idiopathic. The presence of transependymal reabsorption of CSF, especially demonstrated on MRI FLAIR sequences, suggested that the patient had elevated intracranial pressure associated with the hydrocephalus (Figure 1). Due to the considerable hydrocephalus, a lumbar puncture was not attempted. He was taken for VP shunt placement. Sampling of the CSF showed a high number of leukemic blasts.

At this point, our patient had been on one day of dexamethasone already for treatment of increased cranial pressure (ICP). He underwent bone marrow sampling, which showed 4% blasts, TEL-AML positive. Since this value was obtained after having already started dexamethasone, there was a chance that the percentage of blasts in the bone marrow may have been initially higher. Because there was a concern for both marrow and CNS relapse, the decision was made to treat him as having a combined relapse under protocol ALL-R3 consisting of dexamethasone, mitoxantrone, vincristine, Peg-asparaginase, and radiation during weeks 14-16 of treatment. He began his treatment immediately after laboratory confirmation of his diagnosis and within a week had clinical improvement of his eye movement.

**DISCUSSION**

This case presents a patient with pre-B cell ALL in remission in whom hydrocephalus is the main finding on imaging for CNS relapse. Per review of literature, hydrocephalus has not been reported as the main finding on imaging for CNS relapse. The hydrocephalus was postulated to be caused by leukemic cells impeding the drainage of CSF from the ventricles. Findings on CT and MRI may provide clues for CNS relapse. Leptomeningeal infiltration is the most common finding, with leukemic cells first being seen in the superficial arachnoid veins and invading the surrounding stroma. These cells can affect brain structures via direct infiltration or by mass effect via nodule formations. A retrospective review was done on CT and MR imaging of 9 pediatric patients diagnosed with relapsed CNS leukemia/lymphoma (out of 80 patients total screened) [21]. CT scans, when positive, showed hyperdense tumor masses with contact enhancement. MR imaging also showed tumor masses with meningeal infiltration, as well as 2 cases of hemorrhage. A venous infarct was found in another patient, and one report noted pituitary stalk abnormalities [18].

The highest risk for CNS relapse in pediatrics occurs in T cell ALL with hyperleukocytosis (WBC count ≥100x109/L). Other previously documented risk factors include the presence of the Philadelphia chromosome, t(4;11), t(1;19)/TCF3-PBX1 [22] or polymorphism of the vitamin D receptor locus, which can lead to methotrexate resistance [1]. High expression of interleukin-15 has been associated with increased risk of CNS disease at diagnosis as well as relapse [23]. The presence of blast cells in the CSF at time of initial diagnosis is also a risk factor. Children with shorter length of remission (less than 18 months) had a 4 fold risk of CNS relapse when compared to those...
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Figure 1 | MRI FLAIR of brain prior to ventriculoperitoneal shunt placement. There is early hydrocephalus with transependymal cerebrospinal fluid migration but no evidence for brain herniation. The cortical sulci are bright, although no definite enhancement is present to indicate leptomeningeal involvement. However, this signal is an abnormal finding and may reflect leptomeningeal disease, congestive vessels, oxygen supplementation during the study, or high protein in CSF. There is no indication of blood in the CSF.

children who were able to stay in remission for a longer period of time [24]. Our patient had none of these risk factors, and thus suspicion of relapse was lower.

Risk stratification of CNS disease is based on the presence and number of blast cells in the CSF. At diagnosis, a traumatic lumbar puncture with blasts present increased the risk of CNS relapse in some studies [25, 26], though other studies did not note this association [27]. It is thought that a traumatic tap could introduce circulating blast cells into the CSF or alter the anatomy of the dural space that would affect the delivery of chemotherapy. Anatomical changes to the dural space can affect intrathecal chemotherapy delivery or penetrance, and possibly lead to higher rates of CNS relapse. A traumatic spinal tap can also mask CNS disease status.

The prevention of leukemic spread/relapse into the CNS could be attained by cranial irradiation, but the usefulness of this technique has been limited by the secondary effects of radiation, such as neoplastic, neuropsychological, and even social changes [28-31]. However, in one protocol, the use of 18 Gy cranial irradiation did not result in significant neuropsychological or psychosocial changes, which is encouraging [32, 33]. Secondary neoplasms seen with cranial irradiation include benign CNS tumors, sarcomas and carcinomas. The cumulative risk in irradiated patients for these secondary neoplasms was found to be large when compared to the non-irradiated group, 20.9% versus 0.95%. Current ALL protocols call for irradiation treatment in only 2-20% of patients, such as those with CNS3, hyperleukocytosis at diagnosis, or T cell ALL [34]. In most cases, irradiation is not necessary since high dose methotrexate [35], oral dexamethasone [36], and oral mercaptopurine have been shown to decrease CNS relapse rates, while maintaining an acceptable side-effect profile compared to other options [8, 36]. For many groups, higher CNS disease status or a history of traumatic lumbar puncture calls for a more intense chemotherapy regimen, usually consisting of additional doses of intrathecal (IT) chemotherapy [14, 27]. An algorithm provided by the COG may be used in determining whether a traumatic tap should be treated as overt CNS relapse (CNS3) disease or not [37].

Triple IT chemotherapy had no overall survival advantage over IT methotrexate due to increased rate of relapse [38]. Due to anatomical features such as the blood-brain barrier, the CNS is considered a ‘sanctuary site’ that is hard to access with agents such as chemotherapy. Radiation and direct administration of chemotherapy via an intrathecal route provide ways around this barrier. Current treatment regimens are based on data from a trial of 83 pediatric patients with isolated CNS disease on relapse [24]. These patients received systemic and IT chemotherapy for 6 months followed by cranial/craniospinal irradiation (24 Gy cranial/15 Gy spinal). All 83 pediatric patients in this trial achieved a second remission. Four year event-free survival was 70-80%. Those whose duration of initial remission was 18 months or greater had almost double the 4 year EFS compared to patients with short duration of remission (80% versus 46%) [24], and
this outcome correlated with findings from a POG study [39]. Another study showed that pediatric patients with B cell ALL with late CNS relapse (such as our patient) without cranial radiation during initial treatment had a survival rate of 78% [40]. In summary, CNS relapses occur in up to 8% of patients with lymphoblastic leukemia. Symptoms of increased intracranial pressure and/or endocrinological dysfunction are typical. Radiological studies may show involvement of the dura, bone marrow of the calvarium, or of the leptomeninges. There has been no report in the literature of hydrocephalus or ventriculomegaly without clear LMD as the main presentation of CNS relapse in ALL. Indeed, this presentation initially confused our diagnoses due to the lack of expected CT/MRI findings of leukemic infiltration or tumor nodules. It was not until a VP shunt for severe hydrocephalus was placed that a relapse was discovered.

CONCLUSION

We present a unique case of CNS leukemia presenting with the prominent radiological finding of hydrocephalus. Although there was brightening of the cortical sulci, definitive evidence of LMD was absent. Diagnosis still relies on suggestive signs and symptoms, positive CSF cytology, or a consistent MRI. Until better non-invasive techniques capable of detecting early CNS leukemia are developed, increased awareness of the disease and standardized evaluation are likely to have the greatest impact on improving diagnosis and implementing earlier treatment.

REFERENCES