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Catch-22 Situation with Unexpected Reports in Acute Lymphoblastic Leukemia.

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Abstract

Central nervous system (CNS) infections are relatively common among children receiving treatment for acute lymphoblastic leukemia (ALL). However, diagnosing these infections presents challenges. In this report, we present a case of asymptomatic adenoviral meningitis, which presented a diagnostic challenge as it mimicked CNS involvement in a child undergoing treatment for ALL. Our findings underscore the importance of thorough diagnostic evaluation for CNS infections in children undergoing ALL therapy, whether they present with symptoms or exhibit asymptomatic cerebrospinal fluid pleocytosis. Furthermore, distinguishing between infections and CNS leukemia is critical, highlighting the necessity of employing flow cytometry to mitigate the potential misinterpretation of morphological features.

Keywords
- acute lymphoblastic leukemia
- CSF pleocytosis
- CNS infection
- CNS leukemia.

Introduction

A 3-year-old boy presented with fever, and bone pains for the past 3 months. On examination, he had pallor, petechiae, cervical lymphadenopathy, and hepatosplenomegaly. Clinical investigations revealed the following: hemoglobin, 104 g/L; reticulocyte count, 0.28%; platelet count, 11×10^9/L; and white blood cell count, 22.9×10^9/L with 97% blasts. He was diagnosed with pre-B acute lymphoblastic leukemia (PB-ALL) on flow cytometric immunophenotyping. There were no adverse cytogenetics, and he was risk stratified as a standard risk PB-ALL.[1] He was started on induction phase chemotherapy. A diagnostic lumbar puncture done on day 8 of chemotherapy showed a cell count of 12 cells/mm^3 (neutrophils/lymphocytes: 14/86), and the malignant cytology was negative, consistent with central nervous system (CNS) negative disease. Reassessment bone marrow at the end of induction had 3% blasts. However, the minimal residual disease (MRD) was positive (0.05%), necessitating change to the high-risk arm of therapy. The cerebrospinal fluid (CSF) sample sent for malignant cytology at the end of induction (3rd CSF, intrathecal being administered on days 8, 15, and 35 of induction as per protocol) was reported positive. The child had received multiple intrathecal therapies as depicted in ►**Table 1**, among which the third CSF (end of induction) and the sixth CSF (during consolidation) were reported to be infiltrated by leukemic blasts as shown in ►**Fig. 1**.

The CSF samples showed pleocytosis (predominantly had monocytosis and activated lymphocytes—morphologically mimicking ALL blasts). The possibility of infective/chemical meningitis was considered. However, the patient was asymptomatic during the entire period. A detailed molecular investigation of the CSF, which included cell count, Gram stain/culture, flow cytometry, polymerase chain reaction (PCR) for detection of herpes simplex virus (HSV) DNA, cytomegalovirus (CMV) PCR, adenovirus PCR, Japanese encephalitis (JE) PCR, and enterovirus PCR, was performed. The CSF had a

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Table 1 Serial CSF examination findings

Sl. no.	Cell count/cellularity	CSF—malignant cytology	Flow cytometry
1	12 (N/L, %: 14/86)	Negative	–
2	–	Lymphocytic pleocytosis	–
3	–	Positive (end of induction)	–
4	Moderately cellular	Pleocytosis	–
5	30 (N/M, %: 20/80)	Negative	–
6	–	Positive (during consolidation)	–
7	Highly cellular	Inflammation, no malignant cells	15% monocytes, 77% lymphocytes (45% CD4+, 34% CD8+), no CD34, CD10, CD19 positive cells
8	Moderately cellular	Lymphocytic pleocytosis	–

Abbreviations: CSF, cerebrospinal fluid; N/L, neutrophils/lymphocytes; N/M, Neutrophils/monocytes.

cell count of 491 cells/mm^3 (predominantly had monocytosis and activated lymphocytes), the sugar/protein levels were normal (normal glucose level is 50–80 mg/dL, normal protein level is 20–45 mg/dL in the CSF), Gram stain negative, and the culture was sterile. Flow cytometry revealed no blasts—CD45+ lymphocytes were negative for CD10, CD19, and CD34. The results for HSV PCR, CMV PCR, JE PCR, and enterovirus PCR were negative. However, the result for adenovirus PCR was found to be positive. Pleocytosis was attributed to adenovirus meningitis, and the child was continued on therapy as a case of CNS-negative ALL. The child completed consolidation and interim maintenance phases of chemotherapy uneventfully.

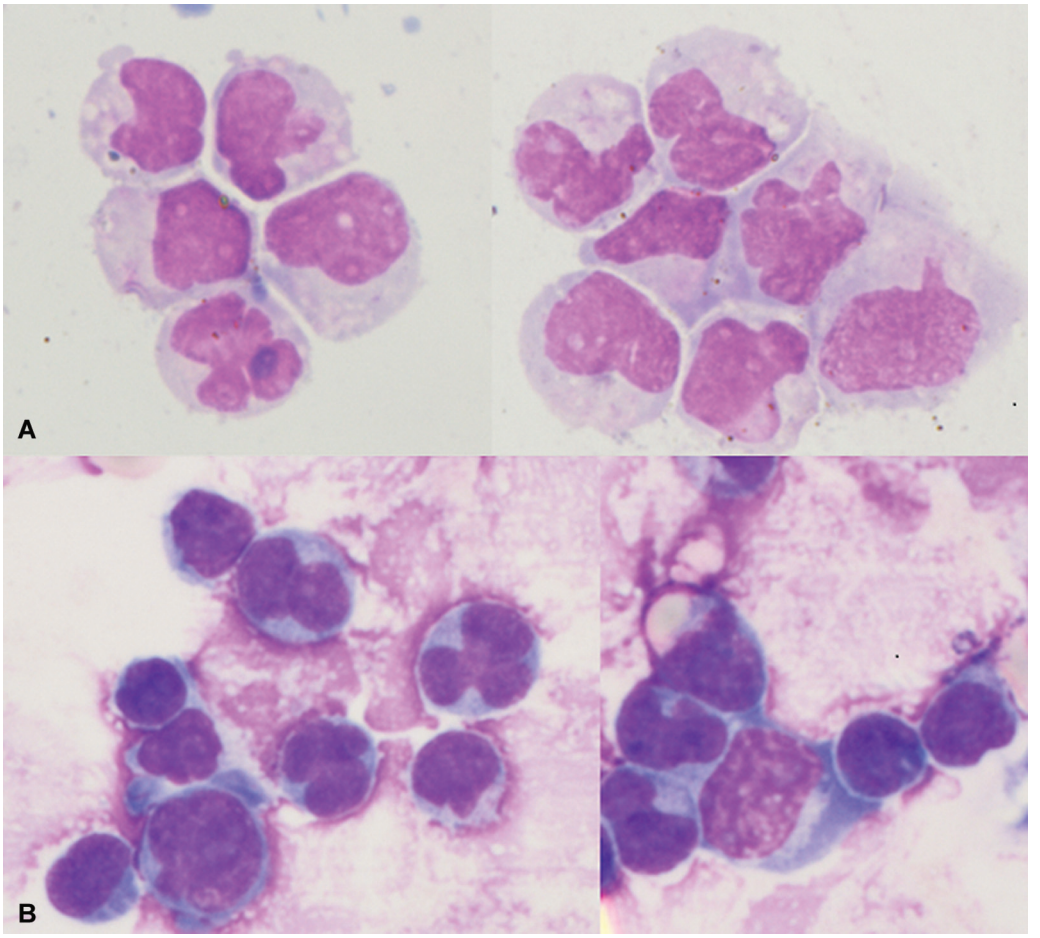

Fig. 1 (**A**) Cerebrospinal fluid (CSF) cytology shows scattered atypical blasts having high nucleus-to-cytoplasm'' ratio (N:C ratio) with opened-up nuclear chromatin, occasional prominent nucleoli, and scant amount of cytoplasm. (**B**) CSF cytology shows infiltration by blasts with high N:C ratio, inconspicuous nuclei, and scant amount of pale basophilic granular cytoplasm.

Unfortunately, he developed fever with loose stools following delayed-intensification therapy and succumbed to possible gram-negative sepsis.

Discussion

CNS involvement at diagnosis in childhood ALL ranges from 3 to 5% in B-ALL and 10 to 15% in T-ALL.[2–4] Being a sanctuary site, CNS-directed prophylaxis is given to all children with ALL. Patients who have CNS disease at diagnosis receive intensive CNS-directed therapy, which may include varying combinations of intrathecal chemotherapy, systemic chemotherapy with high-dose methotrexate (HD-MTX), or Capizzi escalating MTX with Peg-asparaginase, often coupled with cranial irradiation to improve survival.[5,6]

CNS-3 leukemia is often asymptomatic at diagnosis, although some patients present with symptoms such as headache, nausea, vomiting, lethargy, irritability, nuchal rigidity, papilledema, and cranial nerve deficits.[7] CNS infections in immunocompromised children can range from asymptomatic presentations (our index case) to severe symptomatic cases.[2]

Distinguishing CNS infection from CNS leukemia is clinically challenging. CSF cell counts are typically elevated in both scenarios, with neutrophilic predominance observed in bacterial infections and lymphocytic predominance in viral infections and CNS leukemia. Cytomorphology alone may be misleading, as activated lymphocytes and monocytes in viral infections can resemble ALL blasts, potentially resulting in false CNS-positive labeling. Hence, comprehensive infectious workup, including cultures and PCR, are essential for identifying infectious etiologies; however, serology may yield false negatives in immunocompromised patients. CSF flow cytometry with timely processing is crucial for confirming the presence of leukemic blasts in CNS-3 leukemia.[8]

In the index case, as there was clinicopathological discorrelation, efforts were made to confirm the CNS status. Eventually, it was confirmed as negative on repeat morphology and flow cytometry. An extensive infectious workup was done to determine the etiology of the pleocytosis wherein adenovirus PCR was positive. Human adenovirus (HAdv) infections are mostly asymptomatic. Meningoencephalitis is a rare complication of HAdv infection, and it is usually seen in immunocompromised patients. Neurological manifestations range from mild aseptic meningitis as seen in our patient to potentially fatal acute necrotizing encephalopathy.[9]

Conclusion

This case highlights the difficulties faced by the cytopathologist and the dilemma of the clinician in the interpretation and management of a discordant CSF cytology report with repeated pleocytosis. Activated lymphocytes mimic ALL blasts leading to false-positive labeling of the acquired CSF sample. In case of doubt/discrepancy, CSF flow cytometry[8] should always be performed along with cytomorphological diagnosis to confirm the findings, as shown for our index patient since infectious cases necessarily require intensive investigation.

Patient Consent

Author Contributions

S.P. wrote the manuscript, A.T. is the clinician involved in treatment and contributed to betterment of manuscript, P.G. is the Cytopathologist who reported the CSF samples and provided the required images.

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None.

Conflict of Interest

None declared.

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