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CASE REPORT

Extramedullary Relapse of Acute B-Lymphoblastic Leukemia Leading to Paraplegia in a Child with Down Syndrome

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SUMMARY

Background: **Acute B-lymphoblastic leukemia (B-ALL) is a common malignancy in children. Patients with Trisomy 21 (Down syndrome) are at a higher risk of developing hematologic disorders. Despite advances in treatment, extramedullary relapse remains a challenge, particularly when it manifests as spinal cord compression leading to paraplegia, a rare but severe complication.**
Methods: **We describe the clinical course of an 11-year-old male with Trisomy 21, diagnosed with B-ALL. The patient was treated with standard chemotherapy (VDLP regimen) followed by central nervous system prophylaxis through lumbar puncture and intrathecal chemotherapy. Despite achieving minimal residual disease (MRD)-negative status, the patient developed progressive lower back pain and acute paraplegia. Imaging studies and subsequent spinal surgery were performed to diagnose and manage the spinal cord lesion.**
Results: **The patient's spinal pathology confirmed a relapse of B-ALL with extramedullary involvement. Immunohistochemistry of the tumor showed markers consistent with B-lymphoblastic leukemia/lymphoma. Chemotherapy-induced remission was initially achieved, but the patient experienced bone marrow suppression after each cycle, leading to further hospitalization and supportive treatments. Post-surgical findings showed no CNS involvement, and bone marrow MRD remained negative.**
Conclusions: **This case highlights the complexity of managing B-ALL in children with Trisomy 21, who may be prone to extramedullary relapse despite systemic remission. Early recognition of spinal symptoms and prompt surgical intervention are critical in preventing irreversible neurological damage such as paraplegia. This case underscores the need for vigilant monitoring and tailored therapeutic strategies in high-risk populations.**
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KEYWORDS

Acute B-lymphoblastic leukemia, Trisomy 21, extramedullary relapse, paraplegia, spinal involvement, chemotherapy

INTRODUCTION

Acute B-lymphoblastic leukemia (B-ALL) is one of the most common types of childhood leukemia, accounting for approximately 80% of acute lymphoblastic leukemia cases [1]. Advances in the treatment of B-ALL, including intensive chemotherapy protocols, have significantly improved long-term survival rates [2]. However, the

occurrence of extramedullary relapse, particularly involving the central nervous system (CNS) or other non-hematopoietic tissues, remains a formidable challenge [3]. Such relapses often complicate the treatment process and are associated with poor prognosis [4].

Patients with Trisomy 21 (Down Syndrome) are at an increased risk for developing hematological malignancies, including B-ALL. They also face unique therapeutic challenges due to their increased sensitivity to chemotherapy and a heightened risk of treatment-related toxicity [5]. Extramedullary relapse in B-ALL can affect a variety of tissues, including the CNS, skin, and soft tissues, but spinal involvement leading to paraplegia is relatively rare [6]. In cases where extramedullary relapse occurs in the spine, early recognition and prompt intervention are critical for preserving neurological function [7]. Despite prophylactic intrathecal chemotherapy, the risk of CNS or spinal relapse persists. Here, we report a rare case of an 11-year-old male with Trisomy 21, who initially achieved remission following chemotherapy for B-ALL but subsequently developed an extramedullary relapse in the spinal canal. This relapse presented as progressive lower back pain followed by acute paraplegia, ultimately necessitating surgical intervention. This case highlights the clinical challenges of managing relapse in pediatric patients with B-ALL and underscores the need for early detection and treatment of extramedullary disease to prevent severe complications.

CASE PRESENTATION

The patient is an 11-year-old male adolescent with a history of Trisomy 21 syndrome. He presented with acute onset fever, accompanied by cough and sputum production for 4 days. Upon admission, physical examination revealed the patient was alert but had pale mucous membranes, oral ulcers, and atrophy of the tongue papillae.

Initial laboratory tests showed leukopenia (WBC: 3.81 x 10^9/L), neutropenia (0.73 x 10^9/L), anemia (RBC: 2.80 x 10^{12}/L; hemoglobin: 83.00 g/L), and thrombocytopenia (platelets: 17.00 x 10^9/L). Peripheral blood smear revealed 11% blasts. Bone marrow examination demonstrated markedly active cellular proliferation, with 99% lymphocytes, primarily immature lymphoblasts. ANA staining showed 98.2% positivity, consistent with a bone marrow picture of acute lymphoblastic leukemia (ALL).

Flow cytometry of the bone marrow showed 89.61% immature B lymphoblasts, characterized by the following immunophenotype: HLA-DR+, partial CD34+, CD 56-, CD7-, CD117-, CD5-, CD2-, dim CD13-, CD11b-, CD16-, CD14-, CD64-, CD33-, partial CD10+, CD19+, CD20-, CD4-, CD8-, CD3-, MPO+, cCD3-, cCD22+ (Figure 1). These findings supported the diagnosis of B-ALL/lymphoblastic lymphoma (LBL). FISH analysis for TEL/AML1, MLL rearrangement, BCR/ABL1, IGH/BCL2, and iAMP21 was negative. Genetic testing identified mutations in the KRAS and SETD2 genes, while karyotyping revealed no abnormalities.

Chest CT showed no intracranial abnormalities but indicated slight widening of the cranial sutures and heterogeneous bone density, as well as bilateral ear canal nodules. Additional findings included patchy inflammation in the left lower lobe, chronic pleural inflammation in both upper lobes, and a paravertebral soft tissue density near the upper thoracic spine, raising suspicion for extramedullary hematopoiesis. A comprehensive assessment led to the diagnosis of acute B-ALL.

The patient began treatment on June 12, 2022, with the VDLP chemotherapy regimen, including vincristine, daunorubicin, L-asparaginase, and dexamethasone, along with hydration, alkalization, and anti-emetic therapy. He also underwent lumbar puncture with intrathecal chemotherapy for CNS leukemia prophylaxis. Bone marrow examination on day 16 showed active cellular proliferation, with a negative minimal residual disease (MRD) result. He was classified as an intermediate-risk group based on his clinical presentation.

During treatment, the patient developed fever and post-chemotherapy myelosuppression, which was managed with anti-infective therapy and growth factors. He received additional CAM chemotherapy on July 27 and September 12, 2022, with recurrent myelosuppression successfully managed through blood transfusions and white blood cell stimulation. On October 26, 2022, his MRD was again negative, and genetic testing revealed the MTHFR 677C>T mutation in heterozygous form (CT genotype). Subsequently, the patient underwent the mM chemotherapy regimen starting on November 19, 2022, and received a total of 6 lumbar punctures with intrathecal chemotherapy. No abnormalities were found in the cerebrospinal fluid (CSF) analyses during this period.

On February 24, 2024, the patient was admitted to the neurosurgery department with a 2-month history of back pain and 2 days of paraplegia. Magnetic resonance imaging (MRI) revealed an irregular mass at the left paravertebral region from T7 to T10 and intradurally, posterior to the spinal cord from T8 to T10: findings consistent with hematologic malignancy (Figure 2). Under general anesthesia, he underwent spinal lesion resection, spinal decompression, and spinal reconstruction with neurophysiological monitoring. Pathological examination confirmed the diagnosis of B-lymphoblastic leukemia/lymphoma. Immunohistochemical staining revealed TdT(+), CD99(-), CD1a(-), CD7(-), CD3(-), CD21(-), CD20(+), Pax-5(+), with a Ki-67 proliferation index of approximately 60% (Figure 3). Further MRD analysis of the bone marrow was negative and repeat lumbar puncture and intrathecal chemotherapy revealed no leukemia cells in the CSF.

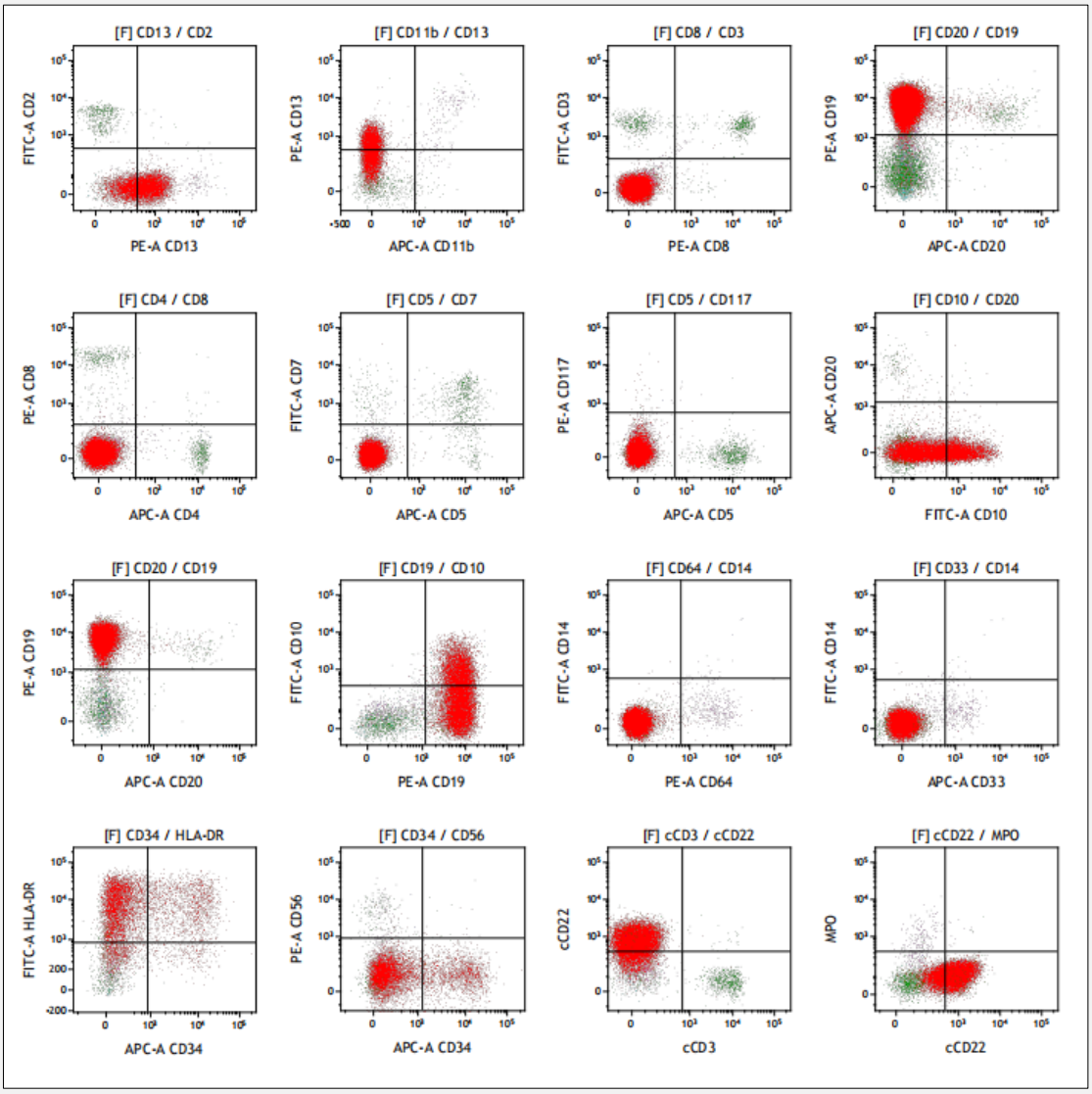

Figure 1. Flow cytometry of the bone marrow showed 89.61% immature B lymphoblasts, characterized by the following immunophenotype: HLA-DR+, partial CD34+, CD56-, CD7-, CD117-, CD5-, CD2-, dim CD13-, CD11b-, CD16-, CD14-, CD64-, CD33-, partial CD10+, CD19+, CD20-, CD4-, CD8-, CD3-, MPO+, cCD3-, cCD22+.

DISCUSSION

This case report highlights several important aspects of managing acute B-lymphoblastic leukemia (B-ALL) in patients with Trisomy 21, particularly the risk of extramedullary relapse and the challenges associated with treatment. The occurrence of spinal involvement leading to paraplegia is a rare but significant complication in B-ALL, and its management requires a coordinated, multidisciplinary approach involving oncologists, neurologists, and surgeons [8]. Patients with Trisomy 21 present unique challenges in the treatment of B-ALL. Due to their underlying genetic and immunological differences, these patients often exhibit heightened sensitivity to chemotherapy, leading to a greater risk of treatment-related toxicities. This patient, for example, experienced delayed clearance of methotrexate during high-dose chemotherapy cycles, requiring adjustments in leucovorin rescue therapy [9]. Such complications necessitate close monitoring of drug metabolism and individualized treatment adjustments to minimize toxicity while maintaining therapeutic efficacy.

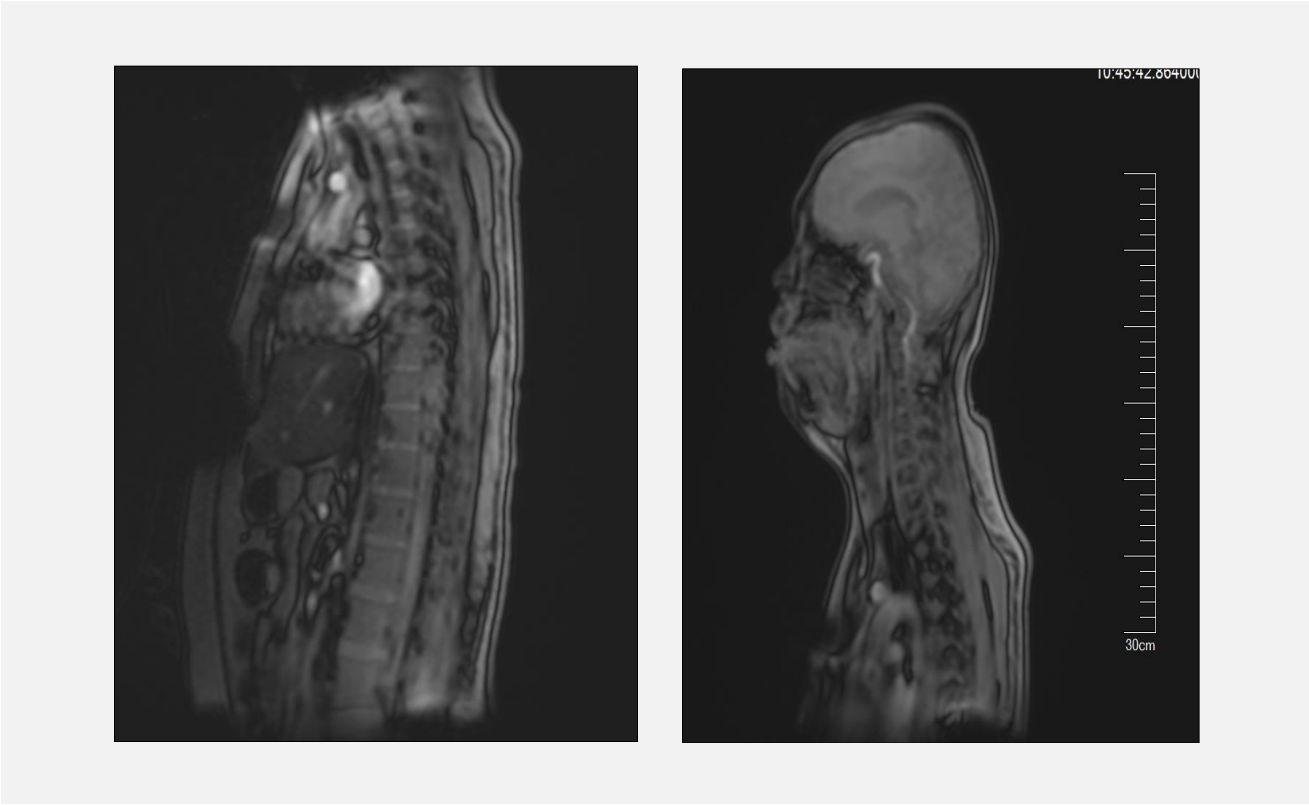

Figure 2. Magnetic resonance imaging (MRI) revealed an irregular mass at the left paravertebral region from T7 to T10, and intradurally, posterior to the spinal cord from T8 to T10: findings consistent with hematologic malignancy.

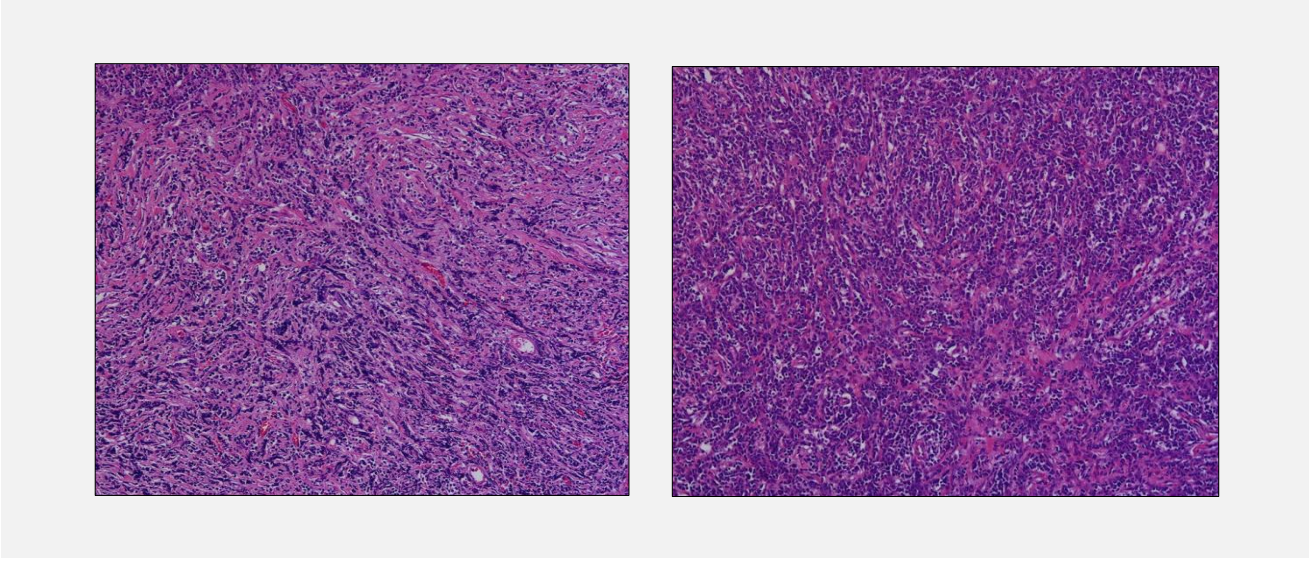

Figure 3. Under general anesthesia, intraoperative neurophysiological monitoring was employed during the intradural lesion resection, spinal canal decompression, and spinal canal expansion procedures.

The pathological diagnosis confirmed B-lymphoblastic leukemia/lymphoma. Immunohistochemical findings were as follows: TdT (+), CD99 (-), CD1a (-), CD7 (-), CD3 (-), CD21 (-), CD20 (clone L26) (+), Pax-5 (+), Ki67 approximately 60% (+), MPO (-), CD34 (-), CD117 (-).

Extramedullary relapse in B-ALL, though rare, can occur in various tissues, and the CNS remains the most common site involved [10]. Despite the use of intrathecal chemotherapy as CNS prophylaxis, the development of spinal cord relapse in this patient underscores the need for vigilant monitoring for extramedullary disease. The pathophysiology underlying extramedullary spread in B-ALL, particularly in the context of Trisomy 21, remains poorly understood [5]. It is hypothesized that the altered immune environment in Trisomy 21, including dysfunction in the immune surveillance mechanisms, may contribute to the increased risk of relapse in non-hematopoietic tissues.

The management of spinal involvement in B-ALL is complex and requires a combination of surgical and medical interventions [11]. In this case, the patient underwent spinal decompression surgery, which successfully relieved the compression on the spinal cord. The subsequent pathology confirmed extramedullary B-ALL relapse. Post-surgical chemotherapy, including high-dose methotrexate, was administered to target residual disease, though the patient again experienced delayed methotrexate clearance, requiring careful management. This case emphasizes the importance of early detection of extramedullary relapses in B-ALL. Regular monitoring through imaging and clinical assessments is crucial for identifying relapses before they cause irreversible damage, such as paraplegia [12]. Furthermore, the case highlights the need for ongoing research into the mechanisms driving extramedullary relapse in B-ALL, particularly in patients with Trisomy 21, who may require modified treatment protocols to reduce relapse risk while minimizing toxicity.

In conclusion, this case illustrates the complexities involved in managing B-ALL in a patient with Trisomy 21, particularly in the context of extramedullary relapse. A multidisciplinary approach is essential for optimizing outcomes, and future research should focus on refining treatment strategies for these high-risk patients.

Declaration of Interest:

None.

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