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## Acute tetraparesis revealing acute lymphoblastic leukemia relapse: A case report and literature review

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### Abstract

Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood. While some 5 to 8% of ALL cases will have neurological involvement at initial presentation, up to 30% of relapses have neurological manifestations. We present the case of a pediatric ALL with meningo-radiculoneuropathy revealing a relapse while on maintenance therapy. Our patient presented the Philadelphia mutation, that is the t(9;22), and thus was at high risk of neurological involvement. The diagnosis of relapse was based on neuroimaging and CSF study. Treatment entailed modified Hyper CVAD chemotherapy with repeated intrathecal treatment until CSF clearance. Outcome was favorable with gradual regression of neurological symptoms.

**Keywords:** acute lymphoblastic leukemia, relapse, polyradiculoneuritis, modified Hyper-CVAD

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### Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood and an important cause of death from cancer during the first two decades of life <sup>[1]</sup>. Global incidence rates have been estimated to be between 1.08 to 2.12 per 100,000 person-years, the condition being four times more frequent in childhood than in adulthood <sup>[2]</sup>. Recent advances in the fields of diagnostics and therapeutics have improved prognostic outcomes in patients <sup>[3, 4]</sup>. Involvement of the nervous system remains, however, an issue of concern, and constitutes a negative prognostic factor <sup>[5, 6]</sup>. While some 5 to 8% of ALL cases will have neurological involvement at initial presentation, up to 30% of relapses have neurological manifestations <sup>[5, 7]</sup>.

We present the case of a pediatric ALL with meningo-radiculoneuropathy revealing a relapse while on maintenance therapy. This case study demonstrates how a thorough neurological examination and appropriate diagnostic workup are required to parse out the various differentials.

### Case Report

A 12-year-old girl, the third of 3 children born to a first degree consanguineous marriage, presented with acute motor impairment of the lower extremities. The patient was followed up for acute B-cell lymphoblastic leukemia (B-cell ALL), treated with the FRALLE 2000 protocol and on the maintenance phase at the time of presentation. The patient had a female maternal cousin with a malignant hemopathy.

The patient presented with acute diplopia, urinary retention and weakness of both lower extremities. On admission, the patient was conscious, stable on cardiorespiratory evaluation, afebrile without pallor or signs of hemorrhage or tumor.

On neurological examination, the patient presented with tetraparesis with decreased muscle tone and absent deep tendon reflexes on all limbs (4/5 proximally and distally, bilaterally on upper extremities; 3-/5 proximally and distally, bilaterally on lower extremities on the Medical Research Council muscle strength grading). Plantar response was equivocal bilaterally. There was reduced pinprick sensation at the pulp of all fingers and in the lower extremities up to the knees with altered position sense of toes and reduced vibration perception up to the knees bilaterally. There was also urinary retention and constipation at presentation. Sensory perception was preserved in the perineal region. There was slight facial and abducens nerves involvement on the right with slight extrinsic third nerve palsy on the left. Brudzinski, but not Kernig sign, was present.

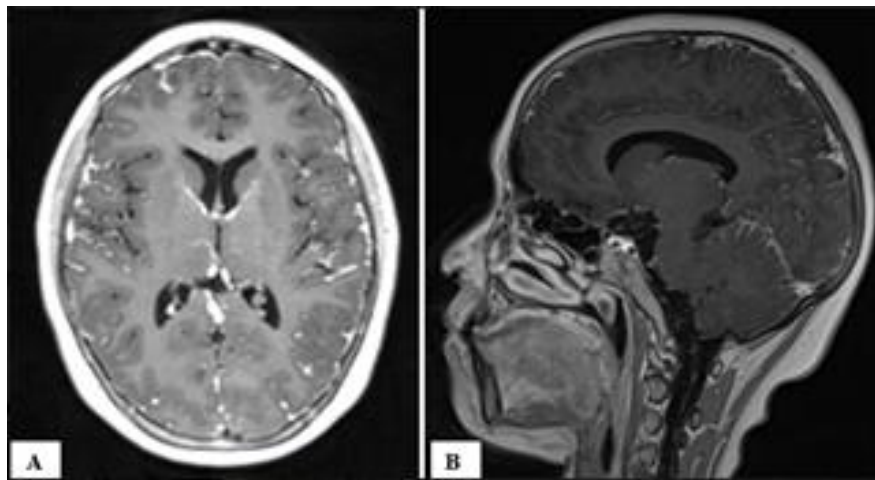
Electromyography revealed axonal polyradiculoneuritis. Brain and spinal magnetic resonance imaging (MRI) revealed diffuse meningeal infiltration in the cranium (Figure 1). Whole body tomography was unremarkable. Cerebrospinal fluid (CSF) study revealed 3590 atypical lymphocytes per mm<sup>3</sup>. Complete blood count (Hemoglobin: 15.2 g/dl; Platelets: 231 000 per mm<sup>3</sup>; White blood cells: 9930 per mm<sup>3</sup>) and peripheral blood smear were unremarkable. Bone marrow examination revealed 15% lymphoblasts (Figure 2). Prothrombin time (PT) was 85%, kaoline clotting time (KCT) was 35.3 seconds compared to a standard of 32 seconds. Fibrinogen was 3.11 g/l. Serum electrolytes, blood urea and nitrates, phosphates and calcium in the blood were

unremarkable except for elevated uric acid (454 mg/l) and lactate dehydrogenase (737 u/l) levels. Immunophenotyping revealed B-cell ALL. Karyotype study of 27 cells using RHG technique revealed 46,XX,t(9;22)(q34;q11)[1]/52,idem,+X,+4,+6,+10,+mar1,mar2[2]/46,XX[24]... a minority pseudodiploid cell clone of 46 chromosomes with a t(9;22) translocation indicating a positive Philadelphia chromosome (1 mitosis). Another hyperdiploidy subclone of 52 chromosomes with trisomies for chromosomes X, 4, 6, 10 and two chromosomes as markers (2 mitoses). A clone without anomalies found on examination (24 mitoses). Molecular biology using multiplex PCR did not find any transcript of BCR-ABL fusion. Human leucocyte antigen (HLA) typing using PCR and reverse dot-blot showed no HLA-A\*29, HLA-B\*27 or HLA-B\*51.

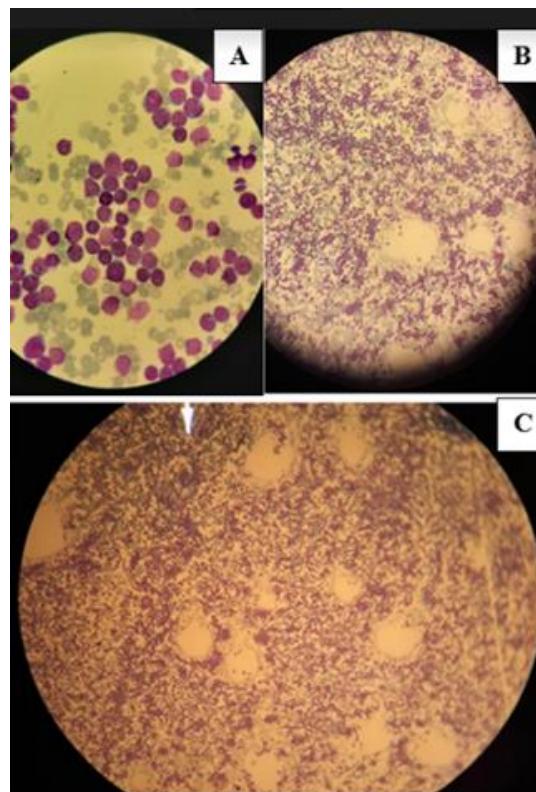
Treatment was started after a pretreatment evaluation involving transthoracic echocardiography, HIV, HVC, HVB, EBV, CMV serologies and Covid-19 PCR was unremarkable. Treatment entailed modified Hyper CVAD chemotherapy with repeated intrathecal treatment (IT) until CSF clearance, hyper hydration, allopurinol, proton inhibitor, prophylaxis with acyclovir and fluconazole

Diplopia resolved after the first cycle of Hyper CVAD and CSF cleared after 4 IT treatments. Post induction bone marrow aspirate showed no excess of blasts.

Consecutive Hyper CVAD cycles were well tolerated. Human Leucocyte Antigen typing of the siblings failed to show compatibility, and the patient is planned to receive pheno-identical stem cell transplantation.



**Fig 1:** Contrast enhanced T1 weighted Brain MRI in (A) Axial and (B) Sagittal planes showing diffuse leptomeningeal enhancement without parenchymal involvement.



**Fig 2:** Bone marrow examination under optical microscope showing infiltration of bone marrow by lymphoblasts (From A to C, X100, X 20, X10 magnification strengths, respectively)

## Discussion

ALL is a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood and extramedullary sites [7]. This transformation is due to chromosomal abnormalities in precursors of B-cell or T-cell lineage. The majority of ALL occur in B-cell lineage as is the case of our patient [8]. Several genetic syndromes have been shown to present a higher incidence of the disease [9-11]. However, the majority of cases are de novo mutations [12]. Other risk factors have been identified such as immunodepression, viral infection, toxic substances and ionizing radiation. Our patient's history of being born to a first degree consanguineous marriage and a cousin with a history of unspecified malignant hemopathy are significant indicators of a possible transmissible genetic aberration. The patient's clinical examination, however, did not reveal any dysmorphic, cutaneous or pre-diagnosis neurological issues suggestive of well-known syndromes such as Down's syndrome, Fanconi's anemia and ataxia-telangiectasia syndrome associated with ALL [9-11].

While neurological manifestations are relatively infrequent at the time of diagnosis, it is classic to find neurological involvement at presentation during relapses [5, 7]. Our patient did not report neurological symptoms at presentation 2 months before at the time the diagnosis of ALL was made. Instead, neurological involvement was the presenting feature of her relapse. The high frequency of these symptoms during relapse makes them important to recognize for early diagnosis and management. Central nervous system (CNS) involvement is a major prognostic factor since it is a primary cause of mortality. CNS involvement entails a pleomorphic presentation. Cranial nerve palsy, signs and symptoms of meningeal irritation and increased intracranial pressure are important to recognize. Parenchymal involvement of the encephalic localization is seen in later stages of ALL [13]. Spinal cord involvement and hormonal deficit due to pituitary infiltration have also been described [14]. Importantly, peripheral involvement, aside from cranial nerves, could also be seen in these patients [15]. Management of these manifestations remains challenging with the risk of neurocognitive complications due to treatment [16].

Several risk factors for neurological involvement in ALL include high leucocyte count on CBC and differential at the time of diagnosis [17]. Cytogenetic types also present differential risk factors for CNS involvement. T (1; 19) and t (9;22) have been shown to be involved with a high incidence of CNS involvement in B-cell ALL [18, 19]. Our patient presented the Philadelphia mutation, that is the t(9;22), and thus was at high risk of neurological involvement.

The diagnosis of relapse was based on neuroimaging and CSF study. Performing lumbar puncture (LP) is an important procedure at the time of diagnosis. Neuroimaging in the form of MRI is required if CNS involvement is suspected. It must be noted, however, that LP has been suspected of being a risk factor of CNS involvement during relapse by the introduction of peripheral malignant cells into the sub arachnoid space during a traumatic tap [20]. This risk was increased with a later timing of intrathecal therapy, multiplicity of traumatic taps and was found to be greater in adult than in pediatric patients [20, 21].

Our patient presented, not only with cranial nerve involvement with meningismus, but also polyradiculoneuritis. While it stands to reason that the context of neoplastic history makes the B-cell ALL a very likely culprit, it must be pointed out that in the case of our patient, other differentials are important to discuss [22]. Given the history of chemotherapy, a toxic etiology should be discussed. Equally likely are immune processes such as para or post infectious mechanisms [23].

An important distinguishing feature of polyradiculoneuritis of neoplastic or para neoplastic origin is the associated constitutional symptoms. In B-cell ALL, non specific 'B symptoms' such as fever, weight loss, fatigue, anorexia and night sweats are frequent but could also be seen in infections such as tuberculosis, Lyme disease and in vasculitis. Tuberculosis is an important diagnosis in our geographic setting. The diagnosis of tuberculosis will require finding decreased CSF glucose and elevated CSF proteins. Also, elevated CSF cells, predominantly lymphocytes will be in favor of the diagnosis. Performing PCR in the CSF (GenXpert) would also be contributory. For Lyme disease, performing *Borrelia* spp. serology, especially in the context of exposure to tick bite would guide diagnosis. Vasculites would be associated with systemic involvement and dermatological manifestations. Peripheral nerve involvement in these pathologies is typically characterized by pain.

Our patient was treated with modified Hyper-CVAD regimen which has been shown to be an effective therapy [24]. The outcome was favorable with sterilization of the subarachnoid milieu as well as gradual recuperation of neurological symptoms.

## Competing Interests

The authors report no conflicts of interest.

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