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CASE REPORT

A Case of Relapsed and Refractory Pediatric Anaplastic Large Cell Lymphoma with Complex Karyotype

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SUMMARY

Background: **Anaplastic large cell lymphoma (ALCL) is a rare type of peripheral T-cell lymphoma, accounting for a small percentage of adult and childhood lymphomas. The scarcity of reports on relapsed or refractory ALCL in children, especially with complex karyotypes, highlights the need for detailed case studies.**
Methods: **We report the case of a 9-year-old girl diagnosed with ALK-positive anaplastic large cell lymphoma, complicated by complex karyotype abnormalities and bone marrow involvement. The patient underwent multiple chemotherapy regimens, including the P regimen, AV1, BV1, AV2, BV2, and AV3 protocols, followed by continuous monitoring through bone marrow biopsies and PET/CT imaging. Despite initial treatment efforts, the disease relapsed, and the patient's condition deteriorated.**
Results: **Initial treatment with chemotherapy led to a transient reduction in disease activity, as evidenced by bone marrow biopsies showing no malignancy. However, PET/CT scans revealed persistent metabolic activity in multiple skeletal sites, indicating incomplete remission. The patient's condition further relapsed with significant disease progression, culminating in sepsis, heart failure, and active bleeding, which were unresponsive to treatment.**
Conclusions: **This case underscores the aggressive nature of pediatric ALCL with complex karyotypes and highlights the challenges associated with its treatment. Despite intensive chemotherapy, the disease exhibited rapid relapse and resistance, ultimately leading to a fatal outcome. This report contributes to the limited literature on pediatric ALCL, particularly in cases with complex cytogenetic profiles, and emphasizes the need for novel therapeutic approaches and early intervention strategies.**
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KEYWORDS

anaplastic large cell lymphoma, complex karyotype, relapsed, pediatric

INTRODUCTION

Anaplastic large cell lymphoma (ALCL) is a type of peripheral T-cell lymphoma that accounts for approximately 3% of adult non-Hodgkin lymphomas and 10 - 15% of childhood lymphomas [1-3]. ALCL is a highly malignant tumor with a wide range of initial symptoms, making diagnosis challenging and often leading to a high rate of misdiagnosis. In its early stages, ALCL can be further complicated by hemophagocytic lymphohis-

tiocytosis (HLH), which adds additional complexity to both diagnosis and treatment. Currently, there are few reports on pediatric ALCL in the domestic literature, with most studies focusing on case analyses at the time of initial treatment. Research on the treatment of relapsed or refractory cases is relatively scarce, and ALCL with complex karyotypes at initial diagnosis is even rarer. This report presents a case of relapsed and refractory pediatric ALCL with a complex karyotype diagnosed at our hospital, aiming to provide insights for clinical diagnosis and treatment.

CASE REPORT

A 9-year-old girl was admitted to our hospital presenting with symptoms of fatigue and fever. A thorough evaluation, including lymph node and bone marrow biopsies, was performed. Immunohistochemical analysis of a left cervical lymph node aspiration revealed the following findings: CD10(-), CD20 (clone L26) (B cells+), CD21(-), CD3 (partial cells+), CD5(+), CD79α (B cells+), Ki-67 (approximately 40%+), CD15(-), CD 30(+), BOB-1(-), PAX-5(-), ALK (clone 5A4) (+), EMA(+), CK(-) (Figure 1A - B). In situ hybridization for Epstein-Barr virus-encoded RNA (EBER) was negative. The pathological findings confirmed a diagnosis of ALK-positive anaplastic large cell lymphoma (ALCL). The bone marrow biopsy showed largely normal marrow architecture (approximately 80%) with extensive proliferation of lymphoid cells. These cells were characterized by large cell bodies, abundant cytoplasm, and kidney-shaped or irregular nuclei. Scattered granulocytes and erythrocytes at various stages of development were observed, but megakaryocytes were absent. Immunohistochemistry results from the bone marrow biopsy were as follows: CD20(-), PAX5(-), CD79a(-), CD3(-), CD5(+), BCL2(-), CD10(-), Ki-67 (70%+), MUM-1(+), BCL-6(-), CD43(-), CD30(+), ALK(+), BOB-1(-), OCT-2(-) (Figure 1C - D). These findings indicated bone marrow involvement by ALK-positive anaplastic large cell lymphoma with secondary myelofibrosis.

Cytogenetic analysis of the bone marrow revealed the following karyotype: 86 - 93, XX, -X, -X, +1, +1, i(1)(q10) x 2, +5, -9, -11, -15, -16, add(16)(p11) x 2, +mar[cp6]/46, XX[14] (Figure 2). PET-CT imaging demonstrated several key findings: Multiple enlarged lymph nodes in the left parapharyngeal space, bilateral cervical regions, and bilateral supraclavicular fossae, with abnormally increased FDG metabolism, suggestive of lymphoma; Abnormal bone density and increased FDG metabolism in the skull, cervical, thoracic, and lumbar vertebrae, right clavicle, bilateral scapulae, bilateral ribs, sternum, pelvis, and the upper segments of both humeri and femurs, consistent with bone marrow infiltration by lymphoma; Splenomegaly with increased FDG metabolism, suggestive of splenic infiltration by lymphoma; hepatomegaly was noted, but no significant abnormalities in FDG metabolism were detected. Based on these comprehensive examinations, a diagnosis of ALK-positive anaplastic large cell lymphoma was established.

The patient was definitively diagnosed and began treatment with the P regimen for tumor reduction on April 24, 2022. Chemotherapy with the AV1 regimen was administered on April 29, 2022, in accordance with the pediatric ALK+ anaplastic large cell lymphoma protocol, including one intrathecal injection. During the subsequent period of bone marrow suppression, supportive treatments, such as transfusions, were provided. Following discharge, the patient developed neutropenia accompanied by fever, which improved with treatment. A bone marrow biopsy conducted in May 2022 revealed no malignancy. However, PET/CT results indicated persistently elevated FDG metabolism in the cranial bones, sacrum, right iliac bone, T3 vertebra, L1 vertebra, and L5 vertebra. Additionally, splenomegaly with mildly increased FDG uptake suggested that the tumor had not achieved complete remission. The BV1 regimen was initiated on June 1, 2022, followed by the AV2 regimen on June 25, 2022. A bone marrow biopsy showed no significant abnormalities, and the karyotype was normal. On July 22, 2022, the BV2 regimen was initiated. During this period, the patient experienced an oral Acinetobacter baumannii infection, which occurred during chemotherapy-induced marrow suppression and was treated with piperacillin and component blood transfusions. After discussions with the patient's mother, autologous hematopoietic stem cell transplantation was recommended; however, the family declined due to financial constraints. The AV3 regimen was started on August 16, 2022, followed by the BV3 regimen on September 7, 2022.

One week ago, the patient developed diffuse bone pain and restricted mobility, which improved after taking ibuprofen capsules. However, one day prior to admission, the patient experienced an unprovoked fever with a maximum temperature of 38.9℃, without chills or shivering, and with mild chest tightness. Upon admission, a PET/CT scan revealed the following: increased radiotracer uptake in multiple bones, including the limbs, skull, spine, humeri, ribs, scapulae, sternum, clavicles, and pelvis, with a soft tissue mass anterior to the sacrum showing abnormally elevated FDG metabolism (SUVmax approximately 18.4). The extent of the disease had significantly increased compared to the most recent prior scan, indicating a relapse. The family decided to discontinue treatment. During hospitalization, the patient received anti-infective therapy with piperacillin, meropenem, and vancomycin, but continued to experience recurrent high fevers. The patient subsequently developed sepsis, heart failure, and active bleeding, with the disease proving unmanageable. The patient was declared clinically deceased one day later.

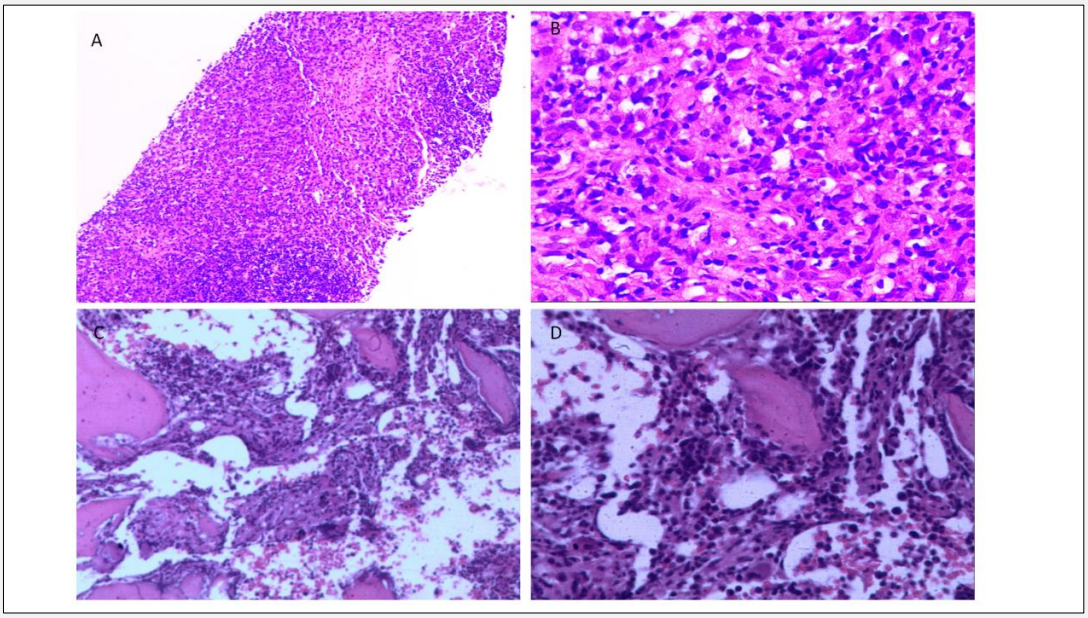

Figure 1. Immunohistochemical analysis of a left cervical lymph node aspiration revealed the following findings: CD10(-), CD20 (clone L26) (B cells+), CD21(-), CD3 (partial cells+), CD5(+), CD79a(B cells+), Ki-67 (approximately 40%+), CD15(-), CD30(+), BOB-1(-), PAX-5(-), ALK (clone 5A4) (+), EMA(+), CK(-)(A-B). Bone marrow biopsy were as follows: CD20(-), PAX5(-), CD79a(-), CD3(-), CD5(+), BCL2(-), CD10(-), Ki-67 (70%+), MUM-1(+), BCL-6(-), CD43(-), CD30(+), ALK(+), BOB-1(-), OCT-2(-) (C - D).

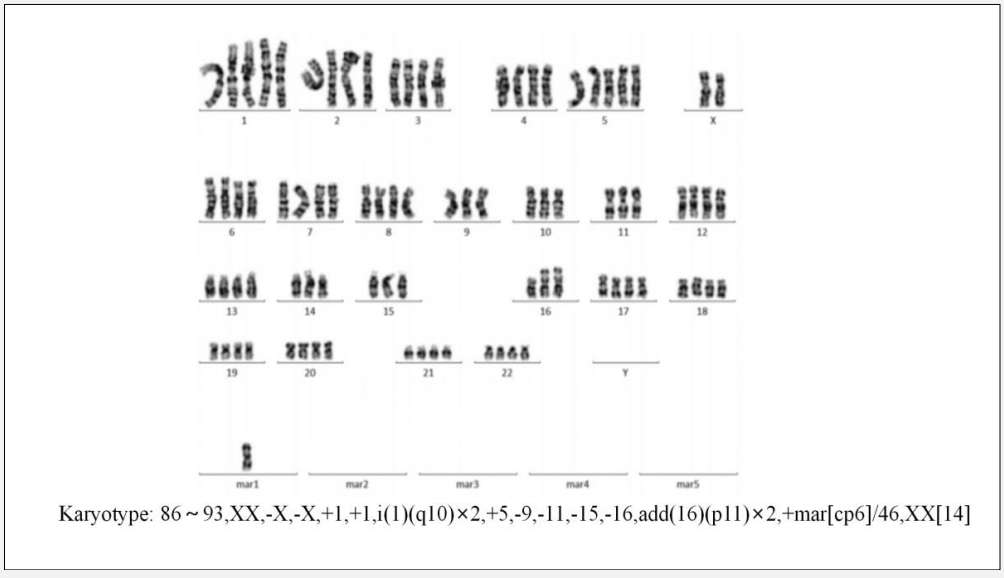

Figure 2. The analysis of 20 metaphase cells showed the presence of polyploidy in some cases, with missing X chromosomes, chromosomes 9, 11, 15, and 16, and an increase in chromosome 1. Marked chromosomes were observed, including an isochromosome 1 and the short arm of chromosome 16 attached to an unknown fragment.

DISCUSSION

ALCL is classified as a peripheral T-cell lymphoma and is rare in children, differing from other common pediatric non-Hodgkin lymphomas. A significant proportion of ALCL cases are associated with the t(2;5)(p23;q35) translocation, leading to abnormal expression of the ALK gene. This aberrant ALK gene expression is closely related to tumor development, biological characteristics, and patient prognosis. Consequently, the World Health Organization (WHO) classifies ALCL into ALK-positive and ALK-negative subtypes [4]. In pediatric and adolescent patients, over 90% of cases are ALK-positive ALCL.

The clinical presentation of pediatric ALCL is diverse and sometimes atypical, making it difficult to diagnose and easily mistaken for other diseases. ALCL with extranodal involvement can sometimes spread to the lungs, presenting as fever, cough, wheezing, and dyspnea, which may lead to misdiagnosis. In this case, the child presented with an acute onset of fever and fatigue, and physical examination revealed multiple enlarged lymph nodes on both sides of the neck and in the supraclavicular fossae. The diagnosis was confirmed only after performing a cervical lymph node biopsy and a bone marrow biopsy.

Regarding the clinical characteristics of ALCL, it typically occurs at a young age, predominantly affecting children and young adults, with a higher incidence in males than in females. The disease often presents with superficial and abdominal lymphadenopathy, frequently involving large masses. At the time of diagnosis, the disease is usually in an advanced stage (Stage III - IV). Extranodal involvement is observed in 60% of cases, with the most common sites being the skin (21%), bone (17%, either solitary or multiple lesions), and soft tissues (17%). Less commonly affected sites include the lungs (11%), liver (8%), and, rarely, the gastrointestinal tract and central nervous system (< 5%). Therefore, in children with recurrent fever and widespread lymphadenopathy, the possibility of lymphoma should be considered, and early lymph node and bone marrow biopsies should be performed to ensure timely diagnosis.

The treatment regimen for ALCL is primarily based on chemotherapy, with a 5-year survival rate of 70% - 85% following chemotherapy [3]. However, approximately 30% of pediatric ALCL patients will experience relapse, and among those who relapse, about 50% can survive and be rescued through aggressive salvage therapy [5-7]. Therefore, early identification and intervention to improve poor prognostic factors in pediatric ALCL will help reduce recurrence and mortality, thereby improving the quality of life and prognosis of patients. In this case, the child presented with a complex karyotype, with molecular biology factors further influencing the disease prognosis. The patient did not achieve complete remission during chemotherapy, and disease progression during treatment indicated a very poor prognosis. Vibutuximab is a novel antibody coupling drug (ADC), which is a humanized anti-CD30 antibody coupled with the anti-mitosis drug MMAE, and has shown excellent efficacy and safety in the treatment of lymphomas, especially metaplastic large cell lymphomas. But due to financial constraints, this treatment option was not utilized.

Declaration of Interest:
The authors declare no competing interests.

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