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ALK-1 positive anaplastic large cell lymphoma in sickle cell trait: A case report and review of literature

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Abstract
Anaplastic large cell lymphoma (ALCL) is a rare subtype of non-Hodgkin lymphoma, with ALK-1 positive ALCL exhibiting an aggressive clinical course. However, it remains potentially curable if diagnosed in a timely manner. We present the case of a 13-year-old boy with coexisting sickle cell trait and ALK-1 positive ALCL, who presented with recurrent fever, progressive weight loss, generalized lymphadenopathy, and severe anemia. Despite aggressive supportive therapy, he succumbed within 32 hours of admission. Postmortem examination revealed extensive lymph node infiltration by tumor cells and widespread multi-organ involvement. This case underscores the diagnostic challenges associated with ALK-1 positive ALCL, particularly in pediatric patients with underlying hematologic conditions, and raises the possibility of a potential association between ALK-1 positive ALCL and sickle cell trait.

Keywords: ALK-1 positive anaplastic large cell lymphoma, sickle cell trait, pediatric lymphoma, systemic ALCL

Introduction

Anaplastic large cell lymphoma (ALCL) is a rare and aggressive subtype of T-cell non-Hodgkin lymphoma, accounting for approximately 10–15% of pediatric lymphomas [1]. It is characterized by large, pleomorphic cells that strongly express CD30, a hallmark of the disease [2]. ALCL is classified into primary cutaneous ALCL, breast implant-associated ALCL (BIA-ALCL), and systemic ALCL, which is further divided into ALK-positive and ALK-negative subtypes based on the presence of an anaplastic lymphoma kinase (ALK) gene rearrangement. The ALK-positive variant is more common in children and young adults [3–5]. The disease typically presents with systemic symptoms such as fever, weight loss, night sweats, and lymphadenopathy, often involving extranodal sites. In advanced cases, bone marrow infiltration may occur, leading to anemia, pancytopenia, eosinophilia, and elevated lactate dehydrogenase (LDH) levels [6].

The relationship between ALCL and sickle cell trait has not been extensively studied. Sickle cell trait is traditionally considered a benign carrier state with minimal clinical implications. However, individuals with sickle cell trait may have an increased risk of certain complications, including thromboembolic events and pulmonary complications, which could potentially influence the progression of malignancies [7]. While sickle cell trait has been associated with an increased risk of ALK-rearranged renal cell carcinoma, its role in the pathogenesis or severity of ALK-positive ALCL remains unclear and warrants further investigation.

This case report describes the aggressive clinical course of ALK-positive ALCL in a child with sickle cell trait, highlighting the diagnostic challenges and rapid disease progression. By presenting this rare occurrence, our findings contribute to the existing literature on ALCL and emphasize the importance of maintaining a high index of suspicion for hematolymphoid neoplasms in individuals with sickle cell trait.

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Case Report

Clinical History

A 13-year-old boy with sickle cell trait presented with a five-month history of progressive abdominal and back pain, recurrent fever, weight loss, intermittent epistaxis, and generalized lymphadenopathy. He had undergone multiple outpatient evaluations where laboratory investigations were significant for elevated ESR (130 mm/hr), and chest X-ray showed hilar lymphadenopathy.

He was empirically started on anti-tuberculosis treatment two weeks prior to admission; however, his symptoms showed no improvement. On arrival at our facility, he appeared moderately pale, wasted, and was actively bleeding from the nose. He had generalized lymphadenopathy involving the cervical, axillary, and inguinal lymph nodes and was febrile (38.8 °C). A preliminary diagnosis of leukemia or lymphoma was considered, and he was initiated on intravenous piperacillin-tazobactam (100 mg/kg/dose), gentamicin (4 mg/kg/day), tranexamic acid, and a nasal pack with adrenaline.

Outcome

Within eight hours of admission, the patient's condition worsened, with a rising fever (39.8°C), increasing restlessness, and severe pallor. He developed respiratory distress with tachypnea (60 breaths per minute), tachycardia (160 beats per minute), and hypotension (88/38 mmHg). Despite aggressive management, including fluid resuscitation (20 mL/kg of normal saline) and transfusion of packed red blood cells (240 mL) and fresh frozen plasma (120 mL), his condition continued to deteriorate, necessitating inotropic support with a noradrenaline infusion (0.5 µg/kg/hr) and oxygen therapy. Laboratory investigations revealed leukocytosis (23.55 × 10^9/L), severe anemia (Hb 4.9 g/dL), and severe thrombocytopenia (38 × 10^9/L). Additionally, there was significant hyperbilirubinemia (99.2 µmol/L) and elevated aspartate aminotransferase (AST) levels (77 U/L) (Table 1). Despite intensive supportive care, the patient remained hemodynamically unstable and succumbed within 32 hours of admission.

Postmortem Findings

Autopsy was requested by the clinical team to ascertain the cause of death as a definitive diagnosis had not yet been established. Before death. Autopsy revealed marked wasting, severe mucosal pallor, generalized lymphadenopathy, and mild jaundice. Notably, there was no evidence of bleeding under the skin or from anybody orifices.

Internal examination showed enlarged mesenteric, para-aortic, and tracheobronchial lymph nodes with a fleshy cut surface (Fig. 1A & 1B). The largest lymph node (Mesenteric) measured 3.2 × 2.1 × 1.5 cm. Small tumor nodules were observed on the epicardium, aortic arch, and visceral pleura of both lungs. Additionally, multiple petechial hemorrhages were noted on the epicardium and pleural surfaces. The spleen and liver were congested, while the rest of the internal organs appeared grossly normal.

Histopathological examination revealed partial effacement of the lymph node architecture, with sheets of atypical lymphoid cells infiltrating the interfollicular T-zones and subcapsular sinuses. The tumor cells were predominantly large to medium-sized (Fig. 2). Characteristic hallmark cells with abundant eosinophilic cytoplasm, prominent Golgi zones, and nuclei displaying an embryo/kidney shape or wreath-like arrangement were observed, consistent with anaplastic large cell lymphoma (ALCL). Immunohistochemical analysis confirmed the diagnosis, with tumor cells expressing CD30, EMA, CD3, CD45, and ALK-1, while staining negative for CD20. The tumor exhibited a high proliferative index (80%) on Ki-67, further supporting a diagnosis of ALK-1 positive ALCL (Fig. 3).

The bone marrow was diffusely infiltrated by sheets of tumor cells with similar morphology. Multifocal tumor cell infiltrates were also detected in the lung parenchyma, the splenic white pulp, and the epicardium. The splenic red pulp displayed congested sinusoids with sickled red cells.

Given these findings, the cause of death in this adolescent was determined to be systemic ALK-positive anaplastic large cell lymphoma (ALK-positive ALCL) with extensive disease involvement.

Discussion

Anaplastic large cell lymphoma (ALCL) is an uncommon subtype of T-cell non-Hodgkin lymphoma (NHL), accounting for approximately 3% of adult NHLs and 10–15% of pediatric lymphomas [8, 9]. It is classified into ALK-positive and ALK-negative subtypes based on the expression of anaplastic lymphoma kinase (ALK), with ALK-positive ALCL primarily affecting children and young adults [10].

The clinical presentation of ALCL typically includes weight loss, fever, and night sweats. While enlarged, easily accessible peripheral lymph nodes can facilitate a prompt diagnosis, cases with a nonspecific presentation and hard to access lymph nodes pose a significant diagnostic challenge, often leading to delays [11]. In our patient, constitutional symptoms, lymphadenopathy, and multi-system involvement initially raised suspicion of an infectious etiology, particularly tuberculosis (TB), given its endemicity in sub-Saharan Africa. Misdiagnosis of ALCL as an infection has been reported in previous studies, with many patients receiving empirical treatment for infections before a definitive lymphoma diagnosis is established [12, 13]. The gold standard for diagnosing ALCL is an excision biopsy of the affected lymph node or tissue, followed by immunohistochemical analysis [14]. Other diagnostic modalities like peripheral blood smears commonly used in hematolymphoid neoplasms play a limited role in ALCL, as it rarely presents in a leukemic phase

The pathogenesis of ALK-positive ALCL is driven by chromosomal rearrangements involving the ALK gene, most commonly the t(2;5) (p23;q35) translocation, which results in the formation of the NPM1-ALK fusion protein [15]. This fusion protein activates multiple oncogenic pathways, including JAK/STAT3, PI3K/AKT, and MAPK, promoting cell proliferation, survival, and resistance to apoptosis [16]. The aggressive nature of ALK-positive ALCL is supported by the high proliferative index (>80%) observed in our patient, as determined by Ki-67 immunostaining [17]. Laboratory findings in ALK-positive ALCL typically include leukocytosis, anemia, thrombocytopenia, and elevated inflammatory markers, all of which were present in our case [18].

Postmortem examination revealed extensive lymphadenopathy, visceral organ infiltration, and disseminated tumor nodules, consistent with advanced-stage

ALCL [19]. Histopathological findings, including the presence of hallmark cells with eccentric nuclei and prominent Golgi zones, confirmed the diagnosis, in line with previous case reports [20].

Interestingly, genetic alterations involving the ALK gene have been identified in individuals with sickle cell trait. One notable example is the VCL-ALK fusion, associated with ALK-rearranged renal cell carcinoma, which results from a t(2;10) (p23; p22) translocation between the VCL (Vinculin) and ALK genes [21]. This fusion leads to the production of an oncogenic protein that drives tumor progression. However, no other ALK-related malignancies have been reported in individuals with sickle cell trait. A review of English literature found no previously documented cases of ALK-positive ALCL in individuals with sickle cell trait.

To our knowledge, this is the first reported case of ALK-positive ALCL in a patient with sickle cell trait. Our findings highlight the need for further next-generation sequencing (NGS) and cytogenetic studies to explore the role of ALK gene rearrangements in malignancies affecting individuals with sickle cell trait. Understanding these molecular mechanisms may provide new insights into the pathogenesis of ALCL and other ALK-related neoplasms in this unique population [22, 23].

Table 1: Laboratory findings from day one to day two

Parameter	Day 1 (Admission)	Day 1 (12 Hours)	Day 2	Normal Range
White Cell Count	17.93x10^9/L	23.55x10^9/L	18.69x10^9/L	3-15x10^9/L
Hemoglobin	5.1g/dL	4.9g/dL	5.6g/dL	11.5-17g/dL
Platelets	39x10^9/L	38x10^9/L	38x10^9/L	150-450x10^9/L
Neutrophils	14.98x10^9/L	18.2x10^9/L	13.81x10^9/L	1.5-7.0x10^9/L
Lymphocytes	2.21x10^9/L	4.14x10^9/L	3.87x10^9/L	1.0-3.7x10^9/L
Monocytes	0.72x10^9/L	1.17x10^9/L	0.97x10^9/L	0-0.7x10^9/L
ALT	--	--	Normal	up to 35U/L
AST	--	--	77U/L	up to 35U/L
Total Bilirubin	--	22.2umol/L	99.2umol/L	up to 17umol/L
Direct Bilirubin	--	15.4umol/L	70.1umol/L	up to 5.1umol/L
Albumin	--	25g/L	28g/L	38-54g/L
Protein	--	47g/L	54g/L	66-87g/L
Phosphate	--	2.1mmol/L	--	0.9-1.5mmol/L
Potassium	--	--	2.8mmol/L	3.1-5.1mmol/L
Uric Acid	--	--	36.2mg/L	up to 11.0mg/L

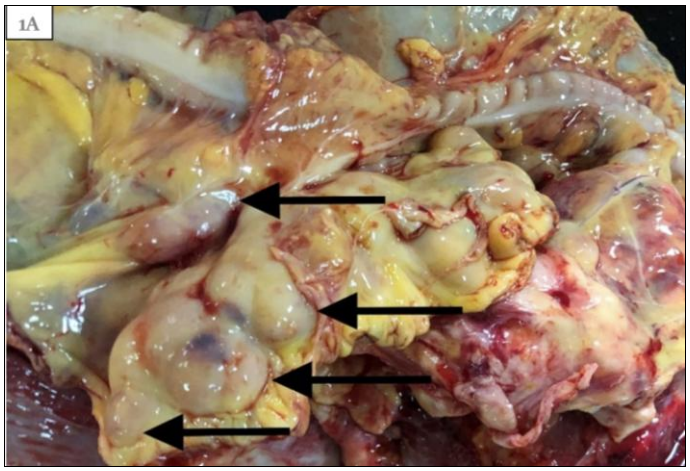

Fig 1A: Gross images of enlarged matted mesenteric lymph nodes noted at autopsy. The largest node measured 3.2x2.1x1.5cm.

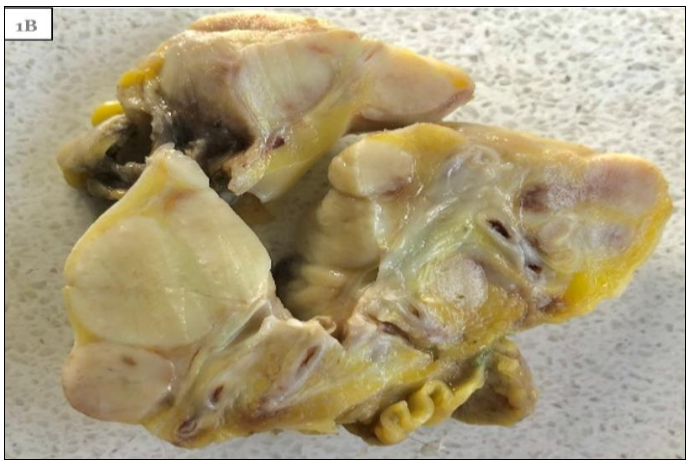

Fig 1B: Shows a fleshy cut surface of the mesenteric lymph nodes

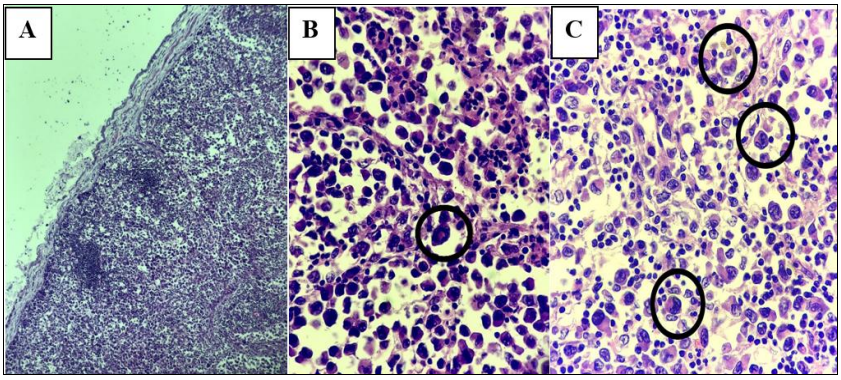

Fig 2: Histology from the mesenteric lymph nodes sampled at autopsy: A) diffuse sheets of atypical lymphoid cells infiltrating the interfollicular T-zones and subcapsular sinuses with partial preservation of the lymph node architecture. B) Hallmark cell with a wreath-like nucleus. C) Hallmark cells with embryo/kidney-shaped nuclei and prominent Golgi zones (Perinuclear eosinophilic regions)

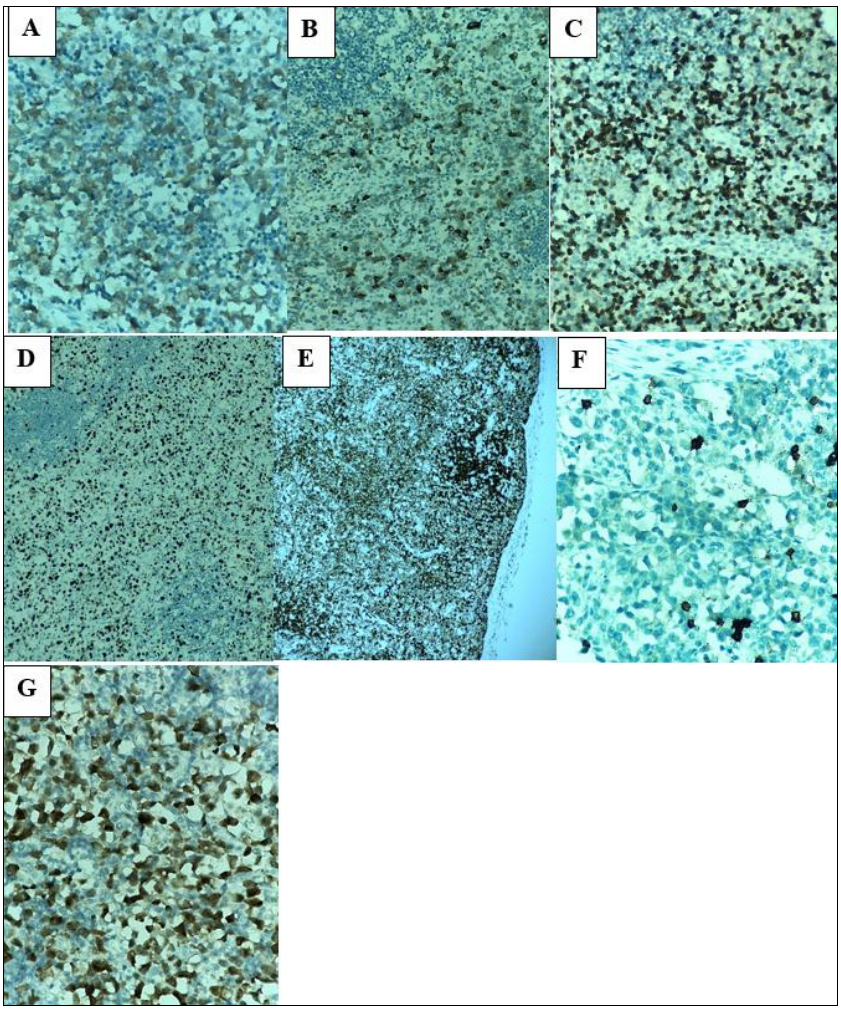

Fig 3: Immunohistochemistry. A) Neoplastic cells are positive for CD30 (X400). B) Neoplastic cells are positive for EMA (X200). C) Neoplastic cells are diffusely positive for CD3 (X200) D) High (>80%) proliferative index on ki-67 (X100). E) Neoplastic cells are positive for CD45 (X100). F) Neoplastic cells are negative for CD20 (X400). G) Neoplastic cells are diffusely and strongly positive for ALK-1.

Conclusion

This case highlights the aggressive nature of ALK-positive ALCL and the diagnostic challenges associated with its varied clinical presentation. The potential association between ALCL and sickle cell trait is intriguing and may provide novel insights into lymphoma pathogenesis. Early recognition, prompt diagnosis, and initiation of targeted therapies remain crucial in improving outcomes for patients with this rare but treatable malignancy.

Consent: The authors retain informed consent signed by the deceased's next of kin authorizing the data publication, and the manuscript is by the Institutional Ethics rules

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Data Availability: All data is available in hard copy and further information can be obtained from the corresponding author upon request.

Author Contributions

O.P. was responsible for conceptualization, methodology, investigation, and data curation. M.S. contributed to the methodology and performed the initial pathological diagnosis. B.M. performed literature review & drafted the manuscript. T.O., M.A., A.I., O.M., G.A., O.J.K., O.P.B., W.E., B.E., M.J.D., N.J., K.M., A.R., N.G., L.R., B.F., Y.M.., O.M., participated in manuscript review and methodology. T.A. performed the special stains. T.O., N.S. performed the surgery and removed the biopsy, and K.S. provided the final pathological diagnosis. All authors reviewed and approved the final manuscript.

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