

Anaplastic Large Cell Lymphoma: A Series of Four Cases

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ABSTRACT

Anaplastic Large Cell Lymphoma (ALCL) is a distinct subtype of mature T-cell lymphoma characterised by uniform and strong CD30 expression across all neoplastic cells, along with wide clinicopathological heterogeneity. It encompasses biologically and prognostically distinct subtypes, namely Anaplastic Lymphoma Kinase (ALK)-positive and ALK-negative ALCL, in addition to the primary cutaneous variant. Despite sharing certain morphological and immunophenotypic features, these subtypes differ considerably in their clinical behaviour, treatment response and overall prognosis. This case series aims to illustrate the diverse clinicopathological manifestations of ALCL encountered in routine diagnostic practice and to highlight the challenges faced in reaching a timely and accurate diagnosis. This retrospective case series includes four patients (3 males, 1 female) diagnosed with ALCL at a tertiary care Government Medical College Hospital over a defined study period. Clinical presentation, haematological and biochemical laboratory parameters, radiological findings, histopathological features and Immunohistochemistry (IHC) results were systematically analysed and documented. The patients ranged from eight to 63 years of age, reflecting the broad age distribution seen in ALCL. Clinical presentations were varied and included prolonged fever with bilateral cervical lymphadenopathy, enlarging soft-tissue swellings, non healing cutaneous ulcers and an ulceroproliferative lesion involving the lip. Extranodal involvement was a prominent feature in three out of four cases. Notably, one paediatric patient fulfilled the established diagnostic criteria for secondary Haemophagocytic Lymphohistiocytosis (HLH), an uncommon but life-threatening complication. Histopathological examination revealed variable morphology with sheets of large pleomorphic cells showing hallmark cell morphology in the majority of cases. On immunohistochemistry, all four cases demonstrated strong CD30 positivity; two cases were ALK-positive and two were ALK-negative. This series underscores the importance of maintaining a high index of suspicion for ALCL across diverse clinical scenarios and age groups and reiterates the indispensable role of integrated histopathological and immunohistochemical evaluation in establishing a definitive diagnosis. The novelty of the present case series is that it highlights the protean clinical and pathological manifestations of ALCL encountered in routine practice. The inclusion of an ALK-negative ALCL with retained CD3, CD5 and CD8 expression which is seen in less than 50% of ALK-negative ALCL, alongside cases with varied extranodal presentations and HLH-associated disease, underscores the diagnostic challenges posed by this lymphoma and emphasises the need for careful clinicopathological correlation and comprehensive immunohistochemical workup for accurate diagnosis. ALCL demonstrates marked clinicopathological heterogeneity and frequently masquerades as other disease entities. Adequate tissue sampling and immunohistochemistry are essential for early and accurate diagnosis.

Keywords: Anaplastic lymphoma kinase, Diagnostic challenge, Immunohistochemistry, Morphologic heterogeneity, T-cell lymphoma

INTRODUCTION

The ALCL comprises a distinct group of mature T-cell lymphomas characterised by strong and uniform CD30 expression and characteristic morphological features [1]. Globally, ALCL accounts for approximately 3% of all non-Hodgkin lymphomas and up to 10-15% of peripheral T-cell lymphomas, with a bimodal age distribution predominantly affecting children, adolescents and young adults [1,2]. The clinical presentation of ALCL ranges from lymphadenopathy and constitutional symptoms to predominant extranodal involvement involving skin, bone, lung and soft-tissue [2,3].

Recent advances in molecular pathology have clarified the pathogenetic mechanisms underlying ALCL. ALK-positive ALCL is characterised by chromosomal rearrangements involving the ALK gene on chromosome 2p23, most commonly the NPM1::ALK fusion, resulting in constitutive kinase activation. In contrast, ALK-negative ALCL demonstrates recurrent genetic alterations including Dual Specificity Phosphatase 22 (DUSP22) rearrangements and activation of the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signalling pathway [4]. ALK status carries significant prognostic implications: ALK-positive ALCL is associated with a more favourable prognosis (5-year survival rate approximates 80%) compared to ALK-negative ALCL (approximately 50%) [5].

Current classifications, including the 2022 World Health Organisation framework, recognise four major entities: ALK-positive ALCL, ALK-negative ALCL, primary cutaneous ALCL and breast implant-associated ALCL [5]. The diagnosis of ALCL rests on careful histomorphological evaluation supported by a comprehensive immunohistochemical panel. Extranodal presentations may clinically mimic inflammatory conditions, infections, or epithelial malignancies, leading to diagnostic delay [6]. Targeted therapy incorporating brentuximab vedotin has improved outcomes particularly in paediatric ALK-positive ALCL [7].

The following case series highlights four diagnostically challenging cases of ALCL with diverse extranodal manifestations, underscoring the critical role of integrated clinicopathological assessment and comprehensive immunohistochemical evaluation in establishing an accurate diagnosis and guiding appropriate management.

CASE SERIES

Case 1

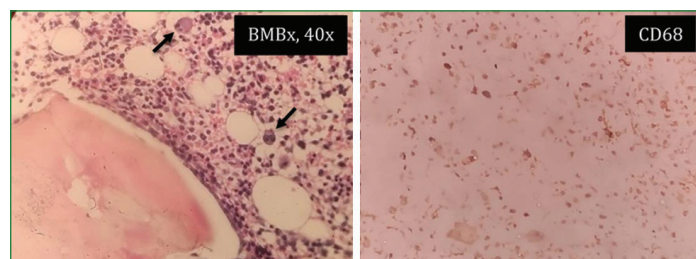
A 10-year-old female child presented with complaints of fever for one month, which was high grade and intermittent, not associated with chills or rigours and partially relieved with medications. She also

had a history of bilateral cervical lymphadenopathy of one-month duration, insidious in onset and gradually progressive, without associated breathing or swallowing difficulty.

There was a significant history of vesicles in the skin that initially appeared on the face and subsequently progressed to involve the neck, trunk and upper and lower limbs, sparing the palms and soles. At presentation, the lesions were in the healing stage. The patient also had a history of productive cough.

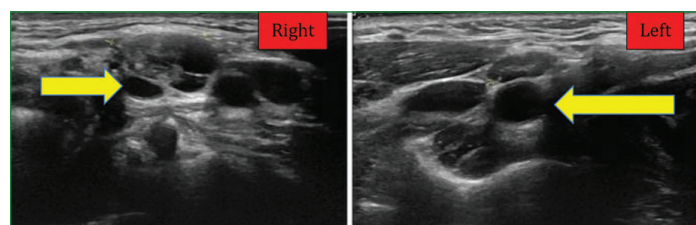
The patient had been previously admitted to another Government Medical College hospital and was referred due to persistent high fever spikes. Laboratory investigations revealed elevated inflammatory markers with Lactate Dehydrogenase (LDH) of 562 U/L (normal range: 100-330 U/L), ferritin of 3792 ng/mL (normal range: 7-140 ng/mL), C-Reactive Protein (CRP) of 48.4 mg/L (normal range: <8 mg/L) and triglycerides of 338 mg/dL (normal range: <130 mg/dL). Complete blood count and peripheral smear showed pancytopenia. These laboratory findings, in conjunction with bone marrow evidence of haemophagocytosis, fulfilled the HLH-2004 diagnostic criteria, confirming secondary HLH [8]. Serological tests for Hepatitis B Surface Antigen (HBsAg), Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Widal test and tropical infections were negative. Mycobacterium tuberculosis was not detected on Cartridge-Based Nucleic Acid Amplification Test (CBNAAT). Blood culture showed no growth.

Bone marrow aspiration and biopsy showed normocellular marrow with increased number of marrow macrophages demonstrating phagocytosis of haematopoietic elements. Immunohistochemistry in bone marrow biopsy revealed cytoplasmic positivity for CD68 in macrophages exhibiting haemophagocytosis [Table/Fig-1a,b]. No lymphomatous infiltration was identified in the bone marrow. Based on radiological, laboratory and bone marrow findings, this patient was staged as Ann Arbor stage III, with bilateral nodal involvement on both sides of the diaphragm (cervical and hilar nodes). Hepatosplenomegaly with ascites was documented on imaging; however, tissue confirmation of hepatic or splenic infiltration was not performed and reactive organomegaly secondary to HLH could not be excluded. Pericardial effusion cytology was not performed and reactive effusion could not be ruled out.



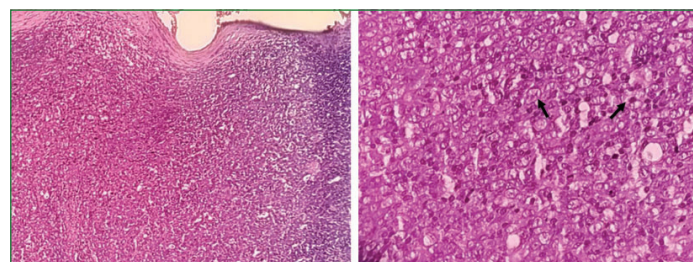
[Table/Fig-1]: a) Bone marrow biopsy showing haemophagocytosis by macrophages (black arrows); and b) Increase in macrophages as demonstrated by cytoplasmic positivity for CD68.

Ultrasonography (USG) of the neck showed left level V lymph nodes measuring 2.4×1.5 cm with necrotic areas and multiple enlarged bilateral level II, III and IV lymph nodes [Table/Fig-2]. Ultrasonography of the abdomen and pelvis revealed mild hepatosplenomegaly with mild ascites. Echocardiography showed trivial pericardial effusion. CT chest demonstrated bronchial wall thickening in the right perihilar region and hilar node enlargement.

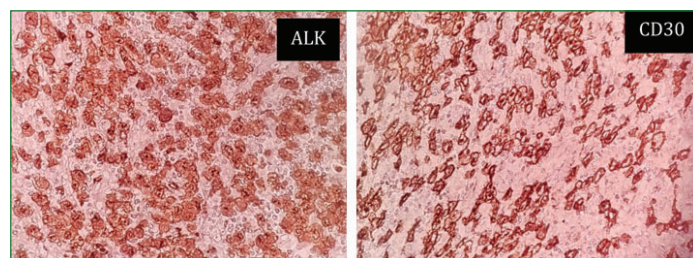


[Table/Fig-2]: Ultrasonogram of cervical nodes showing bilateral lymphadenopathy.

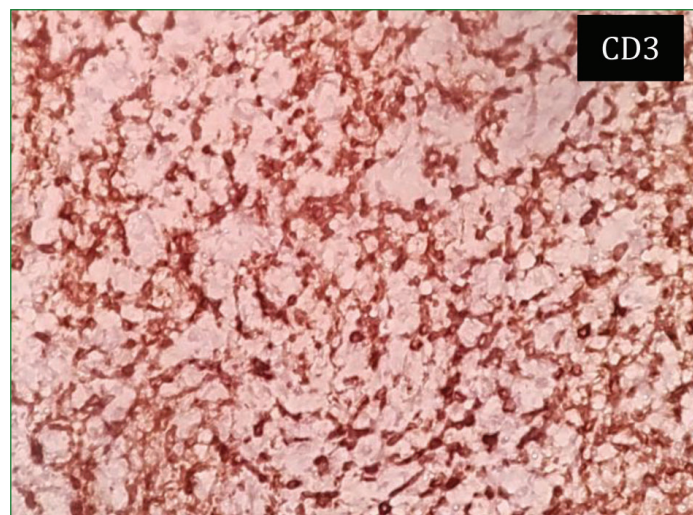
Fine Needle Aspiration Cytology (FNAC) of the cervical lymph node was not performed. Lymph node biopsy revealed effacement of architecture by sheets of large atypical cells having moderate eosinophilic cytoplasm and large round vesicular nuclei with prominent nucleoli. Hallmark cells with abundant cytoplasm and horseshoe-shaped nuclei were also identified. Immunohistochemistry revealed diffuse strong membranous positivity for CD30 in more than 80% of tumour cells. ALK showed diffuse strong nuclear and cytoplasmic positivity (consistent with NPM1::ALK pattern) in more than 80% of tumour cells. CD3 showed diffuse positivity in large cells favouring T-cell lineage [Table/Fig-3-5]. CD20 and panCK were negative, ruling out B-cell neoplasm and epithelial malignancy respectively. PAX5 and CD15 were negative in tumour cells. PAX5 and CD15 negativity, along with Diffuse CD30 positivity in tumour cells ruled out Hodgkin lymphoma and diffuse large B-cell lymphoma. Absence of necrosis and mixed inflammatory infiltrates ruled out Kikuchi disease and infective lymphadenitis, respectively. As the presence of large pleomorphic cells admixed with hallmark cells, diffuse and strong positivity of tumour cells for CD30 and ALK fulfills the essential criteria for diagnosis of ALK positive ALCL [5], additional IHC markers including Epithelial Membrane Antigen (EMA), Cluster of Differentiation 4 (CD4), Cluster of Differentiation 8 (CD8), Cluster of Differentiation 43 (CD43), T-cell Intracellular Antigen-1 (TIA-1), Granzyme B, and Ki-67 Proliferation Marker (Ki-67) were not performed in the present case. Fluorescence In Situ Hybridisation (FISH) for the Nucleophosmin 1 (NPM1):ALK fusion was not performed; this is acknowledged as a limitation.



[Table/Fig-3]: Section shows sheets of large cells showing atypia and prominent nucleoli (black arrows) (H&E, 10x & 40x, respectively) Images from left to right.



[Table/Fig-4]: Immunohistochemistry showing positivity for: a) ALK; and b) CD30 (10x, IHC).



[Table/Fig-5]: Immunohistochemistry showing CD3 positivity in tumour cells (IHC, 10x).

Final Diagnosis was given as ALK-positive ALCL.

The patient was given induction chemotherapy according to ALCL-99 protocol, comprising cyclophosphamide, vincristine and methotrexate, for a period of three days. On day 4, despite intensive treatment measures, the child succumbed to illness.

Case 2

An eight-year-old male child presented with a single swelling over the right shoulder region since the past two months which was insidious in onset and progressively increased in size. The swellings were progressively increasing in size. Local examination revealed a fluctuant swelling of size 8×7 cm was present in the right scapular region, associated with tenderness.

Provisional differential diagnoses considered at presentation included cold abscess (tuberculous origin), soft-tissue sarcoma and lymphoma.

Complete blood count was normal. Mantoux turned out to be negative. Ultrasonogram of right supra scapular region revealed a hypoechoic lesion in the subcutaneous and intramuscular plane [Table/Fig-6]. Magnetic Resonance Imaging (MRI) of right shoulder region revealed T2-weighted/Short Tau Inversion Recovery (T2/STIR) hyperintensity lesions in right back in the subcutaneous plane, intramuscular plane involving latissimus dorsi muscle and in the medial aspect of left thigh [Table/Fig-7].



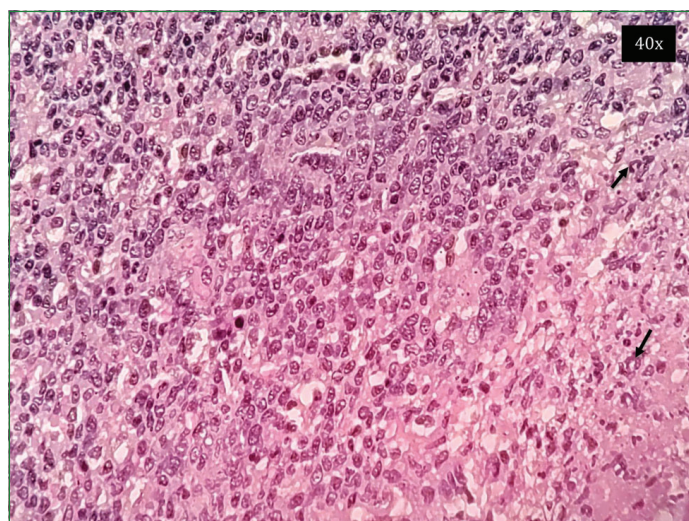
[Table/Fig-6]: USG showing right shoulder swelling abscess (yellow arrow).



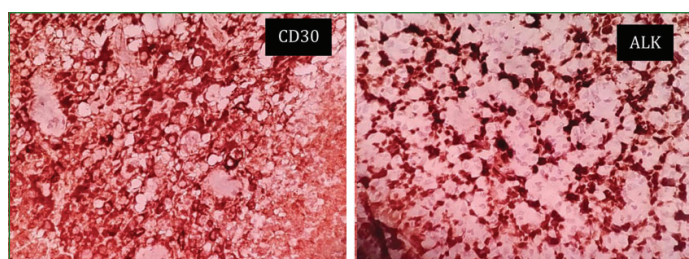
[Table/Fig-7]: MRI showing right shoulder swelling abscess (yellow arrow).

Histopathological examination of the excision biopsy from the shoulder swelling showed a malignant neoplasm composed of sheets of medium to large atypical cells with predominantly pleomorphic nuclei with occasional round forms. Some of the large cells showed abundant cytoplasm with horseshoe-shaped nuclei (hallmark cells) [Table/Fig-8]. Also seen are areas of neutrophilic infiltrates, increased apoptosis with nuclear dust and extensive necrosis. Two to three mitotic figures per five high power field. Ki67 proliferation index was 50-60%. Immunohistochemistry revealed strong diffuse membranous positivity for CD30 in more than 90% tumour cells and diffuse strong nuclear positivity for ALK in more than 80% tumour cells [Table/Fig-9], diffuse membranous positivity

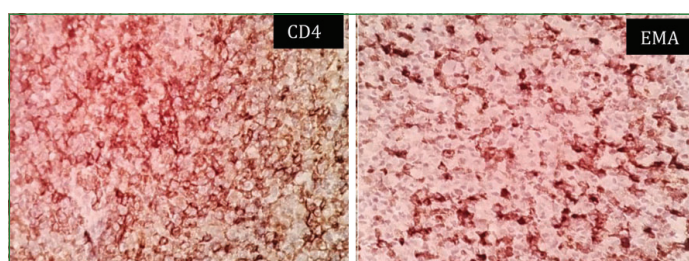
for CD4 and EMA in more than 70% of tumour cells [Table/Fig-10]. CD5 was also focally positive [Table/Fig-11]. CD3, CD2 and CD7 were negative. As the presence of hallmark cells with strong and diffuse positivity of tumour cells for CD30 and ALK fulfills the essential criteria WHO 2022 classification of haematolymphoid tumours) for diagnosis of ALK positive ALCL, Cytotoxic markers TIA-1, granzyme B and perforin were not done. IHC for Tdt and CD34 were negative and hence lymphoblastic lymphoma was ruled out.



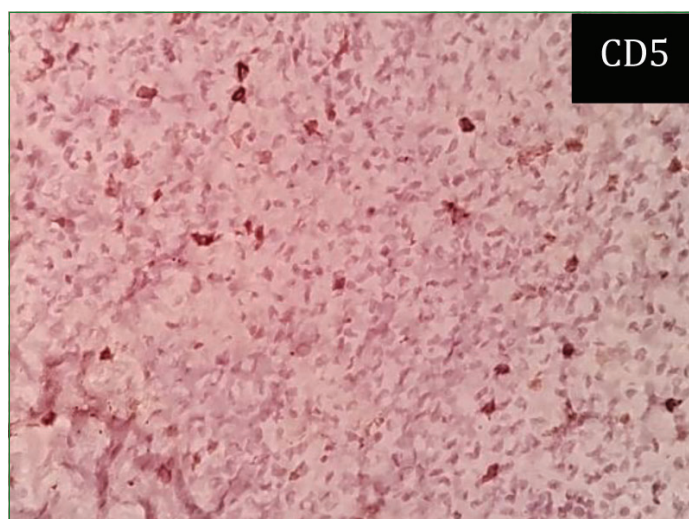
[Table/Fig-8]: Histopathological section showing sheets of medium to large atypical cells with round to pleomorphic nuclei. Some cells show horseshoe-shaped nuclei (H&E, 40x) (black arrows).



[Table/Fig-9]: IHC for CD30 and ALK showing strong positivity (H&E, 10x).



[Table/Fig-10]: IHC for CD4 and EMA showing diffuse positivity (H&E, 10x).



[Table/Fig-11]: IHC for CD5 showing scattered focal positivity (H&E, 10x).

Final Diagnosis was given as ALK-positive ALCL

The patient was started on chemotherapy based on ALCL-99 protocol. During the pre-phase, Dexamethasone is administered from days 1 to 5, followed by Cyclophosphamide on days 1 and 2 and Triple intrathecal therapy on day 1.

The AM courses (AM1, AM2, AM3) each consist of Dexamethasone from days 1 to 5, Methotrexate on day 1 at 3 g/m² infused over three hours with Folinic acid rescue, an intrathecal injection on day 1, Ifosfamide from days 1 to 5 with Mesna cover and Cytarabine along with Etoposide administered on days 4 and 5.

The BM courses (BM1, BM2, BM3) each consist of Dexamethasone from days 1 to 5, Methotrexate on day 1 with Folinic acid rescue, Cyclophosphamide from days 1 to 5 and Doxorubicin on days 4 and 5. After induction, the child received maintenance therapy. The child is on regular follow-up and remains recurrence-free at one year of follow-up [Table/Fig-12].



[Table/Fig-12]: Intra-op and post-chemotherapy images showing involvement of deeper tissues and resolution after chemotherapy, respectively.

Case 3

A 10-year-old boy presented with an ulcer over the right-side of the neck of two weeks' duration. The lesion initially started as a small swelling which subsequently ulcerated and accompanied by bleeding. There was a history of night sweats and evening rise of temperature. The clinical differential diagnoses considered at presentation included tuberculosis of the lymph node with collateral skin ulceration, cutaneous leishmaniasis and a malignant ulcer. Local examination revealed an ulcer measuring 2×2 cm in size, with raised and indurated edge, central umbilication, floor covered with granulation tissue and a non indurated base [Table/Fig-13].

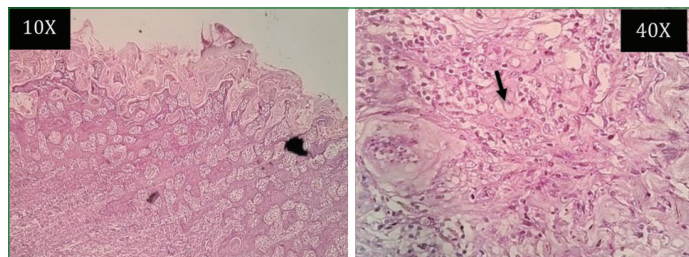


[Table/Fig-13]: Image shows a non healing ulcer with everted edges.

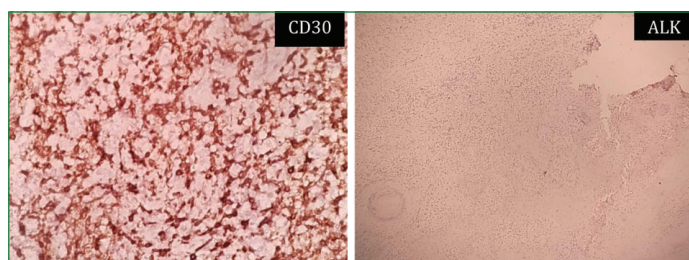
Ultrasonogram abdomen and x-ray chest revealed no abnormality. Mantoux was negative.

Wedge biopsy from the ulcer edge showed epidermis exhibiting epithelial hyperplasia with underlying dermis infiltrated by sheets of round to oval cells with moderate eosinophilic cytoplasm having vesicular nuclei and prominent nucleoli [Table/Fig-14]. Immunohistochemical analysis revealed diffuse strong membranous

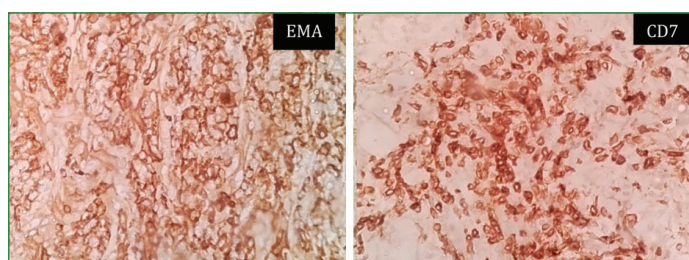
positivity for CD30 and CD7 in more than 70% of tumour cells, focal positivity for EMA and CD5, with IHC for ALK was negative. Ki 67 was positive in more than 60% tumour cells [Table/Fig-15,16]. This immunoprofile was consistent with Alk-negative ALCL. CD5 was scattered positive [Table/Fig-17]. Also, IHC for SALL4, CD20, CK5/6 were all negative ruling out germ cell tumour, b cell lymphoma and epithelial malignancy respectively.



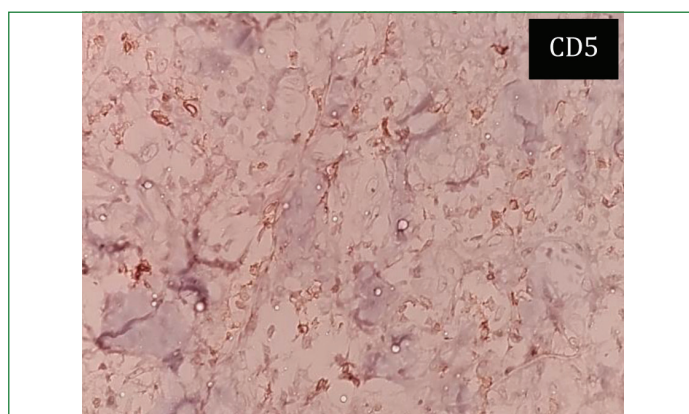
[Table/Fig-14]: Histopathological section showing skin with epidermis, with dermal infiltrates of round to oval cells with moderate eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli (H&E, 10x).



[Table/Fig-15]: IHC showing CD30 positivity and Alk-negative (H&E, 10x).



[Table/Fig-16]: IHC showing EMA and CD7 positivity (H&E, 10x).



[Table/Fig-17]: IHC showing scattered CD5 positivity in tumour cells.

Final diagnosis was given as ALK-negative ALCL.

The patient was started on chemotherapy based on ALCL-99 protocol. During the pre-phase, Dexamethasone is administered from days 1 to 5, followed by Cyclophosphamide on days 1 and 2 and Triple intrathecal therapy on day 1.

The AM courses (AM1, AM2, AM3) each consist of Dexamethasone from days 1 to 5, Methotrexate on day 1 at 3 g/m² infused over three hours with Folinic acid rescue, an intrathecal injection on day 1, Ifosfamide from days 1 to 5 with Mesna cover and Cytarabine along with Etoposide administered on days 4 and 5.

The BM courses (BM1, BM2, BM3) each consist of Dexamethasone from days 1 to 5, Methotrexate on day 1 with Folinic acid rescue,

Cyclophosphamide from days 1 to 5 and Doxorubicin on days 4 and 5. After induction, the child received maintenance therapy. The child is followed-up till date for a period of three years and is recurrence free.

Case 4

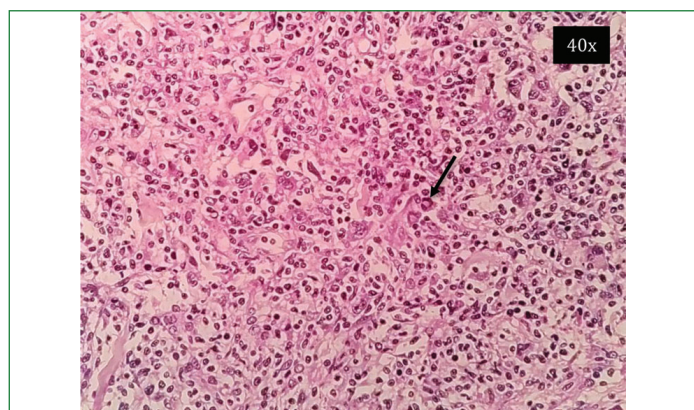
A 63-year-old male patient presented with an ulceroproliferative lesion over the right upper lip which started as a slowly progressive swelling over the right upper lip of three months duration, which had subsequently ulcerated over the past six weeks. He reported associated pain, bleeding on touch and difficulty in eating. There was no history of fever, weight loss, or night sweats. He had no significant past medical history and was not on any long-term medications. He was a chronic beedi smoker with a 30 pack-year history, though no tobacco chewing habit was reported.

Local examination revealed a 3x2.5 cm ulceroproliferative lesion on the right-side of the upper lip, with irregular everted edges, an indurated base and a necrotic slough-covered center [Table/Fig-18]. The lesion bled on probing. The lesion was initially assessed at an outside institution prior to referral.



[Table/Fig-18]: Image showing ulceroproliferative lesion in the right-side of upper lip.

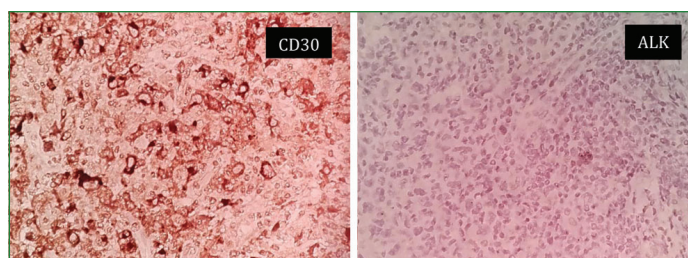
On review and opinion at the present study Institute, histopathological examination revealed sheets of pleomorphic cells with predominantly pleomorphic nuclei and occasional round forms [Table/Fig-19]. Immunohistochemistry demonstrated diffuse strong membranous positivity for CD30 and positivity for CD3, CD4, CD5, CD8, EMA with negative staining for ALK favouring diagnosis of ALK-negative ALCL [Table/Fig-20-22]. Pax5 was negative ruling out Hodgkin lymphoma. CD30 showed strong and scattered positivity in reed Sternberg cells in Hodgkin lymphoma, whereas it is strong and diffuse positive in ALCL. It is noteworthy that CD3, CD5 positivity are seen in <50% of ALK-negative ALCL and CD8 positivity is rarely observed [5].



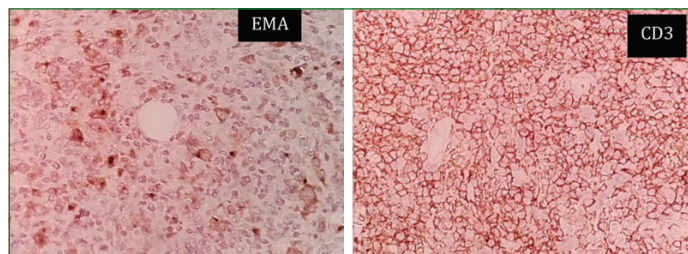
[Table/Fig-19]: Histopathological section shows sheets of large pleomorphic cells with hallmark cells (H&E, 40x) (black arrow).

Final diagnosis was given as ALK-negative ALCL.

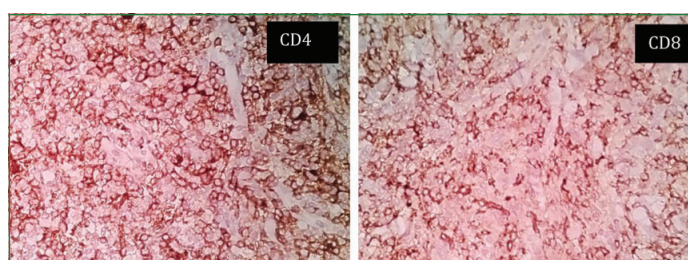
The patient was started on chemotherapy based on ALCL-99 protocol. During the pre-phase, Dexamethasone is administered from days 1 to 5, followed by Cyclophosphamide on days 1 and 2 and triple intrathecal therapy on day 1.



[Table/Fig-20]: IHC for CD30 showing strong positivity. IHC for ALK was negative (H&E, 10x).



[Table/Fig-21]: IHC for EMA and CD3 showing strong positivity (H&E, 10x).



[Table/Fig-22]: IHC for CD4 and CD8 showing positivity in tumour cells (H&E, 10x).

The AM courses (AM1, AM2, AM3) each consist of Dexamethasone from days 1 to 5, Methotrexate on day 1 at 3 g/m² infused over three hours with Folinic acid rescue, an intrathecal injection on day 1, Ifosfamide from days 1 to 5 with Mesna cover and Cytarabine along with Etoposide administered on days 4 and 5.

The BM courses (BM1, BM2, BM3) each consist of Dexamethasone from days 1 to 5, Methotrexate on day 1 with Folinic acid rescue, Cyclophosphamide from days 1 to 5 and Doxorubicin on days 4 and 5. After induction, the patient received maintenance therapy. The patient is on regular up till date for a period of about eight months.

Currently, patient is recurrence free. All four cases have been summarised in [Table/Fig-23].

DISCUSSION

The ALCL is a diagnostically challenging peripheral [9] T-cell lymphoma due to its morphological diversity and variable clinical manifestations. Unusual histological variants, including clear cell morphology, further expand its spectrum [10].

The pathogenesis of ALCL is driven by genetic alterations that activate oncogenic signalling pathways, leading to uncontrolled proliferation and survival of neoplastic T cells. ALK rearrangements involve over 20 distinct partner genes, with NPM1 being the most frequently encountered. The recurrent t(2;5)(p23;q35) translocation results in formation of the NPM1::ALK fusion protein, which is aberrantly expressed. Most ALK-negative ALCLs exhibit clonal TR gene rearrangements. Activating mutations of JAK1 and STAT3, as well as oncogenic tyrosine kinase fusions unrelated to ALK, contribute to persistent STAT3 pathway activation. DUSP22 rearrangements are present in 20-30% of cases, whereas TP63 rearrangements, usually involving Transducin Beta-Like 1 X-Linked Receptor 1 (TBL1XR1) through a 3q28 inversion, occur in approximately 5%. About 30% of cases show copy-number abnormalities, including TP53 loss due to deletion of 17p13. Gene expression studies indicate that ALK-ALCL shares some molecular characteristics with ALK+ ALCL but remains biologically distinct from Peripheral T-cell Lymphoma-Not Otherwise Specified (PTCL-NOS) [10].

Case	Age/Sex	Presentation	Site of biopsy	Imaging	Histopathology	IHC profile	Treatment and outcome
1	10y/F	Fever, bilateral cervical lymphadenopathy, vesicles/bullae (healed), productive cough, secondary HLH	Left level V cervical lymph node	USG neck: bilateral necrotic nodal enlargement; CT chest: bronchial wall thickening, hilar nodes; Echo: pericardial effusion	Sheets of large atypical cells with moderate eosinophilic cytoplasm, large round vesicular nuclei, prominent nucleoli; hallmark cells	CD30+, ALK+ (nuclear and cytoplasmic), CD3+; CD20–, panCK–. FISH/ NPM1::ALK not done.	ALCL-99 Protocol regimen-based induction (cyclophosphamide, vincristine, methotrexate); patient succumbed despite treatment
2	8y/M	Single fluctuant swelling right scapular region (8×7 cm), 2-month duration, tenderness	Right scapular region excision biopsy	USG: hypoechoic lesion subcutaneous and intramuscular; MRI right shoulder region: T2/STIR hyperintensity right back subcutaneous and intramuscular (latissimus dorsi) and medial left thigh	Sheets of medium to large atypical cells with predominantly pleomorphic nuclei with occasional round forms; abundant cytoplasm; hallmark cells; increased apoptosis; extensive necrosis	CD30+ (>90%), ALK+ nuclear (>80%), CD4+, EMA+; TdT–, CD34–	ALCL-99 Protocol regimen, RECURRENCE FREE AT 1 YEAR OF follow-up
3	10y/M	Non healing ulcer right-side of neck, 2-week duration; night sweats, evening rise of temperature	Wedge biopsy from ulcer edge	USG abdomen and X-ray chest: no abnormality detected; Mantoux negative	Epithelial hyperplasia overlying dermis infiltrated by sheets of round to oval cells with moderate eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli	CD30+ (>70%), CD7+, EMA focal+, CD5 focal+; ALK–; Ki67 >60%; SALL4–, CD20–, CK5/6–	ALCL-99 Protocol regimen, RECURRENCE FREE AT 3 YEARS OF follow-up
4	63y/M	Ulceroproliferative lesion over right upper lip; duration- 3 months, ulceration- 6 weeks duration; referred from outside institution	Right upper lip biopsy	Not performed at the present study Institute (outside referral)	Sheets of pleomorphic cells with predominantly pleomorphic nuclei with occasional round forms; hallmark cells present	CD30+ (diffuse strong membranous), EMA+, CD3+, CD4+; ALK–; PAX5–, CD5+, CD8+ (note: CD3, 5, 8 are typically negative or lost in ALCL — clinical context required)	ALCL-99 Protocol regimen, on regular follow-up and is recurrence free at 8 months of follow-up

[Table/Fig-23]: Summary of present cases.

Author and Year	Age/Sex	Clinical features	Site of biopsy	Radiological findings	Histopathological findings	IHC
Miranda JA et al., 2023 [2]	67 y/F	Rapidly growing painful ulcerated lesion on back	Ulcer from back	USG soft-tissue: nodular mass with cystic/necrotic areas	Dermal perivascular infiltration of large atypical lymphoid cells extending into subcutaneous fat	CD30+; ALK–
Lozano-Jaramillo DA et al., 2023 [6]	12 y/M	Pain, paresthesia and limitation of movement in right lower extremity	Pelvic mass	CT abdomen: pelvic mass in right ilio-psoas region with multiple nodal enlargement	Small round blue cell tumours	CD30+; ALK+
Sharma A et al., 2024 [9]	22 y/M	Painless erythematous noduloplaque on chest wall, ulcerated within a month	Exophytic ulcerated lesion on chest wall	X-ray chest: normal	Dermal infiltrates of sheets of atypical large lymphoid cells with pleomorphic hyperchromatic nuclei, irregular nuclear membrane and moderate to abundant clear cytoplasm	CD30+; ALK-
Ahuja R et al., 2023 [12]	48 y/M	Asymptomatic erythematous nodules in left arm and chest	Erythematous nodule on chest	—	Diffuse dermal infiltrates of atypical intermediate to large lymphocytes with prominent nucleoli, frequent mitotic activity and apoptosis mixed with mature lymphocytes	CD30+; ALK-

[Table/Fig-24]: Comparison with published literature [2,6,9,12].

In the present series, ALK-positive ALCL was observed predominantly in paediatric patients, whereas adult cases were ALK-negative. This age-related distribution aligns with previously reported prognostic stratification, wherein ALK-positive disease generally demonstrates a more favourable outcome compared to ALK-negative ALCL, with 5-year overall survival rates of approximately 80% and 50%, respectively [11]. The molecular basis of this prognostic difference lies in constitutive ALK kinase activation driving oncogenesis in ALK-positive disease, which is targetable with brentuximab vedotin in combination with standard chemotherapy.

Cutaneous and extranodal presentations frequently mimic inflammatory or infectious conditions. Zosteriform nodules, ulcerative lesions and inflammatory-appearing masses have been described in systemic ALK-negative ALCL [12].

Histomorphologically, sheets of large pleomorphic cells with hallmark cells, frequent mitoses and extensive apoptosis represent classic features of ALCL and have been consistently described across both large reviews and individual case reports [13,14]. Radiological-pathological correlation was achieved in the present cases: USG-guided identification of necrotic lymph nodes in Case 1 and MRI-defined intramuscular extension in Case 2 directed appropriate biopsy sites, reinforcing the role of imaging in surgical planning. Present case has been compared with published literature in [Table/Fig-24] [2,6,9,12].

Ulcerative facial and soft-tissue masses similar to those observed in cases 3 and 4 have been reported and are often initially misdiagnosed as epithelial malignancies or chronic inflammatory lesions [15]. Rare ALK-negative variants with distinctive immunophenotypic features have also been documented, underscoring the need for careful immunohistochemical interpretation [16].

The differential diagnosis of ALCL is broad and must be approached systematically, with careful attention to ALK status, site of disease and the clinical context, as misclassification carries significant therapeutic implications.

For ALK-positive ALCL, confirmation of ALK expression by immunohistochemistry alone is insufficient for diagnosis, since several non T-cell neoplasms can aberrantly express ALK. These include ALK-positive large B-cell lymphoma, inflammatory myofibroblastic tumour, carcinomas, particularly lung carcinoma and rare ALK-positive histiocytoses. Unlike ALK-positive ALCL, these entities characteristically lack hallmark cells and are typically CD30-negative, though exceptions exist. ALK-positive large B-cell lymphoma deserves special mention, as it may completely downregulate B-cell lineage markers while co-expressing EMA and ALK, creating a phenotypic profile indistinguishable from ALCL without a comprehensive immunohistochemical panel. The morphological variants of ALK-positive ALCL further compound

diagnostic difficulty, the small cell variant, in which hallmark cells are scarce and CD30 expression can be focal or weak and the lymphohistiocytic variant, where abundant reactive histiocytes mask the neoplastic population, are both frequently mistaken for PTCL-NOS at nodal sites. Extranodal involvement, most commonly of the skin, soft-tissues and bone, is characteristic of ALK-positive ALCL and is proportionally more frequent than in its ALK-negative counterpart; cutaneous involvement by systemic disease must be distinguished from primary cutaneous T-cell neoplasms that may aberrantly express ALK [17].

For ALK-negative ALCL, the diagnostic boundaries are less sharply defined and the most clinically relevant distinction is from CD30-positive PTCL-NOS. Both entities present predominantly with nodal disease in adults, often with advanced-stage involvement. In favour of ALK-negative ALCL are the presence of hallmark cells, a cohesive or sinusoidal growth pattern, strong and uniform CD30 expression with the characteristic membranous and Golgi pattern and frequent loss of pan-T-cell antigens. PTCL-NOS, by contrast, tend to show variable CD30 expression and retained T-cell antigen expression including TCR proteins. Supporting markers such as clusterin, EMA and cytotoxic markers may help, though their absence does not exclude ALCL- particularly in cases harbouring DUSP22 rearrangements, which typically lack cytotoxic marker expression but carry a favourable prognosis. The further distinction from nodular sclerosis classical Hodgkin lymphoma represents another significant pitfall at nodal sites, as both entities may co-express CD30 and CD15 with variable T-cell antigen loss. In this context, markers such as CD43, clusterin and EMA favour ALCL, while {Epstein-Barr virus-encoded small Ribonucleic Acid (RNA) (EBER)} positivity strongly supports CHL. An equally treacherous overlap occurs in extranodal settings, where loss of T-cell antigens combined with sinusoidal growth and occasional aberrant cytokeratin expression- as seen with Anti-cytokeratin antibody cocktail AE1/AE3 (AE1/AE3) can lead to misdiagnosis as metastatic carcinoma, particularly in soft-tissue or bone biopsies [17].

For primary cutaneous ALCL (pcALCL), the central diagnostic challenge lies not in identifying the neoplasm, but in correctly establishing its localised nature. The morphology and immunophenotype of pcALCL are essentially identical to those of cutaneous involvement by systemic ALCL and morphological or immunohistochemical criteria alone cannot reliably distinguish the two. Within the spectrum of primary cutaneous CD30-positive T-cell lymphoproliferative disorders, pcALCL must be differentiated from LyP, particularly type C, which can show identical histology; clinical parameters- notably lesion size, spontaneous regression and disease chronicity are the deciding factors. Accurate clinicopathological correlation and thorough clinical staging, including Positron Emission Tomography (PET) scan and bone marrow evaluation, are therefore indispensable before rendering a diagnosis of pcALCL, as systemic ALCL with cutaneous involvement would mandate aggressive systemic chemotherapy rather than the conservative local approach appropriate for the localised primary cutaneous form. This distinction carries direct prognostic and therapeutic consequences that underscore the critical importance of integrating pathological findings with clinical history in every case [17].

Overall, the findings are concordant with previously published literature and reinforce the necessity of adequate tissue sampling, careful morphological evaluation and comprehensive immunohistochemistry in suspected cases of ALCL. The present case series contributes to the literature by illustrating the spectrum of ALCL presentations in a resource-limited tertiary

care setting and highlights the diagnostic pitfalls encountered in routine practice. Key learning points include: (a) secondary HLH may be the presenting manifestation of ALCL in the paediatric age group and should prompt urgent lymphoma workup; (b) extranodal ALCL can mimic tuberculosis, soft-tissue tumours and metastatic carcinoma; and (c) ALK status remains the single most important prognostic marker and must be documented in all cases of ALCL.

CONCLUSION(S)

The ALCL poses a significant diagnostic challenge due to its broad clinical spectrum and histomorphological diversity, necessitating a high-index of clinical suspicion. Histopathology supported by comprehensive immunohistochemistry remains the diagnostic cornerstone. Early recognition and accurate subclassification based on ALK status are crucial for guiding therapy and improving patient outcomes. Secondary HLH as a presenting feature of paediatric ALCL and extranodal involvement mimicking common benign conditions are important learning points highlighted by the present case series.

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