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DECODING ANAPLASTIC LARGE CELL LYMPHOMA : A CLINICO-PATHOLOGICAL STUDY ON HISTOLOGICAL PATTERNS AND OUTCOMES

Oncopathology

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ABSTRACT

Anaplastic large cell lymphoma (ALCL) is a rare and heterogeneous T-cell lymphoma characterized by CD30 expression and variable ALK status. This retrospective study analyzed 60 systemic ALCL cases diagnosed over a 5.5-year period, focusing on demographic, morphological, immunohistochemical, and prognostic parameters. The cohort showed a slight adult predominance and a male-to-female ratio of 2:1. ALK positivity was seen in 78.3% of cases and was significantly associated with younger age. Histologically, the common subtype was most frequent, with a substantial proportion displaying small cell, lymphohistiocytic, or composite variants, which often demonstrated aberrant immunophenotypes. Although ALK-positive and early-stage cases showed better survival trends, no parameter was statistically significant in predicting overall survival. The median survival was six months. Findings highlight the diagnostic complexity of ALCL and the importance of comprehensive immunohistochemistry. Incorporating molecular prognostic markers such as minimal disseminated disease (MDD) and ALK antibody titers could improve risk stratification and guide therapy in future studies.

KEYWORDS

Anaplastic large cell lymphoma, ALK expression, prognosis

INTRODUCTION:

Anaplastic large cell lymphoma (ALCL) is a distinct subtype of T-cell non-Hodgkin lymphoma (NHL) characterized by strong CD30 expression and variable ALK gene rearrangement. Systemic ALCL primarily affects children and young adults, with a male predominance, and displays heterogeneous morphology and immunophenotypic features [1,2]. The World Health Organization (WHO) classifies ALCL into ALK-positive, ALK-negative, primary cutaneous and breast implant associated subtype, each with different clinical behavior and prognostic implications [3]. ALK-positive ALCL, frequently associated with the t(2;5) (p23;q35) NPM-ALK translocation, typically has a more favorable prognosis, especially in pediatric populations [4]. Recent studies have emphasized the significance of minimal disseminated disease (MDD), measurable residual disease (MRD), and anti-ALK antibody titers as independent prognostic markers in pediatric ALCL [5]. Additionally, histologic variants such as small cell and lymphohistiocytic subtypes often exhibit aggressive clinical behavior and aberrant immunoprofiles, making diagnosis more complex [6,7]. This study evaluates the clinical, pathological, and immunophenotypic spectrum of systemic ALCL in an Indian cohort and explores the prognostic significance of ALK status, histologic subtype, and disease site.

MATERIALS AND METHODS

This retrospective study was conducted at our institution over five and a half years, from January 2017 to June 2022. All histologically confirmed ALCL cases were retrieved and reviewed by two oncopathologists. Morphological subtypes and IHC panels were recorded, with attention to aberrant marker expression and ALK staining patterns wherever applicable. Cases of primary cutaneous ALCL, those with incomplete IHC workup, or those lacking histological confirmation were excluded. Statistical analysis was conducted using software "R" with Pearson chi-square test and Fisher exact test used to test the associations between variables. A p-value <0.05 was considered statistically significant. Overall survival (OS) was estimated using Kaplan-Meyer analysis. Overall survival was defined as the time from study entry until death or last follow-up.

RESULTS:

Clinico-pathological And Demographic Parameters

This retrospective study included 60 patients diagnosed with systemic anaplastic large cell lymphoma (ALCL) over 5.5 years. The age distribution was nearly equal, with 48.3% aged ≤18 years and 51.7% >18 years. The mean age was 31.45 years (median: 19 years). Males predominated (66.7%), with a male-to-female ratio of 2:1.

Disease Distribution

showed nodal involvement in 58.3% and extranodal disease in 41.7%. Cervical lymph nodes were most frequently involved (35%), followed by inguinal (13.3%), axillary (5%), supraclavicular (3.3%), and preauricular (1.7%). Extranodal sites included soft tissue (18.3%), bone (8.3%), and scalp (5%). Rare sites included sinonasal region, orbit, breast, trachea, mediastinum, and endobronchial areas (collectively 10%). Four patients had both nodal and extranodal disease; nine had multiple nodal sites. Bone marrow (n=6), spleen (n=4), and CNS (n=1) were also involved. Diagnosis was established via biopsy in 41 cases and excisional specimen in 19. B symptoms were noted in 61.5% of patients (32/52 with available data). Elevated LDH levels were observed in 84.6% (44/52).

Staging (Ann Arbor): Stage III was most frequent (33.3%), followed by Stage II (26.7%), Stage I (23.3%), and Stage IV (16.7%) (Table 1).

Table 1: Clinicopathological Characteristics Of ALCL Cases:

Parameter	Category	Frequency (n=60)	Percentage
Age	≤18 years	29	48.3%
	>18 years	31	51.7%
Sex	Male	40	66.7%
	Female	20	33.3%
Site of Involvement	Nodal	35	58.3%
	Extranodal	25	41.7%
Ann Arbor Stage	I	14	23.3%
	II	16	26.7%
	III	20	33.3%
	IV	10	16.7%
ALK Status	Positive	47	78.3%
	Negative	13	21.7%
Histological Subtype	Common	29	48.3%
	Small cell	8	13.3%
	Lymphohistiocytic	14	23.3%
	Hodgkin-like	2	3.3%
	Composite	7	11.6%

Histomorphology And Immunohistochemistry:

The most common histological pattern was the classic (48.3%), followed by lymphohistiocytic (23.3%), small cell (13.3%), composite (10%), and Hodgkin-like (5%). 78.3% were ALK-positive (n=47) and 21.7% ALK-negative (n=13). Among ALK+ cases, staining was nuclear and cytoplasmic in 34, purely cytoplasmic in 12, and membranous in one. **CD45** was expressed in 58/60 cases (96.7%); the two CD45-negative cases were of small cell and lymphohistiocytic variants. **CD3** negativity (null-cell phenotype) was observed in 16 cases (27.1%). Among other T-cell markers, **CD4** was positive in 79.2% (19/24 tested), and **CD8** in 66.7% (8/12). **CD30** was positive in all cases (diffuse in 57, focal in 3), and **EMA** was expressed in 58 cases. Focal CD30 staining was common in Hodgkin-like and

lymphohistiocytic subtypes possibly due to the sparse distribution of tumor cells in these subtypes. **Proliferation index (Ki-67)** ranged from 30% to 90%, with 93.3% of cases (56/60) showing >40%, consistent with aggressive disease. Additional cytotoxic or T-cell associated markers were also expressed in a subset of cases, including **CD5 (n = 12)**, **CD7 (n = 5)**, **perforin (n = 5)**, and **granzyme B (n = 17)**. Interestingly, **aberrant expression of non–T-cell lineage markers** was observed in several cases. These included **B-cell markers** such as **CD20 (n = 6)**, **PAX5 (n = 2)**, **CD79a (n = 1)**, and **BCL6 (n = 3)**; **plasma cell markers** including **CD138 (n = 3)** and **MUM1 (n = 4)**; and **other aberrant antigens** such as **CD15 (n = 2)**, **LMP-1 (n = 2)**, **P63 (n = 1)**, **CD43 (n = 3)**, **CD117 (n = 1)**, **CD56 (n = 2)**, **CD99 (n = 2)**, **BCL2 (n = 3)**, **CD68 (n = 2)**, and **C-MYC (n = 2)**. These findings highlight the immunophenotypic heterogeneity of ALCL and underscore the need for comprehensive immunohistochemical panels in its diagnosis.

Statistical Comparison Of Clinico-pathological Parameters:

Statistical analysis using the Chi-square test was employed to explore associations between various clinicopathological parameters. A significant association was identified between age group and ALK status (Pearson Chi-square = 7.215, p = 0.007; Fisher's Exact Test = 0.011). ALK positivity was predominantly seen in the younger age group (≤18 years), accounting for 57.4% of ALK-positive cases, whereas ALK negativity was more frequent in patients aged >18 years (84.6%). However, no significant association was found between ALK status and other variables including gender (p = 0.268), disease distribution (nodal vs. extranodal, p = 0.125), Ann Arbor stage (p = 0.637), or histological subtype (p = 0.421).

Secondary analyses further revealed no statistically significant associations between age and Ann Arbor stage (p = 0.331), age and disease distribution (p = 0.631), or age and histological subtype (p = 0.123). Similarly, no significant correlation was noted between histological subtype and Ann Arbor stage (p = 0.181), between site of involvement and stage (p = 0.154), or between histological subtype and site of involvement (p = 0.965) (Table 2).

Table 2: Overall Statistical Comparison

Comparison	Chi-square (χ^2)	Degree of freedom (df)	p-value
Nodal vs Extranodal	0.133	1	0.715
Ann Arbor Stage	1.399	3	0.706
ALK Status	1.574	1	0.210
Gender	1.990 (approx.)	1	0.158
Age (≤18 vs >18)	0.990 (approx.)	1	0.321
Histological subtype	0.182	1	0.670

Treatment And Follow-up Details With Survival Analysis:

All patients underwent a multimodality treatment approach. Pediatric patients were treated with the ALCL-99 protocol, while adults received CHOP-E chemotherapy, with the addition of Brentuximab vedotin, methotrexate, or rituximab in selected cases. Radiotherapy was administered in three cases, and one patient underwent surgical excision. During the course of treatment, 19 patients died, 7 defaulted, and 33 patients completed therapy without any evidence of disease progression or recurrence. One patient exhibited disease progression during treatment, and one case was lost to follow-up.

Kaplan–Meier survival analysis was performed for 59 patients (excluding the one lost to follow-up) and outcomes were compared using the log-rank (Mantel–Cox) test. At the end of follow-up, 26 events (deaths) had occurred, and 33 cases (55.9%) were censored. The median overall survival was 6.0 months (95% CI: 3.6–8.4), and the mean survival time was 5.25 ± 0.42 months. Survival analysis showed no statistically significant difference between age groups (≤18 vs. >18 years; p = 0.921), sex (p = 0.960), or site of disease (nodal vs. extranodal; p = 0.715). Although survival was slightly lower in the extranodal group after six months, the visual difference was minor and not statistically significant. Similarly, no significant difference in survival was observed across the Ann Arbor stages I–IV (p = 0.706), although patients with advanced-stage disease showed a trend toward reduced survival.

To explore prognostic significance based on morphology, histological patterns were grouped into two categories: Subtype 1 (common and Hodgkin-like patterns) and Subtype 2 (lymphohistiocytic, small cell, and composite variants). The median survival for Subtype 1 was 6.0 months (95% CI: 3.39–8.61) and for Subtype 2 was 7.0 months (95% CI: 2.72–11.28), with mean survival times of 5.10 ± 0.60 months and 5.55 ± 0.60 months, respectively. The difference in survival between these groups was not statistically significant (Log-rank $\chi^2 = 0.182$, p = 0.670). ALK-negative cases had a shorter mean survival (3.96 months) compared to ALK-positive cases (5.56 months), but the difference did not reach statistical significance (p = 0.210)(Table 3). Although no statistically significant differences in survival were observed across age, sex, disease site, stage, histological subtype, or ALK status, trends indicating poorer outcomes in ALK-negative cases and those with advanced-stage disease were noted.

Table 3: Kaplan–Meier Survival Summary

Group	n	Events	Mean Survival (±SE)	Median (±SE)	95% CI for Median	p-value
Nodal	35	15	5.15 ± 0.57	6.0 ± 1.76	2.54 – 9.46	0.715
Extranodal	24	11	5.50 ± 0.66	7.0 ± 2.75	1.61 – 12.39	
Stage I	14	3	4.20 ± 0.41	Not reached	-	
Stage II	16	7	4.34 ± 0.56	4.0 ± 1.30	1.44 – 6.56	
Stage III	19	10	4.86 ± 0.73	6.0 ± 2.75	0.61 – 11.39	
Stage IV	10	6	5.60 ± 1.04	8.0 ± 0.00	Not estimable	0.706
ALK+	47	19	5.56 ± 0.48	7.0 ± 1.81	3.45 – 10.55	0.210
ALK–	12	7	3.96 ± 0.66	4.0 ± 1.39	1.27 – 6.73	
Male	39	20	5.12 ± 0.50	6.0 ± 1.52	2.99 – 9.01	0.158
Female	20	6	5.62 ± 0.70	7.0 ± 2.02	3.11 – 10.88	
≤18 yrs	12	4	6.22 ± 0.72	7.0 ± 1.10	4.91 – 8.99	0.321
>18 yrs	47	22	5.01 ± 0.44	6.0 ± 1.26	3.22 – 8.01	
Histological subtype Type 1	30	15	5.10 ± 0.60	6.00 ± 1.33	3.39 – 8.61	
Type 2	29	11	5.55 ± 0.60	7.00 ± 2.18	2.72 – 11.28	0.670

DISCUSSION

This 60-case retrospective study provides insight into the heterogeneity of systemic ALCL in the Indian context. ALK positivity was seen in 78.3% of cases and significantly associated with younger patients (≤18 years), reaffirming global findings that ALK-positive ALCL is predominantly a pediatric disease [1,5]. Our findings also corroborate reports that ALK positivity is associated with better survival outcomes, though the difference did not reach statistical significance in our cohort—possibly due to high-stage presentation and treatment attrition [4,5].

Histologically, the classic pattern was most frequent, but a considerable proportion exhibited small cell, lymphohistiocytic, and composite variants. These subtypes often presented with diagnostic challenges due to sparse tumor populations and unusual immunophenotypes, including loss of T-cell markers and aberrant expression of B-cell (CD20, PAX5), plasma cell (CD138, MUM1), or myeloid markers (CD15, CD43) [7]. These patterns mirror prior reports that emphasize the diagnostic complexity of ALCL, particularly in small biopsies or extranodal sites [6,7].

All cases showed CD30 positivity, and most expressed EMA. ALK-positive cases demonstrated predominantly nuclear and cytoplasmic staining, consistent with NPM-ALK rearrangement. Despite the lack of statistical survival differences across age, sex, stage, and histological subtypes, ALK-negative and advanced-stage cases showed poorer trends—findings also reported in multicenter trials such as ALCL99 [2].

Recent advancements in ALCL risk stratification, particularly the evaluation of MDD at diagnosis and MRD during treatment, have significantly improved outcome prediction in children [5]. Patients with MDD and persistent MRD have a high relapse risk and may benefit from therapy intensification [5]. Similarly, high anti-ALK antibody titers have been shown to correlate with favorable prognosis in pediatric ALK-positive ALCL [8].

Our study did not include MDD or antibody testing due to logistical limitations, but the results highlight the urgent need to incorporate molecular prognostic markers into clinical practice, especially in developing regions. Furthermore, emerging therapies such as Brentuximab vedotin and ALK inhibitors (e.g., crizotinib) have improved outcomes in relapsed/refractory ALCL and are reshaping

treatment paradigms [9,10].

CONCLUSION

This study underscores the clinical and pathological heterogeneity of systemic ALCL and the central role of ALK expression in diagnosis and prognosis. Variant morphologies and aberrant immunophenotypes pose diagnostic challenges, necessitating comprehensive IHC panels. Although ALK positivity trends toward better survival, our findings emphasize the need for molecular prognostic tools like MDD, MRD, and ALK antibody levels to enhance risk stratification. Incorporating these markers, alongside evolving targeted therapies, will enable personalized treatment and improve outcomes, particularly in resource-limited settings

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