

# Challenges in utilizing ALK expression to distinguish primary cutaneous from systemic anaplastic large cell lymphoma

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**Abstract.** Anaplastic large cell lymphoma (ALCL) is a CD30<sup>+</sup> peripheral T-cell lymphoma with a clinical spectrum including cutaneous and systemic presentations. While primary cutaneous ALCL (pcALCL) has a favorable prognosis, systemic ALCL (sALCL) has poorer survival outcomes. Expression of anaplastic lymphoma kinase (ALK) by malignant cells has been suggested to distinguish sALCL from pcALCL. However, there have been documented cases of ALK-positive ALCL confined to the skin. The present study reviewed characteristics of published cutaneous ALK-positive ALCL cases to distinguish between these two entities. In 23 identified adults with ALK-positive pcALCL, 26% developed systemic involvement and 74% had skin-limited disease. In 14 pediatric patients, 36% had both cutaneous and systemic involvement and 64% had cutaneous disease only. This analysis revealed that pcALCL and sALCL could not reliably be distinguished by ALK expression or nuclear vs. cytoplasmic localization. Localized treatment with frequent monitoring may be

sufficient in ALK-positive pcALCL until there is evidence of progression. Physicians should be aware of the overall spectrum of ALCL, including cutaneous limited disease, systemic disease, disease with NPM-ALK translocation, disease with ALK positivity and disease with skin recurrence.

## Introduction

Primary cutaneous anaplastic large cell lymphoma (pcALCL) is classically characterized as a solitary papulonodule that often enlarges, ulcerates, and can be locally destructive. The lesions can undergo partial or complete regression, but skin relapses frequently occur (1,2). It is estimated that pcALCL has a 90% 5-year overall survival (2). However, large solitary tumors, multifocal disease, and extensive limb involvement tend to exhibit a more aggressive course and have a higher risk of developing extracutaneous involvement (1).

In patients who develop systemic involvement following initial cutaneous manifestations, it is difficult to determine if the systemic disease is a primary occurrence or a presentation of pcALCL with secondary systemic involvement. Use of immunohistochemistry (IHC) in other non-Hodgkin's lymphomas aids in stratifying diagnostic subtypes and distinguishing systemic vs. cutaneous disease (3,4). Similarly, in ALCL, evaluation of anaplastic lymphoma kinase (ALK) and epithelial membrane antigen (EMA) expression by IHC performed on initial skin biopsies has been used to distinguish between cutaneous and systemic forms (5). ALK expression results from translocation of a tyrosine kinase implicated in uncontrolled cell proliferation and survival while EMA is a glycoprotein with roles in tumorigenesis (6). Thus, patients with a diagnosis of ALK-positive and/or EMA-positive ALCL on skin biopsy typically undergo further workup to evaluate for systemic disease.

Although rare, there have been several documented cases of ALK-positive pcALCL (pcALCL) diagnosed on skin biopsy without evidence of secondary systemic involvement. This paradox poses several challenges in the classification, prognostication, treatment, and follow-up of these patients (4, 7-9). Here we present a review of current literature regarding adult and pediatric ALK-positive ALCL without evidence of systemic involvement on initial diagnosis. We sought to

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**Abbreviations:** ALCL, anaplastic large cell (CD30<sup>+</sup>) lymphoma; sALCL, systemic anaplastic large cell lymphoma; pcALCL, primary cutaneous anaplastic large cell lymphoma; EMA, epithelial membrane antigen; NPM, nucleophosmin; ALK, anaplastic lymphoma kinase; TRAF, tumor necrosis factor-receptor associated factor; ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase; TPM3, tropomyosin 3; CHOP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (oncovin) and prednisone; CHOPe, CHOP plus etoposide; MTX, methotrexate

**Key words:** anaplastic lymphoma kinase, anaplastic large cell (CD30<sup>+</sup>) lymphoma, systemic anaplastic large cell lymphoma, primary cutaneous anaplastic large cell lymphoma

determine whether ALK expression, localization within the cell (nuclear vs cytoplasmic), translocation type, and initial treatment in all previously reported cases had any correlation with the progression of pALCL to sALCL.

## Materials and methods

We searched for ALK-positive ALCL cases diagnosed on skin biopsies cutaneous ALCL (cALCL), with and without systemic involvement in the English literature. The MEDLINE database (1946-2022) was searched using the terms and synonyms for ‘anaplastic lymphoma kinase’, ‘anaplastic lymphoma kinase positivity’, ‘anaplastic large cell lymphoma’, ‘skin limited’, ‘cutaneous limitation’, and ‘systemic involvement’. In addition, we performed a manual review of the reference lists of the articles to identify additional articles that could conform to our inclusion criteria. All article types reporting on one or more cases of skin-limited ALK-positive ALCL were included. From these articles, ALK expression, translocation type, EMA positivity, and initial treatment were recorded. Patients' demographic and oncologic characteristics, including age, sex, ethnicity, tumor distribution, and recurring skin lesions were noted. Cases were classified as sALCL if there was evidence of the disease in the lymph nodes, blood, bone marrow or extracutaneous organs. Chi square analysis was performed to compare the categorical variables between the adult and pediatric patients separately. The adult and pediatric populations within each respective group were also compared using Chi square analysis.

## Results

Table I summarizes studies reporting adult and pediatric ALK-positive cALCL published in the English literature. Information about age, sex, presentation and cutaneous distribution, ALK staining and molecular studies, systemic work up, initial treatment course, follow-ups, and outcomes were recorded. We identified 23 adults (age > 18) with ALK-positive cALCL (10-24). We categorized patients into those who developed systemic disease (26%) and patients with skin-limited disease (73%). In pediatric patients, we were able to identify 14 individuals who developed ALK-positive cALCL (5,15,25-29). Of these, nine never had systemic involvement (64%) and five had both cutaneous and systemic involvement (35%). All cases that reported the histologic morphology included a description of large pleomorphic, anaplastic, or reed-Sternberg-like cells with no epidermotropism observed. All reported CD30-positivity. Other specific morphologic and phenotypic trends observed in cALCL are presented in Table I.

**Nuclear vs. cytoplasmic ALK staining pattern.** In cases that reported the location of ALK staining in adults (19/23, 82%), cytoplasmic-only ALK staining was more common in systemic disease (5/6, 83%). The most frequent staining pattern in cases from the cutaneous limited group, was nuclear and cytoplasmic staining (7/13, 54%). Specific ALK translocations were only reported for 32% of patients. In children, cytoplasmic ALK staining was the most reported staining pattern in the systemic group (2/3, 66%) Whereas in the cutaneous group, nuclear and cytoplasmic staining was most common (6/7, 85%). There were no significant differences between the staining patterns in the

cutaneous and systemic groups in either adult or pediatric populations. Comparing adults and children for each group did not yield significant results.

**EMA positivity.** EMA staining was reported in a minority of adult patients (5/23, 21%) and just over half of pediatric patients (8/14, 57%). All patients with systemic disease and a reported EMA had positive staining (4/4, 100%). There were 7/9 patients in the cutaneous-limited groups that had positive EMA staining (78%), however, 2/9 had negative EMA staining (22%) (Table I).

**Treatment.** In adults, the most frequently reported initial treatment method was localized therapies such as excision, resection, or radiation (systemic group: 4/6, 67%; cutaneous-limited group: 11/16, 69%). Chemotherapy was given to the remaining 2/6 patients in the systemic group (33%) and 4/16 patients in the cutaneous limited group (25%). One patient in the cutaneous limited group was treated with methotrexate and retinoids (6%). Regarding reported initial treatments in children, localized approaches were utilized most in both groups (systemic: 3/5, 60%; cutaneous limited 7/9, 78%). In the systemic group, 2/5 patients received chemotherapy (40%) and in the cutaneous limited group, 2/9 received it (22%). The differences in initial treatment were not found to be statistically significant between the systemic and cutaneous groups or between adults and children in each group.

**Outcomes.** There were 6 cases of systemic involvement in the adult population with an estimated mean time of transformation at 16.7 months, and there were equal outcomes of death (3/6, 50%) and remission (3/6, 50%). The patients in remission received follow-up for 7-18 months. Of the patients who survived, 2/3 received initial treatment with chemotherapy (67%), and one patient received localized treatment (33%). Of the patients that died, all three received localized therapy as an initial treatment. All the cutaneous-limited patients survived except for one who received chemotherapy and died due to severe infection (10). The range of follow up was 3.5 to 240 months. Of the five cases with systemic involvement in the pediatric population, two were diagnosed on presentation (40%). Including those cases, the estimated mean time of transformation was 2.6 months. The mean follow-up period was 26 months (range: 14-37 months). There was one death due to disease in the systemic group (20%). There were no deaths in the cutaneous-limited group. The nine patients in the cutaneous-limited ALCL group did not progress regardless of whether initial treatment was chemotherapy or localized therapy. These patients received follow-up for a range of 12-96 months. Finally, comparing outcomes between adult and pediatric populations, 3/23 (13%) adult patients died of the disease and 1/14 (7%) patients died of the disease in the pediatric group. There was no significant difference in deaths between adult and pediatric cases. All patients who died of the disease had systemic manifestations.

## Discussion

There has been a continuous discussion on the theoretical risks and clinical implications of ALK-positivity in cALCL

Table I. Characteristics of ALK-positive ALCL in adult patients  $\geq 18$  years old (10-24) and pediatric patients  $< 18$  years old (5,15,25-29) published to date.

| Characteristics   | Adult patients                                |   |         | Pediatric patients                            |   |         |
|---|---|---|---------|---|---|---------|
|   | Patients who developed systemic disease (n=6) | Patients without clinical evidence of systemic disease (n=17) | P-value | Patients who developed systemic disease (n=5) | Patients without evidence of systemic disease (n=9) | P-value |
| Age range, years  | 22-54   | 21-70   |         | 5-16  | 7.5-16  |         |
| Mean age, years   | 43  | 43  |         | 11.6  | 10.5  |         |
| Sex   |   |   |         |   |   |         |
| Female  | 5   | 8   |         | 4   | 5   |         |
| Male  | 1   | 9   |         | 1   | 4   |         |
| Ethnicity   |   |   |         |   |   |         |
| Japanese  | 3   | 0   |         | 0   | 0   |         |
| Filipino  | 0   | 1   |         | 0   | 0   |         |
| Chinese   | 0   | 1   |         | 0   | 0   |         |
| Caucasian   | 0   | 2   |         | 1   | 3   |         |
| DNR   | 3   | 13  |         | 5   | 6   |         |
| Distribution at presentation  |   |   | 0.64    |   |   | 0.44    |
| Solitary  | 4   | 13  |         | 5   | 8   |         |
| Multifocal  | 2   | 4   |         | 0   | 1   |         |
| Histological morphology and phenotype <sup>a</sup>                                  |   |   |         |   |   |         |
| Pyogenic  | 2   | 1   |         | 1   | 2   |         |
| Pseudo-epitheliomatous  | 0   | 1   |         | 1   | 3   |         |
| CD30 <sup>+</sup>   | 3   | 12  |         | 5   | 9   |         |
| Loss of a pan T-cell Ag   | 3   | 8   |         | 2   | 3   |         |
| ALK localization  |   |   | 0.13    |   |   | 0.10    |
| Nuclear and cytoplasmic   | 1   | 7   |         | 1   | 6   |         |
| Cytoplasmic   | 5   | 6   |         | 2   | 1   |         |
| DNR   | 0   | 4   |         | 2   | 2   |         |
| EMA positivity  |   |   | 0.36    |   |   | 0.54    |
| EMA <sup>+</sup>  | 2   | 2   |         | 2   | 5   |         |
| EMA <sup>-</sup>  | 0   | 1   |         | 0   | 1   |         |
| DNR   | 4   | 14  |         | 3   | 3   |         |
| Translocations  |   |   |         |   |   |         |
| NPM-ALK   | 2   | 2   |         | 2   | 3   |         |
| Other translocations  | 3   | 2   |         | 0   | 0   |         |
| DNR   | 1   | 13  |         | 3   | 6   |         |
| Initial treatment   |   |   | 0.76    |   |   | 0.48    |
| Localized treatments (excision +/- radiation or radiation alone)                    | 4   | 11  |         | 3   | 7   |         |
| Chemotherapy  | 2   | 4   |         | 2   | 2   |         |
| Other or DNR  | 0   | 2   |         | 0   | 0   |         |
| Recurrent skin lesions  |   |   | 0.2     |   |   | 0.16    |
| Recurrence  | 3   | 5   |         | 1   | 0   |         |
| No recurrence   | 2   | 12  |         | 4   | 9   |         |
| Mean time to when systemic involvement occurred (from initial presentation), months | 16.7 months (5.5-29 months)                   | Never   |         | 2.6 months (0-12 months)                      | Never   |         |
| Systemic involvement at diagnosis   | 0   | 0   |         | 2   | 0   |         |

Table I. Continued.

| Characteristics    | Adult patients                                |   |         | Pediatric patients                            |   |         |
|--------------------|---|---|---------|---|---|---------|
|                    | Patients who developed systemic disease (n=6) | Patients without clinical evidence of systemic disease (n=17) | P-value | Patients who developed systemic disease (n=5) | Patients without evidence of systemic disease (n=9) | P-value |
| Range of follow-up | 7-18 months                                   | 3.5-240 months  |         | 14-37 months                                  | 12-96 months  |         |
| Outcomes           |   |   |         |   |   |         |
| Remission          | 3   | 0   |         | 4   |   |         |
| Mortality          | 3 <sup>b</sup>                                | 1 <sup>c</sup>  |         | 1 <sup>d</sup>                                |   |         |

<sup>a</sup>All cases with histological morphology reported dense infiltrate composed of large pleomorphic, anaplastic, or reed-Sternberg-like cells with no epidermotropism observed. <sup>b</sup>mortalities due to disease (all patients received localized treatments); <sup>c</sup>patient treated with chemotherapy died from severe infection; <sup>d</sup>mortality death due to disease. F, female; M, male; DNR, did not report; ALCL, anaplastic large cell (CD30<sup>+</sup>) lymphoma; EMA, epithelial membrane antigen; NPM, nucleophosmin; ALK, anaplastic lymphoma kinase; TRAF, tumor necrosis factor-receptor associated factor; ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase; TPM3, tropomyosin 3; CHOP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (oncovin) and prednisone; CHOPE, CHOP plus etoposide; MTX, methotrexate.

among treating physicians and researchers (30). A consensus statement by multiple lymphoma research organizations noted the presence of ALK positivity in the skin may confer an underlying systemic disease as most cases of pcALCL are ALK-negative (29,30). However, article by Geller *et al* suggested that the mere presence of ALK positivity in cALCL does not necessarily indicate systemic disease (21). Of ALK-positive patients who developed systemic disease after having cutaneous manifestations, it is difficult to determine if systemic disease is an underlying, undetectable primary occurrence or an evolution of the cutaneous disease. Of note, systemic ALK-positive ALCL with t (2,5) and ALK-negative ALCL with DUSP22 rearrangement (to a lesser extent) have been associated with a favorable prognosis (30). The majority of patients we found to be ALK-positive had cutaneous disease only, even after lengthy follow-ups. Therefore, one must question if there are alternative factors to signal systemic involvement rather than ALK positivity alone.

Analysis of previous cases revealed that relying on ALK expression alone may not aid in the stratification of pcALCL subtypes and prognosis. Overall, our comprehensive review suggests that two distinct variants of ALK-positive cALCL exist: pcALCL that will not progress and pcALCL with the inclination to progress to sALCL. Regarding ALK localization, while most patients that progressed to sALCL had cytoplasmic localization (5/6 adults, 2/3 children), those who did not progress did not show a predominance of either nuclear or cytoplasmic localization. Additionally, specific translocations did not favor any outcomes. Overall, ALK expression and localization may be a finding without prognostic significance in pcALCL with initial cutaneous involvement.

EMA, another diagnostic marker in ALCL, is generally assumed to be expressed only on epithelial cells. However, EMA is also found on reactive and neoplastic plasma cells, particularly cases of T-cell lymphoma (30-33). Studies show that tumors of T-cell origin commonly express EMA (31). It was not widely used for c-ALCL as less than half of the cases

reported its use. All reported patients in this study with systemic disease and a reported EMA had positive staining (n=4). There were patients in the cutaneous-limited groups that had positive staining (n=7), however, two had negative EMA staining. While this may indicate the presence of EMA is associated with systemic disease and absence of EMA is associated with cutaneous-limited disease, more studies of c-ALCL with EMA staining are needed to determine its implication in this disease entity.

If CD30-positive ALCL, ALK negative is diagnosed, testing for DUSP22-IRF4 Gene Rearrangement via fluorescence in situ hybridization is considered useful under certain circumstances for the diagnosis of primary cutaneous CD30<sup>+</sup> T-cell lymphoproliferative diseases. ALCL, ALK negative with DUSP22 rearrangement has preliminarily been associated with a favorable prognosis, however the impact of this on choice of therapy is not currently known. TP63 gene rearrangements encoding p63 fusion proteins define a subset of ALK-negative ALCL cases and are associated with aggressive course in systemic ALCL (33).

As for overall survival, our data suggests ALK-positive cALCL had an overall survival of 87%, excluding the patient that died of other causes. The age of the patient may also influence disease presentation and outcomes, as we found there to be higher survival among the ALK-positive pediatric patients (92%), with only one patient dying of systemic disease. A significant mortality of 50% was observed in adult patients who progressed to sALCL, highlighting the importance in prognosticating these patients early.

The decision to treat ALK-positive pcALCL with chemotherapy vs. localized treatment is nuanced. The majority of adult patients with ALK-positive pcALCL reviewed in the literature did not progress to systemic disease (17/23) including those reported as being treated with localized or skin-directed therapies (11/16). Additionally, of the ALK-positive pcALCL patients who never progressed to systemic disease but received chemotherapy (4/16), one patient died of complications of

chemotherapy (10). This calls into question the beneficial role of chemotherapy in patients with ALK-positive pcALCL. While 2/6 patients who received chemotherapy progressed to systemic disease, none died of the disease. Once patients progress to systemic disease, chemotherapy had a clearer benefit as 2/3 patients who received chemotherapy survived. It is reasonable to attempt treatment for ALK-positive pcALCL with chemotherapy as a potential means to increase survival. However, localized treatment with frequent monitoring may be sufficient until there is concrete evidence of systemic involvement given the adverse effects of chemotherapy.

The limitations of this review include its retrospective nature, the rarity of the disease subtype and the heterogeneity of information in the published cases. We endeavored to determine if ALK localization or translocation influenced disease progression. Although we wished to analyze specific translocations and their tendency to result in disease progression, less than half of the cases reported them. While more cases reported ALK localization, this information was not available in 22% of articles reviewed. In addition, we were unable to adequately evaluate if EMA expression could differentiate systemic vs. cutaneous ALCL, due to the low rates of EMA staining in our cohort. A further aim was to evaluate how initial treatment approaches influenced the progression and survival of patients with pcALCL; fortunately, 97% of the literature provided this information. As there is a need to further characterize the role of ALK and other biomarkers in the disease course of pcALCL, large, prospective multi-institutional studies would be extremely impactful.

Our final analysis revealed that ALK-positive pcALCL presents with two distinct entities: cutaneous-limited disease that will not progress and progressive systemic disease. Although trends can be identified, the two entities cannot reliably be distinguished solely by ALK expression or localization. Therefore, larger sample sizes and further studies are needed to distinguish between pcALCL and sALCL. There is a need to prospectively characterize biomarkers in addition to ALK to distinguish between these two entities. It is important for physicians to be aware of the wide clinical spectrum and outcomes associated with pcALCL so that they are conscious of the benefits and drawbacks of treatment options and are vigilant for systemic progression.

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## Availability of data and materials

All data generated or analyzed during this study are included in this published article or may be found in the cited manuscripts.

## Authors' contributions

LG, LA, LB, and ST participated in the research design and analysis of publicly available data, wrote and edited the

manuscript. LB and ST confirm the authenticity of all the raw data. DJ, SB, OA, and PP edited the manuscript. NN participated in research design, reviewed data, edited the manuscript and supervised the overall production of this manuscript. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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