

**Society for Hematopathology Companion Meeting**  
**CD30+ Lymphoproliferative Disorders of the Skin**  
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Primary cutaneous CD30+ lymphoproliferative disorders (LPD) are relatively common, comprise approximately 30% of lymphoid neoplasms primary in the skin, and are second in frequency only to mycosis fungoides.<sup>1</sup> Cutaneous CD30+ LPD represents a biologic and histologic spectrum with lymphomatoid papulosis (a benign disorder with spontaneous regression) at one end<sup>2</sup> and primary cutaneous anaplastic large cell lymphoma (C-ALCL, an indolent CD30+ lymphoma usually treated with local therapy) at the other end.<sup>3,4</sup> In between are borderline lesions that may defy definitive classification until time passes and the lesion “declares itself”. The classification of CD30+ LPD is predominantly based of the number and size of lesions, number of large CD30+ cells, and the clinical evolution of the lesion (progression versus regression). It is extremely important to distinguish C-ALCL from secondary involvement of the skin by systemic ALCL, an aggressive disease that requires multiagent, systemic chemotherapy.

**Topics for Discussion:**

- Clinical and pathologic features of primary cutaneous ALCL
- Pathogenesis of primary cutaneous ALCL
- Distinguishing primary cutaneous ALCL from systemic ALCL
- Treatment of primary cutaneous ALCL
- Clinical and pathologic features of LyP
- Relationship of primary cutaneous ALCL to LyP
- Other lymphomas and reactive processes in the differential diagnosis of CD30+ LPD

**Primary Cutaneous ALCL**

**Definition of primary cutaneous ALCL:**<sup>1,5</sup>

- Skin involvement without evidence of systemic disease \*
- No antecedent history of LyP, mycosis fungoides, Hodgkin lymphoma, or other cutaneous T-cell lymphoma

\*Cases with regional (draining) node involvement are problematic; it is uncertain if they have a different prognosis or if they should be included as primary cutaneous ALCL.<sup>5</sup> One recent study has shown only a slightly decreased overall 5-year survival for primary cutaneous ALCL versus cutaneous ALCL with regional node involvement (83% vs. 76%, respectively); however, it should be noted that 82% of the patients with regional node involvement received multiagent chemotherapy.<sup>6</sup>

**Clinical features of primary cutaneous ALCL:**<sup>7-13</sup>

- Older age, median 40-67 yrs (range 2-95 yrs; most over 50 yrs); pediatric C-ALCL is rare (< 2% of cases of C-ALCL)<sup>6, 12, 14, 15</sup>
- Male to female ratio of 2-3:1
- Nodule (1 - 2 cm)>tumor (>2 cm rapidly growing)>papule (< 1 cm) or plaque (3-5 cm)
- Solitary>multiple; regional>generalized; multifocal disease is seen in approximately 20% - 25%
- Larger lesions are often ulcerated

- Extremities>head and neck>trunk>genitalia
- Rarely described in the post transplant setting<sup>16-19</sup> and in HIV+ patients<sup>20-22</sup>

**Note:** Localized disease refers to a few clustered lesions restricted to one anatomic area, and generally not exceeding 15 x 15 cm. Multifocal disease has skin involvement of two or more anatomic sites.<sup>6</sup>

### **Histologic features of primary cutaneous ALCL:**<sup>8, 9, 11</sup>

- Dense and diffuse dermal infiltrate often extending into subcutaneous tissue
- Epidermal ulceration in 30%-50%; no significant epidermotropism
- Pseudoepitheliomatous epidermal hyperplasia may mimic carcinoma<sup>23, 24</sup>
- Tumor cells are present in sheets or large clusters
- Most cases are anaplastic with large cells having folded or indented nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm
- 10% -25% have non-anaplastic morphology (pleomorphic folded nuclei with denser chromatin or an immunoblastic appearance)
- Vascular invasion or perivascular cuffing, but not destruction, by tumor cells can be seen<sup>11, 25, 26</sup>
- Variable numbers of multinucleated, Reed-Sternberg-like giant cells
- Neutrophils and/or eosinophils may be prominent and a pyogenic form of C-ALCL has been described<sup>5, 20, 27</sup>
- Reactive lymphocytes are often present at the periphery of the lesion
- Large numbers of eosinophils may be predictive of subsequent lymph node disease<sup>8</sup>

**Note:** Regressing atypical histiocytosis is now considered as ALCL<sup>8, 28-30</sup>

### **Immunophenotype of primary cutaneous ALCL:**

- Strong CD30 expression in virtually all (>75%) tumor cells
- CD4+>> CD8+ (< 5%); variable loss of pan T-cell antigens CD2, CD3, CD5
- EMA+ in ≤32% of cases; CD15+ in <10%<sup>9, 31</sup> †
- CD56+ in 12% - 75%; does not appear associated with a worse prognosis as seen in ALCL at other extranodal sites or in systemic ALCL<sup>32-35</sup>
- Roughly 75% express at least one cytotoxic protein (TIA-1, granzyme B, perforin)<sup>36, 37</sup>
- ALK protein expression is uncommon, but is seen in rare cases of primary cutaneous ALCL;<sup>38-40</sup> In most cases ALK positivity suggests systemic disease<sup>41</sup>
- EBV- in > 90%<sup>42-44</sup>
- Clusterin + (41% - 100%)<sup>45-47</sup>
- Fascin+ in 64% of C-ALCL<sup>48</sup>
- C-ALCL has higher expression of apoptosis signaling molecules than systemic ALCL<sup>49</sup>
- Cutaneous lymphocyte antigen (CLA) expression as detected by antibody HECA-452 is reported in 44% C-ALCL in most tumor cells<sup>7</sup>

† Cytoplasmic (not membrane) CD15 expression has been reported in up to 40% of cases

**Note:** Two molecules have been identified as important in predicting whether cutaneous lesions may or may not regress. BCL-2 expression correlates with non-regression;<sup>50</sup> CD30L (ligand) correlates with regression.<sup>51</sup>

### **Pathogenesis of primary cutaneous ALCL:**

As primary cutaneous ALCL is ALK negative, the pathogenesis is different from the usual systemic ALCL. HOX homeobox gene *HOXC5* is preferentially expressed in primary cutaneous ALCL and

MALT lymphoma. HOX genes are important in regulating trafficking, as their target is genes encoding adhesion molecules.<sup>52</sup>

JunB is expressed in virtually all CD30+ tumors including Hodgkin lymphoma, ALK+ and ALK-ALCL, C-ALCL, and LyP.<sup>6, 53, 54</sup> Amplification of *JunB* has been reported in 70% of primary cutaneous ALCL and JunB protein expression has been detected in 100% of C-ALCL in the small number of cases tested.<sup>53, 55</sup> JunB is a component of the AP-1 transcription factor complex that binds to an AP-1 site within the microsatellite region (that is normally repressive) in the CD30 promoter thus allowing transcription of the CD30 gene. In addition, CD30 signaling activates the ERK1/2 MAPK pathway that increases JunB creating an autocrine loop.<sup>56</sup> It is interesting that this “amplifying loop” is not present in normal cells where expression of CD30 is too weak to transduce self-activating signals. Recent studies have also shown polymorphisms in the CD30 promoter microsatellite repressive element (30M377 in LyP and 30M362 in ALCL or HL arising in LyP) suggesting a possible predisposition in these patients to develop a CD30+ LPD.<sup>57</sup>

## Distinguishing Primary Cutaneous ALCL from Systemic ALCL

### Importance of distinguishing primary versus secondary ALCL:

Skin involvement is seen in approximately 15% - 25% of systemic ALCL.<sup>58, 59</sup> Primary cutaneous ALCL has an excellent prognosis (83% - 100% overall 5 year survival; disease related survival is > 90%), whereas the prognosis of systemic ALCL with associated skin involvement is much less favorable<sup>8, 10</sup> (see Table 1).

**Table 1. Five-Year Cumulative Survival in Various Cutaneous Forms of ALCL**<sup>6, 8, 10</sup>

Clinical type of ALCL	5-year cumulative survival (%)
Primary cutaneous	83% - 100%
Skin involvement in systemic disease	24% - 44%
Simultaneous presentation of skin and extracutaneous lesions	15%
Cutaneous ALCL following LyP/MF/Hodgkin lymphoma	65% - 85%*

\*ALCL developing in LyP appears to have a good prognosis<sup>6</sup>

**Note:** Most series report overall 5-year survival for systemic ALCL (includes adults and children, all clinical types) as 65% - 85%.

### How to distinguish primary cutaneous ALCL from systemic disease:

- Careful staging is imperative; there are no foolproof markers to distinguish
- ALK expression correlates with systemic disease (but is rarely seen in primary cutaneous ALCL)<sup>39-41</sup>
- Monomorphic histology is more often seen in systemic disease
- C-ALCL more pleomorphic, more RS-like cells and acute inflammatory cells
- Clusterin was initially reported as being exclusively expressed in systemic ALCL; Wellman et al., 2000<sup>60</sup> reported 100% of systemic ALCL and no primary cutaneous ALCL were positive, however a small number of cases were tested. Recent larger studies have shown clusterin expression in approximately 41% - 100% of cases of primary cutaneous ALCL.<sup>45-47</sup>
- Cutaneous lymphocyte antigen (CLA) is more frequent in C-ALCL than systemic ALCL (44% vs. 18%, respectively)<sup>7</sup>

- Rashes are rare in ALCL overall and are more often seen in reactive CD30+ infiltrates (see below); but, if present in lymphoma suggest systemic disease

**Note:** EMA expression is not useful in distinguishing primary cutaneous disease versus systemic ALCL as it has been reported in 54% of simultaneous cutaneous and systemic ALCL, 100% of secondary skin involvement, and up to one third of primary cutaneous ALCL.<sup>31</sup>

**Note:** Remember primary cutaneous ALCL is uncommon in children; careful staging and follow-up to rule out systemic disease are important.

## Outcome in Primary Cutaneous ALCL

### Disease course, prognosis, and treatment:

- Spontaneous regression (partial or complete) in up to 23% - 44%<sup>6, 8, 31</sup>
- Indolent course<sup>7, 8, 13, 31, 61</sup>
  - Overall 5 year survival (83% - 100%) with a disease related survival > 90% versus ~65% - 85% in nodal (systemic) ALCL<sup>6, 62</sup>
  - Cutaneous relapse common (32% - 44%)<sup>6, 8, 63</sup>, particularly with multifocal disease and in the pediatric population<sup>14, 64</sup>
- Overall, 10% - 25% (17% - > 40% in patients with multifocal disease) develop nodal (or other extracutaneous) disease<sup>6, 9, 64</sup>
  - Median of 24 months (range 2-117 mos.) after initial diagnosis
  - Aggressive disease appears associated with early spread to nodes other than regional nodes; approximately 50% with disseminated disease die

**Note:** In the new WHO-EORTC classification of C-ALCL, the requirement for disease to be limited to the skin for six months has been dropped; however, as a subset of patients develop nodal involvement close clinical follow-up is indicated.

- Sentinel lymphadenectomy for staging of C-ALCL has been described<sup>65</sup>
- Treatment varies with extent of disease:
  - Excision, with or without radiation in localized lesions is usual
  - Imiquimod (Aldara) an immune response modifier may be helpful<sup>66</sup>
  - Generalized cutaneous disease appears to be more aggressive and at greater risk to develop extracutaneous disease; low dose methotrexate, systemic retinoids w/ or w/o interferon alpha; monoclonal anti-CD30 therapy may be used with multicentric disease; combination chemotherapy and bone marrow transplant have not been shown to prevent relapse; at relapse the disease may remain indolent<sup>6, 62, 64, 67, 68</sup>
  - Photodynamic therapy with topical 5-aminolevulinic acid has been used for debulking<sup>69</sup>
  - Development of extracutaneous disease or rapid progression is currently treated with doxorubicin-based multiagent chemotherapy<sup>1</sup>

**Remember:** Patients with systemic ALCL and secondary skin lesions require aggressive multi-agent chemotherapy.

**Note:** Primary cutaneous ALCL in children has a high relapse rate despite systemic chemotherapy; however there is no systemic spread and the course is still favorable.<sup>14</sup> Optimal therapy is not known.<sup>12</sup>

**Note:** No prognostic difference is seen in anaplastic vs. pleomorphic vs. immunoblastic morphology

## Lymphomatoid Papulosis

Overlapping clinical and pathologic features indicate LyP and some cutaneous ALCL represent a continuous spectrum<sup>70, 71</sup>

### Clinical features of LyP:<sup>1, 6</sup>

- Adults (median age 45 years; male: female ratio 1.5:1)
- May occur in children<sup>6, 72, 73</sup>
- Multiple papular, papulonecrotic, or nodular lesions, usually <1 cm
- Extremities and trunk >> face, genitalia
- Lesions usually ulcerate and heal with a scar in 3-12 weeks
- Chronic, recurrent lesions; duration of several months to more than 40 years<sup>1</sup>
- Treatment:<sup>1</sup>
  - None if few lesions and little scarring
  - Low dose methotrexate (5-20 mg/wk) helps suppress development of new lesions
  - PUVA and topical chemotherapy (relapses generally occur after the discontinuation)
- 5% - 20% are associated with lymphoma (MF, ALCL, or HL) after, concurrent with, or before the diagnosis of LyP<sup>6, 74, 75</sup>
- Lymphomas arising in LyP (ALCL and MF) do not appear to have a more aggressive course<sup>6, 76</sup>

### Histologic features of LyP:

- Large atypical cells mixed with small lymphocytes, acute inflammatory cells
- Variable appearance depending on the stage of evolution (i.e., age) of the lesion
- Three histologic types<sup>72, 77</sup>
  - Type A
    - Wedge shaped infiltrate, perivascular
    - Scattered CD30+ large atypical cells
    - Dense background of inflammatory cells; neutrophils, and/or eosinophils may be particularly prominent
  - Type B (less common, <10%)
    - Band-like dermal distribution
    - Lymphocytes with convoluted “cerebriform” nuclei
    - Some epidermotropism may be present
    - Large CD30+ cells are rare or absent
    - Distinguished from mycosis fungoides on clinical parameters; LyP remits spontaneously and does not have extensive patches and plaques
  - Type C (diffuse large cell type)
    - Indistinguishable from ALCL except invasion of the subcutis is minimal or absent
    - **History of regression is the most important distinguishing feature**
    - May have extracutaneous spread, so true “borderline” lesion
- Variants include: follicular<sup>78, 79</sup> and granulomatous eccrinotropic<sup>80</sup>

### Immunophenotype of LyP:

- Most series report predominance of CD4+ phenotype, but some report CD8+<sup>1, 37, 72</sup>
- EMA present in up to 31% of LyP<sup>31</sup>
- CD15+ in up to 33% in frozen tissue<sup>81</sup>
- TIA-1 and/or granzyme B expressed in 74% - 100% of LyP<sup>36, 37, 72</sup>

- CD56 in 0% - 50%<sup>72, 82</sup>
- Fascin+ in 24 % LyP, but is present in 60% of LyP associated with systemic lymphoma and may be a predictor of disease progression<sup>48</sup>
- Cutaneous lymphocyte antigen (CLA) is present on most large cells in LyP (82% +/- 6%) as compared to weaker expression in C-ALCL (13% +/- 7%)<sup>83</sup>

### Molecular findings in LyP:

- Clonal T-cell populations have been demonstrated in 38% - 100% of LyP<sup>76, 84, 85</sup> and the same clone is present in LyP and the lymphomas that develop in some cases.<sup>76, 86</sup> Other studies report polytypic large CD30+ T-cells in LyP with a clonal population of small CD3+ T-cells.<sup>87</sup>

**Clinical (Table 2) and pathologic (Table 3) features are used to distinguish ALCL and LyP:**

**Table 2. Clinical Features Useful in Distinguishing ALCL and LyP**

Clinical Features	LyP	ALCL
Type of lesion	Papules, nodules	Nodules, tumors, rarely rash
Number	Multiple	Single or grouped
Size	Usually < 1 cm*	> 2 cm*
Sites	Extremities, trunk	Extremities, head and neck
Regression	Yes, usually with scar	~ 25% of cases

\* > 3 cm more predictive of lymphoma; borderline lesions are usually intermediate in size, 1-2 cm.

**Table 3. Pathologic Features Useful in Distinguishing ALCL and LyP**

Histology/ Immunophenotype	LyP	ALCL
Pattern of infiltration	Wedge-shaped perivascular/periadnexal	More diffuse
Subcutaneous involvement	Absent (or minimal)	Present
Mixed inflammatory cells	Many	Few to many
CD30+Cells	Scattered single or small clusters	Large groups or sheets
EMA	Present in 10% to 30% of cases	Present in 10% to 30% of cases
ALK	Usually negative	Usually negative
Fascin	Present in 25%*	Present in 50% - 75%

EMA = epithelial membrane antigen

\* 60% of LyP that progress to ALCL are fascin+

## Differential Diagnosis of CD30+ Lymphoproliferative Disorders

### Primary Cutaneous ALCL versus Transformed Mycosis Fungoides (MF):

#### *Transformation of mycosis fungoides to large cell lymphoma:*<sup>88-90</sup>

- Occurs in ~20-25% of cases of MF at a median of 12 months (range 0-128 months)
- Large cells form microscopic nodules or represent >25% of total cells
- Epidermotropism may be absent
- CD30+ in 25%-50% of cases
- Aggressive disease
  - Median survival 29-37 months from diagnosis compared to 163 months for MF without transformation
  - Median survival after transformation 12-19 months

**Features useful in distinguishing transformed mycosis fungoides (MF) and primary cutaneous ALCL:**

- Antecedent or coexistent patch or plaque stage lesions
- Small residual cerebriform lymphocytes usually present

**Remember:** Do immunohistochemistry for CD4 and CD8; Small, reactive CD8+ lymphocytes with irregular, sometimes “cerebriform appearing”, nuclei may surround and infiltrate primary cutaneous ALCL.

**Primary Cutaneous ALCL versus Primary Cutaneous Hodgkin Lymphoma:**

Hodgkin lymphoma (0.5%-3.4%) may secondarily involve the skin as secondary retrograde lymphatic spread from involved lymph nodes or infiltration of soft tissue in advanced (terminal) disease; primary cutaneous Hodgkin lymphoma is very rare.

**Primary cutaneous Hodgkin lymphoma:** <sup>91-93</sup>

- Very rare
- Clinical course is variable; usually indolent; can develop nodal involvement 2 mos-46 years; rare cases with aggressive course
- Extremities >>trunk
- Tumor cells are scattered, not sheet-like
- Diagnostic, multinucleate RS cells present
- CD45-, CD30+, CD15+, EBV+/-

**Table 4. Pathologic Features Useful in the Differential Diagnosis of CD30+ Cutaneous lymphomas/LyP**

Type of lesion	# of Tumor Cells	RS-cells	CD15	CD30	EMA	CD45	EBV	T cell Antigens	Other
ALCL	Many	+/-	-/+	+	-/+	+/-	-	+	
LyP	Few	Rare	+/-*	+	-/+	+	-/+	+	Multiple papules with regression
Transformed Mycosis Fungoides	Many	Rare	-/+	+/-	NT	+	NT	+	Admixed cerebriform lymphocytes; history of patches and plaques
Hodgkin Lymphoma	Few	+	+	+	-	-	+/-	-	Very rare

+ = >50% of cases; +/- = 25% - 49%; -/+ = 5% - 24%; - < 5%

\* frozen tissue<sup>81</sup>

**Beware:** CD30 expression has been reported in granulocytic sarcoma, which can occur in the skin<sup>94</sup>; CD30 can be weakly expressed in malignant melanoma.<sup>95</sup> CD30 expression in these other tumors is usually weak and more diffuse.

**Primary Cutaneous ALCL versus Cutaneous Nasal Type NK/T Cell Lymphoma:**

- ALCL may show vascular invasion (angiocentricity) but lacks angiodestruction
- Zonal necrosis is rare or absent
- EBV expression is uncommon in ALCL
- The immunophenotype is not definitive; CD56 is present in some cases of ALCL and CD30 expression is seen in ~20% of nasal type NK/T cell lymphoma

**Note:** ALCL often involves the subcutaneous tissue, but the sheet-like growth of large tumor cells and strong CD30 expression distinguishes it from subcutaneous panniculitis-like T-cell lymphoma.

### **Primary Cutaneous ALCL versus Reactive Infiltrates:**

***Reactive cutaneous T-cell infiltrates often have CD30+ large cells and may mimic ALCL or LyP in the following circumstances:***

- After multiagent chemotherapy for large cell lymphoma or leukemia<sup>96</sup>
- Following marrow ablative therapy and growth factor administration at the time of lymphocyte recovery (eruption of lymphocyte recovery)<sup>97</sup>
- Hypersensitivity reaction to carbamazepine<sup>98</sup> Rare C-ALCL have been described in patients on carbamazepine<sup>99</sup>
- Herpesvirus or parapoxvirus infection<sup>100, 101</sup>
- Reactive cutaneous infiltrates that contain a prominent neutrophilic or eosinophilic component including insect and spider bites, hidradenitis suppurativa, Sweet syndrome<sup>102, 103</sup>

**Note:** These reactions often have the gross appearance of a rash and CD30+ cells are often scattered rather than sheet-like; however, some may have a perivascular distribution with clustering of CD30+ cells<sup>97</sup>

## **Summary**

1. A diagnosis of primary cutaneous ALCL can only be made after careful staging. Regional node involvement is controversial and currently most cases are treated with systemic chemotherapy.
2. ALK expression is rarely present in primary cutaneous ALCL and usually indicates systemic disease.
3. Borderline lesions between ALCL and LyP should be diagnosed as LyP type C if there is a clinical history of regression and lack of involvement of the subcutaneous tissue.
4. If CD4+ cerebriform small lymphocytes are present, or if there is an antecedent history of patch or plaque lesions, transformation of mycosis fungoides to “secondary” ALCL should be considered.
5. The treatment of primary cutaneous ALCL is conservative and usually local (complete excision with or without local irradiation); systemic treatment may be indicated in multicentric disease.
6. Close clinical follow-up is recommended as 10% - 25% of C-ALCL (particularly multicentric disease) develop extracutaneous disease.
7. CD30+ large cells may be present in reactive conditions; the CD30+ cells are usually scattered and do not form large clusters.

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