OVERVIEW & DEFINITION

- **Primary cutaneous CD30+ T-cell lymphoproliferative disorders (LPDs) represent a spectrum that includes primary cutaneous anaplastic large cell lymphoma (ALCL), lymphomatoid papulosis, and "borderline" cases with overlapping clinical and histopathologic features.[a,b]**
- **Clinical correlation with histopathologic features is essential for establishing the diagnosis of primary cutaneous CD30+ T-cell LPDs; diagnosis cannot be made based on pathology review alone.**

Differential diagnosis

- **It is critical to distinguish CD30+ T-cell LPDs from other CD30+ processes involving the skin that include:**
  - **Systemic lymphomas (eg, systemic ALCL, ATLL, PTCL),**
  - **Other cutaneous process such as other CD30+ skin lymphomas such as mycosis fungoides (MF), especially transformed MF, cytotoxic T-cell lymphomas, and**
  - **Benign disorders such as lymphomatoid drug reactions, arthropod bites, viral infections, and others.**
- **Lymphomatoid drug reactions have been linked with certain drugs (eg, amlodipine, carbamazepine, cefuroxime, valsartan) and are associated with CD30+ atypical large cells in histology**
- **MF and primary cutaneous CD30+ T-cell LPD can coexist in the same patient.**

- **Primary cutaneous ALCL (PC-ALCL)**
  - **Represents about 8% of cutaneous lymphoma cases.[b]**
  - **Unlike systemic ALCL, PC-ALCL typically follows an indolent course and although cutaneous relapses are common an excellent prognosis is usually maintained.[c]**
  - **Histologically characterized by diffuse, cohesive sheets of large CD30-positive (in >75%) cells with anaplastic, pleomorphic, or immunoblastic appearance.[a,b]**
  - **Clinical features typically include solitary or localized nodules or tumors (often ulcerated); multifocal lesions occur in about 20% of cases. Extracutaneous disease occurs in about 10% of cases, usually involving regional lymph nodes.[a,b] Patches and plaques may also be present and some degree of spontaneous remittance in lesions may also be seen.**

- **Lymphomatoid papulosis (LyP)**
  - **LyP has been classified (WHO-EORTC) under lymphomas but may be best classified as a LPD as it is a uniformly spontaneously regressing process.[b]**
  - **LyP has been reported to be associated with other lymphomas such as MF, PC-ALCL, systemic ALCL, or Hodgkin lymphoma.[d,e]**
  - **Histologically heterogenous with large atypical anaplastic, immunoblastic, or Hodgkin-like cells in a marked inflammatory background;[a] several histologic subtypes (types A to D and other types, with CD30-positive cells) defined based on evolution of skin lesions.[d]**
  - **Clinical features characterized by chronic, recurrent spontaneously regressing papulonodular (grouped or generalized) skin lesions.[a,b,d]**

See Diagnosis (PCTLD-2)

[a]Ralfkiaer E, Willemze R, Paulli M, Kadin ME. Primary cutaneous CD30-positive T-cell lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (ed 4th). Lyon: IARC; 2008:300-301.

[b]Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785.

[c]Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol 2009;145:1399-1404.

[d]Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118:4024-4035.

[e]Due to overlapping immunophenotype and morphology, need to use caution to *not* diagnose CD30+ T-cell in lymph nodes as HL (Eberle FC, Song JY, Xi L, et al. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Amer J Surg Pathol 2012;36:716-725.)

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DIAGNOSIS

ESSENTIAL:

- **Clinical presentation: see Overview and Definition**
- **Clinical pathologic correlation is essential**
- **Complete skin examination for evidence of MF**
- **Biopsy of suspicious skin sites**
  - **Histopathology review of adequate biopsy (punch, incisional, or excisional).**
  - **Review of all slides with at least one paraffin block representative of the tumor should be done by a pathologist with expertise in the diagnosis of cutaneous T-cell lymphoma. Rebiopsy if consult material is nondiagnostic.**
  - **Biopsy of all types of clinical lesions present will aid in final diagnosis.**
- **Adequate immunophenotyping to establish diagnosis[f,g] on skin biopsy:**
  - **IHC: CD3, CD4, CD8, CD20, CD30, CD56, ßF1, ALK[h]**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **On skin biopsy:**
  - **Expanded IHC: CD2, CD5, CD7, CD25, TIA1, granzyme B, perforin, GM1, EBER-ISH**
  - **Molecular analysis to detect gene rearrangements: TCR[i] (assessment of clonality)**
- **Excisional or incisional biopsy of suspicious lymph nodes**
- **Assessment of HTLV-1 serology in at-risk populations to identify CD30+ ATLL**

- **Cutaneous ALCL**
- **LyP[j]**

→ **See Workup (PCTLD-3)**

CD30+ transformed mycosis fungoides → **See Mycosis Fungoides Guidelines (MFSS-1)**

[f] See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[g] Typical immunophenotype: CD30+ (>70% cells), CD4+ variable loss of CD2/CD5/CD3, CD8+ (<5%) cytotoxic granule proteins positive.
[h] ALK positivity and t(2;5) translocation is typically absent in PC-ALCL and LyP.
[i] TCR gene rearrangement results should be interpreted with caution. TCR clonal rearrangement can be seen in non-malignant conditions or may not be demonstrated in all cases of MF/SS. Demonstration of identical clones in skin, blood, and/or lymph node may be helpful in selected cases.
[j] LyP is not considered a malignant disorder; however, there is an association with other lymphoid malignancy (mycosis fungoides or PC-ALCL). Staging studies are done in LyP only if there is suspicion of systemic involvement by an associated lymphoma.

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WORKUP

Cutaneous ALCL

ESSENTIAL:
- Complete physical examination including entire skin;[k] palpation of peripheral lymph node regions; liver or spleen enlargement
- CBC, differential
- Comprehensive metabolic panel
- LDH
- Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT
- Biopsy suspicious nodes[e,l,m]

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age[n]
- Bone marrow aspiration and biopsy optional for solitary C-ALCL or C-ALCL without extracutaneous involvement on imaging

- Primary cutaneous ALCL → See Primary Treatment (PCTLD-4)
- Cutaneous ALCL with regional node → See Primary Treatment (PCTLD-4)
- Systemic ALCL → See Peripheral T-cell Lymphoma (TCEL-1)

LyP[j]

ESSENTIAL:
- Complete physical examination including entire skin;[k] palpation of peripheral lymph node regions; liver or spleen enlargement
- CBC, differential
- Comprehensive metabolic panel
- LDH

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age[n]
- Chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET-CT[j,o]
- Bone marrow aspiration and biopsy (not done for typical LyP)[j,o]

→ See Primary Treatment for LyP (PCTLD-5)

[e]Due to overlapping immunophenotype and morphology, need to use caution to *not* diagnose CD30+ T-cell in lymph nodes as HL (Eberle FC, Song JY, Xi L, et al. Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Amer J Surg Pathol 2012;36:716-725.)
[j]LyP is not considered a malignant disorder; however, there is an association with other lymphoid malignancy (mycosis fungoides or PC-ALCL). Staging studies are done in LyP only if there is suspicion of systemic involvement by an associated lymphoma.
[k]Monitoring the size and number of lesions will assist with response assessment.
[l]Consider systemic ALCL, regional lymph node involvement with PC-ALCL, or lymph node involvement with transformed MF.
[m]Consider PC-ALCL if in draining lymph nodes only.
[n]Many skin-directed and systemic therapies are contraindicated or of unknown safety in pregnancy. Refer to individual drug information.
[o]Only done to exclude an associated lymphoma.

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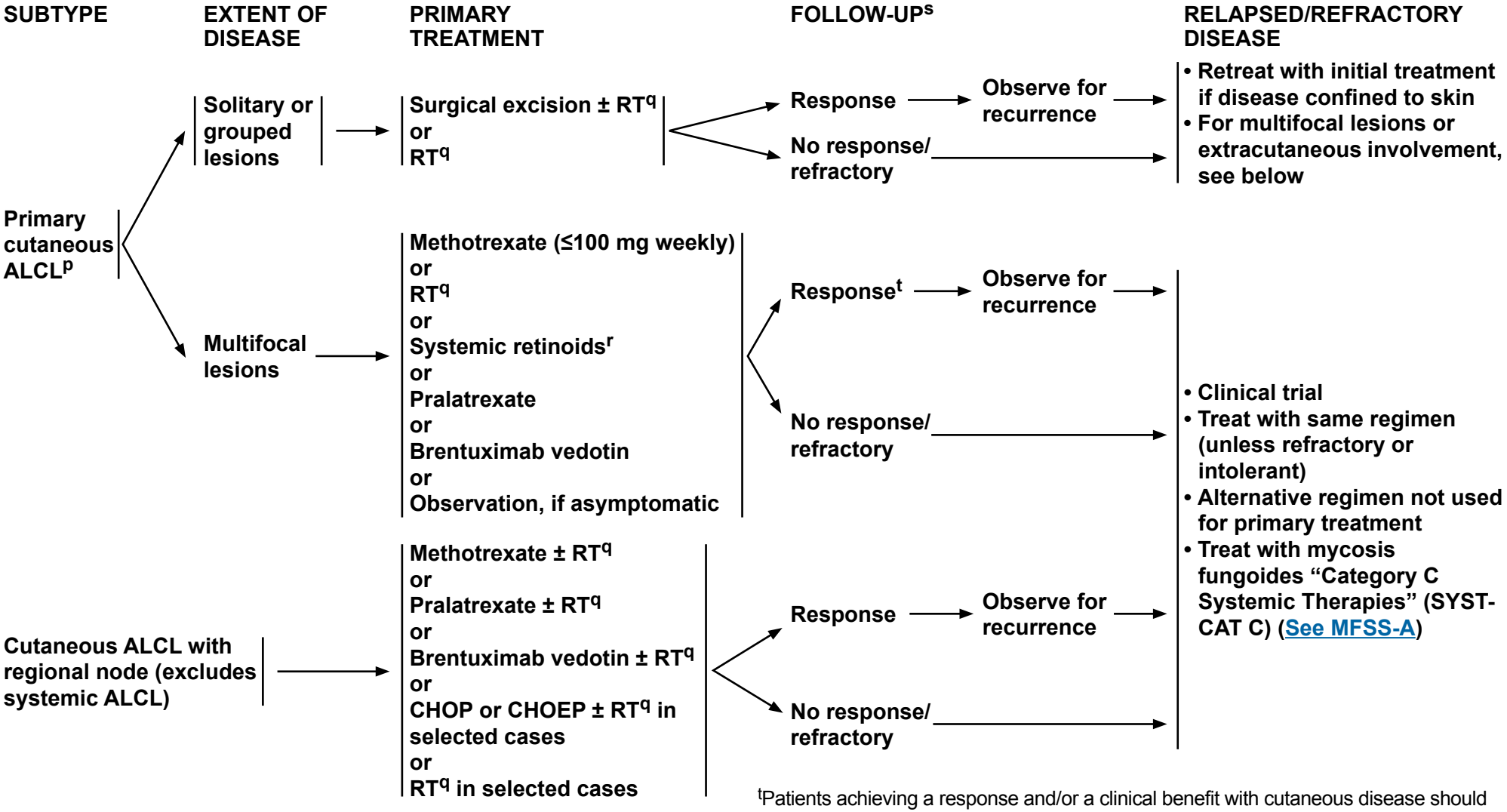

[p]Regression of lesions may occur in up to 44% of cases.
[q]See Principles of Radiation Therapy (NHODG-D).
[r]Limited data from case reports (eg, bexarotene).
[s]Mycosis fungoides can develop over time; continue to conduct thorough skin exam during follow-up.
[t]Patients achieving a response and/or a clinical benefit with cutaneous disease should be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

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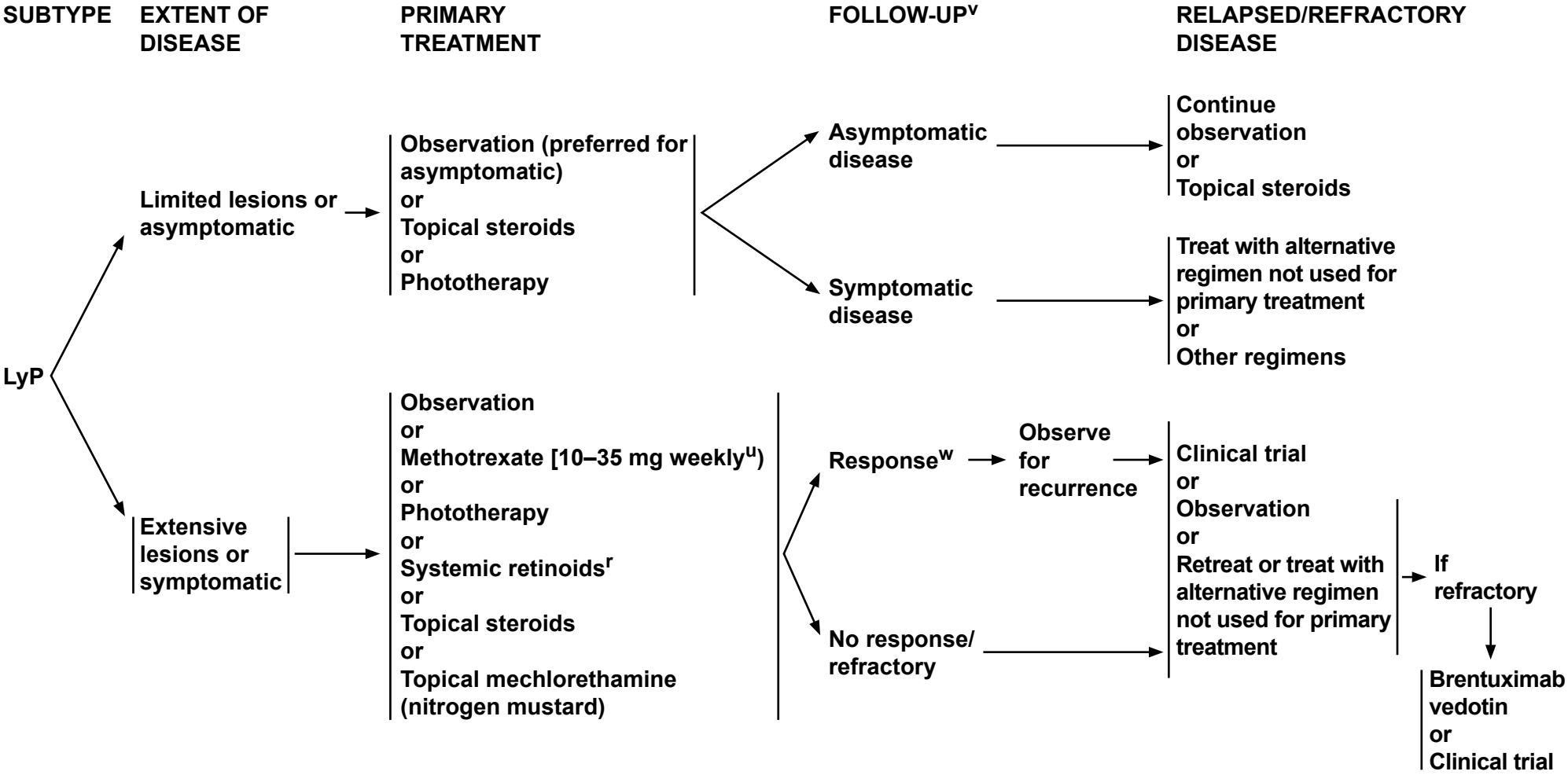

[r]Limited data from case reports (eg, bexarotene).

[u]Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 2011;118:4024-4035.

[v]Life-long follow-up is warranted due to high risks for second lymphoid malignancies; continue to conduct thorough skin exam during follow-up.

[w]Patients achieving a response and/or a clinical benefit may be considered for maintenance or taper regimens to optimize response duration. Patients who relapse often respond well to the same treatment. Patients with a PR should be treated with the other options in the primary treatment list to improve response before moving onto treatment for refractory disease. Patients with relapse or persistent disease after initial primary treatment may be candidates for clinical trials.

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General approach/overview of management

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