

SECONDARY LYMPHOMAS OF THE SKIN

Daniel A. Arber, MD
Stanford University

Malignant lymphomas that secondarily involve the skin are relatively common and may be difficult to distinguish from primary skin lymphomas. While the morphologic features of primary and secondary lymphomas of the skin are often very similar, the clinical behavior of primary and secondary disease is often dramatically different.¹ Although large series of secondary cutaneous lymphomas are uncommon, secondary lymphomas or lymphomas that involve both nodal sites and the skin at presentation appear to represent approximately 25% of all cutaneous lymphomas and up to 50% of cutaneous lymphomas other than mycosis fungoides.^{2,3} In a recent survey of cutaneous lymphomas diagnosed at Stanford University, 24.6% were considered secondary based on a prior or simultaneous diagnosis of non-cutaneous lymphoma. The frequency of each lymphoma type among secondary cutaneous lymphomas at Stanford is given in parentheses after each disease type below.

In contrast to primary cutaneous lymphoma, secondary cutaneous lymphomas show a B cell predominance. Similar to other sites of lymphoma, diffuse large B cell lymphoma and follicular lymphoma secondarily involving the skin are relatively common. However, secondary cutaneous involvement by T and NK cell proliferations is still more common in the skin than the frequency of primary nodal NK and T cell lymphomas.

B cell lymphomas (65.8%)

Diffuse large B cell lymphoma (26.8%)

It is not surprising that diffuse large B cell lymphoma, the most common type of nodal non-Hodgkin lymphoma, is also one of the most common lymphoma types to secondarily involve the skin. The main differential diagnosis of this lymphoma is with diffuse primary follicular center cell lymphoma of the skin and primary cutaneous diffuse large B-cell lymphoma of the leg type. Both primary and secondary diffuse large B cell lymphomas commonly involve the head and neck regions or the extremities, but trunk involvement may be more characteristic of secondary disease. While the morphologic features of these entities are similar, both clinical behavior and gene expression profiling find clear differences in primary and secondary types.⁴ Other than clinical features, there are few clues to secondary cutaneous disease. The most common primary large B cell neoplasms of the skin are usually CD10 negative and lack t(14;18).⁵ Therefore, expression of CD10 or t(14;18), common findings in a subset of nodal diffuse large B cell lymphomas, should warrant further investigation for systemic disease. However, both CD10 expression and t(14;18) may occur in primary disease and these features should not be considered as definitive evidence of a secondary lesion.^{6,7}

Follicular lymphoma (21.4%)

Both primary and secondary cutaneous follicular lymphomas frequently involve the head and neck region.⁸ Both show the presence of large centrocytes as well as cells with irregular nuclear contours. Either type may have a diffuse or nodular appearance in the skin. While some studies have found distinctive immunophenotypic and molecular

genetic differences between primary and secondary follicular lymphoma, these are more striking in European studies than in series of patients from North America, suggesting a possible geographic difference in the primary diseases.⁸⁻¹¹ BCL6 expression is common in both primary and secondary disease, but expression of BCL2 and CD10 tends to correlate more with secondary disease. Expression of BCL2 and CD10 in primary disease, however, is frequent enough to make use of any one of these markers as a discriminator of primary versus secondary disease unreliable. The combined expression of BCL6, BCL2 and CD10 appears to a much stronger predictor of secondary disease than any one alone.¹²

Detection of t(14;18) has also been reported to be fairly specific for secondary disease, but this is also controversial.^{8-11,13} While most studies show a clear increase in the frequency of this translocation in secondary cutaneous follicular lymphoma, it is well documented in some primary cases. These t(14;18) positive primary cases are less frequent in European studies than in North American studies.

Marginal zone lymphoma (6.8%)

Marginal zone lymphomas are often primary cutaneous lymphomas, but may also be secondary. Distinct morphologic differences between primary and secondary cases are not well described, and the differential diagnosis of secondary marginal zone lymphoma of the skin would include primary marginal zone lymphoma, follicular lymphomas and reactive proliferations. In one series, primary or concurrent tumors involving the ocular adnexa or salivary glands seemed to occur more commonly with skin disease than gastric primaries.¹⁴ Secondary disease appears to be more commonly associated with multifocal skin disease when compared to primary marginal zone lymphomas, and the age of development of skin lesions was later in secondary versus primary disease (64 vs. 54 years) in one series.¹⁵ The molecular genetics of primary cutaneous marginal zone lymphoma appears to differ from other extranodal marginal zone lymphomas, in that the t(14;18)(q32;q21) of the *IGH/MALT1* fusion is relatively common, but the t(11;18)(q21;q21) of *API/MALT1* or the t(1;14)(p22;q32) of *IGH/BCL10* are uncommon in the skin.^{16,17} This might suggest that the detection of the later translocations would support secondary disease, but this hypothesis has not been adequately tested.

Small lymphocytic lymphoma/chronic lymphocytic leukemia (5.5%)

Small lymphocytic lymphoma/chronic lymphocytic leukemia may present as a skin lesion, but is not considered a primary cutaneous lymphoma. Patients may present with erythematous papules, plaques, nodules or large tumors which are usually not ulcerated.¹⁸ The lesions may be generalized or localized and virtually any site may be involved. A predilection for prior sites of herpes infection has been suggested in some cases.^{18,19} Virtually any pattern of infiltration of the dermis may be seen, including patchy, nodular, diffuse or band-like. Proliferation centers are often not seen, but the infiltrate has the characteristic CD20 (weak), CD5, CD43 and CD23 expression profile of CLL. Cutaneous involvement by CLL does not appear to impact prognosis.

T and NK cell lymphomas (34.2%)

Peripheral T cell lymphoma, unspecified (14.1%)

Peripheral T cell lymphomas (PTCLs) in the “unspecified” group of the WHO secondarily involve the skin or have cutaneous involvement at the time of diagnosis in 19-55% of cases.²⁰⁻²⁴ Essentially all subtypes of peripheral T cell lymphoma can present with skin involvement. The clinical appearance of the lesions can be quite variable, ranging from erythematous plaques to distinct tumor nodules. Because of the variable presentation and heterogeneous morphologic features, cases may mimic other conditions including granulomatous infections, granuloma annulare, dermatomyositis, panniculitis, vasculitis and eczema.^{20,25-27} Non-cutaneous peripheral T cell lymphomas with either simultaneous or secondary skin involvement are clinically aggressive when compared to primary cutaneous T cell neoplasms.

Anaplastic large cell lymphoma (9.1%)

Secondary cutaneous involvement by nodal anaplastic large cell lymphoma (ALCL) is distinct from primary cutaneous anaplastic large cell lymphoma and is important to recognize. While both show dermal involvement by CD30-positive large cells, the primary cutaneous disease is relatively indolent compared to the worse prognosis of skin involvement by ALK-positive anaplastic large cell lymphoma and the even more aggressive behavior of ALK-negative, non-cutaneous anaplastic large cell lymphoma.^{28,29} Nodal ALCL shows a bimodal age distribution that includes children, while primary cutaneous disease is primarily a disease of adults. Although rare exceptions are reported, the vast majority of primary cutaneous ALCLs are ALK-negative and lack the t(2;5) or variant *ALK* translocations.^{30,31} The detection of ALK expression in a skin lymphoma should warrant extensive evaluation for extracutaneous ALCL. Skin involvement by nodal ALCL occurs in approximately 30% of children with the disease, and most of these are ALK positive.^{32,33} The lack of ALK in a cutaneous, CD30-positive lymphoma, however, cannot be used as sufficient support for a primary cutaneous ALCL. A significant number of nodal ALCL cases, particularly in adults, will be ALK negative, and other CD30-positive proliferations, such as transformed mycosis fungoides and rare cases of Hodgkin’s disease in the skin may occur. Initial studies of clusterin expression in ALCL suggested that it was restricted to the non-cutaneous ALCL cases, but this was not confirmed in later studies.^{34,35}

NK/T cell lymphoma (5.9%)

Nasal type NK/T cell lymphoma may occur as primary cutaneous disease, may be secondary, or may occur simultaneously with disease at other sites. From 8 to 20% of NK/T cell lymphomas of the nasal type have skin involvement.^{24,36} Some patients with apparent primary cutaneous disease have developed nasal masses within one to seven months of diagnosis,³⁷ and the disease is aggressive no matter what the presentation. While some cases have presented as erythematous eruptions, most form ulcerated tumor nodules that may occur at any cutaneous site.^{37,38} The infiltrate is usually dense, surrounding adnexal structures and vessels and often extending from the dermis into subcutaneous adipose tissue. As in other sites, angioinvasion and necrosis may occur and the infiltrate is composed of medium to large irregular cells. The cells may have intermediate chromatin that is similar to a blastic infiltrate. Similar to other sites, the cells usually express CD2, cytoplasmic CD3, CD56 and are EBV positive.

Angioimmunoblastic T cell lymphoma (3.2%)

Skin lesions are common in patients with angioimmunoblastic T cell lymphoma (AILT), present in approximately half of cases.²⁴ Based on one small series, the majority of skin lesions in this disorder demonstrate T cell clonality although the histologic changes in the skin may be subtle.³⁹ A maculopapular eruption involving the trunk or extremities is the most common presentation, and may be confused with a drug or viral reaction; however, plaque-like and nodular lesions may also occur.³⁹⁻⁴³ Several histologic patterns of AILT in the skin have been described. The infiltrate may be sparse with fairly nonspecific perivascular lymphocytes and eosinophils with associated capillary hyperplasia, with or without obvious abnormalities of the lymphocytes. In most cases, however, enlarged, atypical lymphoid cells, sometimes including cells with a Hodgkin-like appearance, are present and rare cases show a dense superficial dermal lymphoid infiltrate with vascular proliferation similar to nodal AILT. The large atypical cells may show aberrant loss of T cell antigens. EBV has been studied in a small number of cutaneous cases and is usually absent or only present in a small percentage of cells, but one reported case had a large number of EBV-positive cells in a recurrent skin lesion following only sparse EBV positive cells in an initial skin biopsy.⁴¹

Many primary and secondary cutaneous lymphomas have similar names and similar morphologic features, and in some cases, such as NK/T cell lymphoma, AILT and CLL, they represent differing presentations of the same disease. For other entities, however, it is important to recognize the clinical difference between the primary cutaneous disease and systemic disease. This is particularly true for primary cutaneous ALCL, follicular lymphoma and the cutaneous diffuse large B cell lymphomas. In these settings, correlation with more detailed immunophenotyping studies and complete clinical evaluation is essential for proper classification.

Acknowledgment: I would like to thank Drs. Kendall Price, Chris Lai and Uma Sundram for their help in tabulating the Stanford University incidence data for secondary cutaneous lymphomas.

References

1. Willemze R, Jaffe ES, Burg G et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768-3785.
2. Tan SH, Sim CS, Ong BH. Cutaneous lymphomas other than mycosis fungoides in Singapore: a clinicopathological analysis using recent classification systems. *Br J Dermatol*. 2003;149:542-553.
3. Nagasawa T, Miwa H, Nakatsuka S et al. Characteristics of cutaneous lymphomas in Osaka, Japan (1988-1999) based on the European Organization for Research and Treatment of Cancer classification. *Am J Dermatopathol*. 2000;22:510-514.
4. Storz MN, van de RM, Kim YH et al. Gene expression profiles of cutaneous B cell lymphoma. *J Invest Dermatol*. 2003;120:865-870.
5. Kim BK, Surti U, Pandya AG et al. Primary and secondary cutaneous diffuse large B-cell lymphomas: a multiparameter analysis of 25 cases including

- fluorescence in situ hybridization for t(14;18) translocation. *Am J Surg Pathol.* 2003;27:356-364.
6. Hembury TA, Lee B, Gascoyne RD et al. Primary cutaneous diffuse large B-cell lymphoma: a clinicopathologic study of 15 cases. *Am J Clin Pathol.* 2002;117:574-580.
 7. Wiesner T, Streubel B, Huber D et al. Genetic aberrations in primary cutaneous large B-cell lymphoma: a fluorescence in situ hybridization study of 25 cases. *Am J Surg Pathol.* 2005;29:666-673.
 8. Kim BK, Surti U, Pandya A et al. Clinicopathologic, immunophenotypic, and molecular cytogenetic fluorescence in situ hybridization analysis of primary and secondary cutaneous follicular lymphomas. *Am J Surg Pathol.* 2005;29:69-82.
 9. Mirza I, Macpherson N, Paproski S et al. Primary cutaneous follicular lymphoma: an assessment of clinical, histopathologic, immunophenotypic, and molecular features. *J Clin Oncol.* 2002;20:647-655.
 10. Vergier B, Belaud-Rotureau MA, Benassy MN et al. Neoplastic cells do not carry bcl2-JH rearrangements detected in a subset of primary cutaneous follicle center B-cell lymphomas. *Am J Surg Pathol.* 2004;28:748-755.
 11. Cerroni L, Arzberger E, Putz B et al. Primary cutaneous follicle center cell lymphoma with follicular growth pattern. *Blood.* 2000;95:3922-3928.
 12. Hoefnagel JJ, Vermeer MH, Jansen PM et al. Bcl-2, Bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle centre cell origin and differential diagnostic significance. *Br J Dermatol.* 2003;149:1183-1191.
 13. Child FJ, Russell-Jones R, Woolford AJ et al. Absence of the t(14;18) chromosomal translocation in primary cutaneous B-cell lymphoma. *Br J Dermatol.* 2001;144:735-744.
 14. Bailey EM, Ferry JA, Harris NL et al. Marginal zone lymphoma (low-grade B-cell lymphoma of mucosa-associated lymphoid tissue type) of skin and subcutaneous tissue: a study of 15 patients. *Am J Surg Pathol.* 1996;20:1011-1023.
 15. Rijlaarsdam JU, van der Putte SC, Berti E et al. Cutaneous immunocytomas: a clinicopathologic study of 26 cases. *Histopathology.* 1993;23:117-125.
 16. Gronbaek K, Ralfkiaer E, Kalla J et al. Infrequent somatic Fas mutations but no evidence of Bcl10 mutations or t(11;18) in primary cutaneous MALT-type lymphoma. *J Pathol.* 2003;201:134-140.
 17. Schreuder MI, Hoefnagel JJ, Jansen PM et al. FISH analysis of MALT lymphoma-specific translocations and aneuploidy in primary cutaneous marginal zone lymphoma. *J Pathol.* 2005;205:302-310.
 18. Cerroni L, Zenahlik P, Hofler G et al. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia: a clinicopathologic and prognostic study of 42 patients. *Am J Surg Pathol.* 1996;20:1000-1010.
 19. Cerroni L, Zenahlik P, Kerl H. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia arising at the site of herpes zoster and herpes simplex scars. *Cancer.* 1995;76:26-31.
 20. Su IJ, Wu YC, Chen YC et al. Cutaneous manifestations of postthymic T cell malignancies: description of five clinicopathologic subtypes. *J Am Acad Dermatol.* 1990;23:653-662.

21. Nakamura S, Suchi T, Koshikawa T et al. Clinicopathologic study of 212 cases of peripheral T-cell lymphoma among the Japanese. *Cancer*. 1993;72:1762-1772.
22. Bekkenk MW, Vermeer MH, Jansen PM et al. Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. *Blood*. 2003;102:2213-2219.
23. Gisselbrecht C, Gaulard P, Lepage E et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). *Blood*. 1998;92:76-82.
24. Lopez-Guillermo A, Cid J, Salar A et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. *Ann Oncol*. 1998;9:849-855.
25. Scarabello A, Leinweber B, Ardigo M et al. Cutaneous lymphomas with prominent granulomatous reaction: a potential pitfall in the histopathologic diagnosis of cutaneous T- and B-cell lymphomas. *Am J Surg Pathol*. 2002;26:1259-1268.
26. Bhushan M, Craven NM, Armstrong GR et al. Lymphoepithelioid cell lymphoma (Lennert's lymphoma) presenting as atypical granuloma annulare. *Br J Dermatol*. 2000;142:776-780.
27. Rencic A, Laman S, Nousari HC. Peripheral T cell lymphoma presenting as dermatomyositis-like eruption. *J Cutan Med Surg*. 2002;6:218-220.
28. de Bruin PC, Beljaards RC, van Heerde P et al. Differences in clinical behaviour and immunophenotype between primary cutaneous and primary nodal anaplastic large cell lymphoma of T-cell or null cell phenotype. *Histopathology*. 1993;23:127-135.
29. Bekkenk MW, Geelen FA, Voorst Vader PC et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood*. 2000;95:3653-3661.
30. Beylot-Barry M, Groppi A, Vergier B et al. Characterization of t(2;5) reciprocal transcripts and genomic breakpoints in CD30+ cutaneous lymphoproliferations. *Blood*. 1998;91:4668-4676.
31. DeCoteau JF, Butmarc JR, Kinney MC et al. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30⁺ lymphoproliferative disorders: comparison with anaplastic large-cell lymphoma of nodal origin. *Blood*. 1996;87:3437-3441.
32. Alessandri AJ, Pritchard SL, Schultz KR et al. A population-based study of pediatric anaplastic large cell lymphoma. *Cancer*. 2002;94:1830-1835.
33. Sandlund JT, Pui CH, Santana VM et al. Clinical features and treatment outcome for children with CD30+ large-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 1994;12:895-898.
34. Wellmann A, Thieblemont C, Pittaluga S et al. Detection of differentially expressed genes in lymphomas using cDNA arrays: identification of clusterin as a new diagnostic marker for anaplastic large-cell lymphomas. *Blood*. 2000;96:398-404.

35. Lae ME, Ahmed I, Macon WR. Clusterin is widely expressed in systemic anaplastic large cell lymphoma but fails to differentiate primary from secondary cutaneous anaplastic large cell lymphoma. *Am J Clin Pathol*. 2002;118:773-779.
36. Ko YH, Ree HJ, Kim WS et al. Clinicopathologic and genotypic study of extranodal nasal-type natural killer/T-cell lymphoma and natural killer precursor lymphoma among Koreans. *Cancer*. 2000;89:2106-2116.
37. Miyamoto T, Yoshino T, Takehisa T et al. Cutaneous presentation of nasal/nasal type T/NK cell lymphoma: clinicopathological findings of four cases. *Br J Dermatol*. 1998;139:481-487.
38. Kato N, Yasukawa K, Onozuka T et al. Nasal and nasal-type T/NK-cell lymphoma with cutaneous involvement. *J Am Acad Dermatol*. 1999;40:850-856.
39. Martel P, Laroche L, Courville P et al. Cutaneous involvement in patients with angioimmunoblastic lymphadenopathy with dysproteinemia: a clinical, immunohistological, and molecular analysis. *Arch Dermatol*. 2000;136:881-886.
40. Murakami T, Ohtsuki M, Nakagawa H. Angioimmunoblastic lymphadenopathy-type peripheral T-cell lymphoma with cutaneous infiltration: report of a case and its gene expression profile. *Br J Dermatol*. 2001;144:878-884.
41. Brown HA, Macon WR, Kurtin PJ et al. Cutaneous involvement by angioimmunoblastic T-cell lymphoma with remarkable heterogeneous Epstein-Barr virus expression. *J Cutan Pathol*. 2001;28:432-438.
42. Huang CT, Chuang SS. Angioimmunoblastic T-cell lymphoma with cutaneous involvement: a case report with subtle histologic changes and clonal T-cell proliferation. *Arch Pathol Lab Med*. 2004;128:e122-e124.
43. Yoon GS, Chang SE, Kim HH et al. Cutaneous relapse of angioimmunoblastic lymphadenopathy-type peripheral T-cell lymphoma mimicking an exanthematous drug eruption. *Int J Dermatol*. 2003;42:816-818.