

What is Lymphomatoid Papulosis: Lymphoid Hyperplasia or Lymphoma?

Unresolved Quandaries in
Dermatopathology
Can we resolve them?

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What is Lyp?



- Hyperplasia: benign
 - chronic stimulation may lead to "second hit" and malignancy
- Lymphoma: malignant
 - low grade lymphoma, controlled by host
 - indolent end of spectrum of CD30+ LPD
- Heterogeneous entity
- Don't know, yet

Organization



- History
- Clinical presentation
- Histologic features
- Immunophenotype
- Molecular data
- Pathogenesis
- Differential Diagnosis

Lymphomatoid Papulosis

**A Continuing Self-Healing Eruption,
Clinically Benign—Histologically Malignant**

Warren L. Macaulay, MD, Fargo, ND

A 41-year-old woman has an asymptomatic eruption of three years' duration. The clinical course is benign and is characterized by a continuing, random, coming and going of papules, some of which undergo necrosis, and all of which involute spontaneously within three to four weeks. Results of repeated physical examinations and laboratory studies are normal. Yet, biopsies of the skin lesions show an alarming infiltrate of anaplastic cells of disputatious origin, suggesting to most reviewers a diagnosis of malignant lymphoma. A number of comparable cases are reviewed, their similarity implying an uncommon entity.

"Hence, it appears that there exists a dermatologic disorder, the clinical and histologic features of which are variable within limits, whose claim to distinction rests upon the incongruity of a benign clinical course in association with the histopathology of malignant lymphoma."

A continuing self-healing eruption, clinically benign - histologically malignant

Follow-up



- Patient was still alive and well 25 years later
- No treatment
- Eruption continued but diminished

Macaulay WL. Arch Dermatol 1989;125:1387-89.

Clinical Features



- Peak incidence: 4th and 5th decade
 - All ages
- Predilection for trunk and extremities
 - No area spared
- Asymptomatic
- Protracted course (>20 years) more common than self-limited

Morphology



- Red-brown papules and nodules
 - central hemorrhage and necrosis
 - crusting
- Lesions < 3cm
- Involute in 3-8 weeks
 - hypo- or hyperpigmented macules
 - superficial scars
- Number variable (few - >100)
- Lesions in different stages of evolution

Associated Neoplasia

- 10% -20% associated with lymphoma
- Most associated lymphomas occur subsequently
 - Lymphoma may precede Lyp or present simultaneously
- Most common: MF, Hodgkin lymphoma, CD30+ ALCL
- Lyp with and without associated lymphoma indistinguishable

Treatment



- No staging necessary for Lyp (but for ALCL)
- Watch and wait
- No curative therapy available
- Low dose oral methotrexate
- Psoralen-UV-A
- Topical mechlorethamine
- Topical carmustine

Histology



- Type A
- Type B
- Type C
- borderline lesions
- different types coexist in same patient
- clinically indistinguishable

Type A Lyp (>75%)

- variable epidermal changes
- perivascular and interstitial infiltrate
- wedge shaped
- may extend into SQ
- large atypical cells in mixed background
 - neutrophils
 - eosinophils
 - histiocytes
 - small lymphocytes
- mitoses

Type B Lyp (<10%)

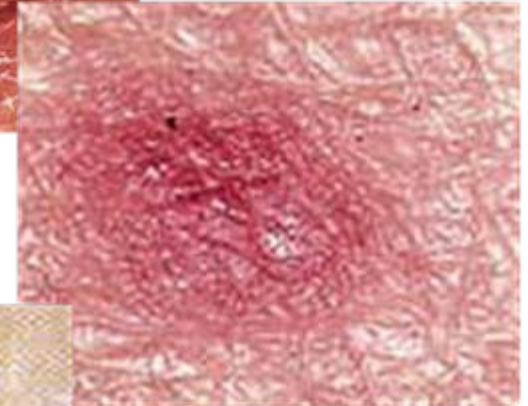
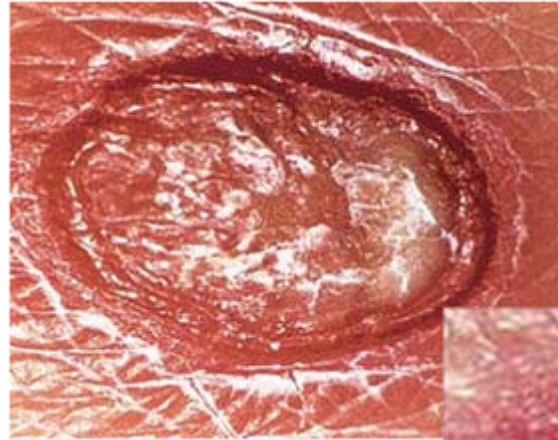
- resembles plaque stage MF
- superficial perivascular to bandlike infiltrate with epidermotropism
- small to medium sized cerebriform cells
- few if any CD30+ large cells
- eosinophils and neutrophils infrequent compared to type A

Type C Lyp (approx. 10%)

- monotonous population of large CD30+ cells
- few admixed inflammatory cells
- indistinguishable from CD30+ ALCL

Histology

- dynamic disease
- age and morphology of lesion will influence histology
- no systematic study relating histology to age of lesion



Histology



- Histologic subtypes clinically and prognostically irrelevant
- CD30+ large cells may be absent in very early lesions, resolving lesions and type B Lyp
- Multiple biopsies will increase diagnostic yield

Variants



- Pseudoepitheliomatous hyperplasia
- Perifollicular
- Syringotropic
- Myxoid
- With follicular mucinosis
- With syringosquamous metaplasia

Immunophenotype

- large cells
 - activated helper cells
 - CD30+
 - CD4+ (<5% of cases CD8+)
 - variable loss of CD2, CD3, or CD5
 - cytotoxic protein expression (TIA-1, granzyme)
 - alk-1 -
 - CD15 -

Immunophenotype




- CD95 + (Fas)
- Fas ligand +
- Occasional coexpression of CD56
- Jun-B +
- c-kit -
- EBV-

CD30



- 1982: H. Stein - Ki-1 antibody (frozen tissue)
- Ki-1 antigen = activation associated antigen
- 120-kd transmembrane cytokine receptor
- Member of TNF superfamily
- Not expressed in normal tissue, except
 - scattered cells around B-cell follicles
 - decidua and decidualized endometrium
- Seen in reactive B- and T-cells exposed to virus, such as EBV or HTLV

Ber-H2



- Antibody for paraffin embedded tissue
- Membrane and golgi staining
 - weak diffuse cytoplasmic staining
insignificant
- Sensitivity subject to antigen retrieval methods

Pathogenesis



- Comparing Lyp, c-ALCL, s-ALCL should provide attractive model for tumorigenesis
- Several studies showed high apoptotic rates in Lyp
- Much research has focused on proliferation, apoptosis and definition of specific pathways
- No clear picture has emerged

Short (and Incomplete) List of Candidate Molecules



- CD44
- CD44v6
- TGF-beta
- CCR3
- Fas/CD95
- PTEN
- Bcl-2
- CD27
- CD40
- granzyme B
- fascin
- C-jun
- CD134
- P21
- Stat3

Jun-B



- Activator protein 1 (AP-1) transcription factor complex
- Members form homo- and heterodimers
- Control cell proliferation and apoptosis
- JunB binds with CD30 promoter in cultured RS and HD cells, inducing CD30 expression
- JunB also expressed in all other CD30+ neoplasms, including Lyp
- ?same role as in HD
- no difference between Lyp and ALCL

Fascin



- Actin-bundling protein
- May have role in cell migration
- Not expressed in normal lymphocytes
- Expressed in RS and EBV-transformed B-cells
- 11/17 (64%) ALCL
- 11/45 (24%) Lyp
- 6/10 (60%) Lyp associated with lymphoma
- ? Marker for progression in Lyp

However...



- Negative fascin expression in Lyp did not exclude associated lymphoma
- 3 patients: lyp - fascin negative, lymphoma - fascin positive
- "...suggests that fascin expression might be associated with progression"
- Later study found fascin in 85% of Lyp, no correlation with associated lymphoma

Fas (CD95) and Fas Ligand (CD95L)

- CD95L = transmembrane protein of TNF family
- Expressed by activated T-cells, NK cells and various tumors
- Binding of CD95L to CD95 induces apoptosis
- CD95/CD95L plays important role in downregulating immune responses and self-tolerance
- Loss of function linked to LPD and autoimmune disorders

Fas (CD95) and Fas Ligand (CD95L)

- CD95 expressed in majority of tumor cells in primary cutaneous CD30+ LPD and in systemic ALCL
- Higher expression of CD95L in background small lymphocytes in primary cutaneous CD30+ LPD

CD30 and CD30L



- CD30-CD30L interaction can lead to cell death or proliferation
- CD30L expressed at higher level in regressing than in growing Lyp lesions
- CD30L appears to be colocalized with CD30 in large cells
- CD30L appears necessary but insufficient

Progression because of Escape from Growth Inhibition?

- TGF-beta is a potent inhibitor of proliferation for most cells
- Mutations in the TGF-beta signaling pathway lead to resistance to growth inhibition
- TGF-beta is expressed in some regressing lesions of Lyp

Progression because of Escape from Growth Inhibition?

- Kadin et al showed that TGF beta failed to inhibit growth of lymphoma cells from advanced disease due to mutation in TGF beta receptor
- Based on experiments in cell lines from two patients

?Viral Etiology



- EBV -
- HHV-6 -
- HHV-7 -
- HHV-8-
- HTLV -

Molecular Data



- No t(2;5) rearrangement
- Approx. 70% of Lyp have detectable clone
- Same clone when spatially or temporally different biopsies are examined
 - Some contradictory studies
- Clonality does not seem to have prognostic implications for lyp

Molecular Data



- Same clone in Lyp and associated MF
 - ? Better clinical prognosis (Zackheim)
- Same clone in Lyp and assoc. HD and ALCL
- Same clone in Lyp and uninvolved BM
- 2 case reports of patients with severe disease and same clone in pb

Which cells are clonal?

- 14 lesions from 11 patients
- Five had h/o lyp for 1-6 months, 6 had h/o lyp for 10 months - 30 years
- only 1 patient had associated lymphoma (MF)
- Single cell analysis of CD30+ large cells and CD2+/CD30- cells for TCR gamma
- CD30+ large cells: 118/123 clonal
- CD30- cells: 4/79 clonal

Steinhoff M, et al. Blood 2002;100:578-84.

Steinhoff M et al. continued

- Amplicon of single cells was identical to amplified product of whole-tissue DNA
- In two cases the CD30+ single cells did not yield a clonal band, however the whole tissue DNA was clonal
 - ? Degradation
- 3 patients had identical clone in anatomically and temporally separate lesions

Steinhoff M et al. continued

- 2 patients had CD30+ cells with unique TCR gamma rearrangements (i.e. different from dominant clone)
- In 4 patients one of the CD30- cells demonstrated the same dominant clone as CD30+ cells (75/79 were unrelated)

Conclusion



- Lyp represents a monoclonal disorder
- CD30+ large cells are clonal
- CD30- cells are polyclonal

Which cells are clonal?



- Four patients with Lyp
- Single cell analysis for TCR gamma and IgH
- Analyzed large cells and small T-cells
- Monoclonal cells restricted to small cell population
- CD30+ large cells polyclonal

Gellrich et al.



- In one patient CD30+ cells were monoclonal B-cells (patient had HD)
- ? Are CD30+ cells polyclonal cells that experience short lived expansion
- ? Do patients harbor an indolent T-cell clone with low proliferative rate that is a component of the T-cell repertoire
- Offers an explanation why B- or T-cell neoplasms may be associated with Lyp

Differential Diagnosis




CD30 +




- Hodgkin lymphoma
- ALCL (systemic and primary cutaneous)
- Large cell transformed MF
- CD30+ B-cell lymphoma
- Embryonal carcinoma
- Viral infection
- Activated cells in reactive infiltrates
- Mycosis fungoides
- CD8+ epidermotropic CTCL
- Pagetoid reticulosis

Type A Lyp



- Reactive CD30+ cutaneous lymphoid proliferations
- ALCL secondarily involving the skin
- Neutrophil rich ALCL
- HD

CD30+ Cutaneous Lymphoid Proliferations



- Arthropod bites
- Tuberculosis
- Molluscum contagiosum
- Orf
- Herpes simplex/ zoster
- Scabies (older lesions>>fresh lesions)
- Drug eruption

Type B Lyp

- Mycosis fungoides
 - MF may be CD30+
- Papular MF
- PLEVA

Lyp vs PLEVA



- both can be clonal
- PLEVA: younger patients
- PLEVA: CD8+
- Lyp: CD4+

Lyp vs PLEVA

Morphology

- **LYP**
 - mixed infiltrate with eos and PMN
 - possible ulceration, but no SNKC
 - large CD30+ cells
- **PLEVA**
 - lymphocytes and histiocytes
 - single necrotic keratinocytes
 - small to medium sized cells

Type C Lyp



- CD30+ B-cell lymphoma (generally EBV+)
- CD30 negative malignant lymphomas
- Primary cutaneous ALCL
- MF with large cell transformation

What is Lyp?




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 - chronic stimulation may lead to "second hit" and malignancy
- Lymphoma: malignant
 - low grade lymphoma, controlled by host
 - Indolent end of spectrum of CD30+ LPD
- Heterogeneous entity
- Don't know, yet

Arguments for Benign Disease



- Excellent prognosis
- Self-regressing
- Sometimes self-limited
- Second-hit theory attractive, similar to MF

Arguments for Malignant Disease



- Distressing with often >50 lesions
- May require MTX
- Clonal
- Loss of pan T-cell antigens
- Morphologically malignant
- Association/ development into lymphoma
- Same clone in associated lymphoma

? Two diseases



- No clinical, histologic, immunophenotypic or genotypic criteria that distinguish between progressors and non-progressors

Spectrum of Disease?



- 20% of ALCL regress (regressing atypical histiocytosis)
- ALCL has excellent prognosis, only small percentage disseminates
- Commonalities:
 - CD30
 - Self regression
 - Clonal
 - CD4 TIA-1 positive
 - Borderline cases
- But: why is Lyp multiple and self regressing?
- Why is Lyp associated with other malignancies (HD and MF)
- LYP and HD: differences in regard to EBV, B-cell and CD15

Why does Lyp not progress?



- Host response
- Mitotic arrest
- Self destruction

Conclusions



- Lyp is a well defined disease entity
- Clinical correlation is paramount for correct diagnosis
- Be aware of mimics in DD
- Best signed out as "CD 30+ lymphoproliferative disorder, see comment"
- Promising model for study of tumorigenesis
- Pathogenetic mechanism is still an enigma

1. When you make a diagnosis of lymphomatoid papulosis (LYP), do you mean to imply that the patient has lymphoma? If not, what is it? *Am J Dermatopathol.* 1995;17:197-208.
2. Bekkenk MW, Geelen FA, van 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;95:3653-61.
3. Bekkenk MW, Kluin PM, Jansen PM, Meijer CJ, Willemze R. Lymphomatoid papulosis with a natural killer-cell phenotype. *Br J Dermatol.* 2001;145:318-22.
4. Boulland ML, Wechsler J, Bagot M, Pulford K, Kanavaros P, Gaulard P. Primary CD30-positive cutaneous T-cell lymphomas and lymphomatoid papulosis frequently express cytotoxic proteins. *Histopathology.* 2000;36:136-44.
5. Cepeda LT, Pieretti M, Chapman SF, Horenstein MG. CD30-positive atypical lymphoid cells in common non-neoplastic cutaneous infiltrates rich in neutrophils and eosinophils. *Am J Surg Pathol.* 2003;27:912-8.
6. Cerroni L. Lymphomatoid papulosis, pityriasis lichenoides et varioliformis acuta, and anaplastic large-cell (Ki-1+) lymphoma. *J Am Acad Dermatol.* 1997;37:287.
7. Cespedes YP, Rockley PF, Flores F, Ruiz P, Kaiser MR, Elgart GW. Is there a special relationship between CD30-positive lymphoproliferative disorders and epidermal proliferation? *J Cutan Pathol.* 2000;27:271-5.
8. Chott A, Vonderheid EC, Olbricht S, Miao NN, Balk SP, Kadin ME. The dominant T cell clone is present in multiple regressing skin lesions and associated T cell lymphomas of patients with lymphomatoid papulosis. *J Invest Dermatol.* 1996;106:696-700.
9. Clarke LE, Bayerl MG, Bruggeman RD et al. Death receptor apoptosis signaling mediated by FADD in CD30-positive lymphoproliferative disorders involving the skin. *Am J Surg Pathol.* 2005;29:452-9.
10. Drews R, Samel A, Kadin ME. Lymphomatoid papulosis and anaplastic large cell lymphomas of the skin. *Semin Cutan Med Surg.* 2000;19:109-17.
11. Drexler HG, Gignac SM, von Wasielewski R, Werner M, Dirks WG. Pathobiology of NPM-ALK and variant fusion genes in anaplastic large cell lymphoma and other lymphomas. *Leukemia.* 2000;14:1533-59.
12. El Shabrawi-Caelen L, Kerl H, Cerroni L. Lymphomatoid papulosis: reappraisal of clinicopathologic presentation and classification into subtypes A, B, and C. *Arch Dermatol.* 2004;140:441-7.

13. Gallardo F, Barranco C, Toll A, Pujol RM. CD30 antigen expression in cutaneous inflammatory infiltrates of scabies: a dynamic immunophenotypic pattern that should be distinguished from lymphomatoid papulosis. *J Cutan Pathol.* 2002;29:368-73.
14. Gallardo F, Costa C, Bellosillo B et al. Lymphomatoid papulosis associated with mycosis fungoides: clinicopathological and molecular studies of 12 cases. *Acta Derm Venereol.* 2004;84:463-8.
15. Gellrich S, Wernicke M, Wilks A et al. The cell infiltrate in lymphomatoid papulosis comprises a mixture of polyclonal large atypical cells (CD30-positive) and smaller monoclonal T cells (CD30-negative). *J Invest Dermatol.* 2004;122:859-61.
16. Gniadecki R, Rossen K. Expression of T-cell activation marker CD134 (OX40) in lymphomatoid papulosis. *Br J Dermatol.* 2003;148:885-91.
17. Greisser J, Doebbeling U, Roos M et al. Apoptosis in CD30-positive lymphoproliferative disorders of the skin. *Exp Dermatol.* 2005;14:380-5.
18. Harvell J, Vaseghi M, Natkunam Y, Kohler S, Kim Y. Large atypical cells of lymphomatoid papulosis are CD56-negative: a study of 18 cases. *J Cutan Pathol.* 2002;29:88-92.
19. Herbst H, Sander C, Tronnier M, Kutzner H, Hugel H, Kaudewitz P. Absence of anaplastic lymphoma kinase (ALK) and Epstein-Barr virus gene products in primary cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis. *Br J Dermatol.* 1997;137:680-6.
20. Herron MD, Bohnsack JF, Vanderhooft SL. Septic, CD-30 positive febrile Ulceronecrotic Pityriasis Lichenoides et Varioliformis Acuta. *Pediatr Dermatol.* 2005;22:360-5.
21. Jang KA, Choi JC, Choi JH. Expression of cutaneous lymphocyte-associated antigen and TIA-1 by lymphocytes in pityriasis lichenoides et varioliformis acuta and lymphomatoid papulosis: immunohistochemical study. *J Cutan Pathol.* 2001;28:453-9.
22. Kadin ME, Levi E, Kempf W. Progression of lymphomatoid papulosis to systemic lymphoma is associated with escape from growth inhibition by transforming growth factor-beta and CD30 ligand. *Ann N Y Acad Sci.* 2001;941:59-68.
23. Kadin ME, Carpenter C. Systemic and primary cutaneous anaplastic large cell lymphomas. *Semin Hematol.* 2003;40:244-56.
24. Kempf W, Kadin ME, Kutzner H et al. Lymphomatoid papulosis and human herpesviruses--A PCR-based evaluation for the presence of human herpesvirus 6, 7 and 8 related herpesviruses. *J Cutan Pathol.* 2001;28:29-33.
25. Kempf W, Levi E, Kamarashev J et al. Fascin expression in CD30-

positive cutaneous lymphoproliferative disorders. *J Cutan Pathol.* 2002;29:295-300.

26. Kummer JA, Vermeer MH, Dukers D, Meijer CJ, Willemze R. Most primary cutaneous CD30-positive lymphoproliferative disorders have a CD4-positive cytotoxic T-cell phenotype. *J Invest Dermatol.* 1997;109:636-40.

27. LeBoit PE. Hodgkin's disease, anaplastic large cell lymphoma, and lymphomatoid papulosis. Another scalpel blunted. *Am J Clin Pathol.* 1995;104:3-4.

28. LeBoit PE. Lymphomatoid papulosis and cutaneous CD30+ lymphoma. *Am J Dermatopathol.* 1996;18:221-35.

29. Liang X, Smoller BR, Golitz LE. Expression of CD44 and CD44v6 in primary cutaneous CD30 positive T-cell lymphoproliferative disorders. *J Cutan Pathol.* 2002;29:459-64.

30. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. *J Am Acad Dermatol.* 2003;49:1049-58.

31. Massi D, Trotta M, Franchi A, Pimpinelli N, Santucci M. Atypical CD30+ cutaneous lymphoid proliferation in a patient with tuberculosis infection. *Am J Dermatopathol.* 2004;26:234-6.

32. McCalmont TH, LeBoit PE. A lymphomatoid papule, but not lymphomatoid papulosis! *Am J Dermatopathol.* 2000;22:188-90.

33. Mori M, Manuelli C, Pimpinelli N et al. CD30-CD30 ligand interaction in primary cutaneous CD30(+) T-cell lymphomas: A clue to the pathophysiology of clinical regression. *Blood.* 1999;94:3077-83.

34. Nijsten T, Curiel-Lewandrowski C, Kadin ME. Lymphomatoid papulosis in children: a retrospective cohort study of 35 cases. *Arch Dermatol.* 2004;140:306-12.

35. Ota M, Sawamura D, Shibaki A, Shimizu H. Bone marrow clonal T-cell population in lymphomatoid papulosis. *J Am Acad Dermatol.* 2005;52:710-1.

36. Paulli M, Berti E, Boveri E et al. Cutaneous CD30+ lymphoproliferative disorders: expression of bcl-2 and proteins of the tumor necrosis factor receptor superfamily. *Hum Pathol.* 1998;29:1223-30.

37. Ranheim EA, Jones C, Zehnder JL, Warnke R, Yuen A. Spontaneously relapsing clonal, mucosal cytotoxic T-cell lymphoproliferative disorder: case report and review of the literature. *Am J Surg Pathol.* 2000;24:296-301.

38. Rassidakis GZ, Georgakis GV, Oyarzo M, Younes A, Medeiros LJ.

Lack of c-kit (CD117) expression in CD30+ lymphomas and lymphomatoid papulosis. *Mod Pathol*. 2004;17:946-53.

39. Rassidakis GZ, Thomaidis A, Atwell C et al. JunB expression is a common feature of CD30+ lymphomas and lymphomatoid papulosis. *Mod Pathol*. 2005;18:1365-70.

40. Rubben A, Kempf W, Kadin ME, Zimmermann DR, Burg G. Multilineage progression of genetically unstable tumor subclones in cutaneous T-cell lymphoma. *Exp Dermatol*. 2004;13:472-83.

41. Scarisbrick JJ, Calonje E, Orchard G, Child FJ, Russell-Jones R. Pseudocarcinomatous change in lymphomatoid papulosis and primary cutaneous CD30+ lymphoma: a clinicopathologic and immunohistochemical study of 6 patients. *J Am Acad Dermatol*. 2001;44:239-47.

42. Schultz JC, Granados S, Vonderheid EC, Hwang ST. T-cell clonality of peripheral blood lymphocytes in patients with lymphomatoid papulosis. *J Am Acad Dermatol*. 2005;53:152-5.

43. Sigel JE, Hsi ED. Immunohistochemical analysis of CD30-positive lymphoproliferative disorders for expression of CD95 and CD95L. *Mod Pathol*. 2000;13:446-51.

44. Stein H, Foss HD, Durkop H et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood*. 2000;96:3681-95.

45. Steinhoff M, Hummel M, Anagnostopoulos I et al. Single-cell analysis of CD30+ cells in lymphomatoid papulosis demonstrates a common clonal T-cell origin. *Blood*. 2002;100:578-84.

46. Su LD, Schnitzer B, Ross CW et al. The t(2;5)-associated p80 NPM/ALK fusion protein in nodal and cutaneous CD30+ lymphoproliferative disorders. *J Cutan Pathol*. 1997;24:597-603.

47. Su LD, Duncan LM. Lymphoma- and leukemia-associated cutaneous atypical CD30+ T-cell reactions. *J Cutan Pathol*. 2000;27:249-54.

48. Van Neer FJ, Toonstra J, Van Voorst Vader PC, Willemze R, Van Vloten WA. Lymphomatoid papulosis in children: a study of 10 children registered by the Dutch Cutaneous Lymphoma Working Group. *Br J Dermatol*. 2001;144:351-4.

49. Willemze R, Meijer CJ. Primary cutaneous CD30-positive lymphoproliferative disorders. *Hematol Oncol Clin North Am*. 2003;17:1319-32, vii-viii.

50. Wood GS. Analysis of the t(2;5) (p23;q35) translocation in CD30+ primary cutaneous lymphoproliferative disorders and Hodgkin's disease. *Leuk Lymphoma*. 1998;29:93-101.

51. Zackheim HS, Jones C, Leboit PE, Kashani-Sabet M, McCalmont TH, Zehnder J. Lymphomatoid papulosis associated with mycosis fungoides: a study of 21 patients including analyses for clonality. *J Am Acad Dermatol.* 2003;49:620-3.

52. Zoi-Toli O, Vermeer MH, De Vries E, Van Beek P, Meijer CJ, Willemze R. Expression of Fas and Fas-ligand in primary cutaneous T-cell lymphoma (CTCL): association between lack of Fas expression and aggressive types of CTCL. *Br J Dermatol.* 2000;143:313-9.