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

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%)
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

Rassidakis GZ et al. Mod Path 2005;18:1365
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

Dalton, S et al. Abstract at 2005 ASDP, Seattle
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

Sigel JE, His ED Mod Pathol 2000;13:446-51
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

Kadin, ME, Levi E, Kempf W. Ann NY Acad Sci 2001;941:59-68
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. 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?

- 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
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.


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


