

Session 1 – Part 2 Diagnosis Groups

- Plasma cell leukemia
- Plasmablastic and other high grade variants of plasma cell myeloma
 - Extramedullary presentation of high grade plasma cell myeloma
- EBV+ plasma cell neoplasms in immunocompetent patients
- Systemic plasma cell proliferations in HIV+ patients

Session 1 – Part 2 Questions to be answered (if possible)

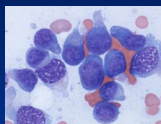
- How do we define/diagnose plasmablastic plasma cell myeloma – and do we need to do it?
- How do we differentiate extramedullary plasma cell myeloma from extramedullary plasmacytoma and plasmablastic lymphoma?
- Does EBV+ plasma cell myeloma exist?
- How do we classify systemic plasma cell neoplasms in immunosuppressed states?

Plasma cell myeloma, plasmablastic

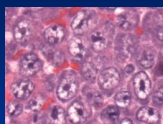
Morphological diagnosis, however, two different definitions in use

- Cytology-based, 2% threshold (Greipp et al)
- Histology-based, pred. cell-type (Bartl et al)

#122
Spier



#351
Djokic



- Do diagnose „plasmablastic“ PCM (but use the correct classification with respect to material!) – probably identifies high risk disease (high risk genetics)
- Other high grade morphology may be identified
- High MIB1 index does not define „plasmablastic“

Differential Diagnosis

	Extram. PCM	Primary EMP	PBL
Morphology	Oftentimes plasmablastic	Mostly plasmacytic	Plasmablastic Large cell /immunobl.
M-protein	Most cases	20-30%, low levels	Rare
Osteolytic lesions	Common	Occasional local bone	Rare
Lymphadenopathy	Rare	Very unusual, usually aerodigestive tract	In minority of cases
Bone marrow	Yes	No	May occur
CD56	70-80%	<20%, weak	Some positive
Cyclin D1 / t(11;14)	15-20%	Neg.	Neg.
C-myc rearrangement	common	Neg	common
P53	Common	Rare	common

Session 2-Summary Hsi/Dogan

- Use of the term 'plasmablastic lymphoma'
- Immunophenotype of plasmablastic lymphoma
- Castleman disease with monotypic plasma cells
- Use of terms 'microlymphoma' and 'germinotropic lymphoma'
- PBL vs plasmablastic plasma cell myeloma
- Plasmablastic lymphoma vs EBV+ LBCL of the elderly

Use of the term 'plasmablastic lymphoma'

- Use the term Plasmablastic Lymphoma for the specific entity described in WHO classification.
- For other lymphomas with plasmablastic phenotype use the specific terms assigned by WHO
 - LBCL arising in HHV8+ MCD
 - ALK pos. LBCL
 - PEL
 - DLBCL with plasmablastic differentiation

Immunophenotype of Plasmablastic Lymphoma

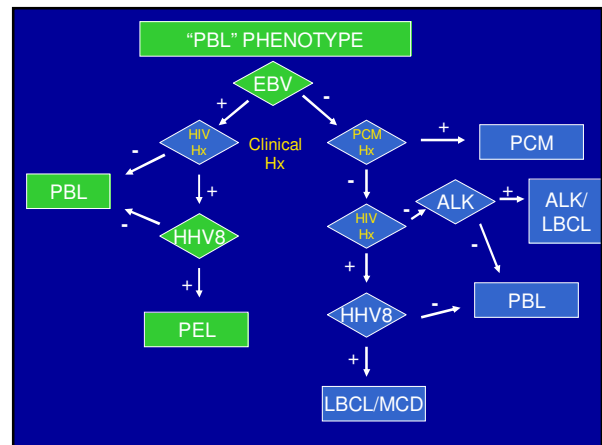
- Positive
 - CD138
 - CD38
 - IRF4/MUM1
 - Blimp-1
 - XBP-1
 - clg
 - (EBV)
- Neg
 - CD20
 - Pax5
 - (LMP1)
- Variable
 - CD79a
 - CD56
 - CD10
 - CD30
- Aberrant
 - CD4
 - Keratin

Castleman disease

- Castleman disease with monotypic plasma cells
 - Consider a diagnosis of plasma cell neoplasm with Castleman Disease like follicles
- HHV8+ multicentric Castleman disease
 - Do not use the term 'microlymphoma' or 'germinotropic' for collections of plasmablasts in the follicles

PBL differential diagnosis

- PBL vs PCM
 - Knowledge of clinical features is critical
 - EBV? More work needed...
- PBL vs EBV+ DLBCL of the elderly
 - If the features are typical for PBL in an "older" patient, make a diagnosis of PBL



Immunophenotype of Plasmablastic Lymphoma

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Lymphoplasmacytic lymphomas

Summary of the summaries

Steven H. Swerdlow, M.D.



What I am not going to do

- Still not going to give a lecture on lymphoplasmacytic lymphomas – already heard one this AM from someone who knows a lot more about them than I do.
- Attempt not to repeat my introduction & original summary dealing with this topic and the cases that were submitted to the workshop (although I was tempted to).

What I will attempt to do

- Summarize my sense of the mainstream way in which hematopathologists are dealing with these cases.
 - What should we do when we all go back to work next week in terms of diagnosing lymphoplasmacytic lymphomas?
 - Dealing with life in an imperfect world.
- Briefly look at the areas of ongoing need and interest.

How can we best apply the WHO criteria which remain all we have at the current time?

- LPL is a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and spleen, which does not fulfill the criteria for any of the other small B-cell lymphoid neoplasms that may also have plasmacytic differentiation.
- Although often associated with a paraprotein usually of IgM type, it is not required for the diagnosis.

The 2008 WHO recognizes the need to equivocate in some cases but doesn't mean that one should never render a diagnosis of LPL or strongly favor LPL.

- “Because the distinction between LPL and one of these other lymphomas, especially some marginal zone lymphomas (MZL), is not always clear-cut, some cases may need to be diagnosed as a small B-cell lymphoma with plasmacytic differentiation and a differential diagnosis provided.”

Critical 1st step

- Adequately worked up cases with full knowledge of the clinical history and additional laboratory findings (some may come after a case is initially reviewed and signed out).
- Uncertainty in some of the workshop cases arose solely because of insufficient information.

Cases that will be the most confidently diagnosed as LPL

- BM-based neoplastic lymphoplasmacytic proliferations that have an interstitial marrow growth pattern (at least in part), appear relatively monotonous, don't have clinical/morphologic/phenotypic/cytogenetic features to suggest another specific neoplasm.

High confidence level diagnoses of LPL

- We've seen a significant amount of acceptable phenotypic variation but again will feel most confident in the absence of strong/extensive CD5 staining, in the absence of CD10 and possibly in the absence of strong/extensive CD23 expression.
- The presence of a significant IgM paraprotein will increase one's confidence level even if not required for the diagnosis nor sufficient.

In these circumstances, what should you still worry about?

- Findings you don't know about or didn't look for would have suggested a different diagnosis.
 - Is there disease elsewhere that might suggest one of the marginal zone lymphomas?
 - Would additional workup that didn't seem necessary suggest a different type of lymphoma?
- Plasma cell neoplasms which can co-exist with distinct lymphoid neoplasms.

What about at extramedullary sites?

- LPL is a diagnosis to make only infrequently.
- The cases one can be most confident about are the lymph node biopsies with sinus preservation, a relatively monotonous lymphoplasmacytic proliferation, relatively inconspicuous follicular structures, an acceptable phenotype/genotype and lacking any other features that might suggest another well-defined type of B-cell neoplasm.
- The most definite cases will also have bone marrow involvement and an IgM paraprotein.

But many cases will not have all of these features – including cases from this workshop

- Go back to the basic definition and ask yourself with what degree of confidence can you exclude other B-cell/plasmacytic neoplasms with the most problematic, as we have seen here, being marginal zone lymphomas with plasmacytic differentiation.
- We don't want MZL to become a wastebasket diagnosis either!

LPL are being diagnosed with

- Follicular structures present
- A greater degree of pleomorphism than in the most typical cases
- Phenotypic variation – not all CD5- & CD10- and many are CD23 at least partially positive.
- Paraproteins other than IgM or no paraprotein at all
- Involvement at MALT sites

What about cytogenetic studies?

- Continued interest in this area & more to learn but at the moment while 6q deletions are the most common abnormality and can qualify for "comfort food" for the hematopathologist, they are not specific for LPL.
- Useful to help exclude other neoplasms.
- Perhaps other high throughput technologies could help as well????

At the end of the day

- Need to use wording that you feel comfortable with and conveys to the clinician in some way your confidence level in the diagnosis.

What else to worry about?

- Usually fixate on ddx with MZL, but in cases with a high proportion of plasma cells or in situations with a possibly distinct plasma cell population, do need to think about plasma cell neoplasms.
 - Discussed potential utility of looking for CD19 on the plasma cells even if not completely specific finding (plus the other things we do to identify pc neoplasms)

More worries

- When do the findings suggest a more aggressive neoplasm? When do you diagnose transformation?
 - Sheets of transformed cells/immunoblasts not a problem but may be other morphologic appearances of higher grade histology (like with other lymphoid and plasmacytic neoplasms).
- How many LPL are HCV-related proliferations & not true neoplasms?

Hopes for the future

- To have a better way to diagnose LPL in a positive fashion because they have specific features, not as an exclusionary diagnosis.
 - What distinguishes the lymphocytes in LPL (or the plasma cells) from those in a MZL (assuming we should distinguish them)?
- When that day comes, we will also better understand the nature of this neoplasm and its relationship to other B-cell neoplasms, not all of which have very specific diagnostic features either.

Session 5 Final Summary

Take Home Messages

Splenic lymphomas

- Cases where we feel best about the diagnosis are those with classic “biphasic” morphology or monophasic, monocytoid morphology
- 2008 WHO classification includes “Splenic lymphoma/leukemia, unclassifiable” to recognize that many cases don't fit our usual criteria and that other yet-to-be clarified entities may exist
- When working with bone marrow alone, caution is warranted

Gamma Heavy Chain Disease

- Much remains to be determined
- Many of these cases appear to be indistinguishable from LPL
 - Should gamma heavy chain disease simply be recognized as a subset of LPL with distinct clinical features, similar to concept of WM as a subset of LPL?
- Checking for SPEP/UPEP info can sometimes change your approach to case!