Pitfalls in Immunohistochemistry in Hematopathology: CD20 and CD3 Can Let Me Down!?

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62 yo man
Orchiectomy:
Testicular tumor
Seminoma?

• CD20 and CD3: most commonly used B and T cell markers
  • Almost always reliable
• When can they let us down?
  • Absence of CD20 in B-cell lymphomas
    • Plasmablastic lymphoma
    • Primary effusion lymphoma and “solid” variants (HHV8+)
    • ALK+ large B-cell lymphoma
    • B-cell lymphomas after rituximab
    • B lymphoblastic lymphoma
• Presence of CD20 when it is unexpected
  • Plasma cell neoplasms
  • T-cell lymphomas
• Presence of CD3 when it is unexpected
  • B-cell non-Hodgkin’s lymphomas
  • Classical Hodgkin’s lymphoma
Diagnosis:
- Plasmablastic lymphoma

Additional clinical history:
- Status post cardiac transplant

Updated diagnosis:
Monomorphic post transplantation lymphoproliferative disorder, consistent with Plasmablastic lymphoma

Plasmablastic Lymphoma
- Rare lymphoma
- Proliferation of large neoplastic cells with morphology of immunoblasts/plasmablasts and immunophenotype of plasma cells
- First described in HIV+ patients, arising in oral cavity
- Strong association with immunosuppression, EBV
- Majority of patients are HIV+
  - Median age, fifth decade, M >> F
- Rarely, HIV+ children develop PBL
- Other PBL patients
  - Older, less striking male predominance
  - Post transplantation (cardiac transplant most common in one study)
  - Other iatrogenic immunosuppression
  - Older adults with immunosenescence of aging
  - Rare cases of plasmablastic transformation of low-grade BCL

Plasmablastic Lymphoma
- Often extranodal
  - Oral cavity and other head and neck sites
  - GI tract
  - Skin, soft tissue
  - Liver
  - Spleen
  - Testis
  - Others
- Lymph nodes in a minority of cases
- Aggressive lymphoma often with stage III/IV disease
- Unfavorable prognosis

Plasmablastic Lymphoma
- Histology:
  - Diffuse proliferation of immunoblasts, plasmaacytoid immunoblasts, plasmablasts +/- plasmaacytic differentiation
  - Frequent mitoses, starry sky pattern +/- necrosis
- Immunophenotype
  - Usually +: CD138, CD38, MUM1, Blimp1, clg, MYC
  - Variable: CD45, CD79a, CD56, CD10, CD30
  - Negative: CD20, Pax5, BCL6, ALK, HHV8
  - High proliferation index
  - Rarely, aberrant expression of keratin
- EBV, Cytogenetics, Molecular genetics
  - EBER+ in 60 – 70% of cases
  - Almost all HIV+ cases are EBV+
  - MYC translocation in ~ 50% of cases, fewer have MYC amplification
  - Complex karyotype
  - Recurrent mutations of PRDM1 (Blimp1), may enhance deregulation of MYC
  - Downregulation of BCR signaling program, upregulation of genes associated with plasma cell differentiation
PBL: Differential Diagnosis

- Plasmablastic myeloma
  EBV-, marrow+, lytic lesions
- DLBCL, NOS
  CD20+
- EBV+ DLBCL, NOS
  Most CD20+; not usually plasmablastic
- Burkitt's lymphoma
  CD20+, simple karyotype
- HHV8+ large B-cell lymphomas
  HHV8+
- ALK+ DLBCL
  ALK+
- EBV+ plasmacytoma in immunocompetent patients (EPIC)*
  
  • Rare
  • Nasal cavity, esophagus, mediastinum
  • Mature plasma cells, admixed CD8+ T cells, no MYC rearrangement
  • Good prognosis

ALK+ Large B-Cell Lymphoma

- Rare, aggressive lymphoma with poor prognosis
- Young to middle-aged adults mostly affected, M > F
- B symptoms, widespread disease: common
- Lymph nodes +/- extranodal involvement
- Sinusoidal involvement in nodes
- Plasmacytoid immunoblasts
- CD45+, CD20-, CD79a-/+, CD138+, CD4+/-, OCT2+, BOB1+, cyto Ig+ (IgA most common), CD30-, HHV8-, EBER-, ALK+
- Clonal IGH
- ALK-Clathrin fusion: t(2;17) in most

Diagnosis:
Lymphoplasmacytic Lymphoma

But:
Giemsa stain:
No increase in mast cells

Flow cytometry:
2% polyclonal B cells
3% clonal plasma cells

Additional information
• Allele specific PCR assay for MYD88 Leu265Pro mutation: wild type only
• FISH: abnormal result including CCND1-IGH fusion; t(11;14)

Diagnosis
• Plasma cell myeloma, IgM+

IgM Plasma Cell Myeloma
• Clinical, laboratory findings: similar to other myelomas
  • IgM M-component
  • Lytic bone lesions common
  • Lymphoplasmacytic morphology is common
  • Cyclin D1+: most cases (73%)*
  • CD20: often + (40%)*
  • CD19 and Pax5: often + (67%, 73%)*
  • Flow: clonal plasma cells, no clonal B cells
  • MYD88 L265P: absent
  • Cytogenetics: as for myeloma, with CCND1-IGH in most
  • Differential: LPL, mantle cell lymphoma

**CD20+ Peripheral T-Cell Lymphoma**

- CD20 co-expression by neoplastic T cells is rare
- Older adults, M>F
- Other pan-B cell markers much less often co-expressed
- Neoplastic transformation of a small normal subset of CD20 dim+ T cells?
- Aberrant antigen expression? Sign of T-cell activation?
- May be seen in many different types of T-cell lymphomas (MF, EATL/MEITCL, PTCL, NOS...)
- CD20 is often patchy, dim, variable from site to site
- May occur in relapses and increase with disease progression
- Associated with a poor prognosis
- Important to avoid misdiagnosis as B-cell lymphoma

Diagnosis:
Anaplastic large cell lymphoma?

Also negative for CD3, CD4, CD5, CD8, CD20, CD79a, rare CD138+.

Diagnosis:
HHV8+, EBV+ large cell lymphoma

But HHV8+ lymphoproliferative disorders are B-lineage, what about CD3??

PCR
- IgH: Clonal pattern, with framework I (330 bp), framework II (285 bp) and framework III (120 bp) primers
- TCRγ: Polyclonal pattern

Final Diagnosis
- HHV8+, EBV+ extracavitary variant of primary effusion lymphoma (aka “solid” PEL) with aberrant expression of CD3 (mimicking ALCL)
- Clues were origin from Cameroon and plasmacytosis

CD3+ B-Cell Lymphomas

- CD3+ BCLs:
  - Uncommon
  - Mostly DLBCLs
  - Often EBV+
  - Immunosuppression common
  - Solid PELs: 29% CD3+

One study found two groups of CD3+ B-lineage neoplasms**
1. 7 DLBCLs, plasmacytic; 4 plasma cell neoplasms; 2 PBLs: Extranodal disease cytoCD3+
2. 5 DLBCLs with anaplastic features, 1 follicular lymphoma: Lymph nodal disease

Membrane CD3

T Antigen+ Classical Hodgkin’s Lymphoma

- Most often nodular sclerosis CHL, NS2 (abundant tumor cells)
- 5% of CHL cases
- CD2, CD4 most commonly expressed
- CD3, CD5, CD7, CD8 also may be expressed
- More than one T antigen may be expressed
- 10-35% of tumor cells T antigen+
- TCR genes almost always germine
- Shorter OS & EFS
- Differential: High-grade PTCL
- Awareness of phenomenon
- Pax5 expression (almost always in CHL) against PTCL
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