Case Presentation: Is This Hodgkin’s or Not?

Patrick Treseler, MD, PhD
University of California San Francisco

Clinical History:

47-year old woman with no history of immunosuppression presented with fevers, night sweats, and right cervical adenopathy (clinical impression: Hodgkin’s lymphoma). A right cervical lymph node was excised. Referring pathologist noted diagnostic Reed-Sternberg cells.
EBV

CD20

CD3

Hodgkin’s or Not?
Immunophenotype of Hodgkin’s/Reed-Sternberg Cells

<table>
<thead>
<tr>
<th></th>
<th>Classical HD</th>
<th>LP HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td>CD15</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>CD45RB (LCA)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD20</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>CD3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EMA</td>
<td>-</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Classical Hodgkin’s Lymphoma: Clonal rearranged Ig genes

Promoter

Structural

Immunoglobulin Gene

Single cell IgH rearrangements by PCR
Classical Hodgkin’s Disease Cases

<table>
<thead>
<tr>
<th></th>
<th>Clonal</th>
<th>Polyclonal</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajewsky et al. (Five reports, 1994-98)</td>
<td>16</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stein &amp; Hummel (1999)</td>
<td>24</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Crippling Mutations in HRS Cells of CHL

CHL cases with crippling mutations 12 (22%)

CHL cases without crippling mutations 43 (78%)

No Ig mRNA or protein produced in either!

Bräuninger et al 118: 1853; 2006
Global downregulation of B-cell antigen expression in CHL

- B-cell antigens absent from HRS cells
  - Immunoglobulin
  - CD19
  - CD20
  - CD79a
  - Oct 2/BOB.1
- A notable exception: Pax-5/BSAP

Pax-5/BSAP

- Pax-5 gene encodes B-cell-Specific Activator Protein (BSAP), a critical nuclear transcription factor for many B-cell genes
- Expression highly specific for B-cell lineage
- Expression begins very early in B-cell development
- Inactivation critical for progression to plasma cell stage
- Present in virtually all B-cell neoplasms (except plasma cell tumors) including classical Hodgkin’s disease (Torlakovic et al. AJSP 26: 1342; 2002)
Classical Hodgkin’s Lymphoma

**Immunophenotype:**
- CD30 + >90%
- CD15 +/- ~80%
- CD20 +/- ~20% (focal, weak)
- CD3 - <10%
- Pax-5 + >90%*
- Oct2 - <10%†

*Staining may be focal and weak
†Focal weak staining present in many cases

“Diagnostic Reed-Sternberg Cells” in Lymphoid Lesions

**Differential diagnosis:**
- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Diffuse large B-cell lymphoma variants
- Peripheral T-cell lymphomas
- Immunosuppression-associated LPDs
- Reactive immunoblastic hyperplasia
“Diagnostic Reed-Sternberg Cells” in Lymphoid Lesions

Differential diagnosis:
- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Diffuse large B-cell lymphoma variants
- Peripheral T-cell lymphomas
- Immunosuppression-associated LPDs
- Reactive immunoblastic hyperplasia

Nodular lymphocyte predominant HL
- Highly atypical CHL-like HRS cells present focally in 55% of cases; such cells may predominate in rare cases*
- Atypical large cells:
  - CD30- CD15-- CD20+ Oct2+ CD79a+
  - EMA+/-

*Blood 96: 1889-1899; 2000

Distinguishing DLBCL from CHL

Potential pitfalls:
- DLBCL can express CD30
  - But will strongly express most B-cell markers (CD20, Oct-2, CD79a) and lack CD15
- Rituximab-treated DLBCL may have partial or total loss of CD20
  - But will strongly express other B-cell markers (Oct-2, CD79a)
- Plasmablastic lymphomas have weak to absent CD20
  - But will strongly express Oct-2 and often lack Pax-5
“Diagnostic Reed-Sternberg Cells” in Lymphoid Lesions

**Differential diagnosis:**
- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Diffuse large B-cell lymphoma variants
  - DLBCL, anaplastic variant
  - T-cell/histiocyte-rich large B-cell lymphoma
  - EBV-positive DLBCL of the elderly
- Peripheral T-cell lymphomas
- Immunosuppression-associated LPDs

---

**Diffuse large B-cell lymphoma, anaplastic**

- Large B-cells include highly pleomorphic giant cells resembling RS cells of CHL
- May grow in cohesive sheets in LN sinuses
- Roughly half CD30+
- CD20+ CD15- Oct2+
- Pure morphologic variant (per WHO)

---

**T-cell/histiocyte-rich large B-cell lymphoma**

- Large B-cells <10%; may resemble RS cells
- Large cells scattered
- Small B-cells rare to absent
- Many cases extranodal
- Most high stage
- CD30- CD15- (rarely CD30+)
- CD20+ Oct2+

---

**EBV-positive DLBCL of the elderly**

- Related to senescence of immune system
- Patients >50 years, with no history of prior immunodeficiency
- EBV+ by definition
- CHL-like HRS cells typically present
- May be CD30+ CD20-
- Oct2+ CD15-
"Diagnostic Reed-Sternberg Cells" in Lymphoid Lesions

Differential diagnosis:
- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Diffuse large B-cell lymphoma variants
- Peripheral T-cell lymphomas
- Immunosuppression-associated LPDs
- Reactive immunoblastic hyperplasia

Distinguishing PTCLs from CHL

Potential pitfalls:
- PTCL can express CD30 (e.g., ALCL)
  - But will generally express CD45, express T-cell markers (possibly including ALK), lack CD15, and lack Pax-5
- PTCL can lose expression of T-cell markers, and B-cell CHL can gain them
  - But Pax-5 expression still common in CHL, uncommon in PTCL (resort to gene rearrangements as needed)

"Diagnostic Reed-Sternberg Cells" in Lymphoid Lesions

Differential diagnosis:
- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Diffuse large B-cell lymphoma variants
- Peripheral T-cell lymphomas
- Immunosuppression-associated LPDs
- Reactive immunoblastic hyperplasia

Anaplastic large cell lymphoma, T-cell type

- May have wreath-like giant cells, reniform large cells ("hallmark cells")
- "Hodgkin-like" variant perfectly mimics CHL
- CD30+ CD3-
- CD15- Pax-5-
- Variably positive for CD4, TIA-1, granzyme B, ALK protein
Angioimmunoblastic T-cell lymphoma

- Patients may present with adenopathy and B symptoms clinically suspicious for CHL
- EBV+ cells typically present, may resemble RS cells of CHL
- Most EBV+ cells usually mature B-cells, but others have full CHL phenotype (composite lymphoma)

“Diagnostic Reed-Sternberg Cells” in Lymphoid Lesions

- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Diffuse large B-cell lymphoma variants
- Peripheral T-cell lymphomas
- Immunosuppression-associated LPDs
- Reactive immunoblastic hyperplasia

Immunosuppression-associated LPDs

- Pts immunosuppressed for allografts/autoimmune disorders may develop EBV+ LPDs with RS-like cells
- Many of these RS cells will have mature B-cell phenotype +/-CD30, others that of CHL
- Even pts meeting criteria for CHL may respond to ↓ immunosuppression

“Diagnostic Reed-Sternberg Cells” in Lymphoid Lesions

- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Diffuse large B-cell lymphoma variants
- Peripheral T-cell lymphomas
- Immunosuppression-associated LPDs
- Reactive immunoblastic hyperplasia
Reactive immunoblastic hyperplasia
- AKA interfollicular or paracortical hyperplasia
- Typically triggered by viral infection or hypersensitivity reaction
- When potent (EBV), can expand T-cell zones to mimic LN effacement
- RS-like cells may be seen, but often “wimpy”
- Cells often CD30+, but mix of B & T-cells

Hodgkin’s or Not?

Immunophenotype Summary:
- CD30  + focal
- CD15  -
- CD20  + diffuse
- CD79a + diffuse
- Pax-5 + diffuse
- Oct-2 + diffuse

Diagnosis?
1. Classical Hodgkin’s lymphoma
2. Nodular LP Hodgkin’s lymphoma
3. Diffuse large B-cell lymphoma
4. Peripheral T-cell lymphoma
5. Reactive immunoblastic hyperplasia
**Diagnosis:**
Diffuse large B-cell lymphoma
- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Peripheral T-cell lymphoma
- Reactive immunoblastic hyperplasia

**Diagnosis:**
Diffuse large B-cell lymphoma
- Anaplastic variant?
- T-cell/histiocyte rich?
- EBV+ DLBCL of elderly?

“There are aggressive B-cell lymphomas, rich in reactive T-cells, in which the neoplastic cells are sparse, and are EBV-positive. In such cases, the neoplastic cells may exhibit a Hodgkin-like morphology. Such cases should not be classified as THRLBCL, and should be considered within the spectrum of EBV-positive DLBLC.”

WHO Classification (2008), p. 238

**Diagnosis:**
Diffuse large B-cell lymphoma, NOS

Comment:
- Strong resemblance to TCHRLBCL
- EBV-related (likely aggressive)
Thomas Hodgkin 1798-1866

“Diagnostic Reed-Sternberg Cells” in Lymphoid Lesions

Differential diagnosis:
- Classical Hodgkin’s lymphoma
- Nodular LP Hodgkin’s lymphoma
- Diffuse large B-cell lymphoma variants
- Peripheral T-cell lymphomas
- Reactivesuppressedlastissuelesions

Making a Diagnosis of Classical Hodgkin’s Lymphoma

Required elements:
- Compatible clinical presentation
- Compatible morphology
- Compatible immunophenotype

It’s a non-Hodgkin’s lymphoma you idiot...