Disclosed of Relevant Financial Relationships

USCAP requires that all planners (Education Committee) in a position to influence or control the content of CME disclose any relevant financial relationship WITH COMMERCIAL INTERESTS which they or their spouse/partner have, or have had, within the past 12 months, which relates to the content of this educational activity and creates a conflict of interest.

Dr. Ohgami declares he has no conflicts of interest to disclose.

Case history

A 32 year old man presents with a 4 month history of isolated left inguinal lymphadenopathy. A physical exam demonstrates no other abnormal findings. The patient has no personal or family history of malignancy. Further workup including CBC, peripheral blood smear and bone marrow biopsy were unremarkable.

Case history

CBC and Differential
WBC: 6.2 K/μL
HGB: 14.3 g/dL
PLT: 210 K/μL
Neutrophils: 65%  
Lymphocytes: 30%  
Monocytes: 3%
Case history

A 32 year old man presents with a 4 month history of isolated left inguinal lymphadenopathy. A physical exam demonstrates no other abnormal findings. The patient has no personal or family history of malignancy. Further workup including CBC, peripheral blood smear and bone marrow biopsy were unremarkable.

A LN biopsy was performed.
What about the atypical spindled cells?
Cytogenetic and molecular studies

• Normal male karyotype: 46,XY[20].
• Molecular studies: Negative for T-cell and B-cell clonality.

Summary

• Clinical
  • Healthy male
  • Prolonged isolated inguinal adenopathy

• Morphology
  • Infiltrate of immature blastic lymphoid cells in sheets and clusters
  • Atrophic “lollipop” follicles with onion skinning mantle zones
  • Effacement by a proliferation of atypical spindled cells, some binucleate

• Immunophenotype
  • Lymphoid infiltrate: CD3+, CD4+, CD8+, CD99+, TdT+
  • Spindled cells: D240+, CD123+, focal dim CD21

• Cytogenetics/Molecular
  • Non-clonal T-cells
  • Normal cytogenetics

Differential Diagnosis

• Thymoma
• T-lymphoblastic lymphoma
• Kaposis Sarcoma
• Castleman disease
• Follicular dendritic cell sarcoma
• Indolent T-lymphoblastic proliferation

Differential Diagnosis

• Thymoma
• T-lymphoblastic lymphoma
• Kaposis Sarcoma
• Castleman disease
• Follicular dendritic cell sarcoma
• Indolent T-lymphoblastic proliferation

Differential Diagnosis

• Thymoma
• T-lymphoblastic lymphoma
• Kaposis Sarcoma
• Castleman disease
• Follicular dendritic cell sarcoma
• Indolent T-lymphoblastic proliferation

Differential Diagnosis

• Thymoma
• T-lymphoblastic lymphoma
• Kaposis Sarcoma
• Castleman disease
• Follicular dendritic cell sarcoma
• Indolent T-lymphoblastic proliferation

Differential Diagnosis

• Thymoma
• T-lymphoblastic lymphoma
• Kaposis Sarcoma
• Castleman disease
• Follicular dendritic cell sarcoma
• Indolent T-lymphoblastic proliferation
Differential Diagnosis

- Thymoma
- T-lymphoblastic lymphoma
- Kaposi Sarcoma
- Castleman disease
- Follicular dendritic cell sarcoma
- Indolent T-lymphoblastic proliferation

Final Diagnosis

- Indolent T-lymphoblastic proliferation
- Castleman disease, hyaline vascular type
- Follicular dendritic cell sarcoma

Castleman disease

Morphology

- Hyaline Vascular
- Intermediate
- Plasma cell

Clinicopathologic

- Unicentric
- Multicentric

HIV

HHV8
Follicular dendritic cell sarcomas

- Spindled proliferation
- Plump, sometimes binucleate cells
- Positive for follicular dendritic cell markers
  - (CD21, CD35, D240, CD23)

Lost CD21 Express CD123

But I’m here to talk about...

Castleman disease – Follicular dendritic cell sarcoma

Indolent T-lymphoblastic proliferation

Robert (Bob) Ohgami, MD, PhD
Stanford University

What they didn’t teach you in fellowship...

- Indolent T-lymphoblastic proliferations
- “Rules”/Dogma can be broken
What they didn’t teach you in fellowship...

• Indolent T-lymphoblastic proliferations

• “Rules”/Dogma can be broken

Indolent T-lymphoblastic Proliferations

• First case in 1999:
  - Healthy patient
  - Proliferation of blastoid lymphoid cells
  - CD3+/TdT+ T-cells
  - Extra thymic expansion
  - Clinical indolence
  - Non-clonal

Similar to...
Malignant T-lymphoblastic lymphoma

EXCEPT...

Since then... 13 other cases in the literature

Summary of cases of indolent T-lymphoblastic proliferations

• Age: ~40 (10-70)
• Male:Female 1:1
• Morphologic: small round or tadpole cells, blastic chromatin
• Immunophenotype: 100% TdT+/CD4+/CD8+/CD3+ T-cells
• Molecular: 100% non-clonal
T-cell development

Summary of cases of indolent T-lymphoblastic proliferations thus far

- Age: ~40 (10-70)
- Male:Female 1:1
- Morphology: small-medium sized cells, blastic chromatin
- Immunophenotype: 100% TdT+/CD3+ T-cells
- Molecular: 100% non-clonal
- Associated diseases: Castleman disease, Follicular dendritic cell sarcoma

TdT+ T-lymphoblastic cells are increased in Castleman disease and FDCS/FDCT
TdT+ T-lymphoblastic cells are increased in Castleman disease and FDCS/FDCT

Ohgami et al., AJSP 2012

TdT+ T-lymphoblastic cells are increased in angioimmunoblastic T-cell lymphoma (AITL)

Ohgami et al., AJSP 2012

Association with CD, FDCS, AITL

• Some have speculated interleukine/cytokines are responsible for cells
  • II-6
  • Still not understood

In 2013...

Diagnostic Criteria

Why are diagnostic criteria needed?

Diagnosis

Reactive

Indolent T-lymphoblastic proliferation

Malignant

T-lymphoblastic lymphoma
Diagnostic Criteria: iT-LBP

**Major Criteria**
- $\text{TdT}^+ \text{T cells in sheets/dense clusters primarily in interfollicular region}$
- Preservation of general follicular lymphoid architecture
- Small-medium sized T cells without significant morphologic atypia
- No aberrant antigen expression
- Non-clonal (TCR)
- No associated thymic epithelium
- Clinical evidence of indolence

**Diseases associated with**
- Castleman disease and/or follicular dendritic cell sarcomas/tumors
- Concurrent angioimmunoblastic T-cell lymphoma (AITL) or history of AITL

What they didn’t teach you in fellowship...

- Indolent T-lymphoblastic proliferations
- “Rules”/Dogma can be broken

Case B
- 49 year woman
- Diffuse lymphadenopathy
- Healthy otherwise

Expression of other antigens, including CD33

CD33 expression odd...
CD33 expression odd... = lymphoma

CD33 expression odd... = lymphoma?

CD33 expression odd...
- Expression can be seen on reactive and highly activated T-cells
- 4 years later patient is still alive without treatment

Diagnosis here:
- Indolent T-lymphoblastic proliferation with CD33 expression
  - Unusual disseminated disease
- Since that report a second case with CD33 has been described

That’s interesting...

But we’re not done yet...
A very recent case...

• Healthy 24 year old male
• Isolated inguinal adenopathy

Additional clinical information

• Clinical indolence: 3 months without progression
• No marrow or peripheral blood involvement
• Radiology: SUV of lymph node was very low, minimally increased.

What they didn’t teach you in fellowship...

• Indolent T-lymphoblastic proliferations
• “Rules”/Dogma can be broken

What they didn’t teach you in fellowship...

• Indolent T-lymphoblastic proliferations
• “Rules”/Dogma can be broken
Is this malignant? Is this reactive?

Non-clonal

TdT

CD56

Is this reactive?

CD56 expression odd...

CD56 expression odd... = ?lymphoma?

T-cell development

<table>
<thead>
<tr>
<th>Protein</th>
<th>Prethymic</th>
<th>Thymus Cortex</th>
<th>Thymus Medulla</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD2/CD3/CD7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TdT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>Single positive</td>
<td>single positive</td>
<td></td>
</tr>
<tr>
<td>CD8</td>
<td>Double positive</td>
<td>Double positive</td>
<td></td>
</tr>
<tr>
<td>CD3a</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

??CD56??

NK/T cell development

<table>
<thead>
<tr>
<th>Protein</th>
<th>Stem cell</th>
<th>NK/T cell precursor</th>
<th>Committed NK/T cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD5a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD56</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NK/T cell development

<table>
<thead>
<tr>
<th>Protein</th>
<th>Stem cell</th>
<th>NK/T cell precursor</th>
<th>Committed NK/T cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD5a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD56</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
More information on the case: Followup

• Many more months, patient is healthy, no disease, no treatment

Diagnosis here?

• Castleman disease, hyaline vascular type
• Unusual CD56+ lymphoblastic proliferation

Koo and Cloetingh et al., in preparation

Indolent NK/T-lymphoblastic proliferation

• Stay tuned...

Summary

• Indolent T-lymphoblastic proliferations
  In the context of science and reason
• “Rules”/Dogma can be broken

Questions remain...

• What is driving these proliferations?
• Do these indolent immature T-cells mature into functional T-cells?
• Why are these associated with Castleman disease? Follicular dendritic cell sarcomas? Angioimmunoblastic T-cell lymphoma?

Returning to Case 1

• What did our panelists think?
Case 1 - Panelists Diagnoses

- Indolent T-lymphoblastic proliferation in the setting of Castleman’s Disease
- TDT+ T lymphoblastic proliferation in Castleman’s disease
- Indolent T lymphoblastic proliferation, Castleman disease and follicular dendritic cell proliferation (recommend more stains to better define follicular dendritic cell proliferation).

Acknowledgements

Stanford University
- Roger Warnke
- Yaso Natkunam
- Michaela Liedtke
- Susan Atwater
- Brent Tan
- Dita Gratzinger
- Jason Kurzer

Colleagues Beyond
- Mark Fleming, CHB/Harvard
- Dan Arber, U Chicago
- Tracy George, UNM
- Milind Velankar, Loyola U
- Larry Weiss, Neogenomics