Case 3

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Massachusetts General Hospital
Harvard Medical School
28 year old man with childhood asthma status post tonsillectomy (pathology showed benign lymphoid hyperplasia).

Six months later he felt a painless lump on the left side of his face.

Imaging found a 2.1 x 2.1 x 1.5 cm preauricular mobile mass within the parotid gland.

FNA showed viably sized atypical lymphocytes, including large cells with irregular nuclei and prominent nucleoli. Flow showed a CD10+ B cell population with monoclonal kappa light chain expression cell population.

Clinical Differential: Follicular lymphoma, DLBCL, Large B-cell lymphoma with IRF4 rearrangement, Burkitt lymphoma
Case 3
Case 3
Case 3
Additional Information

- MUM1 IHC is negative
- FISH for BCL2 and BCL6 gene rearrangements are negative
- Imaging shows that disease is localized

**Diagnosis**: Pediatric-Type Follicular Lymphoma
Follicular Lymphoma Variants and Related Entities

Variants
- In situ follicular neoplasia
- Duodenal-type follicular lymphoma
- Extranodal follicular lymphoma
- FL with predominantly diffuse growth pattern and 1p36 deletion

Distinct Entities
- Primary cutaneous follicle center lymphoma
- Pediatric-type follicular lymphoma *New
- Large B-cell lymphoma with IRF4 translocation *New
Follicular lymphoma

- 20% of All lymphomas
- Mean Age: 6th decade
- M:F = 1:1.7
- Often advanced stage
- Sites: lymph nodes, marrow, spleen;

Photo courtesy of J.A. Ferry
Grade 1-2

Grade 3B

Grade 3A

Photo courtesy of J.A. Ferry
Follicular lymphoma: Grading

<table>
<thead>
<tr>
<th>Grading</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Grade 1-2 (low grade)</td>
<td>0-15 centroblasts per hpf*</td>
</tr>
<tr>
<td>1</td>
<td>0-5 centroblasts per hpf*</td>
</tr>
<tr>
<td>2</td>
<td>6-15 centroblasts per hpf*</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt;15 centroblasts per hpf*</td>
</tr>
<tr>
<td>3A</td>
<td>Centrocytes present</td>
</tr>
<tr>
<td>3B</td>
<td>Solid sheets of centroblasts</td>
</tr>
</tbody>
</table>

Diffuse areas of grade 3 = Diffuse large B-cell lymphoma

<table>
<thead>
<tr>
<th>Reporting of pattern</th>
<th>Proportion follicular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Follicular and diffuse</td>
<td>25-75% **</td>
</tr>
<tr>
<td>Focally follicular</td>
<td>&lt;25% **</td>
</tr>
</tbody>
</table>
**BCL2 Translocations in Follicular Lymphoma**

- Present in up to 85-90% of low grade advanced stage cases; 50% of grade 3 FL

- Translocation t(14;18)(q32;q21) juxtaposes BCL2 on 18q21 to regulatory sequences and enhancer elements of the Ig heavy chain
# Early Series of FL in Children Identify Common Features

<table>
<thead>
<tr>
<th>Series</th>
<th>Cases</th>
<th>Ages</th>
<th>M/F</th>
<th>Site(s)</th>
<th>Stage I</th>
<th>Tx(s)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frizzera 1979</td>
<td>8</td>
<td>3-13</td>
<td>6/2</td>
<td>Mostly LN, 1 ileal mass</td>
<td>75%</td>
<td>All XRT +/- chemo, excision</td>
<td>All alive w/o disease</td>
</tr>
<tr>
<td>Winberg 1981</td>
<td>12</td>
<td>3-19</td>
<td>11/1</td>
<td>All LN, with 8 head/neck</td>
<td>42%</td>
<td>5 XRT, 6 chemo, 1 excision only</td>
<td>All stage I disease-free</td>
</tr>
<tr>
<td>Pinto 1990</td>
<td>20</td>
<td>3-20</td>
<td>15/5</td>
<td>7 tonsil, 13 LN (5 head/neck)</td>
<td>75%</td>
<td>Chemo, excision; 3 tx deferred</td>
<td>All durable remission</td>
</tr>
<tr>
<td>Ribiero 1992</td>
<td>17</td>
<td>11.7 med.</td>
<td>Most M</td>
<td>Most tonsil, head/neck LN</td>
<td>Most</td>
<td>not reported</td>
<td>94% stage I disease-free</td>
</tr>
<tr>
<td>Atra 1998</td>
<td>7</td>
<td>4-13</td>
<td>4/3</td>
<td>All LN, with 5 neck/tonsil</td>
<td>100%</td>
<td>3 excision only, 4 exc+chemo</td>
<td>86% durable remission</td>
</tr>
<tr>
<td>Lorsbach 2002</td>
<td>23</td>
<td>3-20</td>
<td>16/7</td>
<td>LN/tonsil/extranodal</td>
<td>79%</td>
<td>All chemo, 3 also rcv’d XRT</td>
<td>All stage I disease-free</td>
</tr>
</tbody>
</table>

**M>>F**

**Limited stage**

**Head & Neck**

**High histologic grade**

**Commonly lack aberrant bcl2**

**Durable remission**

“Pediatric Follicular Lymphoma” - Provisional Status in 2008

- Pediatric age
- Increased proportion lack BCL2 protein expression and t(14;18)
- Often localized
- Grade 3 morphology
- Tend to have large expansile follicles with architectural effacement
- Excellent Prognosis (the majority disease free at time of last follow-up)

“Pediatric follicular lymphomas have many features indistinguishable from those seen in adults...”
Critical Issues in the Diagnosis of Pediatric FL

1. Evolving management of pediatric FL case
   - Additional experiences demonstrate no progression/recurrence with excision alone

1. Young adults (20’s and 30’s) present with pediatric FL – like lesions
   - Do adult patients have the same highly indolent disease?
   - How should patients be diagnosed and treated?
   - FL, grade 3 - or Pediatric FL?
Pediatric-type nodal follicular lymphoma: an indolent clonal proliferation in children and adults with high proliferation index and no BCL2 rearrangement

Abner Louissaint Jr,1 Adam M. Ackerman,1 Dora Dias-Santagata,1 Judith A. Ferry,1 Ephraim P. Hochberg,2 Mary S. Huang,2 A. John Iafrate,1 Daniel O. Lara,1 Geraldine S. Pinkus,3 Itziar Salaverria,4 Zakir Siddiquee,1 Reiner Siebert,4 Howard J. Weinstein,2 Lawrence R. Zuckerman,1 Nancy Lee Harris,1 and Robert P. Hasserjian1

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BLOOD, 20 SEPTEMBER 2012 • VOLUME 120, NUMBER 12

Follicular Lymphomas in Children and Young Adults
A Comparison of the Pediatric Variant With Usual Follicular Lymphoma

Qingyan Liu, MD,* Itziar Salaverria, PhD,† Stefania Pittaluga, MD, PhD,* Armin G. Jegalian, MD, PhD,* Liqiang Xi, MD,* Reiner Siebert, MD,‡ Mark Raffeld, MD,* Stephen M. Hewitt, MD, PhD,* and Elaine S. Jaffe, MD*

Am J Surg Pathol • Volume 37, Number 3, March 2013
‘Pediatric-type FL’ characterized by high PI and Absence of \textit{BCL2/BCL6/IRF4} rearrangements

![Graph showing survival analysis](image)

<table>
<thead>
<tr>
<th>Graph Description</th>
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<tbody>
<tr>
<td>Percent not progressed or relapsed</td>
</tr>
<tr>
<td>No BCL2 gene rearrangement \textit{and high} proliferation index</td>
</tr>
<tr>
<td>BCL2 gene rearrangement \textit{and/or low} proliferation index</td>
</tr>
</tbody>
</table>

Louissaint \textit{et. al} Blood 2012
Pediatric Follicular Lymphoma

- No BCL2, BCL6, IRF4 or CBFA2T3 Breaks
- Effaced nodal architecture
- Often irregular shaped follicles
- Prominent starry sky pattern, but without polarization

Liu et al AJSP 2013
Unique Cytological Features of PTFL

Typical Centroblasts
Small to medium sized blastoid cells resembling centrocytes

Blastoid Cells of Pediatric-Type FL
Medium-sized to large blastoid cells with finely clumped chromatin

Liu et al. AJSP 2013
Frequency of “Pediatric-type FL” by Age

Pediatric Type FL peaks 2\textsuperscript{nd} Decade

Conventional FL peaks 5\textsuperscript{th} Decade

Louissaint et. al Blood 2012
Genome-wide analysis of pediatric-type follicular lymphoma reveals low genetic complexity and recurrent alterations of TNFRSF14 gene

Janine Schmidt, 1, Shunyou Gong, 2, Teresa Marafioti, 3, Barbara Mankel, 1, Blanca Gonzalez-Farre, 4, Olga Balagú, 4, Ana Mozos, 5, José Cabezas-Díaz, 6, Jon van der Walt, 7, Daniela Hoehn, 8, Andreas Rosenwald, 9, German Ott, 10, Stefan Dojcinov, 11, Caio Miguel Egan, 2, Ferran Nadeu, 4, Joan Enric Rami-Salgado, 4, Guillem Clot, 8, Carmen Bárbara, 12, Vanesa Pérez-Alonso, 12, Volker Endri, 13, Roland Penzel, 13, Carmen Lome-Maldonado, 14, Írisa Bonzheim, 1, Falko Fend, 1, Elias Campo, 4, Elaine S. Jaffe, 2, Izizal Salverria, 4, and Leticia Cuinianilla-Martínez 1.

1Institute of Pathology and Cytogenetics, Eberhard Karls University of Tübingen and Comprehensive Cancer Center, University Hospital Tübingen, Tübingen, Germany; 2Department of Pathology, National Cancer Institute, Bethesda, MD; 3University of Clinical Pathology, Albert Einstein College of Medicine, New York, NY; 4Department of Pathology, European Institute of Oncology, Milan, Italy; 5Department of Pathology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 6Department of Pathology, Instituto de Investigación Sanitaria La Fe, Valencia, Spain; 7Department of Pathology, Klinikum der Universität München, Munich, Germany; 8Department of Pathology, University of Würzburg, Würzburg, Germany; 9Department of Pathology, University of Virginia, Charlottesville, VA; 10Department of Pathology, University of Chicago, Chicago, IL; 11Department of Pathology, University of California, San Francisco, CA; 12Department of Pathology, University Hospital Sant Pau, Barcelona, Spain; 13Department of Pathology, University Hospital of the Saarland, Homburg, Germany; 14Department of Pathology, Instituto Nacional de Cancerología, Tegucigalpa, Honduras.

A study of the mutational landscape of pediatric-type follicular lymphoma and pediatric nodal marginal zone lymphoma

Michael G Ozawa 1,6, Aparna Bhaduri 2,6, Karen M Chisholm 3, Steven A Baker 1, Lisa Ma 1, James L Zehnder 1,4, Sandra Luna-Fineman 3, Michael P Link 5, Jason D Merker 1, Daniel A Arber 1 and Robert S Ogami 3.

1Department of Pathology, Stanford University, Stanford, CA, USA; 2Program in Epithelial Biology, Stanford University, Stanford, CA, USA; 3Department of Laboratory Medicine, Seattle Children’s Hospital, Seattle, WA, USA; 4Division of Hematology, Department of Medicine, Stanford University, Stanford, CA, USA and 5Department of Pediatrics, Stanford University, Stanford, CA, USA

Pediatric-type nodal follicular lymphoma: a biologically distinct lymphoma with frequent MAPK pathway mutations

Abner LouisCant Jr, 1,2, Kristian T. Schafforn, 3, Julia T. Goyor, 4, Alexandra E. Kovach, 5, Mahmoud Ghandi, 6, Dita Gratzing, 7, Christine G. Roth, 8, Christian N. Paxton, 9, SunHee Kim, 8, Chungak Namgyl, 10, Ryan Morin, 11, Elizabeth A. Morgan, 10, Donna S. Neubert, 12, Sarah T. South, 13, Marian H. Harris, 14, Robert P. Hassinger, 15, Ephraim P. Hochberg, 14, Levi A. Garraway, 15, Nancy Lee Harris, 1 and David M. Weinstock 2,6.

1Department of Pathology, Massachusetts General Hospital, Boston, MA; 2Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; 3Department of Pathology and Laboratory Medicine, Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL; 4Department of Pathology and Laboratory Medicine, Weill Cornell Medical College-New York Presbyterian Hospital, New York, NY; 5Department of Pathology, Boston Children’s Hospital, Boston, MA; 6Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA; 7Department of Pathology, Stanford University School of Medicine, Stanford, CA; 8Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; 9ARUP Institute for Clinical and Experimental Pathology, Department of Pathology, University of Utah, Salt Lake City, UT; 10Department of Pathology, Brigham & Women’s Hospital, Boston, MA; 11Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, Canada; 12Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; 13ARUP Laboratories, Department of Pathology, University of Utah, Salt Lake City, UT; and 14Department of Medicine, Massachusetts General Hospital, Boston, MA.
<table>
<thead>
<tr>
<th>PTFL cohort</th>
<th>Criteria</th>
<th>Comparison Group</th>
<th>Assays used</th>
</tr>
</thead>
</table>
| **Schmidt et. Al** | 42 PTFL  
M:F = 20:1  
Ages 5-31 (16)  
30% >18 years | • **WHO 2008**  
• Morphology  
• No BCL2/MUM1 translocation;  
• BCL6 FISH neg (23/23) | 11 Typical FL t(14;18) -  
• Targeted sequencing: **TNFRSF14, MLL2, FOXO1, EP300, MEF2B, GNA13, HIST1H1B-E, EZH2, CREBBP**  
• Copy number alterations |
| **Louissaint et. al** | 26 PTFL  
M:F = 12:1  
Ages 4-60 (16)  
38% >18 years | • **WHO 2016 Criteria**  
• Expansile Follicles;  
• No BCL2, BCL6, IRF4 translocations;  
• High PI; Limited Stage | Limited Stage Typical FL: t(14;18)+ or Low PI  
• Targeted Sequencing (142 genes)  
• Exome Sequencing  
• Copy Number analysis |
| **Ozawa et. Al** | 6 PTFL  
M:F = 5:1  
Ages 12-18 (16) | • **WHO 2008**  
• Morphology | 6 Pediatric NMZL  
22 Adult-type FL  
• Exome Sequencing |
Copy Number Alterations in Pediatric-Type FL

Low Genomic Complexity
- 0.77 Copy number alterations per case (vs. 9 CNA / case) \[Schmidt \text{ et. al}\]
- 0.5% of genome altered by copy number alterations (vs. 10% of the genome in Typical FL) \[Louissaint \text{ et al}\]

Frequent 1p36 alterations
- Recurrent Copy number neutral loss of heterozygosity at 1p36 (40% of cases)
- Deletion at 1p36.32 including \textit{TNFRSF14} (5% of cases)

\textit{Schmidt et. al} Blood 2016
\textit{Louissaint et. al} Blood 2016
Sequencing with Lymphoseq Panel
(142 genes previously reported to be mutated in FL)

Louissaint et. al Blood 2016
Exome Sequencing reveals novel mutations in PTFL

- 50% cases (3 of 6) with **IRF8** Mutations in DNA Binding Domain
  - **IRF8** p.K66R mutation
  - This particular point mutation appears to be specific to pediatric-type FL

- 50% cases (12 of 24) with **MAP Kinase Pathway** mutations (**MAP2K1, MAPK1, RRAS**)
Activating MAP2K1 Mutations in PTFL

(Seen also in Melanoma, Langerhans Cell Histiocytosis, BRAF negative hairy cell leukemia

Louissaint et. al Blood 2016
Recurrent Mutations in PTFL

Schmidt et al. Blood 2017
Louissaint et al. Blood 2016
Ozawa et al. Modern Pathology 2016
# Pediatric-Type Follicular Lymphoma

**WHO 2016 Primary Diagnostic Criteria:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Morphology</td>
<td>At least partial effacement of nodal architecture (required)</td>
</tr>
<tr>
<td></td>
<td>Pure follicular proliferation (required)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Expansile follicles&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Intermediate-sized so-called blastoid cells (not centrocytes)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>BCL6 positivity</td>
</tr>
<tr>
<td></td>
<td>BCL2 negativity or weak positivity</td>
</tr>
<tr>
<td></td>
<td>High proliferative fraction (&gt; 30%)</td>
</tr>
<tr>
<td>Genomics</td>
<td>No BCL2, BCL6, IRF4, or aberrant IG rearrangement</td>
</tr>
<tr>
<td></td>
<td>No BCL2 amplification</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Nodal disease (required)</td>
</tr>
<tr>
<td></td>
<td>Stage I–II disease (required)</td>
</tr>
<tr>
<td></td>
<td>Patient age &lt; 40 years&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Marked male predominance</td>
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</tbody>
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- **Grading is not used**
- **NO advanced stage disease**
- **NO DLBCL component!**

<sup>a</sup> The presence of any component of diffuse large B-cell lymphoma or advanced-stage disease excludes PTFL

<sup>b</sup> These are common features of PTFL, but not required for diagnosis.
Architectural Effacement Distinguishes PTFL from Follicular Hyperplasia with clonal B cells
Missense mutations in BCL2 impact BCL2 staining with standard antibodies
Missense mutations in BCL2 impact BCL2 staining with standard antibodies
BCL2-negative Conventional FL

- 47% early stage conventional FL lack BCL2 rearrangement
- Tendency to express BCL2 despite lacking BCL2 rearrangement
- Often lack CD10 and/or express MUM1/IRF4.

Leich et al Leukemia 2016
25 year old man with cervical lymphadenopathy
Is this a nice classic case of PTFL?

Answer: Do the FISH for $BCL6$ and $BCL2$ rearrangement

No $BCL2$ gene rearrangement; $BCL6$ Rearrangement is present!

This is a conventional $BCL2$ negative Follicular lymphoma

Later: CT shows axillary lymphadenopathy
Morphology and Immunohistochemistry are not sufficient to diagnose PTFL!

Consider all clinical features in the WHO “blue box” and do the appropriate molecular genetic studies to rule out both \textit{BCL2}, \textit{BCL6} and \textit{IRF4} gene rearrangements.
Pediatric-Type Follicular Lymphoma

- PTFL is a clinically and biologically distinct, indolent lymphoma of children and adults, most commonly <40 years of age.
- Benign proliferation with rare progression even after surgical excision alone

Criteria:
- Expansile follicles composed of medium-sized blastoid cells (Grading is not used)
- BCL2 negative/dim; High proliferation fraction (>30%);
- No BCL2, BCL6 and IRF4 rearrangements.
- NO areas of DLBCL
- Not advanced stage

Red flags: Non-peripheral lymphadenopathy; CD10 loss; strong MUM1 expression, Classic grade 1-2 histology

Ages 0 to 18: conventional FL is extremely rare, likely PTFL
Ages 18-40: Rely on criteria
Age >40: Be cautious with diagnosis
Thank you!