Hematopathology Specialty Conference Case

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Case history

• 14 year old boy with isolated right inguinal lymphadenopathy
• 6.0 x 4.3 x 2.5 cm lymph node excised
Ancillary studies

- Flow cytometry not performed
- PCR on paraffin tissue
  - Single intense IGH rearrangement with framework 1 and 2 primers
  - No IGH-BCL2 rearrangement (mbr)
- FISH on paraffin tissue
  - No IGH-BCL2 rearrangement
  - No BCL6 rearrangement

Follicular lymphoma

- Generally considered an indolent but incurable lymphoma of older adults
  - Usually Stage III-IV at diagnosis
  - Multiple relapses after chemotherapy are common
- Special types of follicular lymphoma are clinically distinct, often remaining localized and cured by excision alone
  - Involving intestine (duodenum), skin, gonads
  - Occurring in children (“Pediatric”)

“Pediatric” follicular lymphoma

- Affects children (median age ~14 years), M>>F
- Cervical lymph nodes, Waldeyer’s ring, testis
- Stage I or II
- Large, expansile follicles with frequent “starry-sky” histiocytes
- “Blastoid” histology, often categorized as grade 3, with high Ki67 proliferation index
- Lacks IGH-BCL2 gene rearrangement and is usually bcl2 negative by immunohistochemistry
- Excellent prognosis


Pediatric versus usual FL

Pediatric type | Usual type
---|---
• Stage I | • Mostly Stage III-IV
• Lack *BCL2* rearrangement | • *BCL2* rearrangement in vast majority
• High (>30%) Ki67 proliferation index | • Low (<30%) Ki67 proliferation index
• Monotonous, blastoid appearing follicle center cells | • Mixture of centrocytes and centroblasts, grade 1-2 > grade 3

"BCL2-N & HPI"


**Pediatric nodal FL is a highly indolent disease**

Includes 14 patients treated with excision only

PFL: Reactive LN at periphery

PFL: Expansile follicles

PFL: Small follicles

PFL: Grade 3?
Pediatric type nodal FL can occur in older adults!

Analysis of Stage I nodal FL in adults (≥18 years)

- BFL2/NHP1 vs Other stage (≥18)
- Age (years)
- All stage I and exhibiting highly indolent behavior

Conclusions of Louissaint et al study:
- "Pediatric type" nodal FL is characterized by high Ki67 PI, no BCL2 rearrangement
  - Stage I
  - No BCL6 rearrangement
- Stage I pediatric type nodal FL can occur in older adults and exhibits similar behavior
- "Conventional" FL (BCL2 rearranged and with low Ki67 PI) can occur in young adults (≥17 years) and behaves similarly to FL in older adults.
Use of *BCL2* FISH versus IHC

- Variable bcl2 expression may occur in *BCL2* non-rearranged FL cases (18-55% of cases)
  - Usually weak and/or stains only subset of cells
  - Subjectivity in interpreting degree of bcl2 staining on intrafollicular B cells
- *BCL2* rearrangement status by FISH correlated better with stage and outcome than bcl2 IHC
- Standard bcl2 antibody (clone124) does not detect protein from some *BCL2* rearranged FL cases due to somatic mutations that alter the binding epitope

Extranodal FL in pediatric patients

- Tonsil (13%) and testis (6%) also sites of FL in children/young adults
- Tonsillar FL has distinctive features
  - Morphologically similar to PFL and no *BCL2* rearrangement, but more often bcl2+ by IHC
  - Frequent *IGH-IRF4* rearrangements with strong MUM1/IRF4 expression by IHC
  - Can also have alterations in *BCL6* locus
  - Often associated with DLBCL
  - Probably biologically different from PFL

Differential diagnosis

- Follicular hyperplasia with clonal B cells
- Low-grade FL with high proliferation index
- “Conventional” Grade 3A/3B FL
- Diffuse large B-cell or Burkitt lymphoma (especially on small sample)

Follicular hyperplasia with clonal B-cells

- Affects tonsils and head/neck lymph nodes of young males
- Light chain restricted by flow cytometry (CD10+) and clonal *IGH* rearrangement
- Histology shows follicular hyperplasia without architectural effacement
Low-grade FL with HPI

- Histologically grade 1-2 FL with Ki67 PI >30%
- More aggressive course resembling FL grade 3
- Mostly stage III-IV
- 80% bcl2+ by IHC
- Follicles usually small
- Centrocytes may appear blastoid, but are smaller than in PFL

Wang SA AJSP 2005;29:1490

“Conventional” Grade 3 FL

- >85% of Grade 3A FL have BCL2 rearrangement
  - BCL2 non-rearranged cases tend to have BCL2 gene amplification or BCL6 rearrangement
- Most Grade 3B FL lack BCL2 or BCL6 rearrangements
  - Often CD10 negative and/or MUM1+
  - Usually associated with concurrent DLBCL
  - Monomorphous centroblastic morphology differs from PFL
- Majority are Stage III-IV


Diffuse large B-cell/Burkitt lymphoma

- PFL immunophenotype overlaps with Burkitt lymphoma (CD10+, bcl6+, bcl2-)
- Blastoid morphology, “Starry sky” and high proliferation of PFL may mimic Burkitt lymphoma on FNA samples +/- core biopsy

Beware of diagnosing DLBCL or BL on limited tissue samples from pediatric patients!

Follow up of current case

- Staging studies revealed Stage I disease
- Patient was followed without any additional therapy after surgery and is alive with no evidence of disease 3 years later

Diagnosis

- Pediatric follicular lymphoma
- Key features
  - Localized disease
  - Blastoid centrocytes with high Ki67 proliferation index
  - No BCL2 gene rearrangement
Take home points

- Pediatric FL is a highly indolent clonal follicular proliferation that affects children and young adults
- Similar cases may be seen in older individuals
- High proliferation index and blastoid appearance can lead to erroneous classification as a high-grade lymphoma
- Patients may not require cytotoxic therapy after excision

References-1


References-2

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