

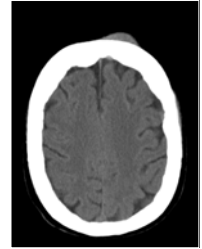
Cytogenetic studies MYC a difference

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Note: any references to the upcoming 2008 WHO Bluebook are unofficial and subject to change.

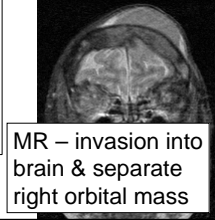
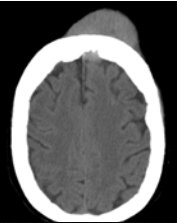
Case 4

- 88 year old woman who hit her head on the sink when she bent to pick up a brush and developed a lump on her forehead. Initial CT was interpreted as a small left frontal scalp hematoma.



Case 4

- She had persistent shoulder/neck pain, went to the ER and her shoulder was injected with steroids and she was given oral steroids as well. After some pain relief, the patient presented again 4 weeks following her injury to the hospital with diplopia, a persistent "hematoma" and severe neck pain & underwent repeat CT plus MR scan.



MR – invasion into brain & separate right orbital mass

Flow cytometric immunophenotypic studies

- CD5-, CD10-, CD20+, kappa monoclonal population with admixed heterogeneous T-cells.
- So, is this a Burkitt lymphoma, or not?

Diffuse proliferation of intermediate sized transformed cells with vacuoles, some with nuclear clefts & some large atypical forms associated with apoptosis & a starry sky.

CD5-, CD10-, CD20+ mcl B-cells

- B-cell lymphoma
 - Burkitt with somewhat atypical morphologic features (atypical Burkitt)
 - DLBCL
 - Cutaneous DLBCL, leg type
 - Blastoid (aggressive pleomorphic) mantle cell lymphoma
 - Unusual lymphoblastic lymphoma

Paraffin section IHC

- CD20+
- CD3-
- CD10 – some possible weak positivity (BL should be clearly positive)
- Bcl6+
- Ki-67, almost all +
- Bcl2+ (unlike BL)
- MUM-1+ (unlike BL)

Cytogenetic FISH analysis

- *BCL6* -- translocated
- *MYC* -- translocated
- *IGH/BCL2* -- no translocation

Major differential diagnosis

- Burkitt with somewhat atypical morphologic features (atypical Burkitt) & atypical phenotype
 - *MYC* rearranged but so is *BCL6*
- DLBCL
 - Major option if not Burkitt – should it be further designated?
- Cutaneous DLBCL, leg type
 - Can occur at sites other than the leg
 - Pure population of transformed cells
 - Phenotype would be typical (CD10-, Bcl-6+, MUM-1+ bcl-2+), *MYC* or *BCL6* translocations reported in many cases
 - But patient had disseminated disease (so not by definition a primary cutaneous lymphoma)

Burkitt lymphoma versus diffuse large B-cell lymphoma

- What are the best criteria to use?
- Some cases seem to have features intermediate between these two entities (“gray-zone” cases).
 - Cases that look like Burkitt but phenotype/genotype/karyotype too “atypical” OR cases with perfect ancillary studies but cytologic features considered beyond what is acceptable for even atypical BL.

Diagnosing Burkitt lymphoma

- Some morphologic variation permitted – “atypical Burkitt” lymphoma can be used but the term is restricted to cases that are otherwise just like a Burkitt lymphoma – not a wastebasket term for lymphomas “sort of like” Burkitts (not equiv to SNC-NB).
- Immunophenotype critical: CD20+, SIg+, CD5-, CD10+, bcl-6+, virtually all cells Ki-67 (MIB-1)+ & bcl-2- (rare exceptions).
- *MYC* rearranged with immunoglobulin gene (HC>LC) & usually without many other abnormalities. *BCL2* & *BCL6* rearrangements absent.

BCL-6 & *MYC* translocation but no *BCL-2* translocation

- *MYC* translocations associated with Burkitt lymphoma and a smaller proportion of other aggressive lymphomas
- *BCL-6* translocation associated with DLBCL and a smaller proportion of other lymphomas, don’t expect to see with Burkitt lymphomas
- DLBCL with *MYC* & *BCL-6* translocations rare but described (JCO 18:510, 2000).

What about just *MYC* R?

- Prognostic implications are controversial – some say adverse, some say doesn’t matter.
- *MYC* with *BCL2* or *BCL6* translocations are associated with very aggressive lymphomas – not clearly of Burkitt type.

What criteria should we rely on?

- Stein & Hummel (2006): “ at present, there are no reliable criteria that can be applied to distinguish BL from DLBCL.”
- One study found no adult patients with BL that fulfilled all the criteria we just reviewed that are characteristic of Burkitt lymphoma.
- Burkitt lymphoma of childhood is a more readily identified lymphoma.
- Considered important to recognize Burkitt lymphomas for clinical purposes.

Suggested criteria

- Haralambieva, et al (2005) used 2 algorithms to divide a group of BL vs DLBCL cases into BL or non-BL category
 - Histopathology, age, site, immunohistochemistry but not molecular
 - BL=Ki-67>90%, Bcl6+, CD10+, bcl2-, MYC but not BCL2 or BCL6 translocation – no additional histopathology review
- Highlighted problems in reproducible histopathologic analysis (4 pathologist agreement with consensus dx in 24% of adult BL)
- Second algorithm slightly more clinically homogeneous group but no real clinical data.
- Among the adult patients entered in this study, BL dx'd in 21 cases by algorithm A, 23 by algorithm B and only 15 (20%) by both.

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And what about the recent gene profiling studies that define “molecular BL”?

- The diagnosis appears to make a difference with therapeutic implications (not prospective studies, small #)

Hummel, et al: survival of molecular BL vs non-BL or intermediate cases (varied rx) but differences largely explained by younger age & lower stage of mBL

Dave, et al : survival of molecular BL – “discrepant” BL rx'd with CHOP did poorly (28 children & adults)

The study by Hummel, et al, (2006) also demonstrates the presence of a true “molecular” gray zone between BL & DLBCL.

In their study, the *BCL-6* translocations were found in the intermediate and non-BL group but not in those with “molecular” BL.

The 2008 WHO monograph on Tumours of the Haematopoietic and Lymphoid disorders will include a chapter on B-cell lymphoma, unclassifiable, with features intermediate between Diffuse Large B-cell Lymphoma and Burkitt Lymphoma

Bottom line

- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (diffuse large B-cell lymphoma with “high grade” features)
- What characterizes these type of cases?
 - Some morphologic features of BL including apoptosis and frequent starry sky although usually with other features unlike BL (larger cells, more prominent single nucleoli, non-amphophilic cytoplasm)
 - Phenotype usually with some features of BL (CD10+, bcl6+, sometimes bcl2-) but with other atypical but inconstant features (eg, bcl2+ (~50%), MUM1+, often Ki-67 not >95% although usually >80%).
 - MYC present in ~35-50% of cases, sometimes with other translocations as well. BCL2 translocations in ~15% sometimes with MYC.
 - Unlike in BL, MYC translocations often with non-IG genes and associated with a complex karyotype.



The patient had disseminated disease, developed a pericardial effusion and expired about one week after her biopsy.

Case that had more than meets the eye!

- A history of trauma doesn't necessarily exclude a neoplasm.
- A starry sky and many intermediate-sized transformed cells do not necessarily make for a diagnosis of classic or atypical Burkitt lymphoma.
- FISHing for *MYC* alone may be misleading.
- On the other hand, there is more to be said about a case like this than simply “DLBCL”.