

GROUND ROUNDS



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Presentation

- CC: “my left eye is pushing out”
- HPI: This is a 47 year old Asian male who was referred to the University of Louisville for abnormal orbital CT findings and Left eye proptosis. On further questioning patient also complained of double vision for the past 1-2 months. More recently patient noted decreased vision in the left eye along with some mild discomfort.
- POH: Non-contributory
- PMH: Non-contributory
- Meds: Artificial tears left eye
- Social History: 20 pack/year smoking history

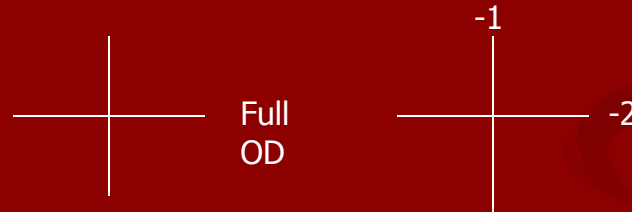
Exam

■ VA 20/30 OD 20/70 OS

■ IOP 18 OD 30 OS

■ Pupils +rAPD OS

■ EOM



Binocular double vision noted on left gaze during the exam

■ Ant. Segment: Edema of left upper eye lid, ptosis and proptosis was noted

■ Normal Dilated Fundus Exam

Photograph of the patient



Photograph at the time of presentation to ER demonstrates fullness of the left upper lid along with some conjunctival injection

CT Imaging



Axial CT imaging of the orbits demonstrates a well circumscribed mass in the suprolateral aspect of the left orbit. Mass appears to be superior to the optic nerve. No invasion of the bony orbit is noted by the mass.

Differential Diagnosis

- Cavernous hemangioma
- Lymphoma
- Benign reactive lymphoid hyperplasia
- Hemangiopericytoma
- Lymphangioma
- Orbital metastasis

Intraoperative Photograph



Lateral orbitotomy via modified Berkes procedure

Intraoperative photographs

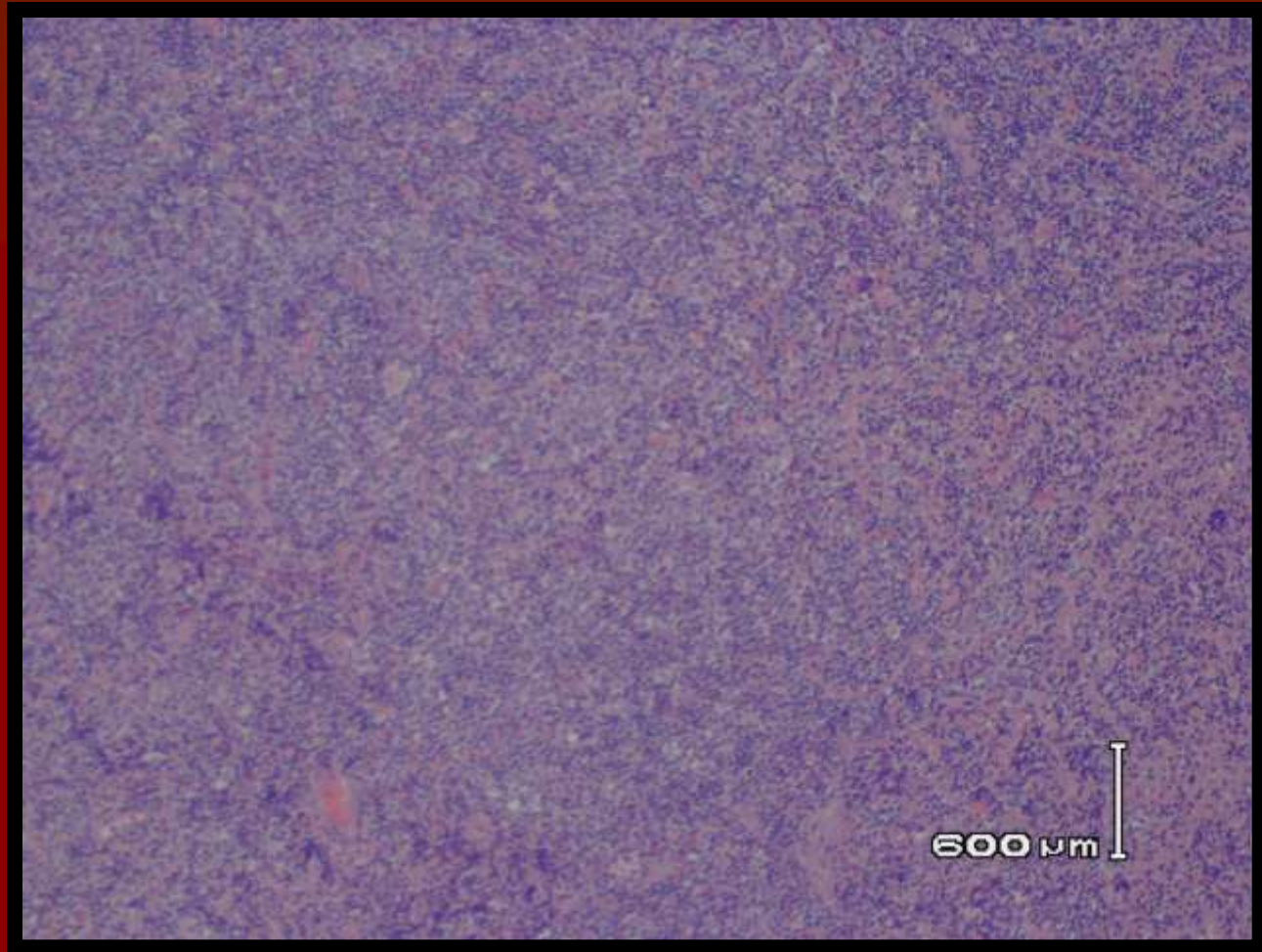


Lateral orbitotomy with more exposure of the orbit. Mass was noted to be encapsulated anteriorly. As dissection was carried out toward the orbital apex the mass was noted to be less encapsulated and more infiltrative

Pathology (frozen section)

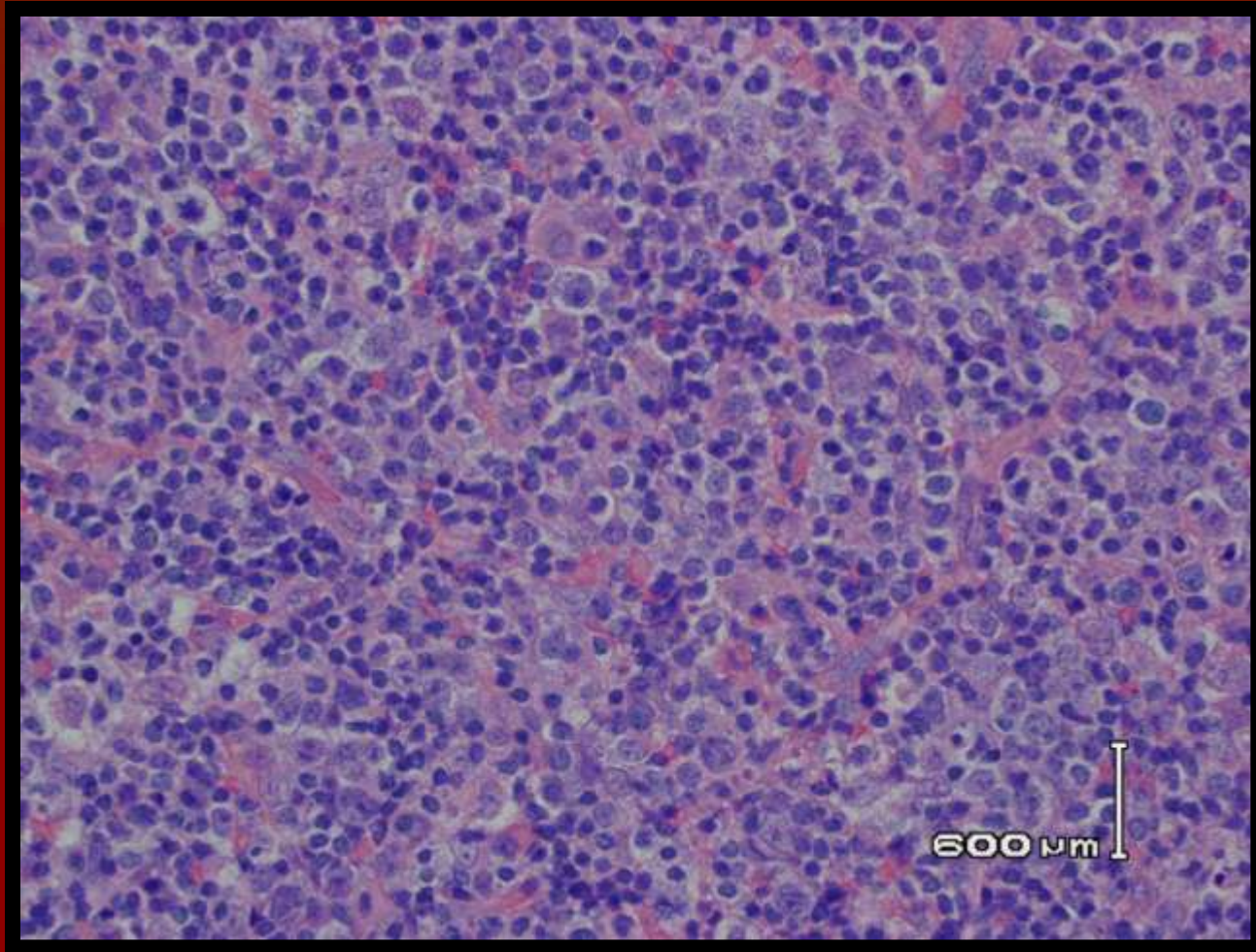
- Frozen section revealed an initial diagnosis of Lymphoma

Pathology slide



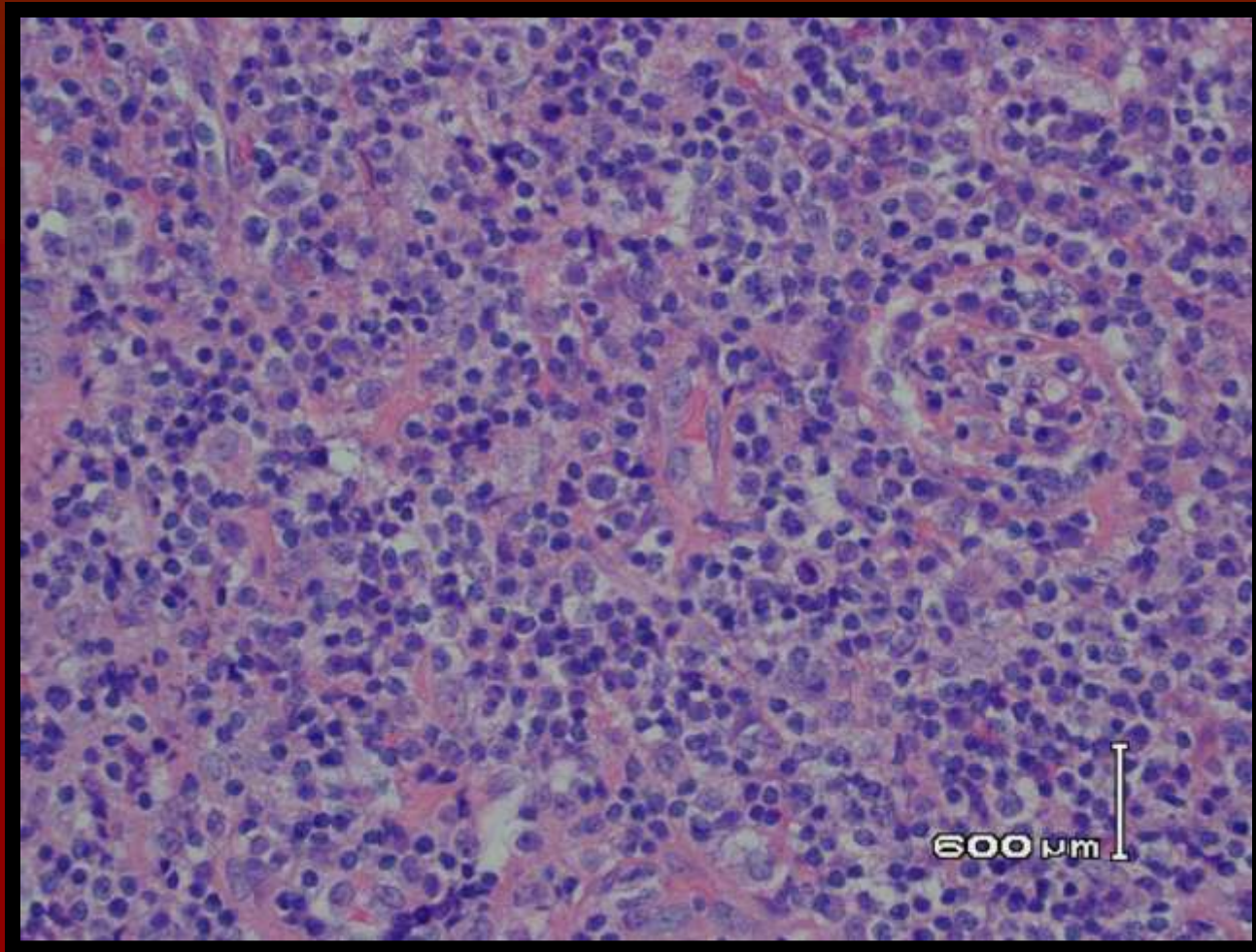
Low magnification of H&E stained specimen. Diffuse lymphocytic infiltrate with a poorly defined germinal center

Pathology slide



Higher magnification of H&E stained specimen revealing numerous small lymphocyte as Marginal zone cells

Pathology slide



High magnification H&E stain. Demonstrating numerous small lymphocytes as well as some plasma cells.

Diagnosis

- Pathological diagnosis of Extranodal Marginal Zone lymphoma was made
- The neoplastic lymphoid cells express CD20 (bright), CD5 (weak), CD19, and BCL-2 but do not express CD3, CD43, CD10, BCL-6, and BCL-1.

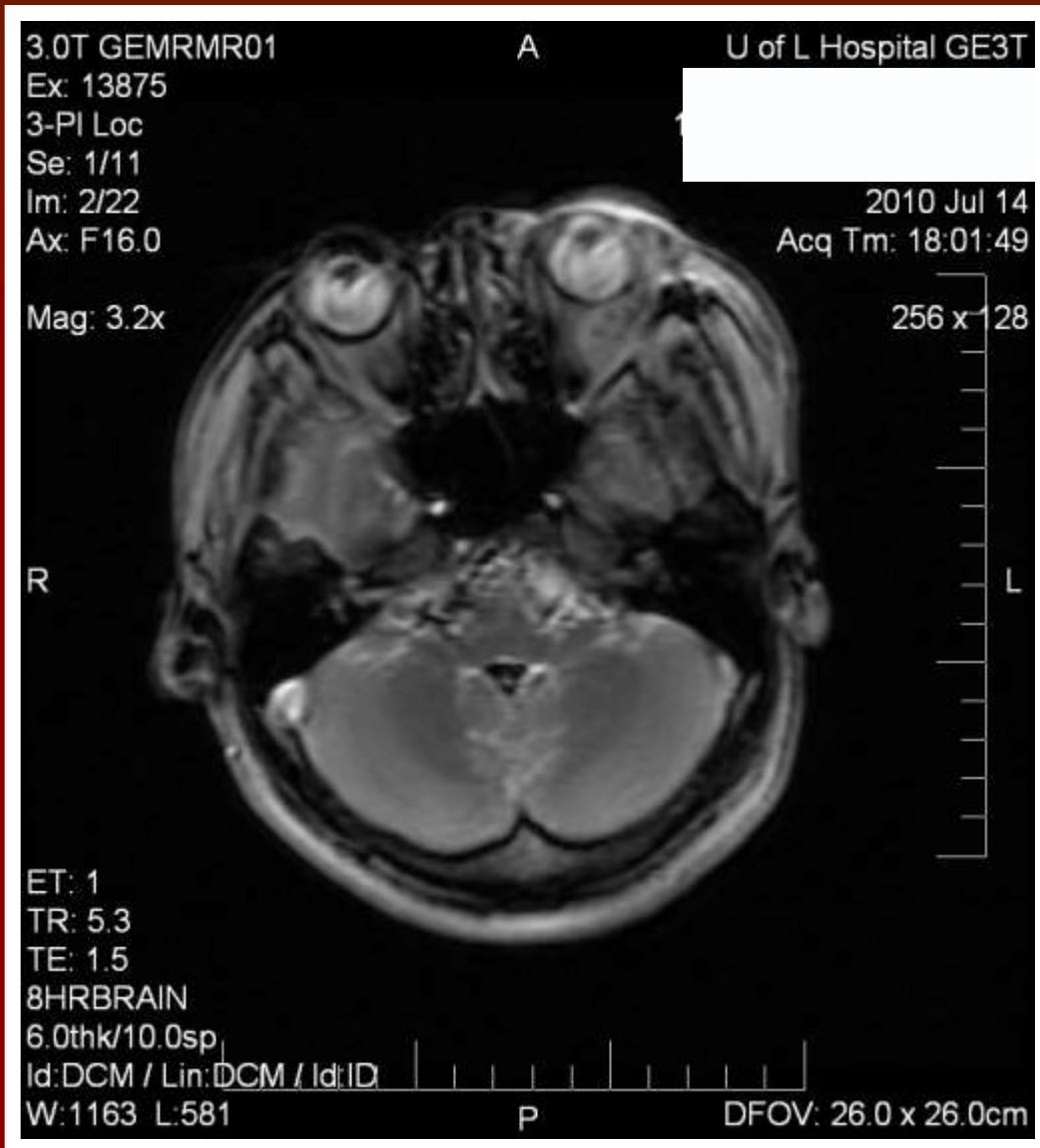
Immunophenotype analysis of ocular adnexal lymphoproliferative lesions

Type	CD3	CD5	CD10	CD20	CD23	CD43	CD79	Bcl-2	Bcl-6
EMZL	–	–	–	+	–	+	+	–	–
Follicular	–	–	+	+	±	–		+	+
Mantle cell	–	+	–	+				–	
Lymphoplasmacytic	–	+	–	+	+				
Diffuse large B-cell lymphoma	–	– (+)	+(25% – 50%)	+			+		

Tumor staging

- Physical exam: no evidence of lymphadenopathy
- CBC with diff: wnl
- DFE: wnl
- Brain and orbital MRI: evidence of residual tumor in the orbit
- Chest CT: wnl
- PET scan: wnl
- LFTs: wnl. ALT:57 AST: 49 Albumin 4.7
- HIV negative. Negative Hepatitis panel

MRI



T2 diffusion weighted image reveals an intraorbital mass in the left orbit.

Orbital Lymphoma

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graph TD; A[Orbital Lymphoma] --> B[None-Hodgkin's (REAL classification)]; A --> C[Hodgkin's Lymphoma]; B --> B1["B-Cell type (97-99%)"]; B1 --> B1a["> Low grade:"]; B1a --> B1a1["1. Extranodal marginal zone lymphoma"]; B1a --> B1a2["2. Follicular cell lymphoma"]; B1 --> B1b["> High Grade:"]; B1b --> B1b1["1. Mantle cell lymphoma"]; B1b --> B1b2["2. Lymphoplasmocytic lymphoma"]; B1b --> B1b3["3. Diffuse large B-cell lymphoma"]; B1b --> B1b4["4. Plasmocytoma"]; B --> B2["T cell type (very rare). 1-3% of all NHL in the orbits"]; C --> C1["Very rare in the orbits. May be seen in endemic areas"];
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None-Hodgkin's (REAL classification)

B-Cell type (97-99%)

➤ **Low grade:**

1. Extranodal marginal zone lymphoma
2. Follicular cell lymphoma

➤ **High Grade:**

1. Mantle cell lymphoma
2. Lymphoplasmocytic lymphoma
3. Diffuse large B-cell lymphoma
4. Plasmocytoma

T cell type (very rare). 1-3% of all NHL in the orbits

Hodgkin's Lymphoma

Very rare in the orbits. May be seen in endemic areas

Epidemiology of Orbital Lymphoma

- Incidence is approximately 1/500,000
- 1% of all non-Hodgkin's Lymphomas
- Comprises 11% of all orbital tumors and 55% of all malignant orbital tumors
- Equal prevalence in males and females

Presenting sign and symptoms

- 91% of all patients are symptomatic. Mean time from onset of symptoms to diagnosis is 4-6 months
- Conjunctival hyperemia (32%)
- Exophthalmos (27%)
- Palpable orbital mass (19%)
- Decreased vision (6%)
- Diplopia (2%)

Tumor Location

- Orbits: most common location. Involved in 46-74%
- Conjunctivae: Involved in 20-33%
- Eyelids: Involved in 5-20%
- Up to 20% of cases may have bilateral involvement. Bilaterality is not necessarily a sign of systemic disease

Site related prognosis

- Prognosis is measured by systemic involvement of the tumor
- Eye lid: carries the worse prognosis. There is a 67-100% chance of systemic involvement
- Orbits: carries a 35% chance of systemic involvement
- Conjunctivae: carries a 25% chance of systemic spread

Primary vs. Secondary

Primary orbital lymphoma	Secondary orbital lymphoma
Isolated to the orbit	Simultaneous discovery of lymphoma in the orbits and systemic lymphoma
Unilateral	Unilateral
Prevalence: 63-78%	Prevalence: 22-36%
Age 50-70, M=F	Age 50-70, M=F
Usually low grade. Extranodal marginal zone, follicular	Intermediated or high grade. Large cell lymphoma

- ❖ With the advancement in imaging modalities more tumors are found to be Secondary

Primary vs. Secondary Orbital lymphoma

Study	Number of patients	Solitary (%)	Extraorbital at diagnosis (%)
Jenkins	192	64	36
Auw	46	78	22
Cahill	20	70	30
Mannami	42	—	—
Fung	84	63	25
Coupland	230	—	—

Classification of orbital lymphoma

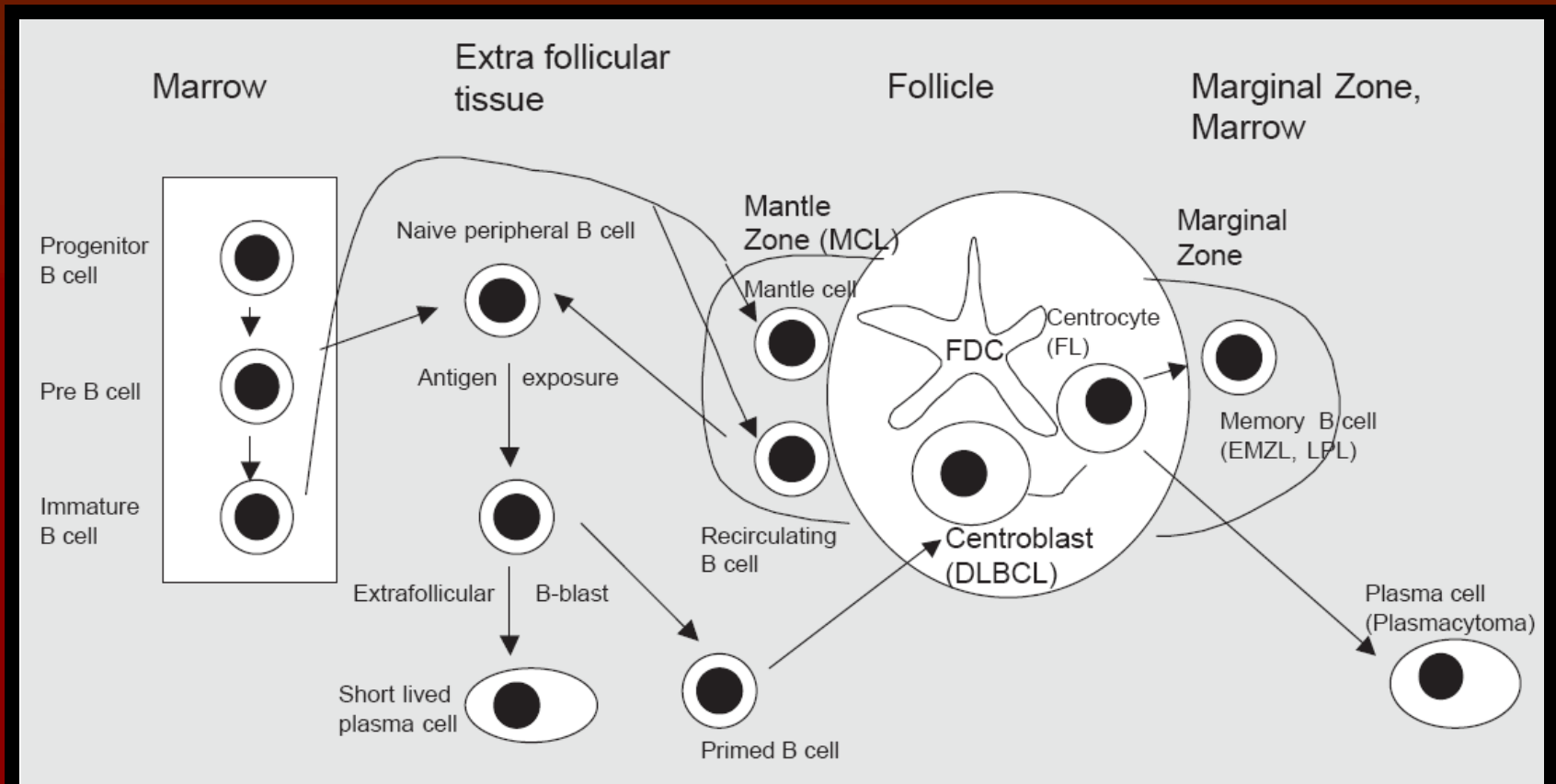


Fig. 1. Simplified model of B-cell development. Tumors arising from a given cell line are shown in parentheses. DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal cell lymphoma; FDC, follicular dendritic cell; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma.

Classification

- **Extranodal Marginal zone Lymphoma:**
 - Most common type of NHL in the orbit
 - Arise from memory B cells
 - Morphologically heterogeneous small B-cells, including marginal zone cells, small lymphocytes and poorly formed follicles
 - May be antigen driven. Chlamydia psittaci has been shown to play a role in development of EMZL
 - Immunohistochemistry is CD20+ and generally CD5- and CD10-
 - 5-10% may undergo spontaneous remission
 - 15-20% transform to Large cell type
 - 50% develop systemic disease in 10 years

Classification

■ Follicular Center Lymphoma:

- Second most common type of orbital lymphoma
- Low grade
- Arise from the cells in the germinal center

■ High-grade lymphomas:

- Large cell lymphoma (arise from cells in the germinal center)
- Mantle cell lymphoma (arise from mature naive B-cells)

Distribution of Orbital Lymphoma

Distribution of types of ocular adnexal lymphoproliferative lesions

Series	Year	OAL							
		patients (no.)	EMZL (%)	Follicular (%)	Mantle zone (%)	Lymphoplasmacytic (%)	Diffuse large B cell (%)	Plasma cytoma (%)	T cell
Coupland	2003	230	59	12	3	4	13	4	3
Fung	2003	98	57	18	4	—	7	—	—
McKelvie	2001	70	63	17	3	—	11	—	1
Shields	2001	117	Not done	—	—	—	—	—	—
Mannami	2001	43	86	—	2	—	12	—	—
Bhatia	2001	47	17	53	—	—	26	—	—
Sharara	2003	17	47	12	18	6	18	—	—
Jenkins	2000	—	54	11	2	24	8	—	<1
Nakata	1999	44(57)	77	—	4	2	14	—	—
White	1995	43	Not done	—	—	—	—	—	—
Cho	2003	57	98	—	2	—	—	—	—
Range			17–98	11–53	2–18	4–24	7–26	4	1

❖ Extranodal marginal zone lymphoma is the most common type

Tumor Related Mortality

Mortality with ocular adnexal lymphoproliferative lesions

Series	EMZL (%)	DLBCL (%)	FCL (%)	MCL (%)	LPL (%)
McKelvie	2	38	33	100	100
Coupland	13	42	37	38	44
Fung	20	25	20	—	—
Jenkins	9	30	21	NA	14
Nakata	0	75	—	75	—

Abbreviations: FCL, follicular lymphoma; MCL, mantle cell lymphoma; NA, not analyzed separately.

❖ Extranodal Marginal Zone Lymphoma has the best prognosis followed by Follicular Cell Lymphoma

Diagnosis

- Ophthalmic exam and physical exam
- Orbital imaging. Characteristic putty like molding of the tumor to the surrounding structures
- Tissue biopsy.
- H &E stain. Blue cells
- Immunohistochemistry: identifies antigenic expression of lymphoma cells and aids in histological classification
- **Flow cytometry**: determines clonality of the lymphocytes
- **Cytogenetic studies**: identifies tumors with characteristic chromosomal abnormality
- **Molecular studies** : PCR

Tumor staging and work-up

- Physical exam
- CBC with differential
- CT imaging of chest, abdomen and pelvis
- Brain MRI
- Bone marrow biopsy
- PET scan

Treatment

- **Surgery:** Excision may be most appropriate for localized lesions of the conjunctiva and orbit
- **Radiation:** Typical doses are 28 to 36 Gy for low-grade lymphomas and 30 to 40 Gy for high grade lymphomas. There seems to be a dose dependent response. The local 5-year control rate of EMZL-MALT was 81% with doses less than 36 Gy but 100% with doses greater than 30 Gy for high-grade disease (1)
- **Brachytherapy:** local recurrence and toxicity is common
- **Chemo/radiation:** used for more histologically aggressive tumor types where systemic involvement may be more likely

Treatment (continued)

- **Monoclonal antibody therapy:** directed against CD20+ cells (Rituximab)
- **Radioimmunotherapy:** Lymphocyte specific monoclonal antibodies are used to deliver radioisotopes to tumor. For example I-131-tositumomab is a murine anti-CD20 monoclonal antibody linked to I-131-radioisotope.
- **Antimicrobial therapy:** directed against *C. psittaci*. In small case series 2 of 4 patients with evidence of *C. psittaci* in tumor and peripheral blood had objective improvement after administration of Doxycycline 100mg 3x a day for 3 weeks.(1)

Thank you

References

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