



Memorial Sloan Kettering
Cancer Center

t(14;18) Negative Follicular Lymphoma with 1p36 abnormality associated with In Situ Follicular Neoplasia with t(14;18) translocation

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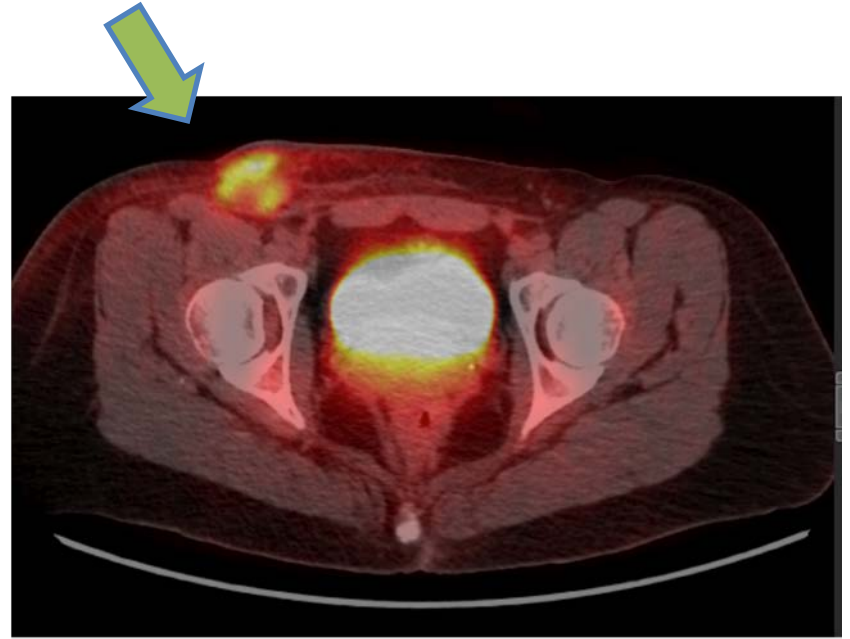
Hematopathology Service
Memorial Sloan Kettering Cancer Center, New York

Clinical History

□ May 2013

- 35 y/o female presented with a painless mass in her right groin.
- No c/o fever, night sweats or unexplained weight loss
- Laboratory Findings :
 - CBC (WBC: 6.6 K/ul; HgB: 13.3 g/dl; Hct: 37.3%; MCV:93 fl; Platelet: 359 K/ul)
 - LDH: 188 U/L

CT and PET Scan Images: May 2013



Localized mass: Right Groin: 3.5 x 2.4 cm; SUV: 4

Clinical History

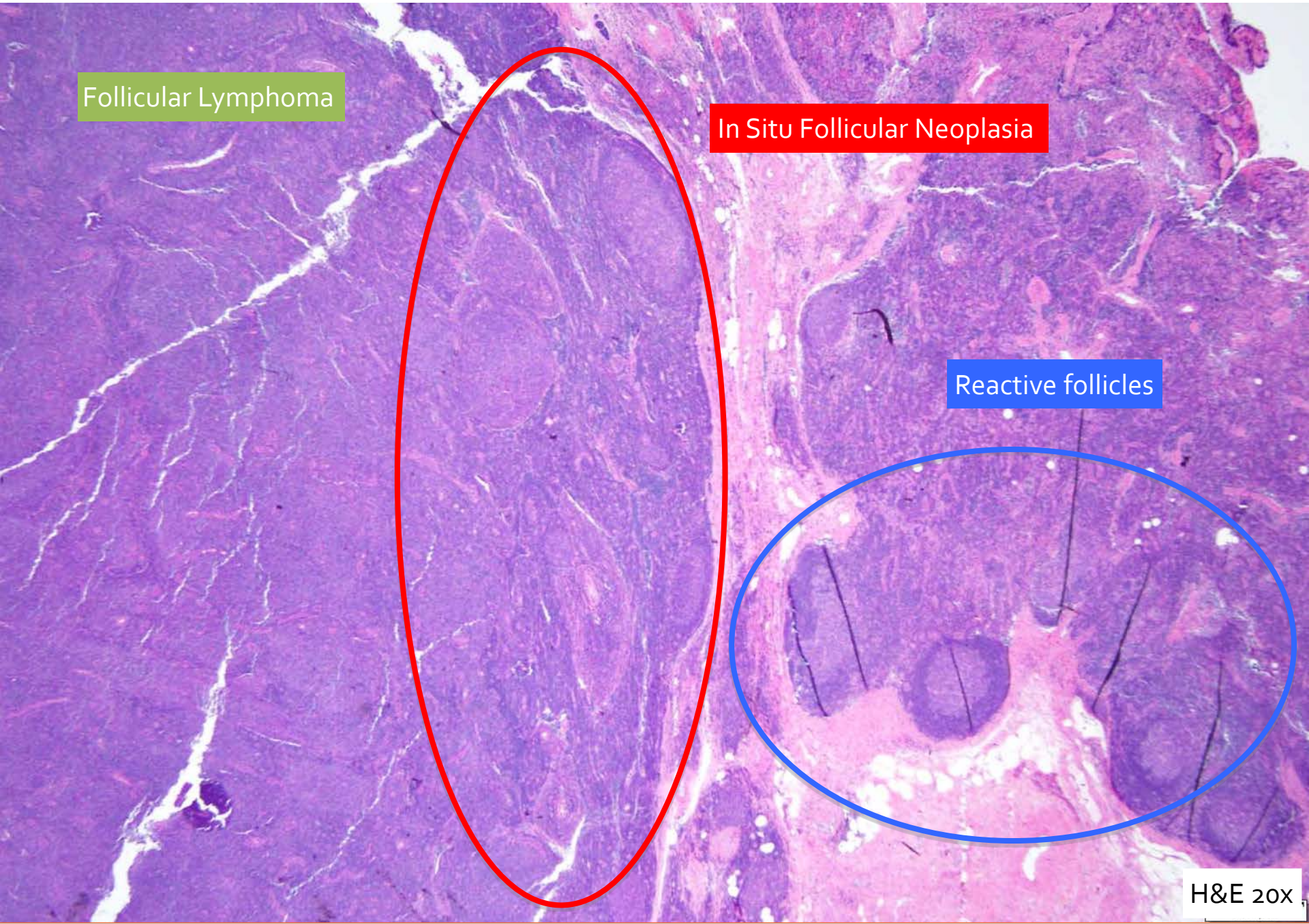
- ❑ Lymph node excision and bone marrow biopsy were performed
- ❑ Diagnosis : At outside institute
 - Lymph node: Marginal zone lymphoma
 - Bone marrow: No morphologic or immunophenotypic evidence of Lymphoma
- ❑ Clinical Stage 1A
- ❑ We received slides for consultation at MSKCC

H&E: Area with Follicular Lymphoma, In Situ Follicular Neoplasia and Reactive Follicles

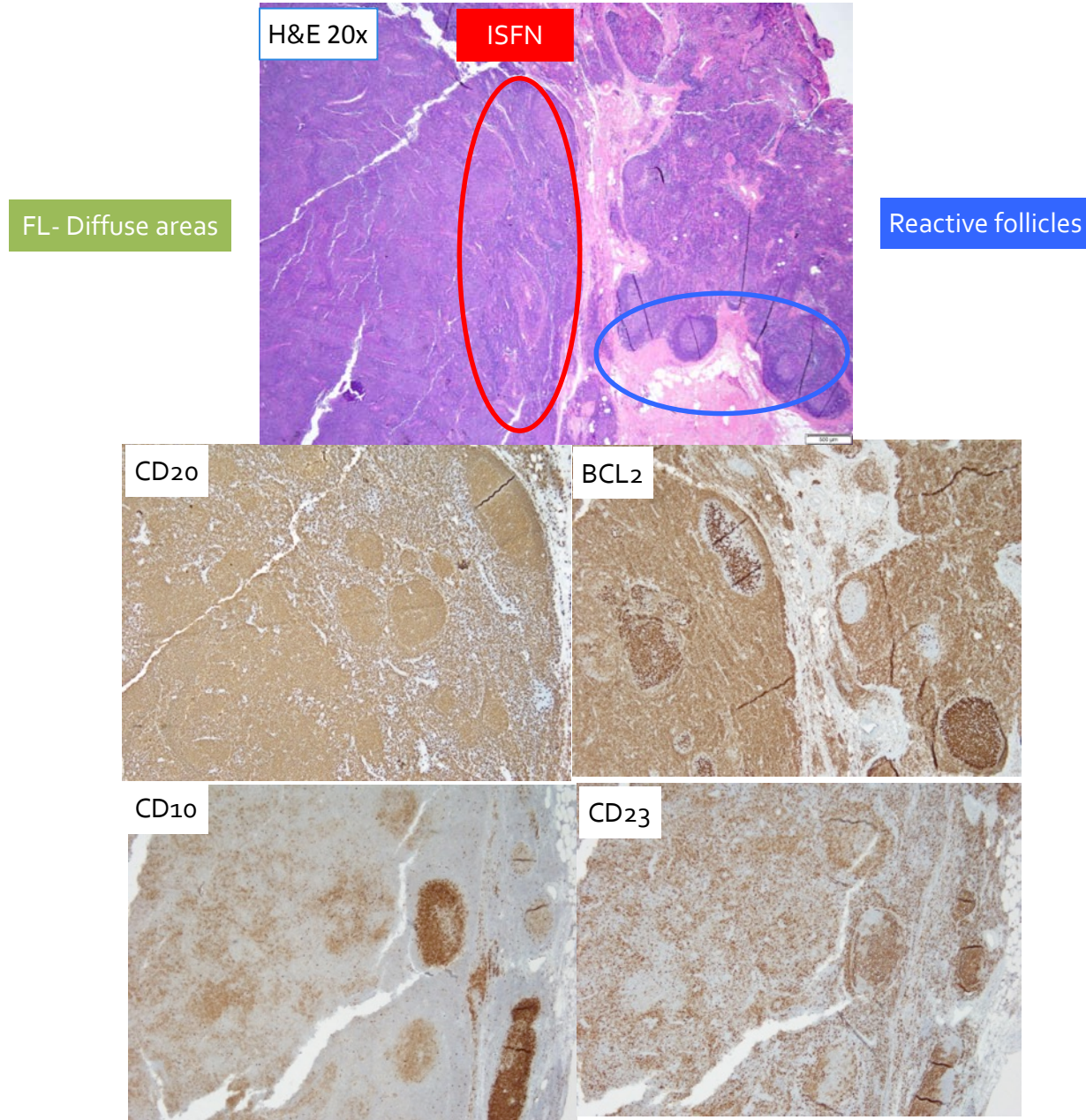
Follicular Lymphoma

In Situ Follicular Neoplasia

Reactive follicles

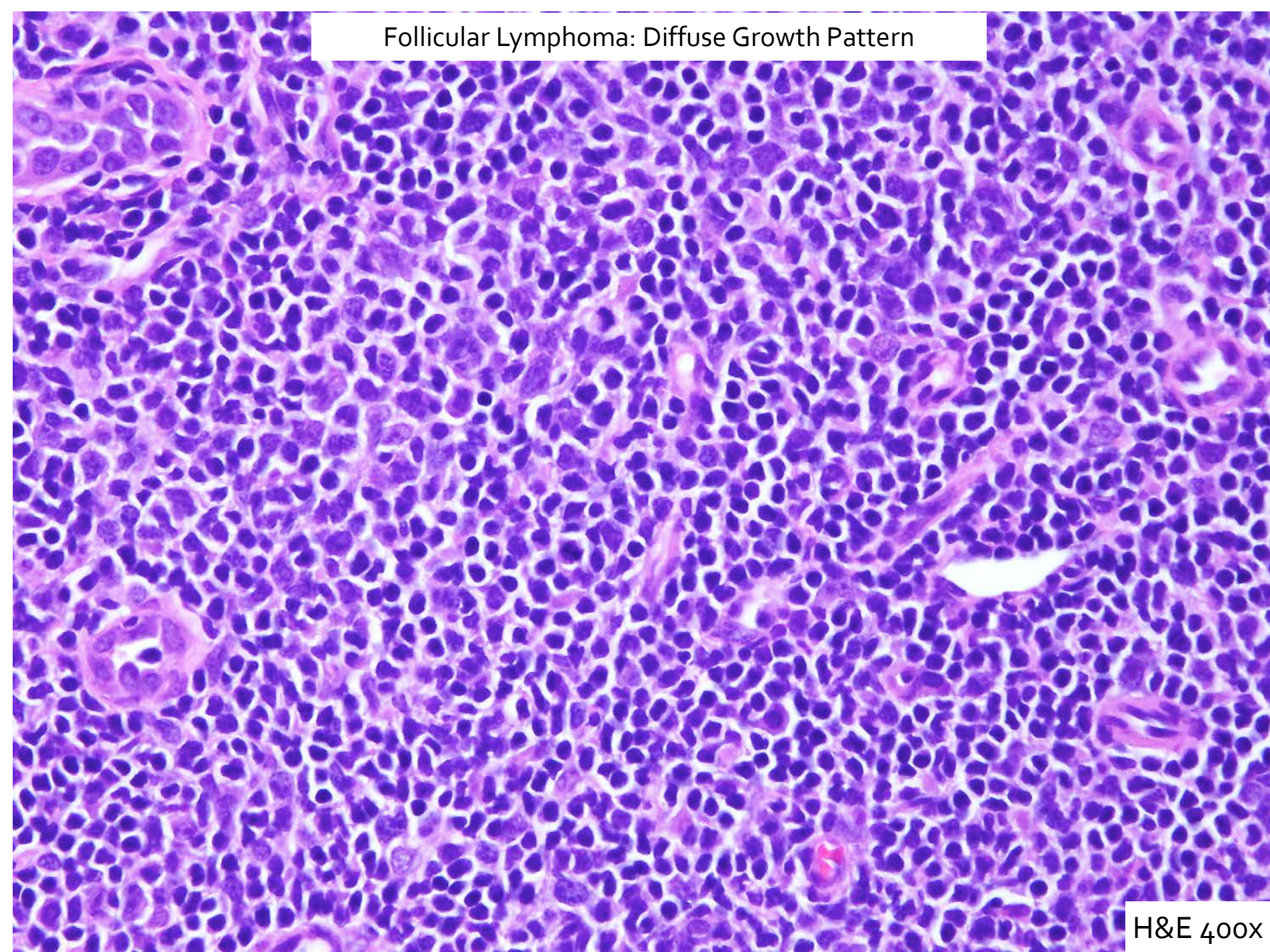


Morphologic and immunohistochemical features of Follicular Lymphoma and In Situ Follicular Neoplasia



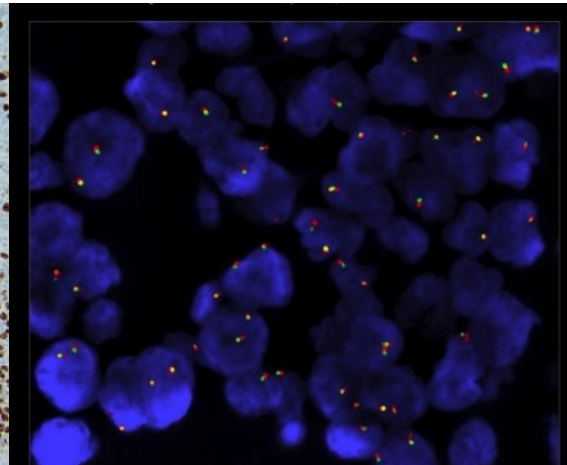
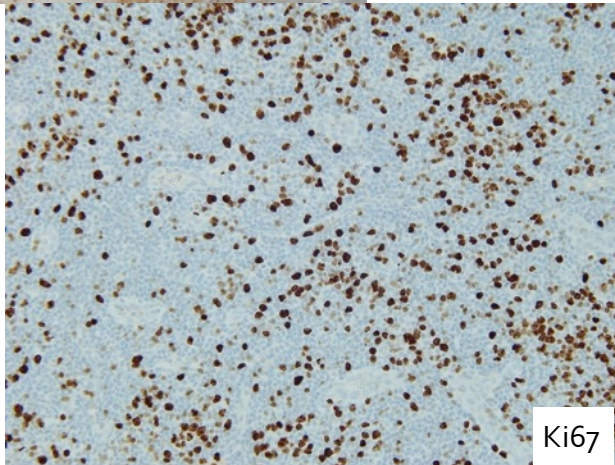
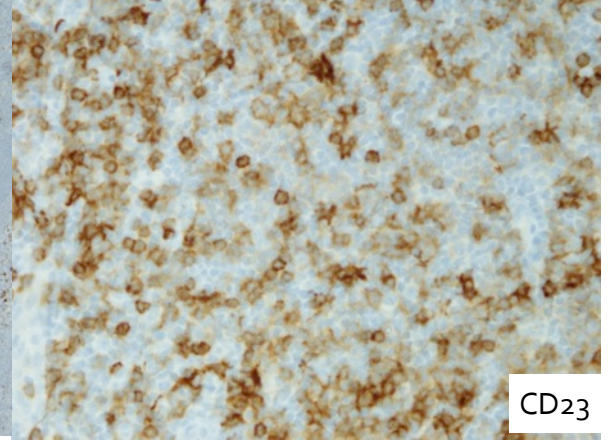
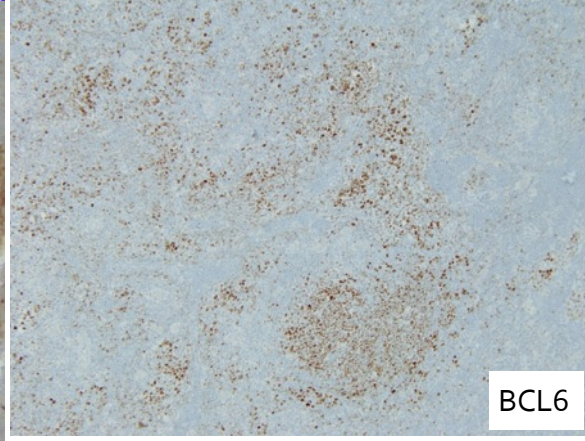
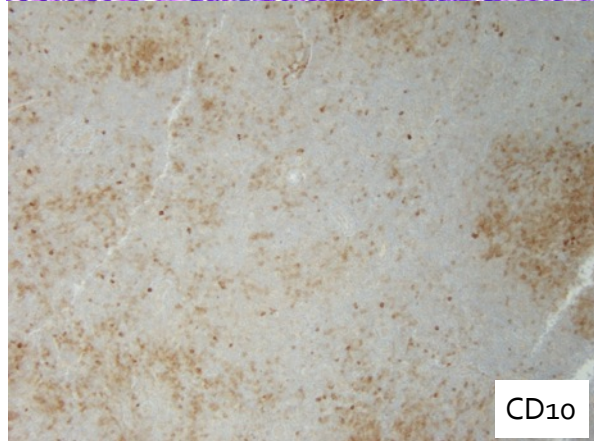
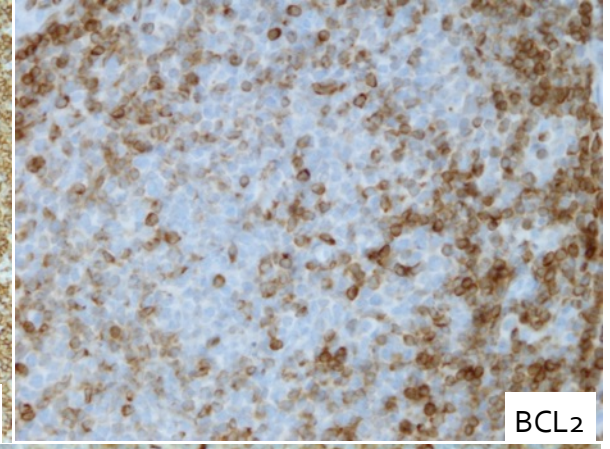
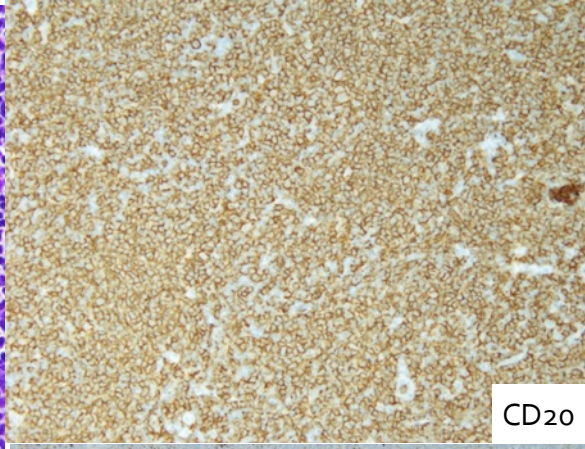
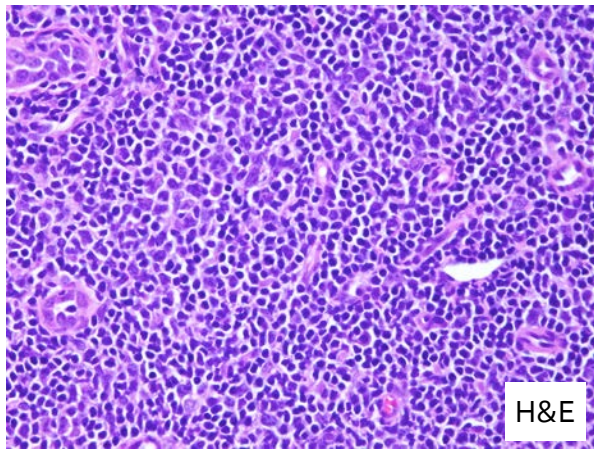
H&E section shows FL with diffuse areas on right, ISFN (center) and reactive follicles on left (20x)

Follicular Lymphoma: Diffuse Growth Pattern



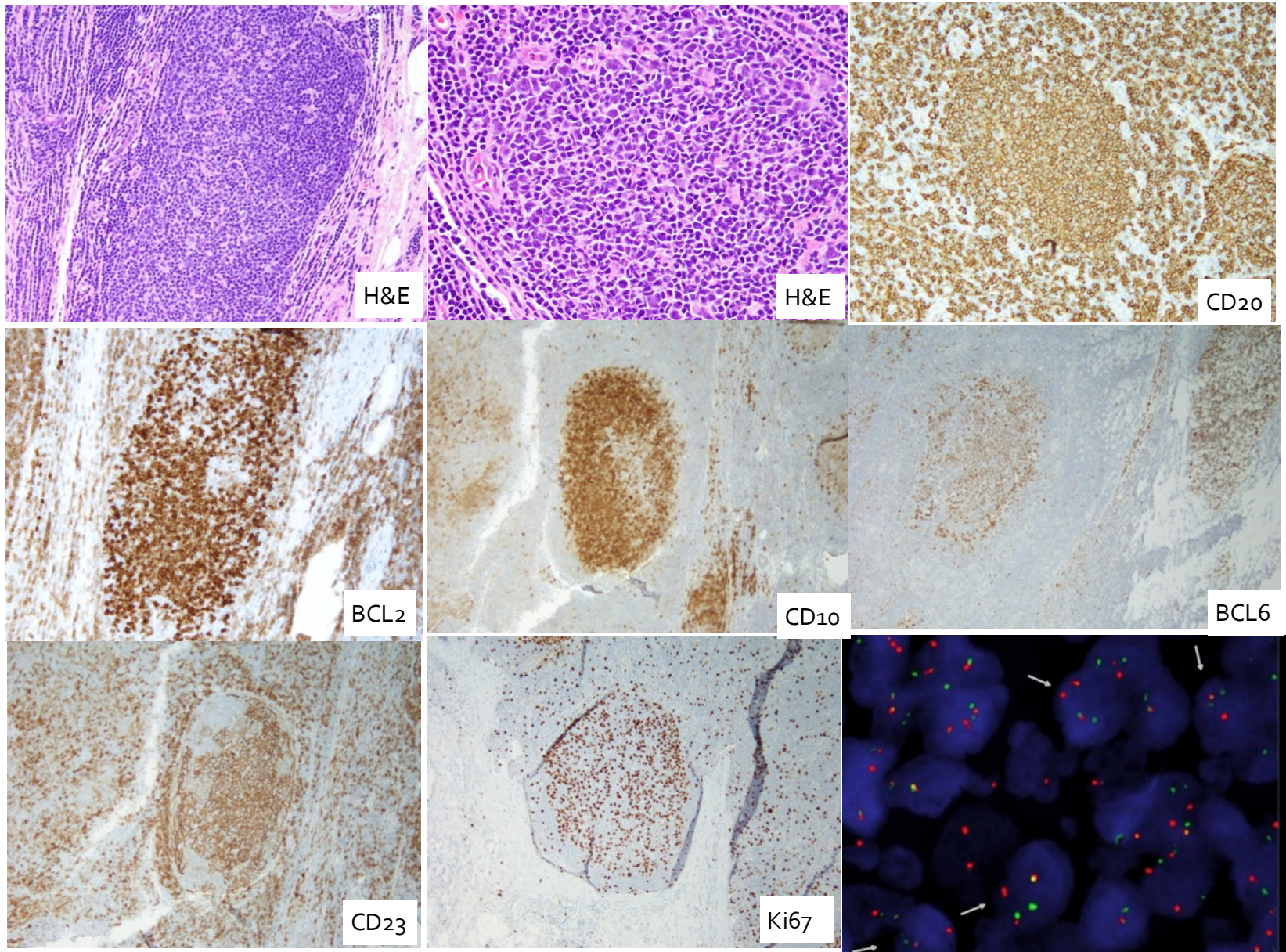
H&E 400x

Morphologic and immunohistochemical features of Follicular Lymphoma (FL)



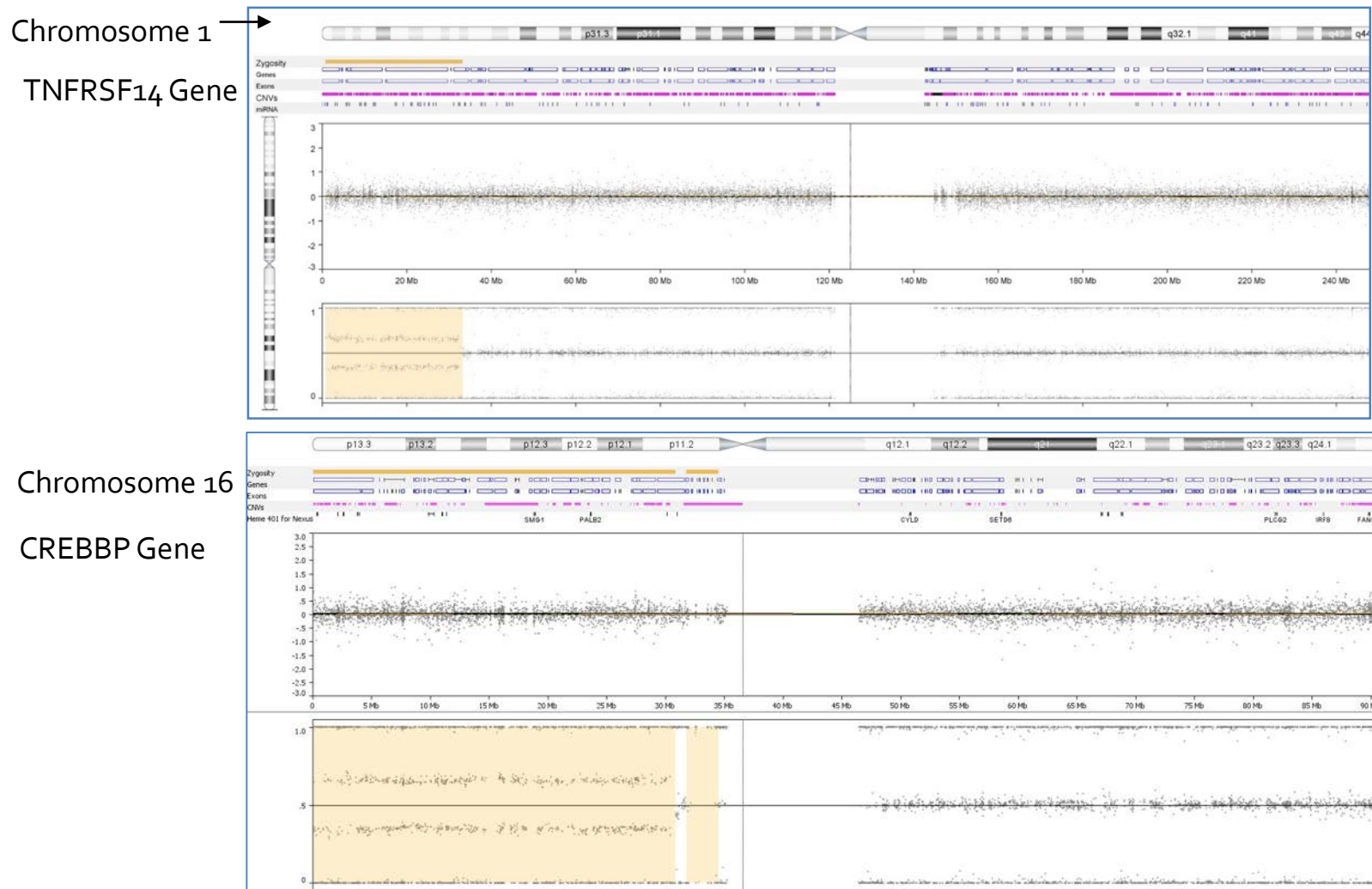
FISH studies using BCL2
Break apart probe:
Negative for BCL2 gene
rearrangement

Morphologic and immunohistochemical features of In Situ Follicular Neoplasia (ISFN)



Genetic Studies

➤ SNP (Single Nucleotide Polymorphism) array analysis



1. Copy Neutral – Loss of Heterozygosity (CN-LOH) in 1p35.1p36.33 that harbors TNFRSF14 gene
2. Coexistence of Copy Neutral – Loss of Heterozygosity (CN-LOH) in 16p involving CREBBP gene

➤ Comprehensive Genomic Analysis:

Chr:Pos	Ref	Alt	Gene	Exon	TxID	cDNA	AA	Variant Class	dbSNP	Method	MAF	VF_N	DP_T	AD_T	VF_T
1:2492074	C	T	TNFRSF14	○	exon5	NM_003820	c.472C>T	p.Q158*	Nonsense_Mutation	M-V	0.00223	831	232	0.27918	
16:3788646	A	C	CREBBP	○	exon26	NM_004380	c.4308T>G	p.S1436R	Missense_Mutation	M-V	0.0	773	228	0.29495	

➤ Two mutations were detected in this patient:

1. TNFRSF14 p.Q158* (A change in nucleotide resulting in a premature stop codon), variant frequency 27.9%
2. CREBBP p.S1436R (Missense mutation), variant frequency 29.5%

➤ Patient's normal control (blood) is also sequenced to filter germline variant.

Summary of Findings

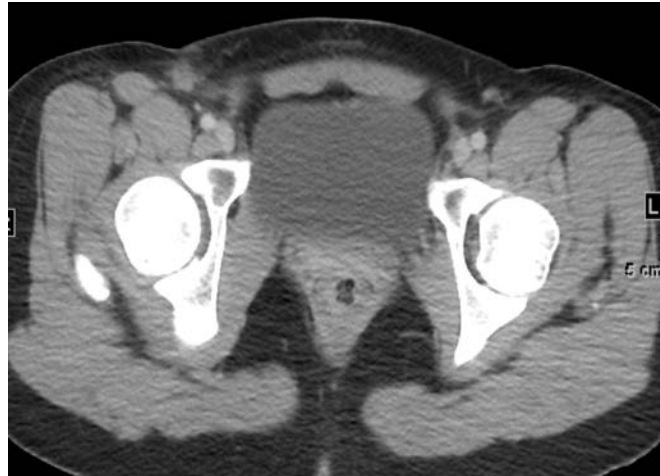
	Follicular Lymphoma Diffuse Growth Pattern	In situ Follicular Neoplasia (ISFN)
❖ Immunostains		
CD20	Positive	Positive
BCL2	Weak to negative	Strong
CD10	Dim	Strong
BCL6	Variable	Variable
CD23	Strong	Negative
❖ Cytogenetic Studies		
BCL2 gene rearrangement	Not detected	Detected (57% of the cells)
SNP array analysis	Detected (CN- LOH in chromosome 1p35.1p36.33 and 16p)	??
❖ Comprehensive Genomic Analysis		
	TNFRSF14 p.Q158*	??
	CREBBP p.S1436R	??

❑ Diagnosis

- **t(14;18) Negative Follicular Lymphoma with 1p36 abnormality associated with In Situ Follicular Neoplasia with t(14;18) Translocation**

❑ Follow Up

- Patient was treated with 24 Gy of involved field radiation therapy (IFRT), completed in August 2013.
- CT scan after treatment- August 2013



- ❑ Follow up examination showed no clinical or radiological evidence of disease- Complete remission after 45 months

In Situ Follicular Neoplasia (ISFN)

- (1) How should in situ follicular neoplasia be defined and diagnosed?
- (2) Is in situ neoplasia an early step of lymphomagenesis?
- (3) How should patients with in situ neoplasia be managed
 - “in situ” follicular neoplasia without overt lymphoma:
 - No evidence for starting therapy: “wait-and-watch policy” is strongly suggested.
 - For patients with concomitant overt lymphoma:
 - Staging and treatment: based on malignant counterpart.

t(14;18) Negative Follicular lymphoma with Diffuse Growth Pattern

- ❑ Presents as large, localized tumors in inguinal region
- ❑ Diffuse growth pattern
- ❑ CD20, BCL2 (dim to negative), CD10 (dim) , BCL6 with CD23 co-expression
- ❑ Lacks BCL2 gene rearrangement
- ❑ Deletion in the terminal parts of the short arm of chromosome 1 (1p36).
- ❑ Low clinical stage, indolent disease

MSKCC t(14;18) Negative Inguinal/ Groin Follicular Lymphoma

- ❑ Inguinal/ groin FL cases were retrieved from archives of Department of Hematopathology at MSKCC
- ❑ Morphologic and immunohistochemical stains were reviewed.
- ❑ FFPE inguinal/ groin follicular lymphoma tissue samples were analyzed by BCL2-rearrangement FISH assay (Abbott molecular).
- ❑ Genomic DNAs extracted from FFPE tumor material were used for copy number and allelic imbalance analysis by SNP-array (OncoScan, Affymetrix).

MSKCC t(14;18) Negative Inguinal/ Groin Follicular Lymphoma Cases

Case No.	FISH studies: BCL2 gene rearrangement	SNP array analysis: Chromosome 1p	SNP array analysis: Chromosome 16p
1	Negative	CN-LOH of 1p	CN-LOH of 16p12.1-ter
2	Negative	CN-LOH of 1p36.23-ter	-
3	Negative	CN-LOH of 1p36.31-ter	CN-LOH of 16p13.13-ter
4	Negative	CN-LOH of 1p35.2-ter	-
5	Negative	CN-LOH of 1p36.11-ter	CN-LOH of 16p11.3-ter
6	Negative	CN-LOH of 1p36.11-ter	-
7	Negative	del of 1p36.33-36.32 (2.7 Mb)	CN-LOH of 16p11.2-ter
8	Negative	CN-LOH of 1p35.2-ter	CN-LOH of 16p11.2-ter
9	Negative	CN-LOH of 1p36	CN-LOH of 16p13.3-p13.11
10	Negative	CN-LOH 1p36.32-ter (2.7 Mb)	-
11	Negative	deletion of 1p36.23-ter	-
12	Negative	deletion of 1p36.23-ter	CN-LOH of 16p11.2-ter
13	Negative	-	CN-LOH of 16p13.13-ter
14	Negative	CN-LOH of 1p34.2-ter	CN-LOH of 16p11.2-ter
15	Negative	CN-LOH 1p36.32-ter (2.9 Mb)	-
16	Negative	CN-LOH 1p33-ter	-
17	Negative	deletion of 1p35.1-ter Focal homozygous deletion of TNFRSF14	-
18	Negative	-	CN-LOH of 16p13.13-ter

Cell Biology of TNFRSF14/HVEM: 1p36 Follicular Lymphoma

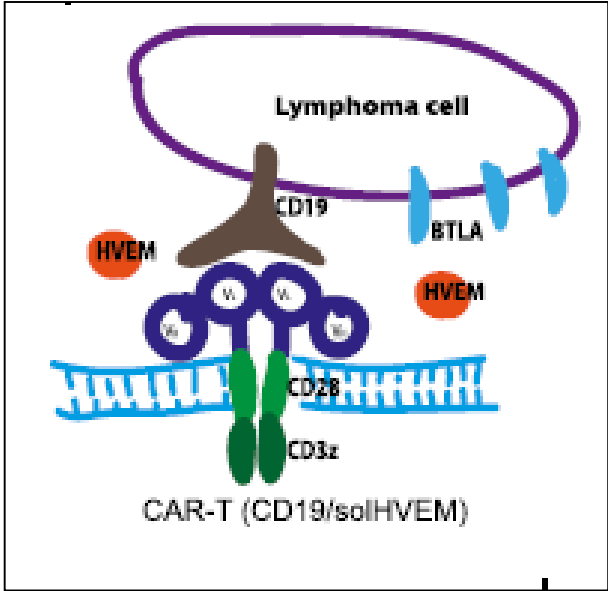
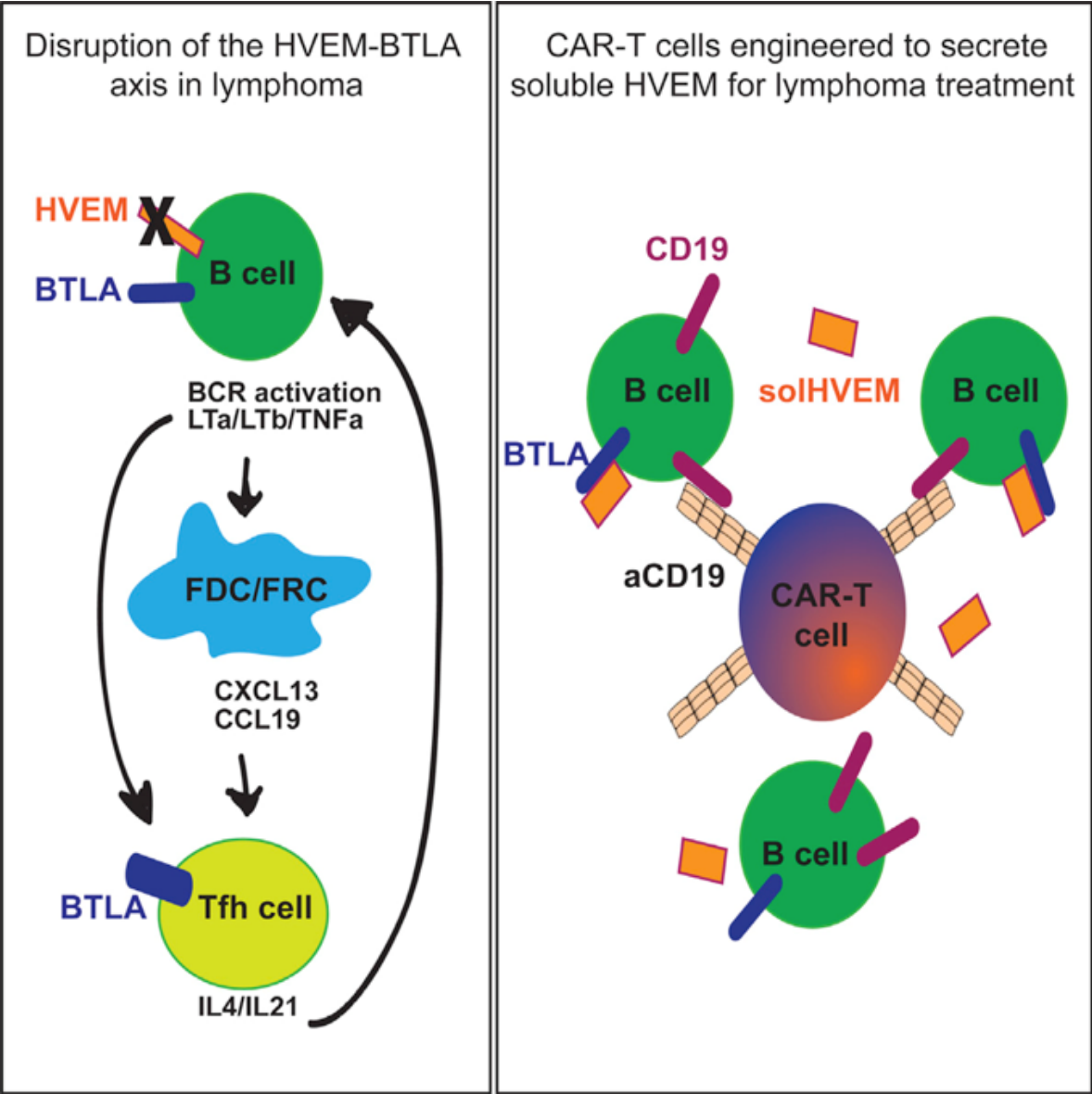


Diagram representing the concept of CAR-T cells that produce solHVEM locally and continuously at the lymphoma site in vivo.

Loss of the HVEM Tumor Suppressor in Lymphoma and Restoration by Modified CAR-T Cells. M. Boice. Cell 2016

Take home message: Inguinal/Groin Follicular Lymphoma with 1p36 abnormality

1. Clinical features

- ❑ Isolated large inguinal/groin mass

2. Phenotype

- ❑ CD20, BCL2 (dim to negative), CD10 (dim), BCL6 with CD23 coexpression

3. Molecular work up

- ❑ FISH Studies: BCL2 gene rearrangement
- ❑ SNP Array: Deletion or CN-LOH in chromosome 1p36
 - SNP array, not FISH would be the test of choice for this aberration.
- ❑ Comprehensive Genomic Analysis: TNFRSF14 gene mutation

Final Panel Diagnosis

t(14;18) Negative Follicular Lymphoma with 1p36 deletion



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Thank You

