Am J Surg Pathol 2020;44:329–339

Unusual Variants of Follicular Lymphoma

Case-based Review

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2020-04-27

Follicular lymphoma (FL)

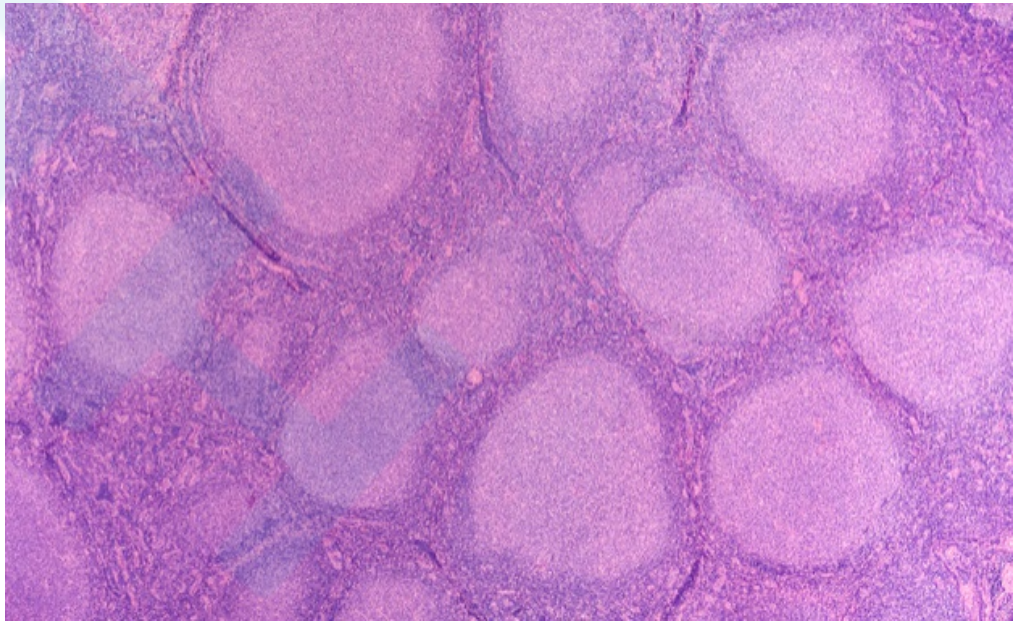
FL is common

- 40% of adult non-Hodgkin lymphomas in US
- Predominantly affects adults (median age 60)
- Generalized peripheral and central lymphadenopathy

  May be accompanied by splenomegaly

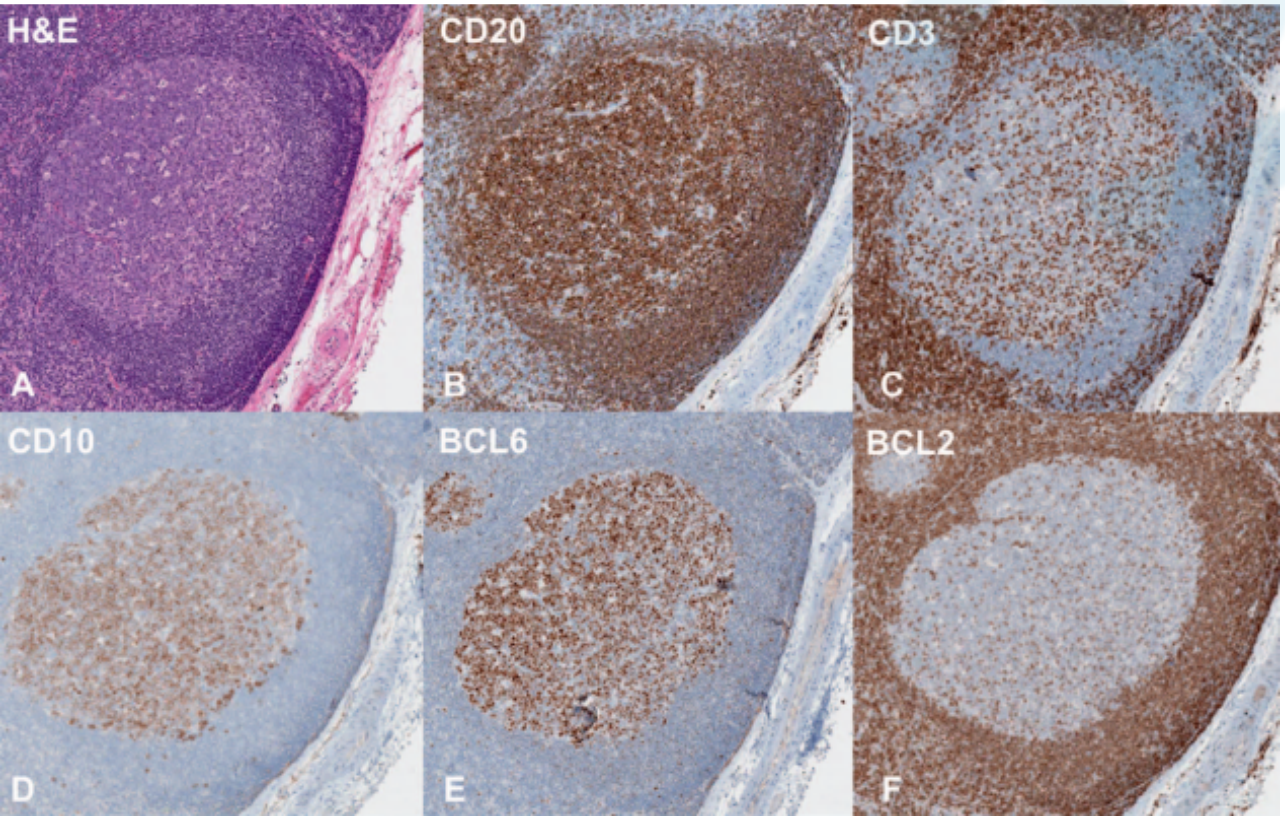
Usual FL

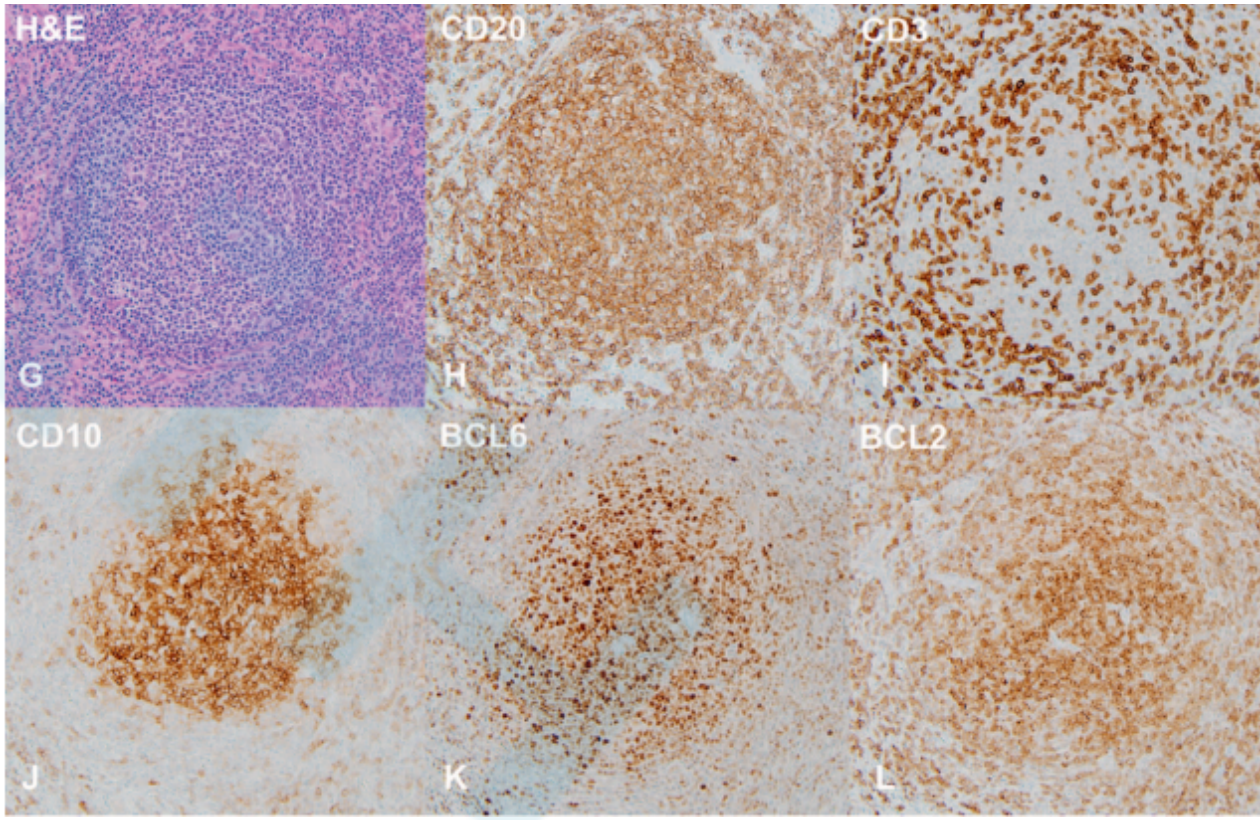
- Derived from germinal center B cells
- Composed of centrocytes and centroblasts
- Characteristic follicular distribution
- Monotonous neoplastic follicles present in a crowded distribution
- Neoplastic follicles lack of well-defined mantle zones and loss of polarization and/or starry-sky pattern



Usual FL

- Germinal center B-cell immunophenotype (CD10, BCL6, HGAL, LMO2)
- Abnormal coexpression of BCL2 (85%)

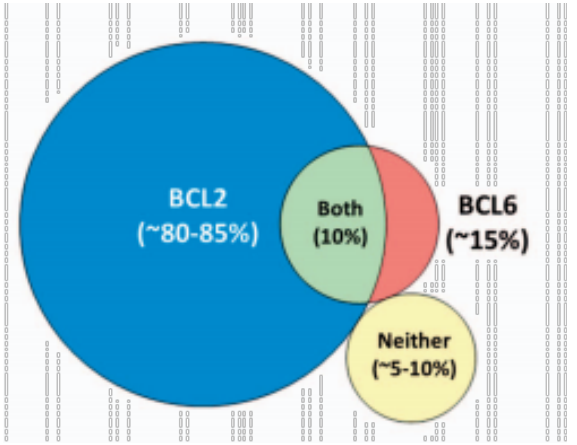


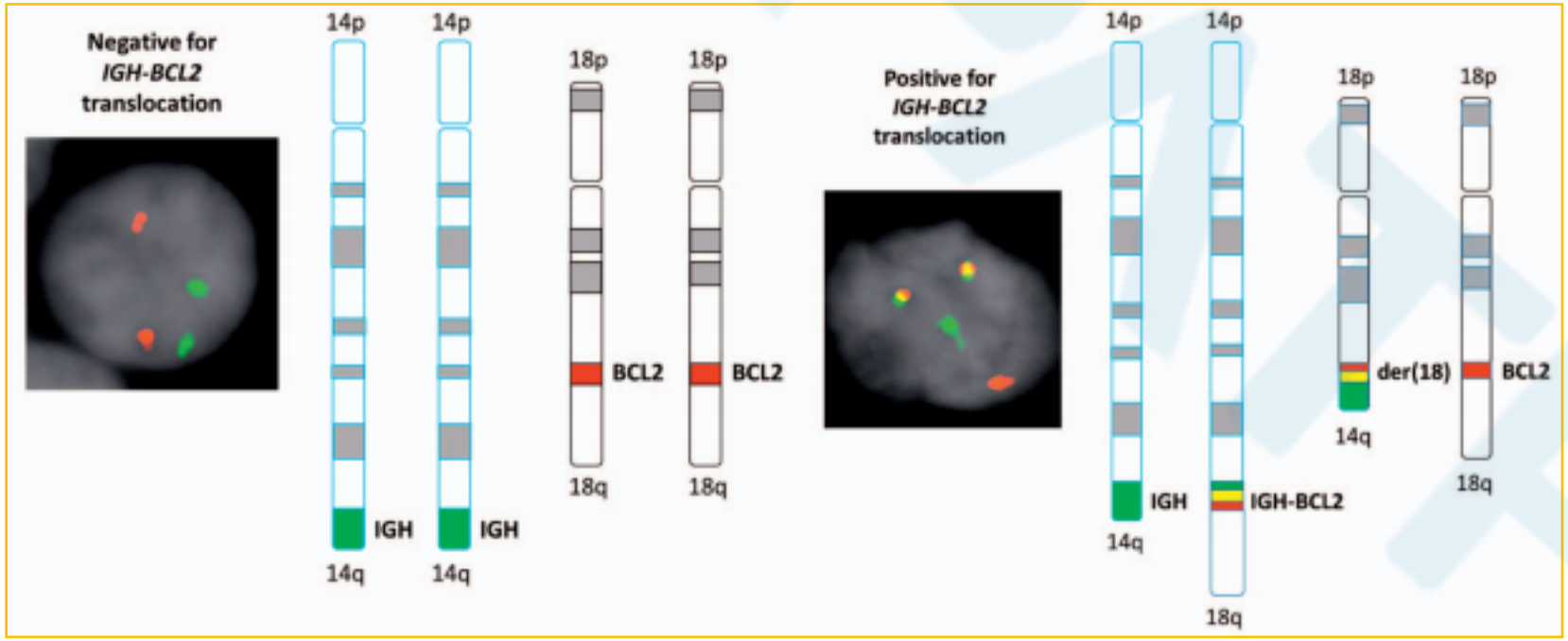


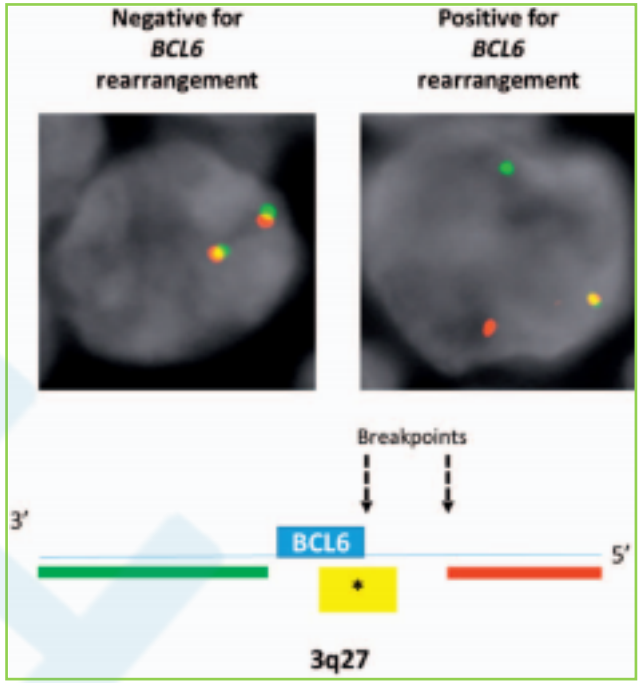
Arch Pathol Lab Med. 2018;142(11):1330-1340

Usual FL

- Usually due to translocation t(14;18)(*IGH-BCL2*)
- FL may also show rearrangements of *BCL6*



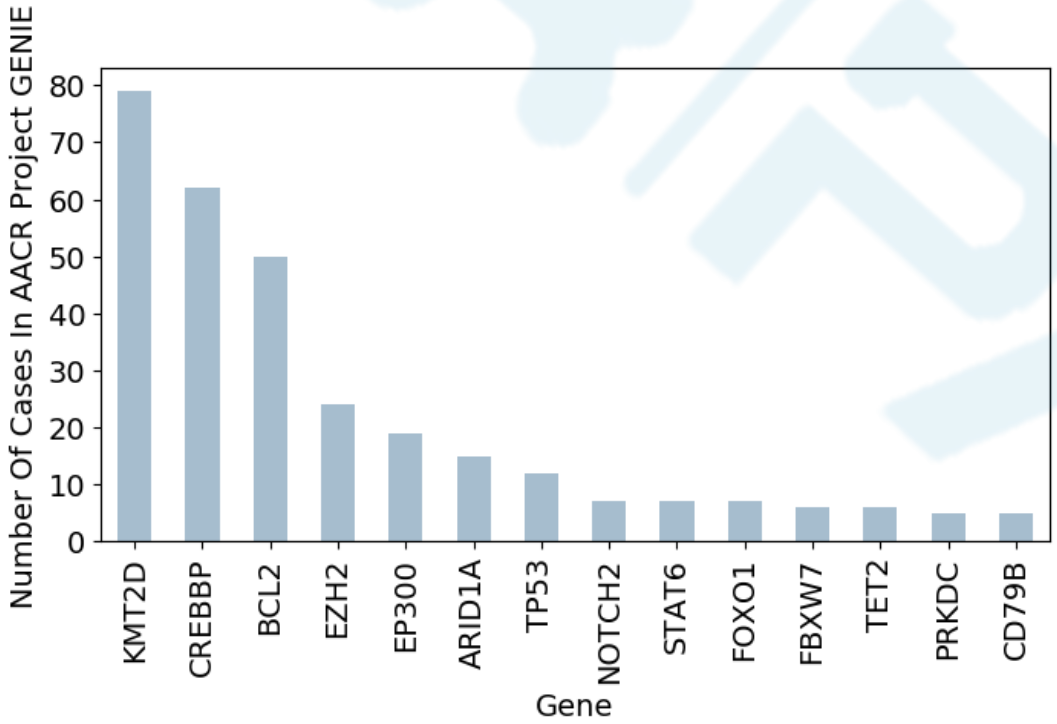


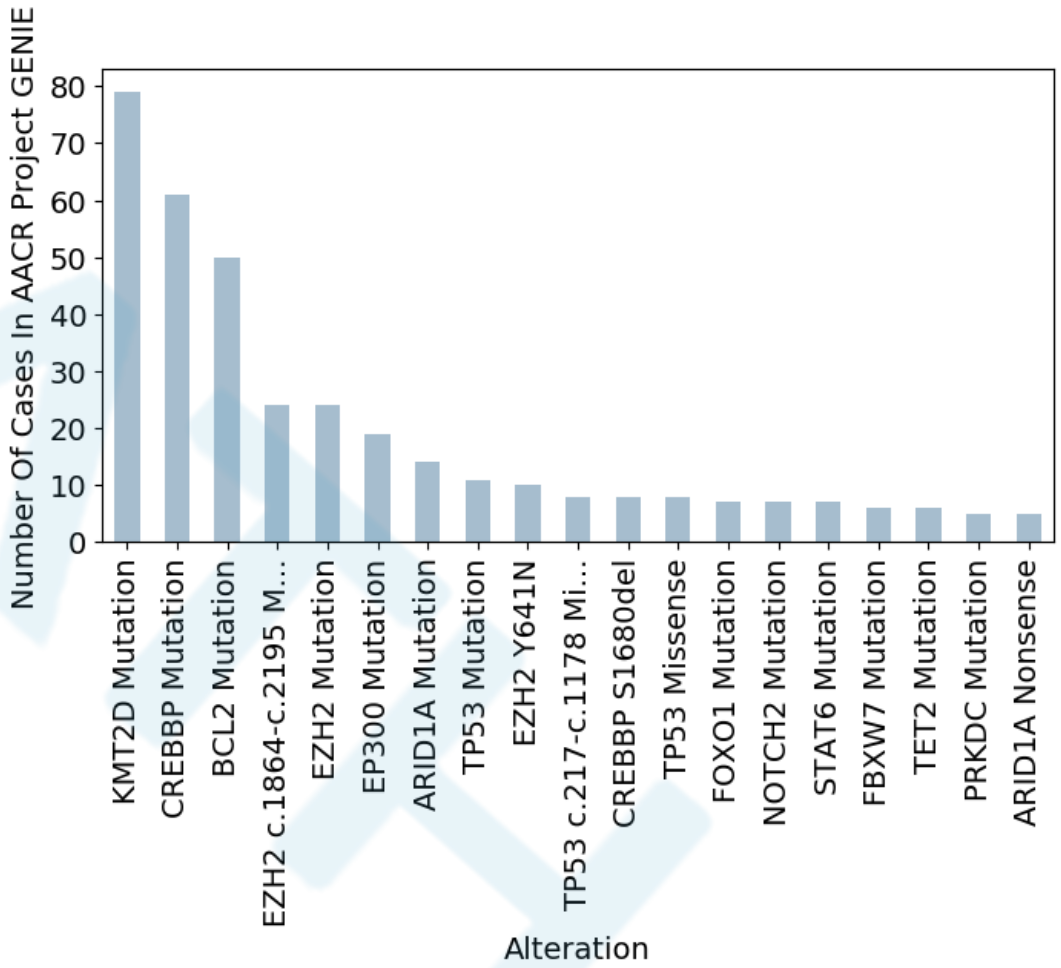


* t(14;18) can be identified in healthy individuals, it follows that additional genomic alterations are required for lymphomagenesis

Arch Pathol Lab Med. 2018;142(11):1330-1340

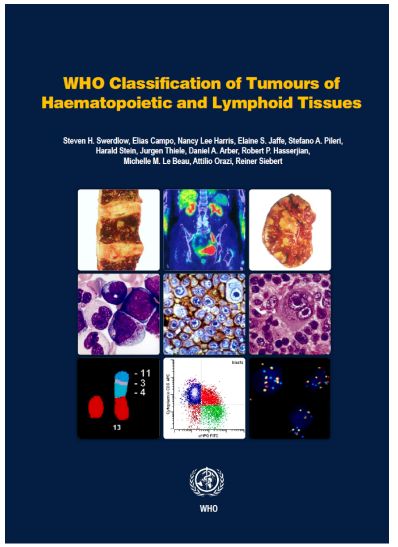
Usual FL





Cancer Discovery. 2017;7(8):818-831

Follicular lymphoma	9690/3
In situ follicular neoplasia	9695/1*
Duodenal-type follicular lymphoma	9695/3
Testicular follicular lymphoma	9690/3
Paediatric-type follicular lymphoma	9690/3
Large B-cell lymphoma with IRF4 rearrangement	9698/3
Primary cutaneous follicle centre lymphoma	9597/3



The focus of this report is to describe cases of FL that are not recognized as distinct FL variants but which have unusual clinical and/or histopathologic features

CASE PRESENTATION & DISCUSSION

01 FL With Castleman-like Changes

02 FL With Plasmacytic Differentiation and IgG4-positive Plasma Cells

03 FL With MZ Differentiation Involving MALT Sites

04 Diffuse FL Variant

05 Mimicry of High-grade FL: Large B-cell Lymphoma With IRF4 Rearrangement

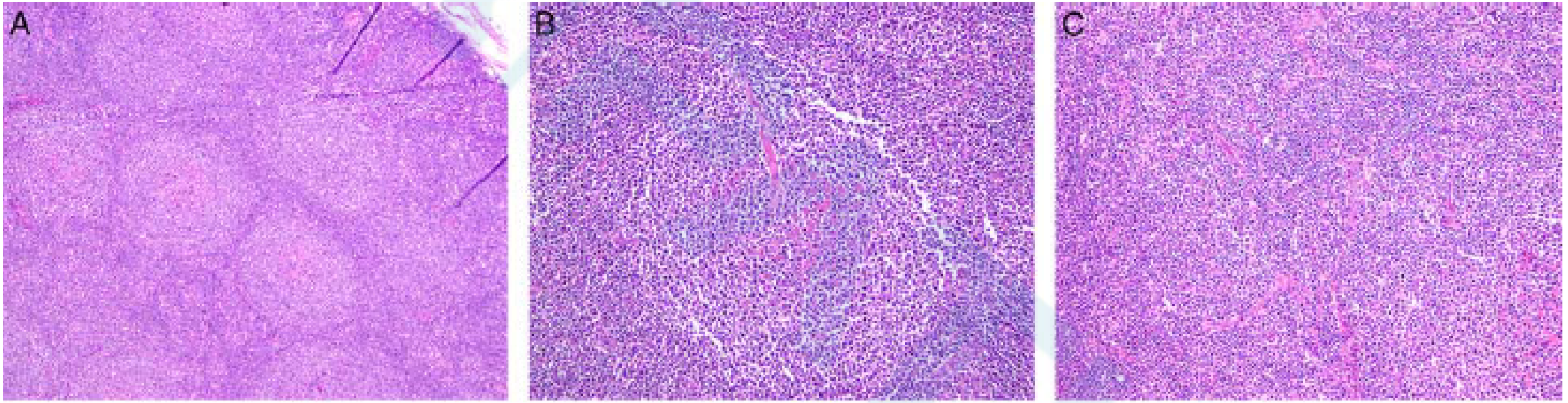
06 FL Negative for CD10, Positive for MUM1

07 Epstein-Barr Virus–positive FL

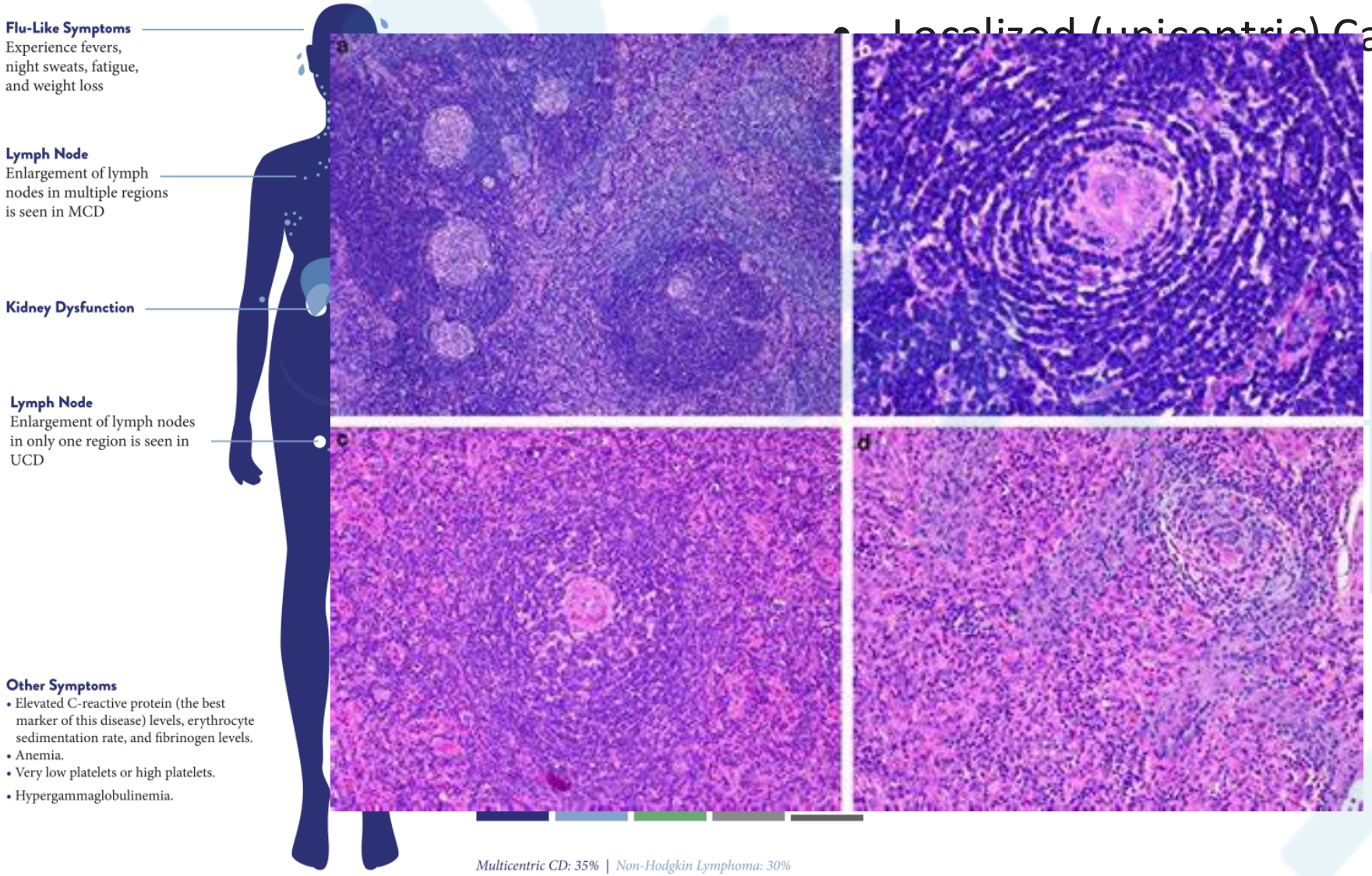
Case 1

- F 83
- left neck lump
- Imaging studies: a 1.3 cm mass in the lower pole of the right thyroid lobe and enlarged cervical lymph nodes, the largest measuring 1.4×1.2 cm
- Weight loss <10%, no other B symptoms
- PET-CT: localized in the left posterior triangle of the neck and right tonsil
- Left cervical lymph node excisional biopsy

Left cervical lymph node



Castleman disease (CD)

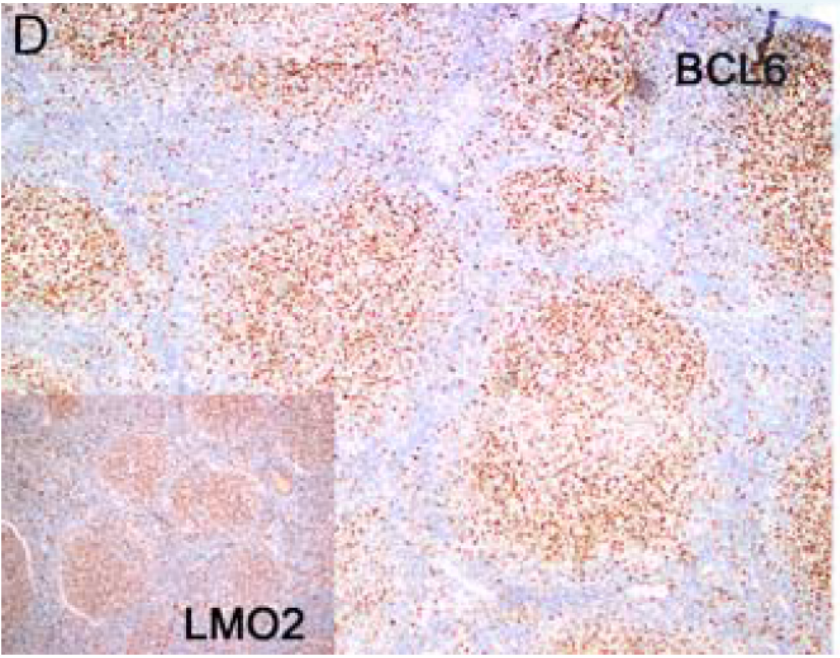


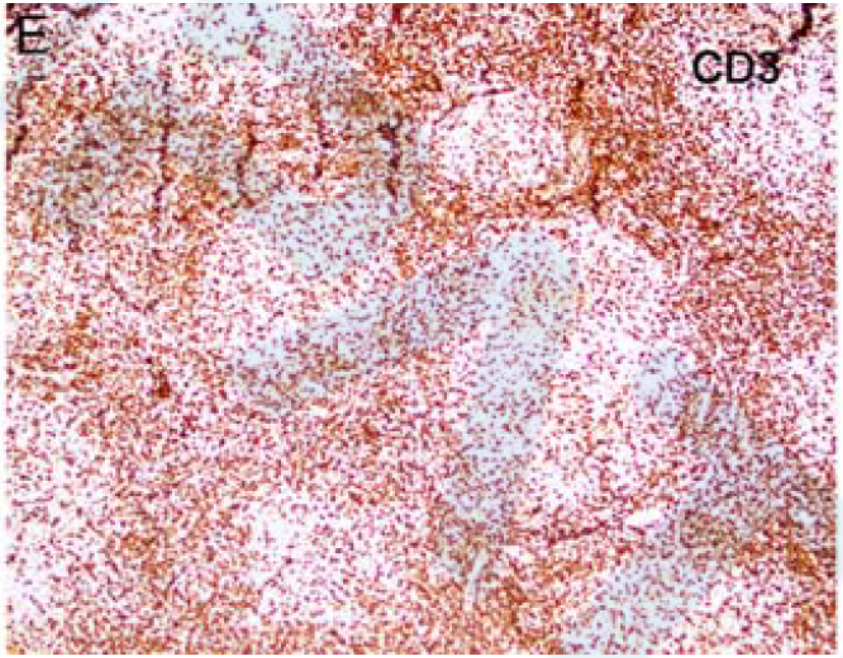
- Localized (unicentric) Castleman disease

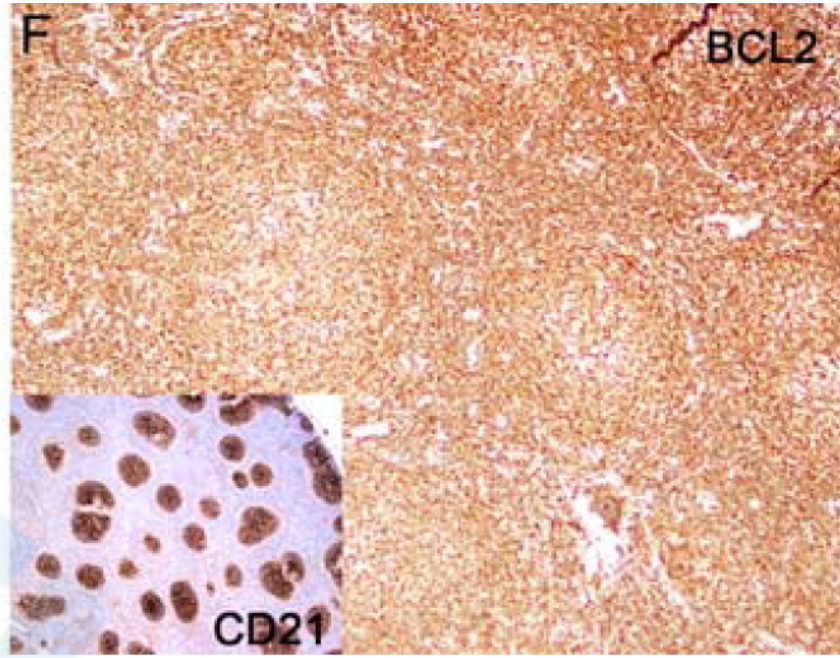
disease

Localized benign mass
Follicular hyperplasia
Atrophic germinal centers
Mantle zone hyperplasia
Hyaline deposits
Vascular proliferation

Left cervical lymph node







01 FL With Castleman-like Changes

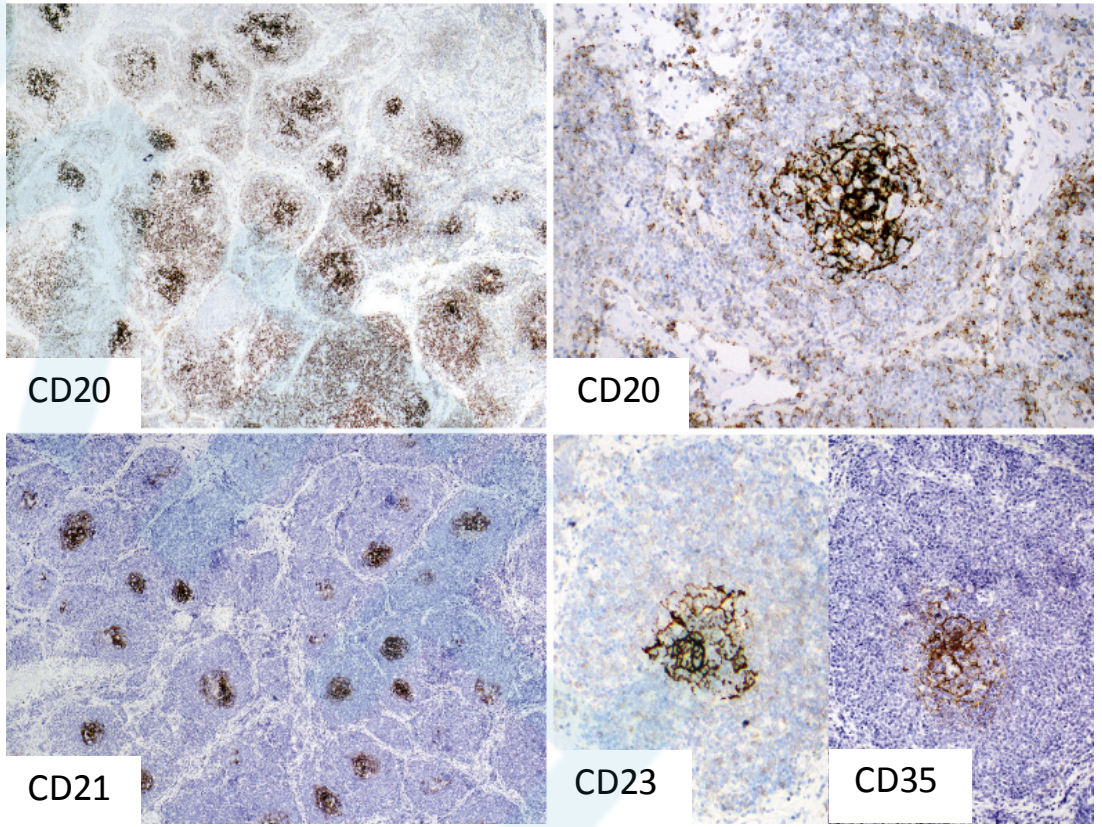
FL with CD-like changes V.S. CD

- Increase in the number of follicular structures
- Atypical follicles containing increased centrocytes
- Bcl6-positive lymphoid cells associated with the atretic follicle center
- Bcl2 expression is variable
- FISH results are also variable

- Pathologists may dominate the histologic picture and mask the presence of lymphoma
- Neoplastic follicles may be absent in core needle biopsies

Pina-Oviedo et al----6 cases report

- 2 showed exclusively atrophic neoplastic follicles and no typical neoplastic follicles
- 1 case FDCs expressed strong coexpression of CD20 and stronger than surrounding lymphoma cells



* Benign lymph node in a FL patient treated with rituximab

Pathology. 2017;49:544–547

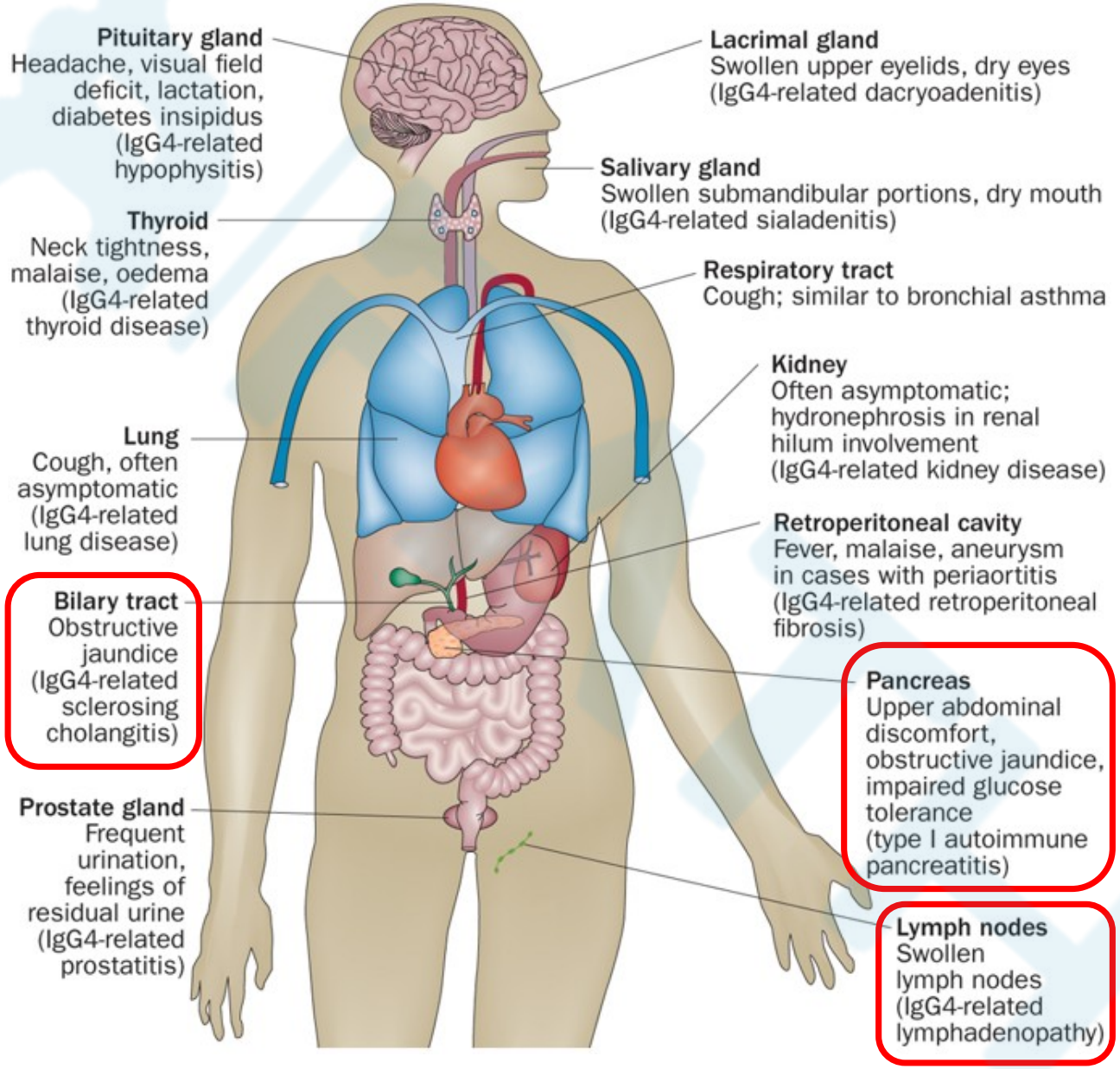
Case 2

- M 61 abdominal pain
- Bile duct obstruction, cholestasis, and progressive hyper-bilirubinemia
- Serum IgG4 361.0 (2 to 96) mg/dL, C reactive protein 1.6 (0.0 to 0.5) mg/dL, Serum IL-6 normal, HHV8 antibody absent
- Imaging: Diffuse enlargement of submandibular lymph nodes (2.9 cm), hepatomegaly (19 cm), thickening of bile duct wall with duct dilatation, mild splenomegaly (13 cm) , 2 diffuse lesions in the pancreas which suggestive of chronic pancreatitis

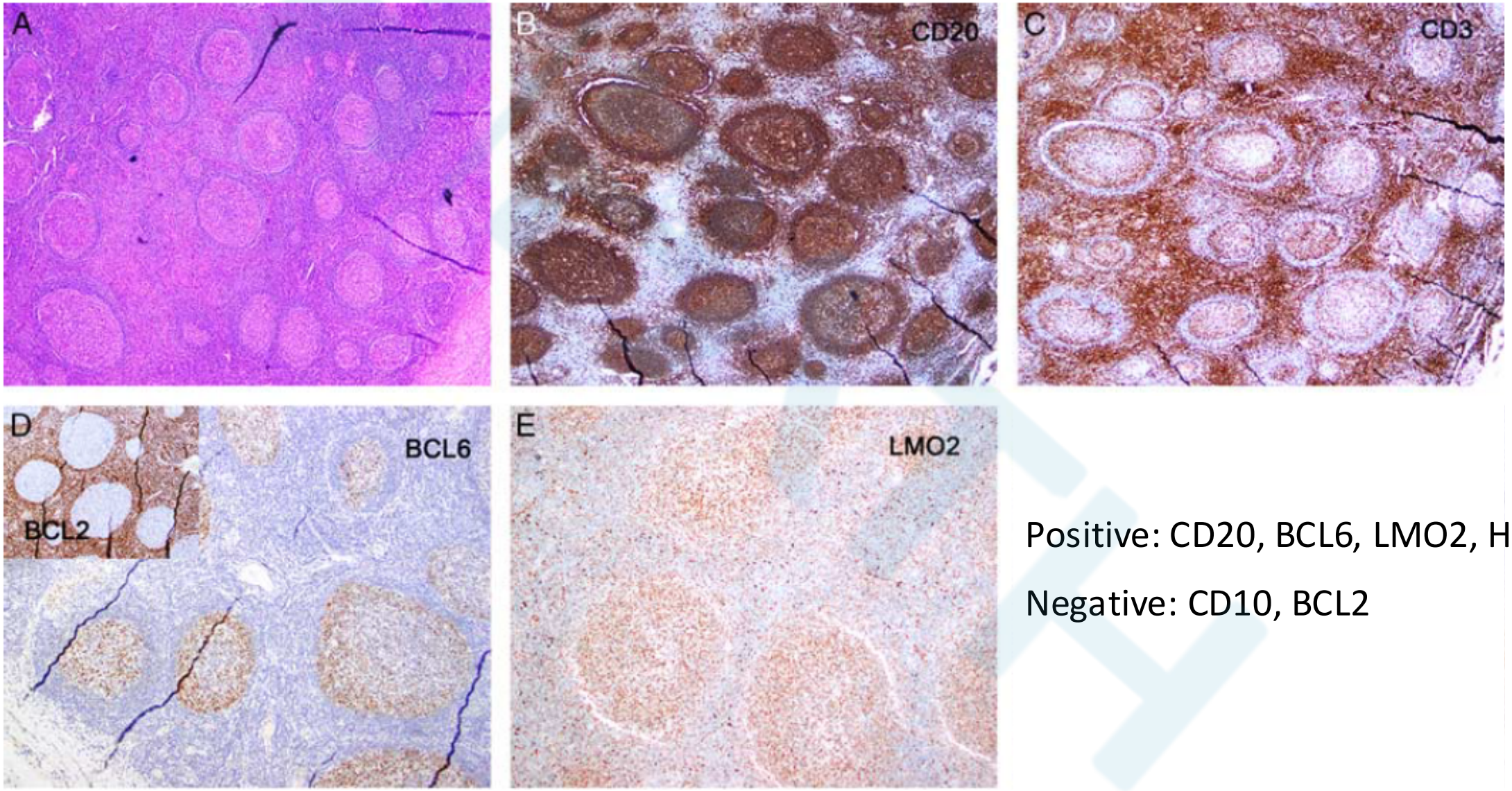
Pancreas biopsy

- Storiform-type fibrosis
- Lymphoplasmacytic inflammation, rich in polyclonal plasma cells
- IgG4-positive plasma cells increased, 65/HPF

IgG4-related disease
(IgG4-RD)

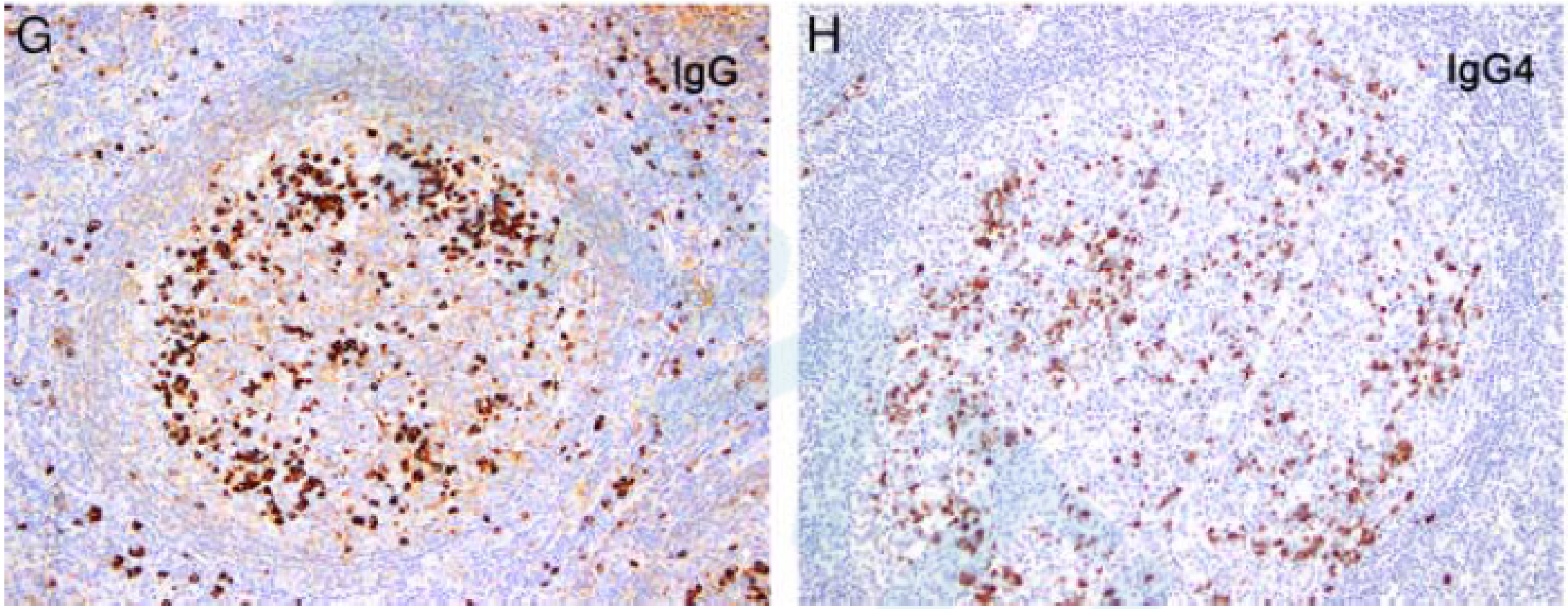

Pituitary gland
Headache, visual field deficit, lactation, diabetes insipidus (IgG4-related hypophysitis)
Thyroid
Neck tightness, malaise, oedema (IgG4-related thyroid disease)
Lung
Cough, often asymptomatic (IgG4-related lung disease)
Bilary tract
Obstructive jaundice (IgG4-related sclerosing cholangitis)
Prostate gland
Frequent urination, feelings of residual urine (IgG4-related prostatitis)
Lacrimal gland
Swollen upper eyelids, dry eyes (IgG4-related dacryoadenitis)
Salivary gland
Swollen submandibular portions, dry mouth (IgG4-related sialadenitis)
Respiratory tract
Cough; similar to bronchial asthma
Kidney
Often asymptomatic; hydronephrosis in renal hilum involvement (IgG4-related kidney disease)
Retroperitoneal cavity
Fever, malaise, aneurysm in cases with periaortitis (IgG4-related retroperitoneal fibrosis)
Pancreas
Upper abdominal discomfort, obstructive jaundice, impaired glucose tolerance (type I autoimmune pancreatitis)
Lymph nodes
Swollen lymph nodes (IgG4-related lymphadenopathy)

Submandibular lymph nodes excisional biopsy

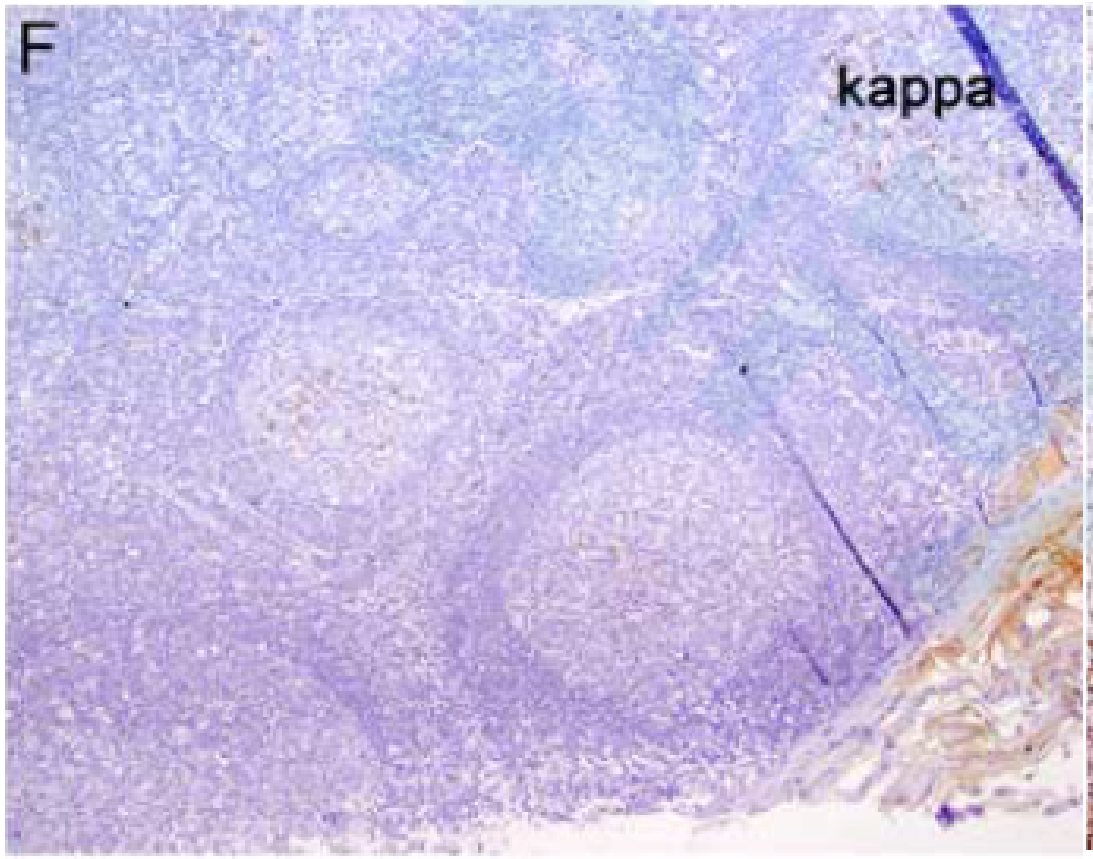


Positive: CD20, BCL6, LMO2, HGAL

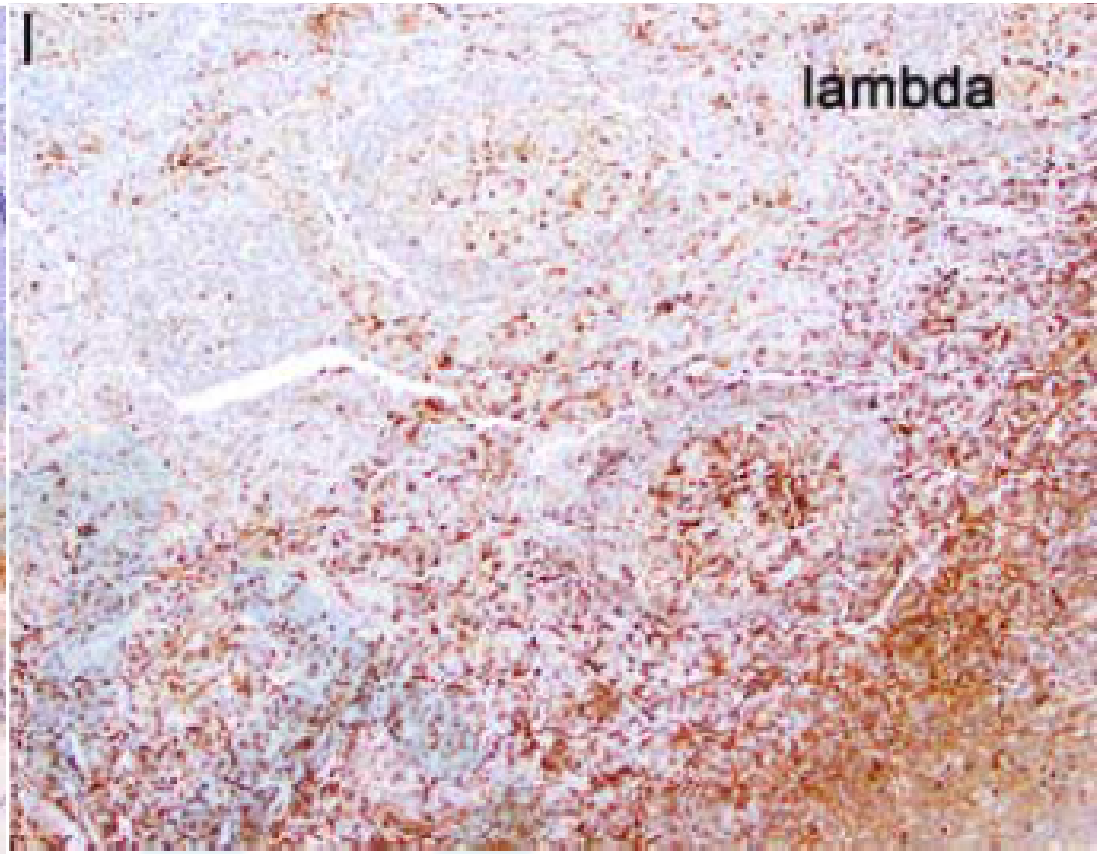
Negative: CD10, BCL2



IgG4-positive plasma cells >70 cells/HPF
IgG4/IgG >90%



Lambda light chain restriction



IgH/BCL2 FISH -
BCL2 translocation -

02

FL With Plasmacytic Differentiation and IgG4-positive Plasma Cells

FL With Plasmacytic Differentiation

Plasmacytic differentiation is seen in ~ 3.5% of FL cases

2 distinct types：

- Typical FL: BCL2 translocation, postfollicular maturation with interfollicular distribution
- Lacking BCL2 translocation, and showing a prominent intrafollicular and perifollicular plasma cell distribution CD10-

The clonal plasma cells in B-cell lymphoma with plasmacytic differentiation are of IgG4+type

Etiologic link between IgG4-RD and malignancy

- Prior studies have suggesting that chronic antigenic stimulation in IgG4-RD may lead to an increased risk of malignancy
- Most lymphomas with IgG4-RD have been described in the ocular adnexa (MALT lymphomas), associated with IgG4-related sclerosing inflammation

Mod Pathol. 2013 Dec;26(12):1568-76

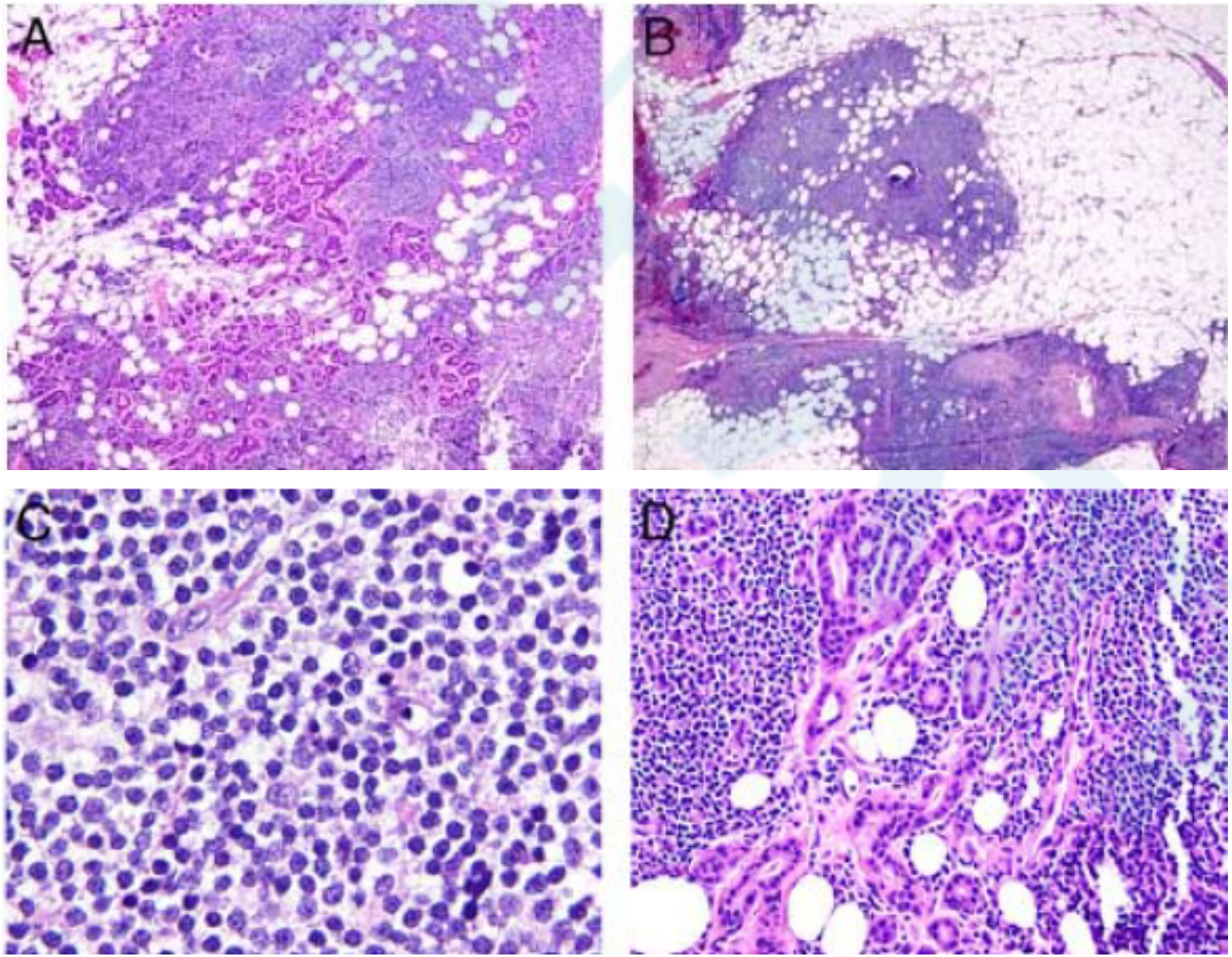
The patient was treated with Prednisone and Rituximab

- Resolution of jaundice and normalization of liver enzymes
- Biochemical remission of IgG4 disease (92 mg/dl) and in lymphoma remission
- ERCP showed resolution of biliary strictures

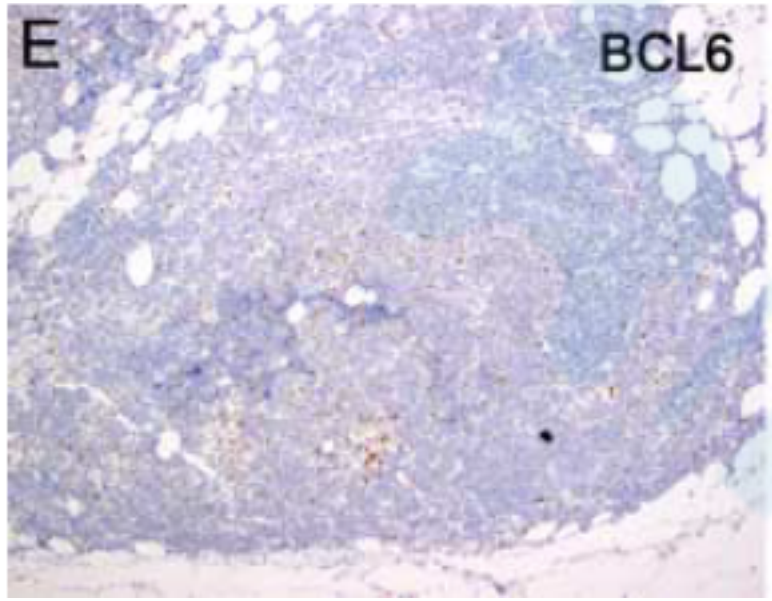
Case 3

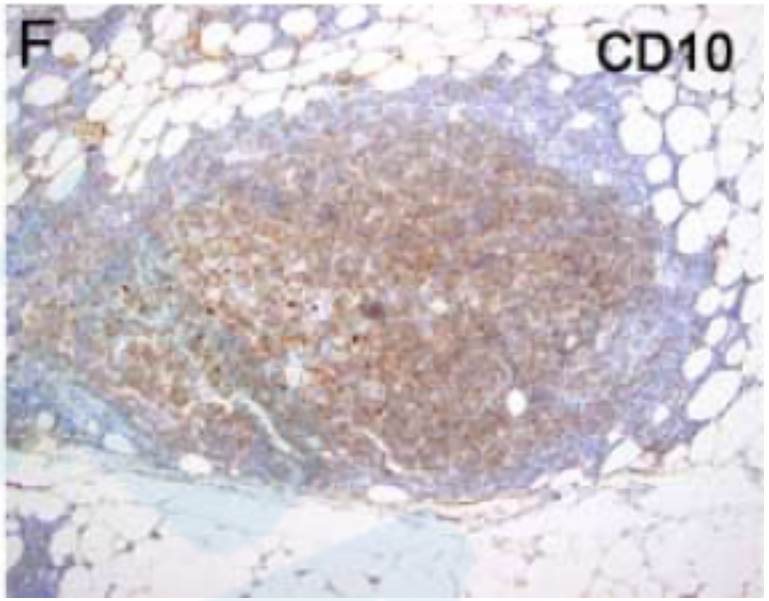
- M 54 Parotid mass (4.2cm)
- Previous history of advanced stage grade 1 FL (2012), complete remission
- No other symptoms and no B symptoms
- PET/CT: extensive lymphadenopathy with standardized uptake value up to 14, largest lymph node 3.1 cm
- Excisional biopsy of parotid gland

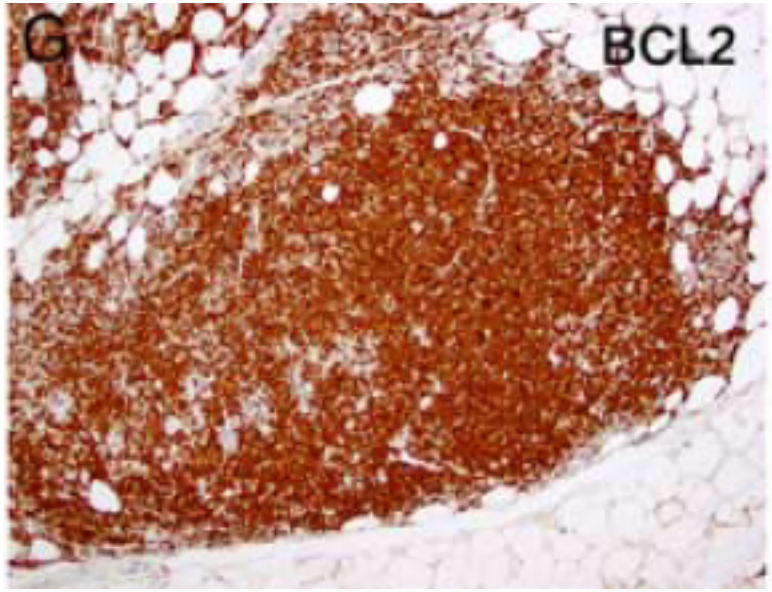
Excisional biopsy of parotid gland

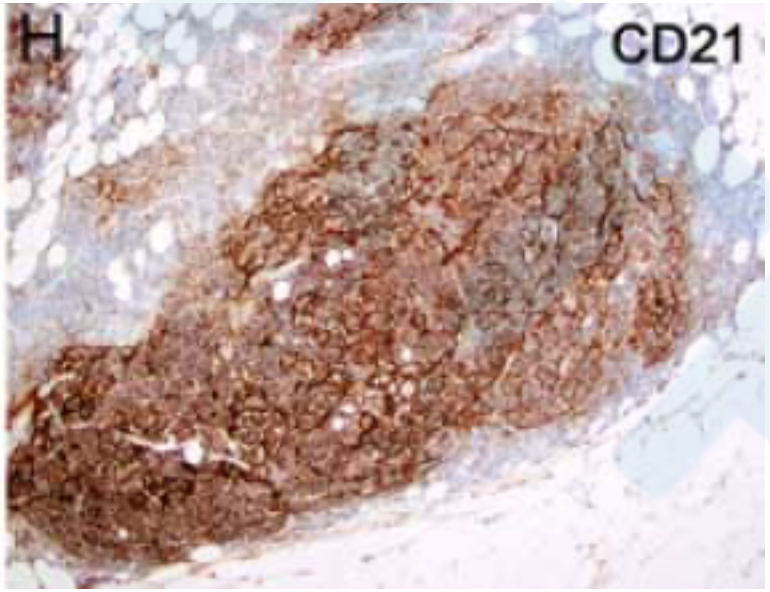


Extranodal MZ lymphomas?









IHC:
Focal BCL6
Dim CD10 and LMO2
Strongly coexpressed BCL2
CD43 negative
Plasma cells were polytypic
IgG4-

NGS:
IGH-BCL2 rearrangement
BCL6 exon 1 deletion
CREBBP E1384fs*75
MLL2 IQ1773*M W5065*,
TBL1XR1 S308fs*1
TNFRSF14 M1I

Recurrent FL

03 FL With MZ Differentiation Involving MALT Sites

FL can have MZ differentiation

- Estimated to occur in 9% of cases
- Histologic features overlapping with MALT lymphoma in FL
  - Predominantly diffuse component
  - Monocytoid differentiation
  - Prominent lymphoepithelial lesions
  - FL involving MALT sites may lack FDC networks or have them distributed and at the periphery of tumor follicles
- Immunophenotypes of the FL cells can be atypical, in particular show diminished or absent CD10 expression

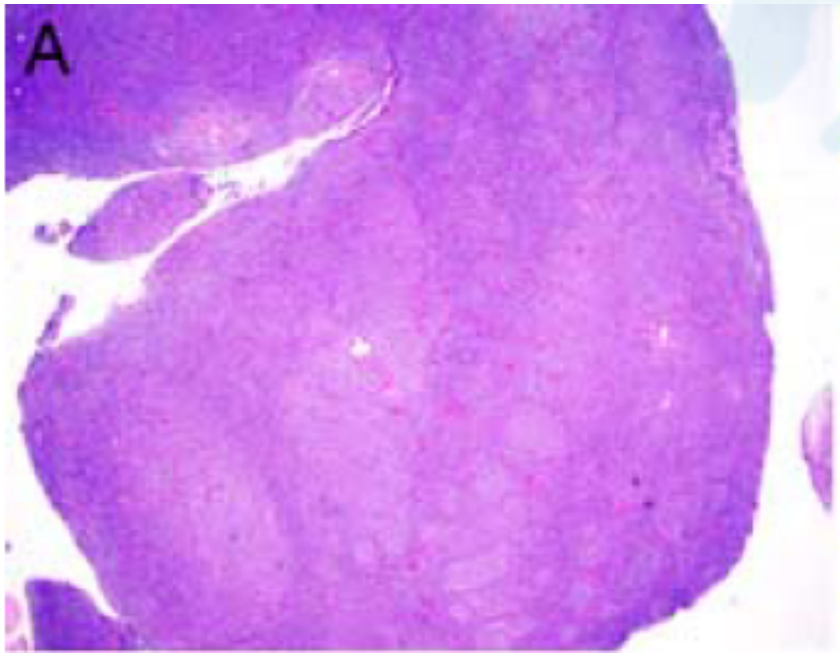
FL involving MALT sites

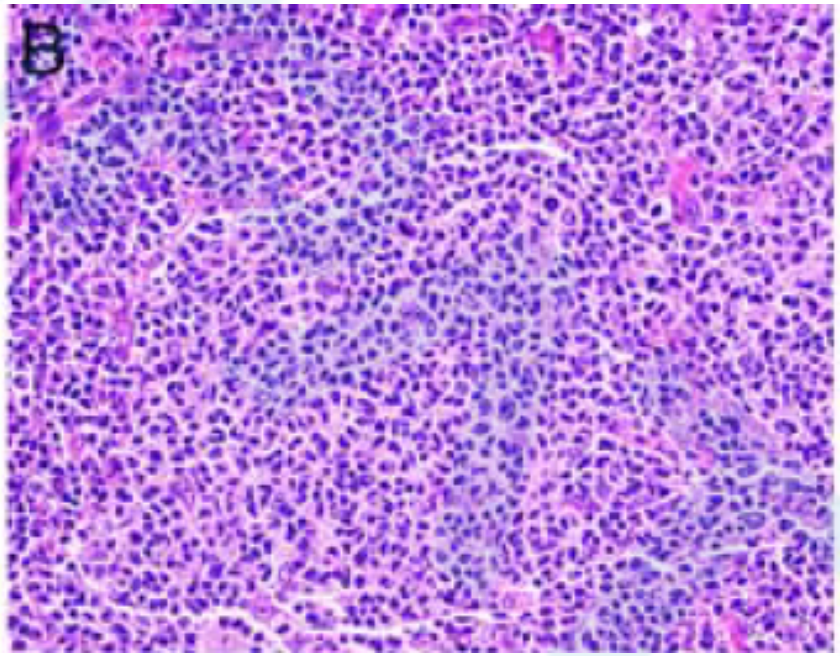
- *IGH-BCL2* rearrangements less frequently than nodal FL (27%)
- *IGHV*: *VH4* predominance, not *VH3* (nodal FL)

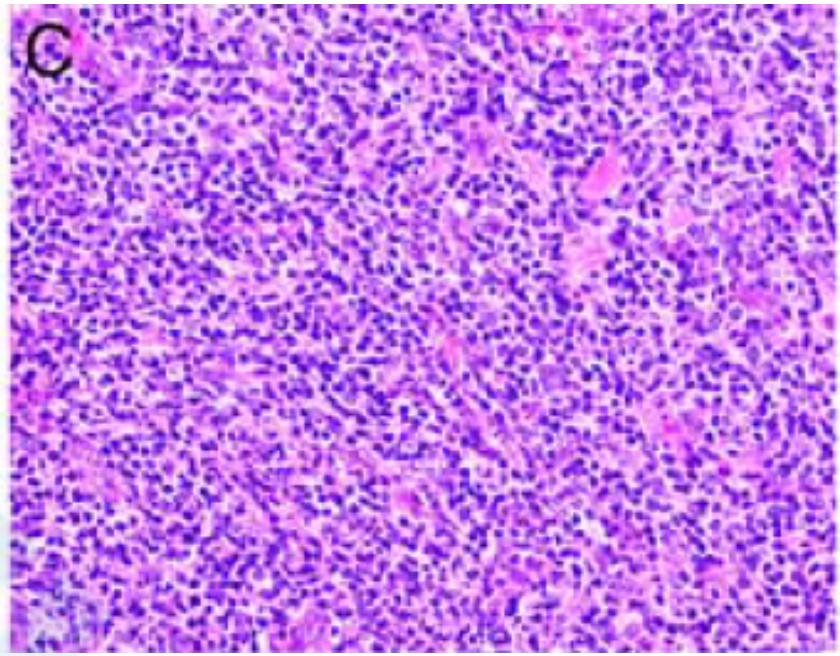
	Similar to usual systemic FL	Overlapping with MZ lymphoma
IGH-BCL2 translocation	high rate	frequently lack
CD10 expression	high rate	frequently lack

Case 4

- M 76
- Asymptomatic inguinal lymphadenopathy
- Excisional lymph node biopsy

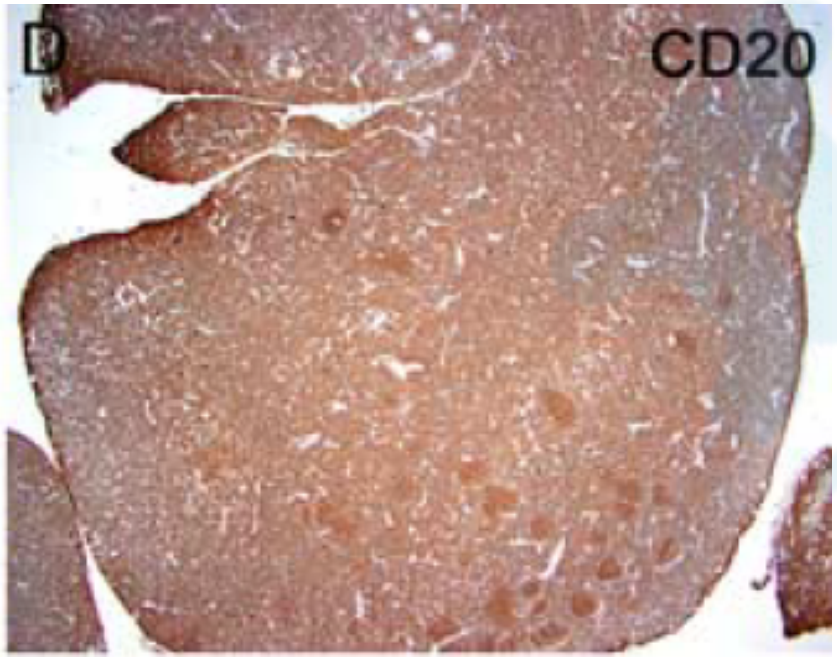


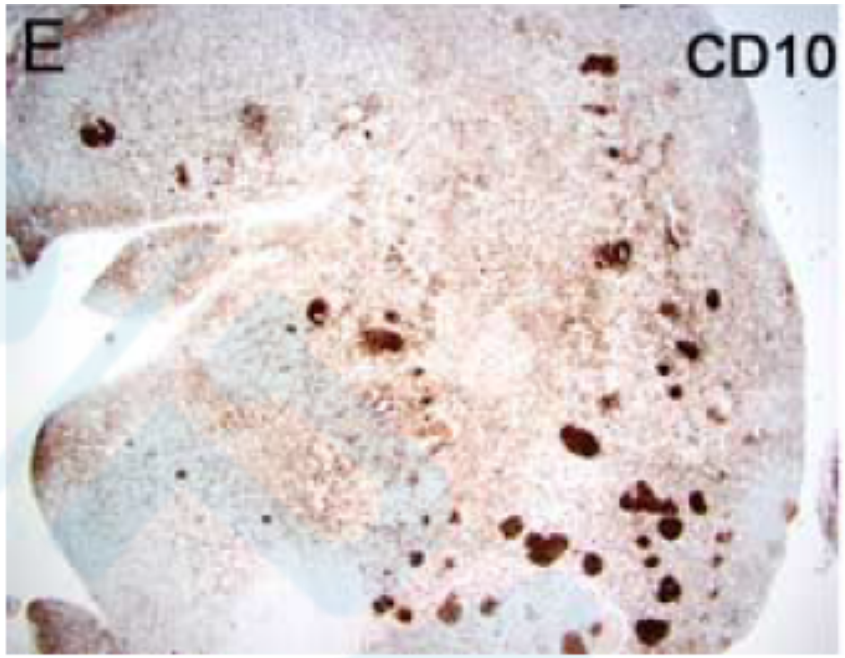


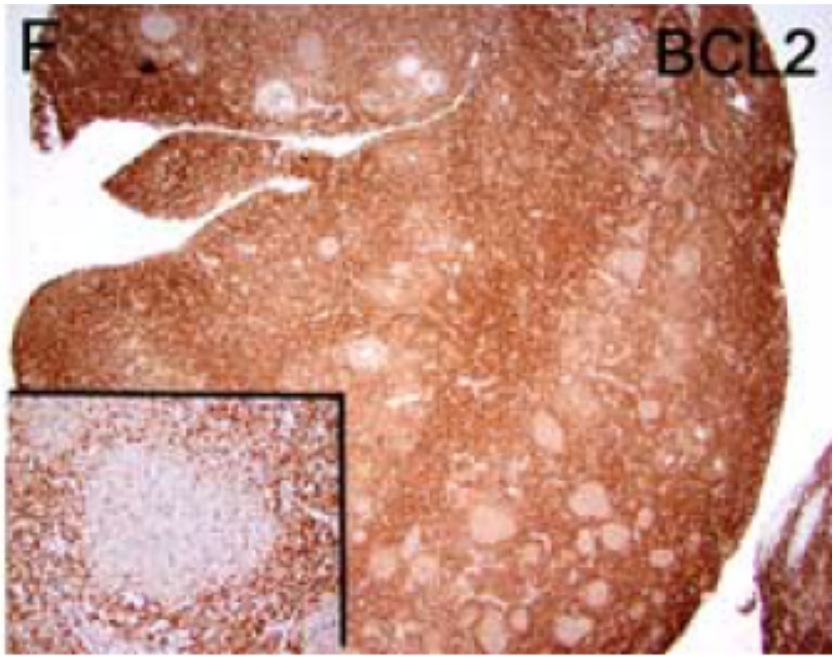


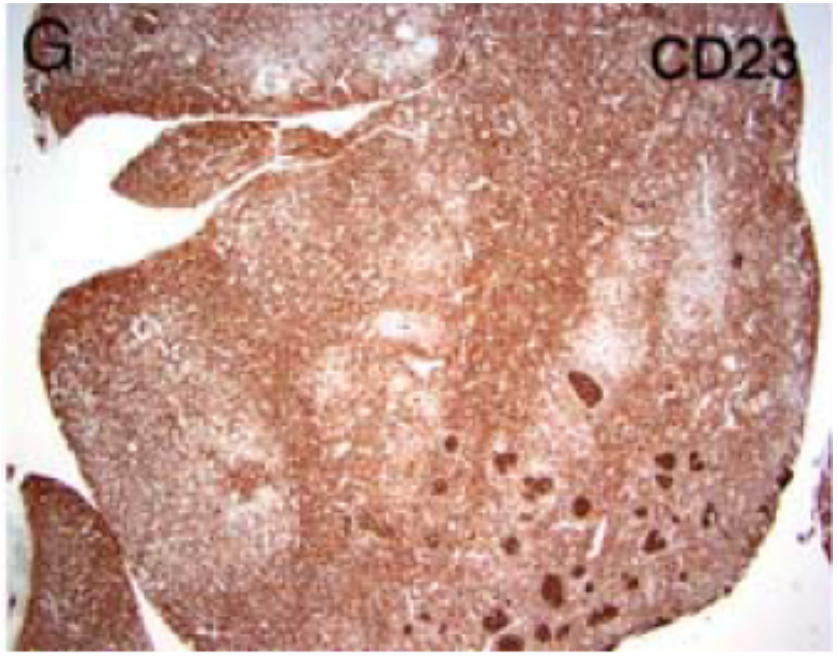
Diffuse pattern (90%)
Vaguely follicular distribution (10%)
Microfollicles

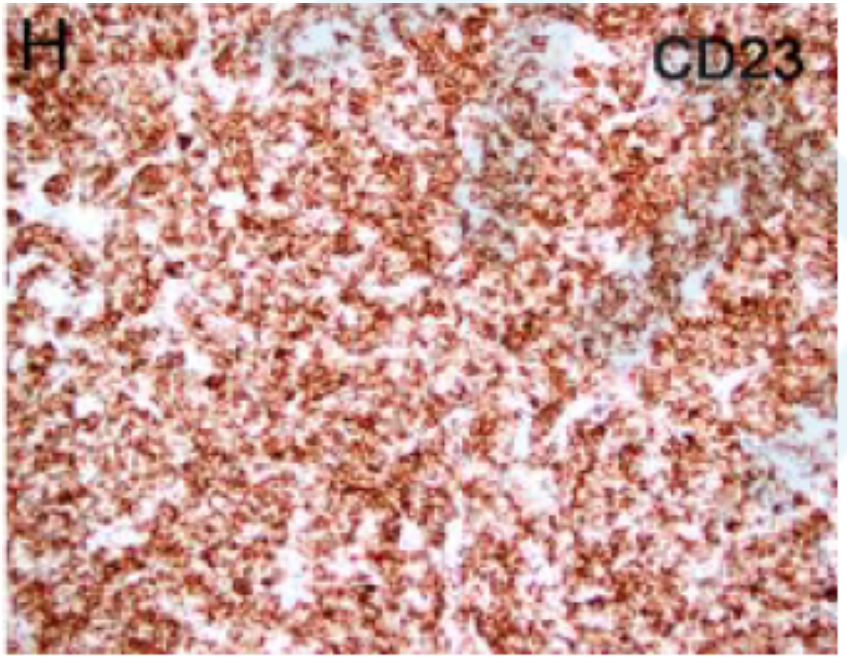
Centrocytic morphologic features











IGH-BCL2 rearrangement negative

NGS:
STAT6 D419G
CREBP S1680del
MLL2 Q2811fs*34
TNFRSF14 loss

04 Diffuse FL Variant

Katzenberger et al. & Siddiqi et al.

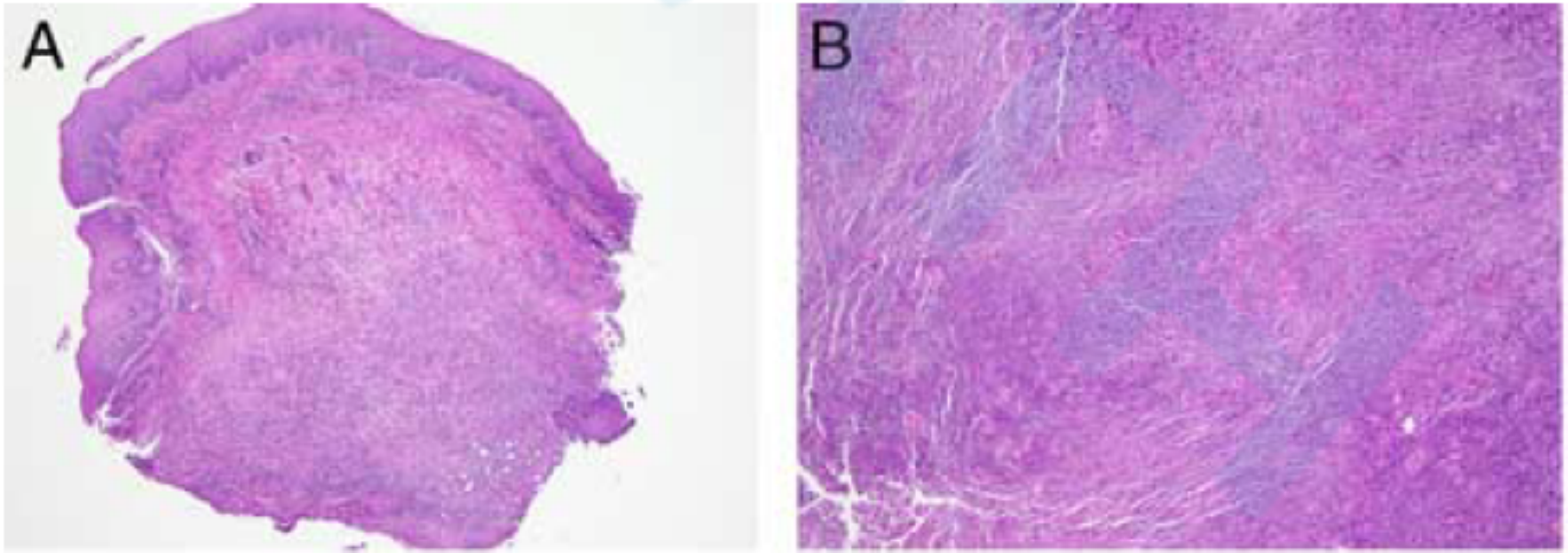
- Predominantly diffuse growth pattern, coexpression of CD23
- Focal follicular cells express germinal center markers
- 37/40 cases lacked t(14;18)(*IGH-BCL2*)
- 35/40 cases showed deletion *1p36* and/or *TNFRSF14* deletions
- STAT6 mutations (82%) is greater than that seen in usual FL (11%)

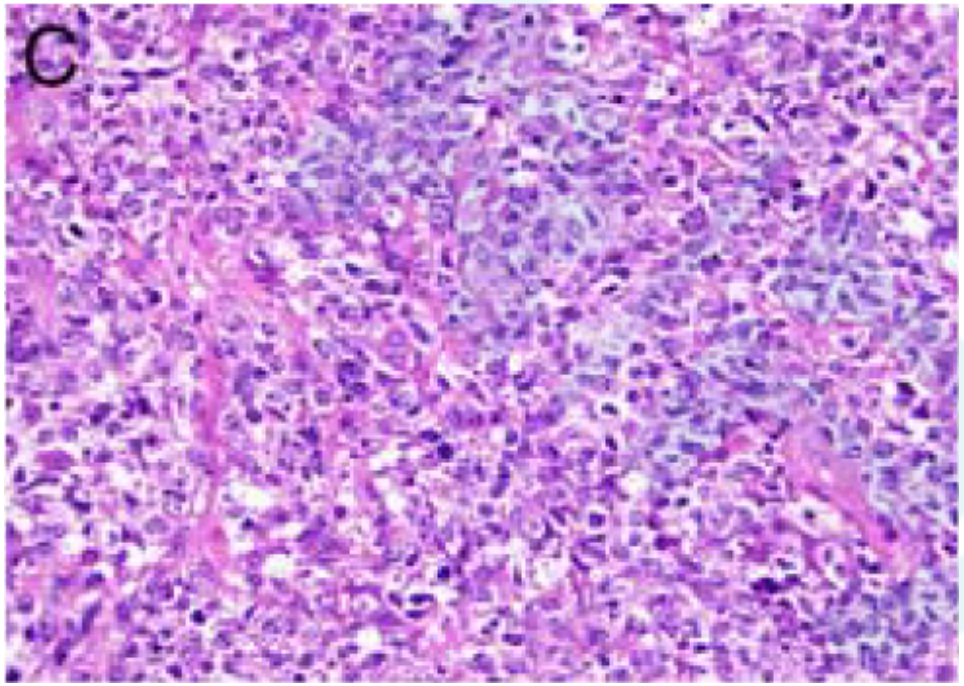
Diffuse FL variant with 1p36 deletion

These FLs usually have an indolent behavior, a tendency to remain localized and respond well to chemotherapy

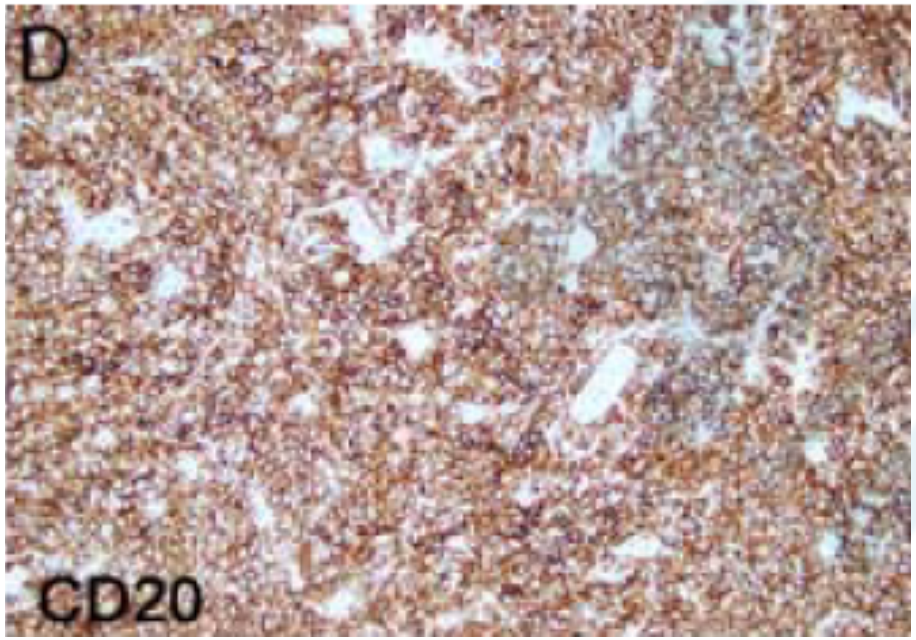
Case 5

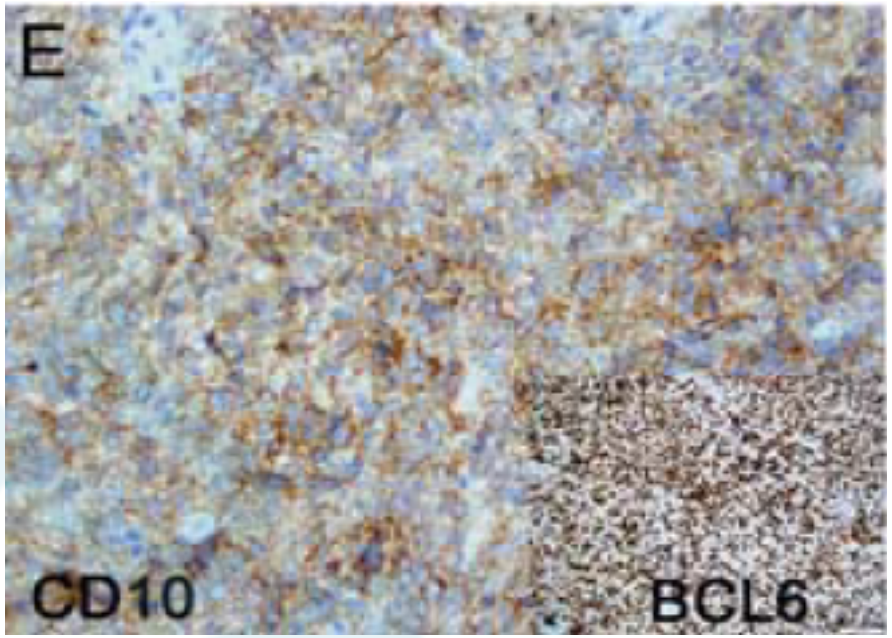
- F 75 Neck pain and difficulty swallowing for 3 mo
- Breast cancer and postchemotherapy
- Imaging: a large (4.0×2.3×2.5 cm) mass on the lateral wall of the hypopharynx

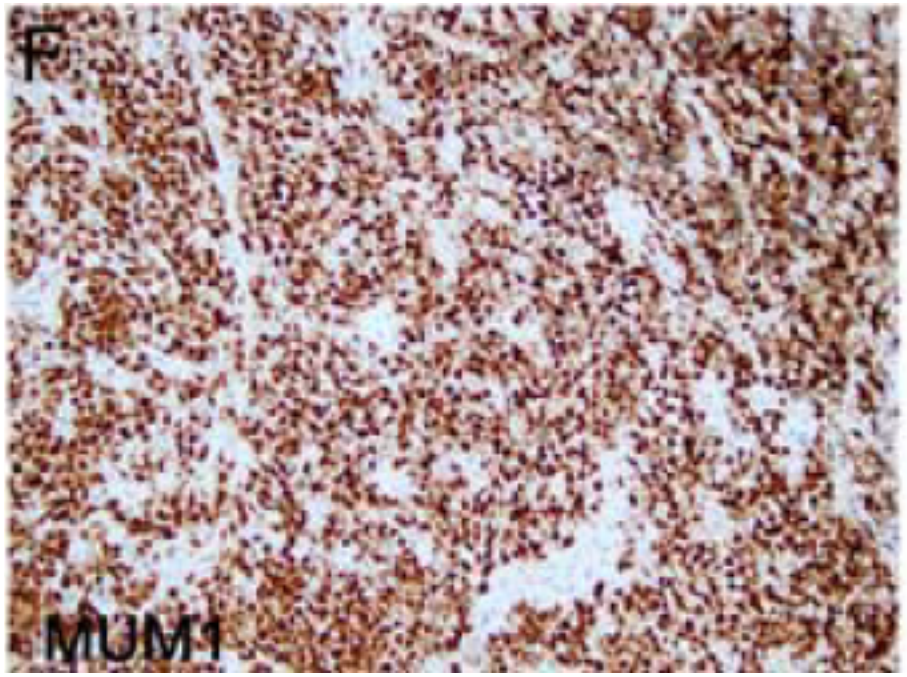


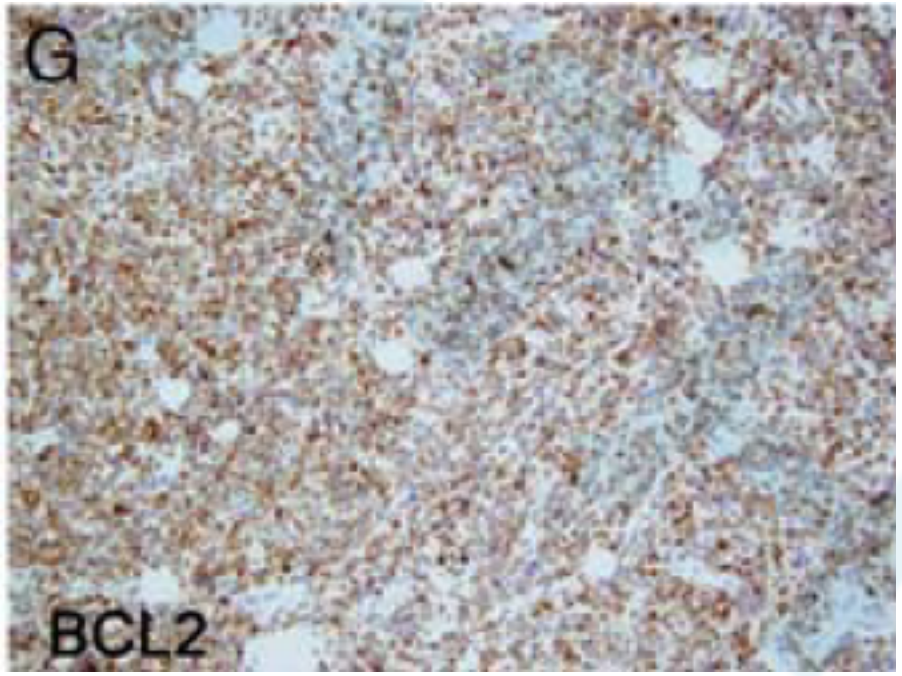


Lymphoma cells are large with open, vesicular chromatin and prominent nucleoli





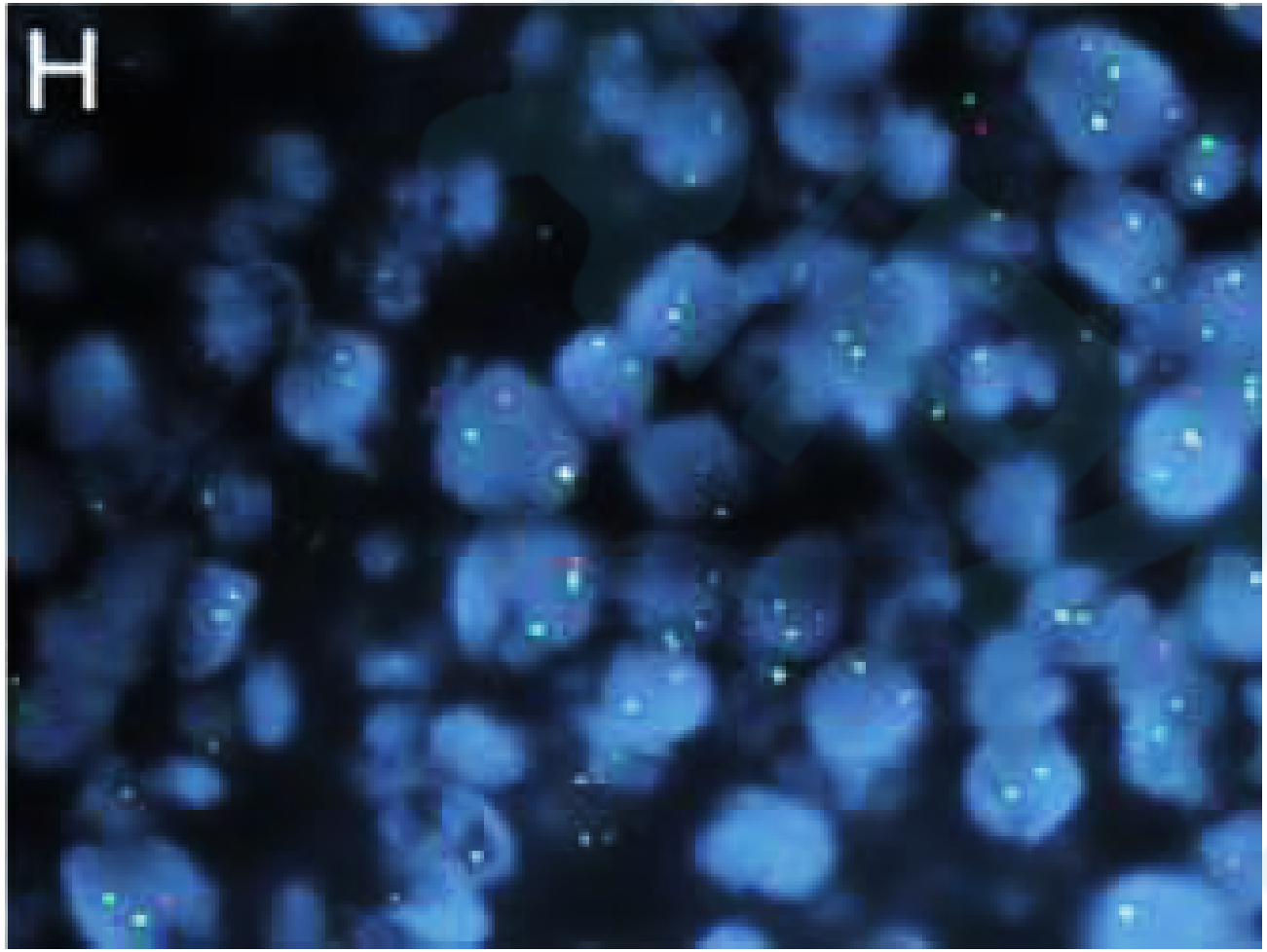




Positive for CD20, CD10 (weak), BCL6, BCL2 (100%), MUM1 (strong and uniform), MYC (60%), and CD19

CD30 and EBER negative

Ki-67 proliferation index was virtually 100%



IRF4 rearrangement

FISH:
t(14;18)(*IGH-BCL2)*
t(8;14)(*IgH-MYC*),
MYC rearrangement
MYC amplification
BCL6 rearrangement

} Negative

NGS:
IGH-IRF4 rearrangement
CCND3 R190fs*53
IRF4 Q60H—subclonal
TP53 L204

LBCL with IRF4 rearrangement

05 Mimicry of High-grade FL: Large B-cell Lymphoma With IRF4 Rearrangement

LBCL with IRF4 rearrangement

- Age range (4 to79 y, median 12 y) with an equal sex distribution
- Predilection for involvement of lymph nodes in the head and neck region

Pattern: entirely diffuse, follicular and diffuse, entirely follicular

- Misdiagnosed as diffuse LBCLs or as FL
- This lymphoma occur more frequent in children, it represents a distinct entity from pediatric-type FL
- 30% of these lymphomas occur in older adults and most patients have localized stage 1 disease
- Patients usually have a favorable outcome following treatment

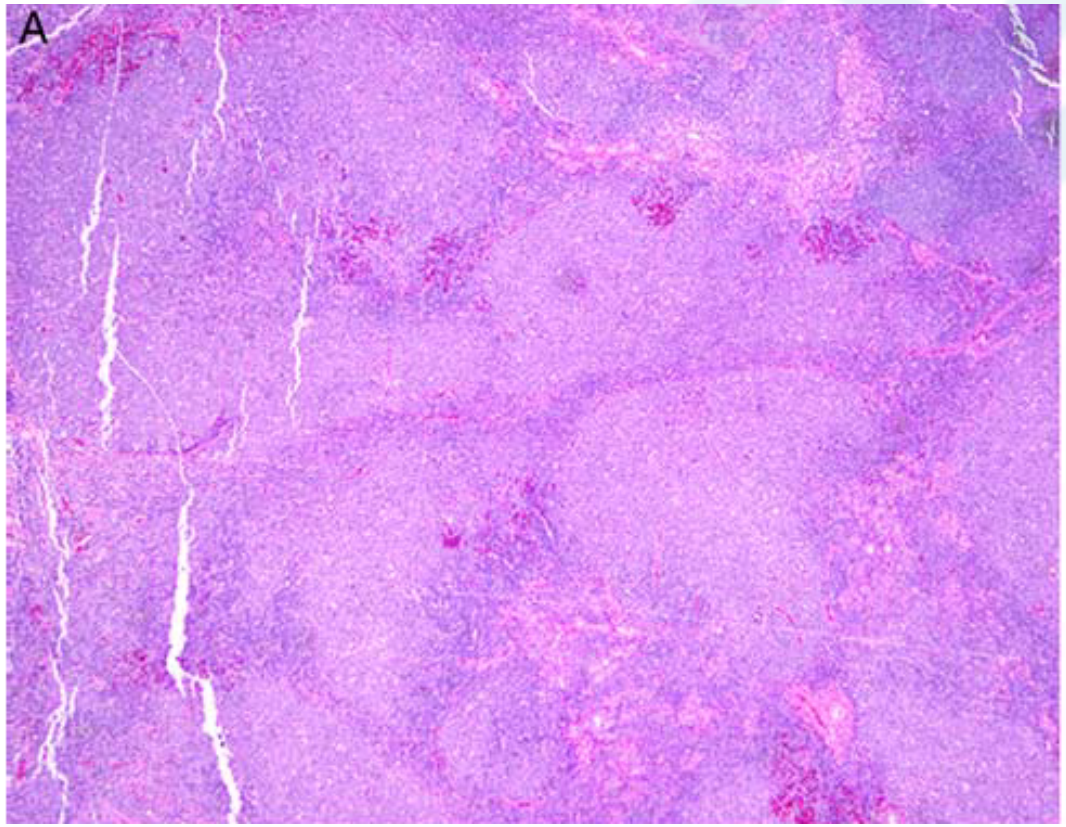
Diagnosis of LBCL with IRF4 rearrangement by FISH or genomic profiling

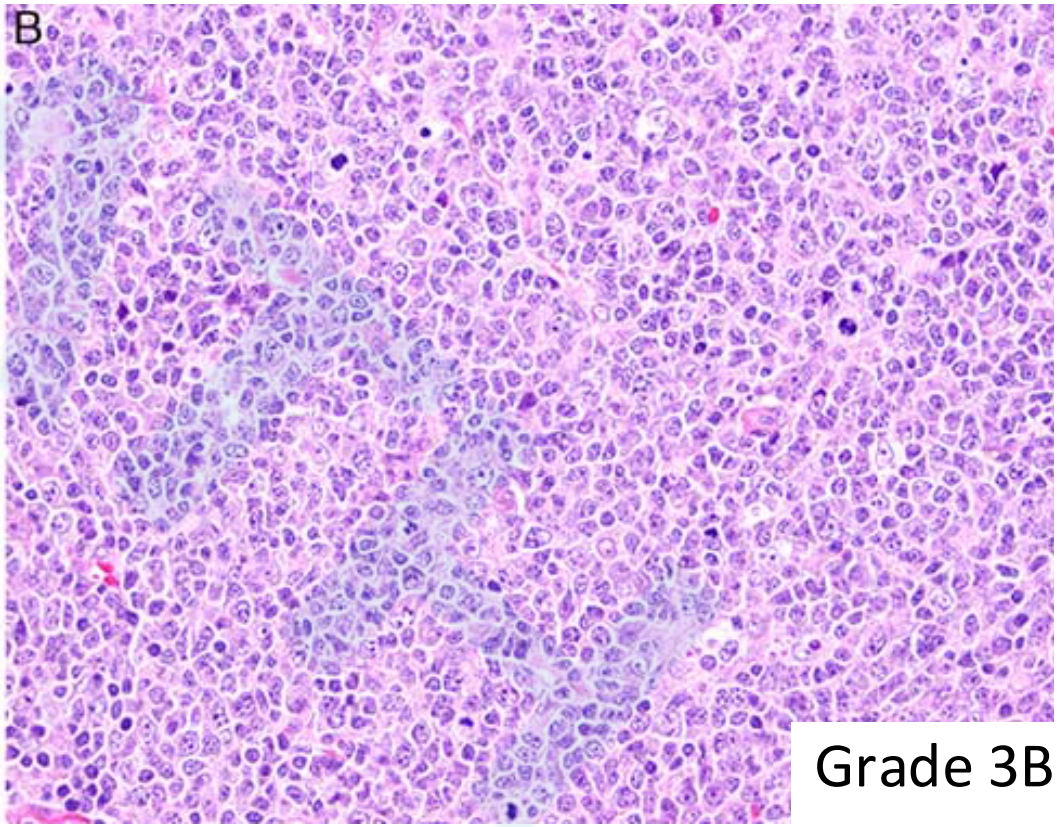
- Rearrangement of *IRF4* with the *IGH* locus
- Rearrangements of *IRF4* involving light chain genes have not been seen
- Concurrent *BCL6* locus rearrangements have been reported
- *MYC* and *BCL2* rearrangements are lacking
- A subset of cases demonstrate genetic changes, but a negative effect on clinical outcome has not been shown
- Gene expression profiling studies have shown the lymphoma cells are of germinal center origin, but these tumors are distinct at the gene expression level from GCB and ABC large cell lymphomas

Strong MUM1 expression in large cell lymphoma with a GCB phenotype involving head and neck or Waldeyer ring should trigger the assessment for rearrangements involving *IRF4* by FISH

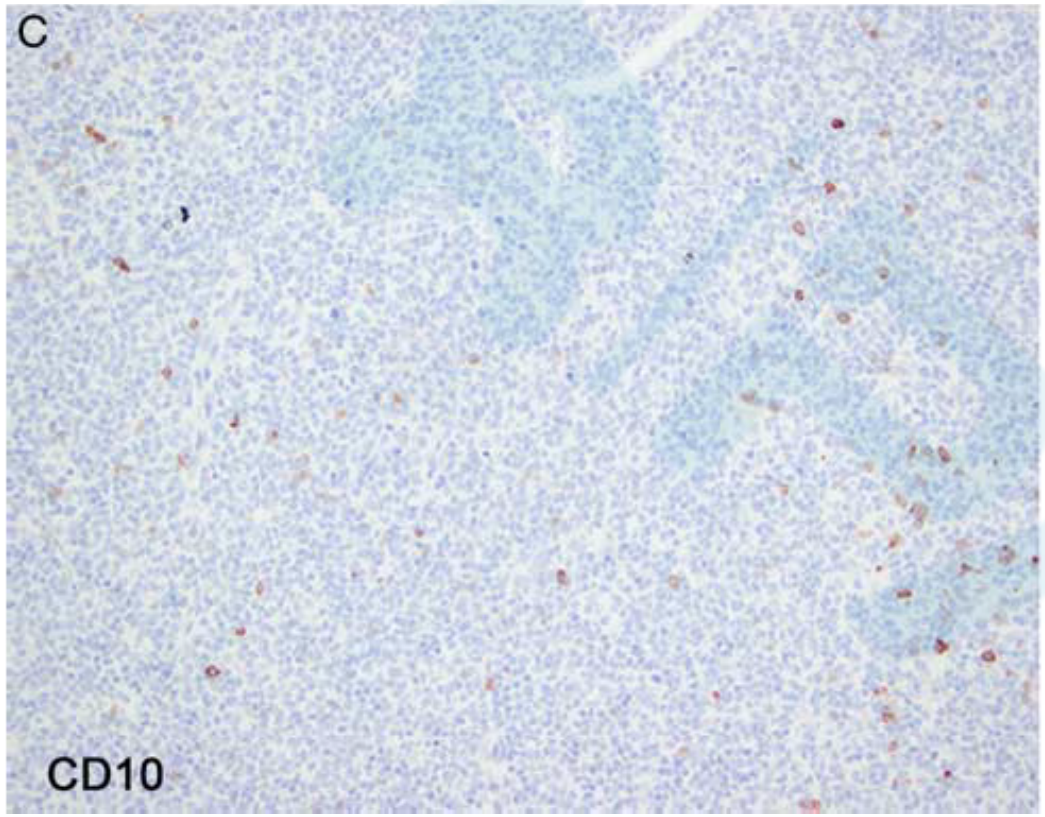
Case 6

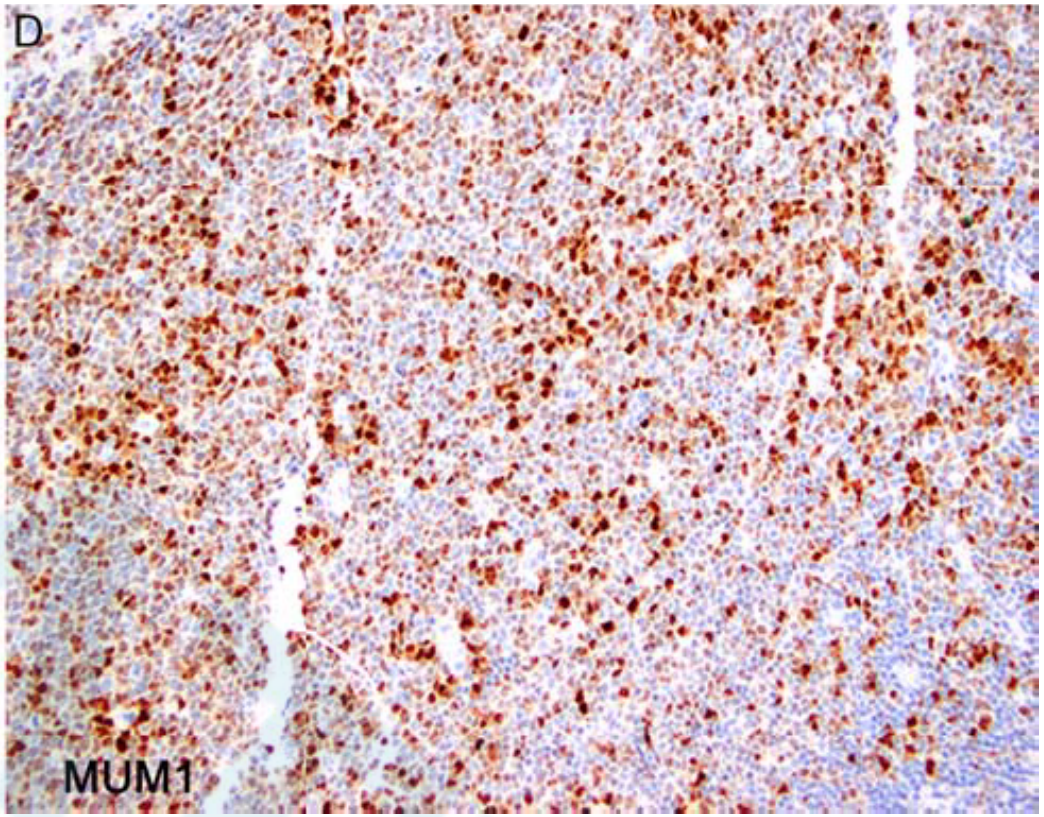
- F 57 Right neck mass
- Involving submandibular gland





Grade 3B FL?





Positive for CD20, BCL6, and BCL2 (dim)

MUM1 was positive ~ 40% with dim to moderate intensity

Ki-67 proliferative index was ~ 90%

Negative for EBER

FISH:

IGH-BCL2, BCL6, and MYC rearrangements were negative

IRF4 rearrangements was negative

BCL6 amplification was not identified

Bone marrow biopsy demonstrated involvement by high-grade FL

The patient was started on R-CHOP therapy

Complete response after the third cycle of therapy

06

FL Negative for CD10, Positive for MUM1 (Usually With Amplification of BCL6)

FL Negative for CD10 and Expressing MUM1

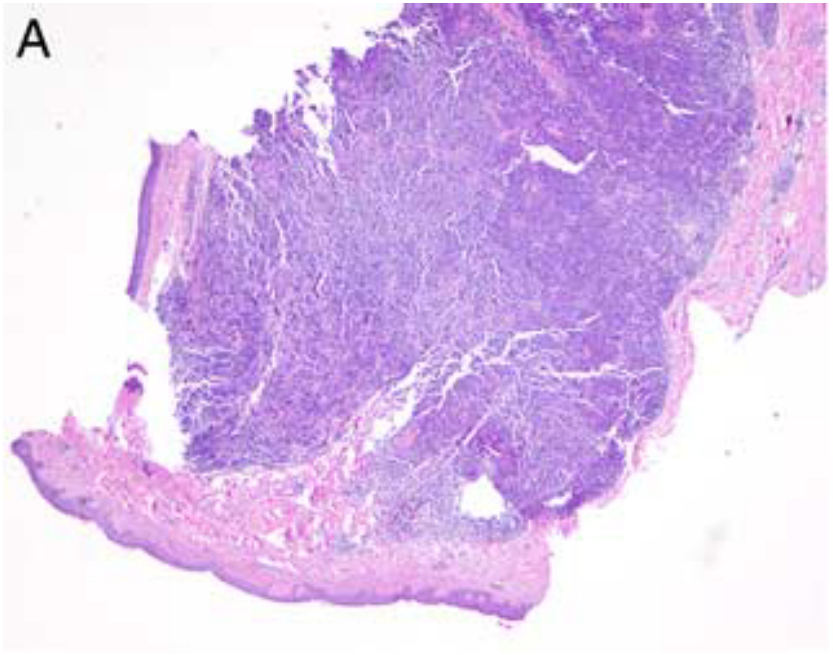
- Tend to occur in more elderly patients
- More frequently in high grade (grade 3A or 3B)
- Typically lack the *IGH-BCL2* translocation
- Amplification of *BCL6* (88%) and *BCL2* amplification/gain

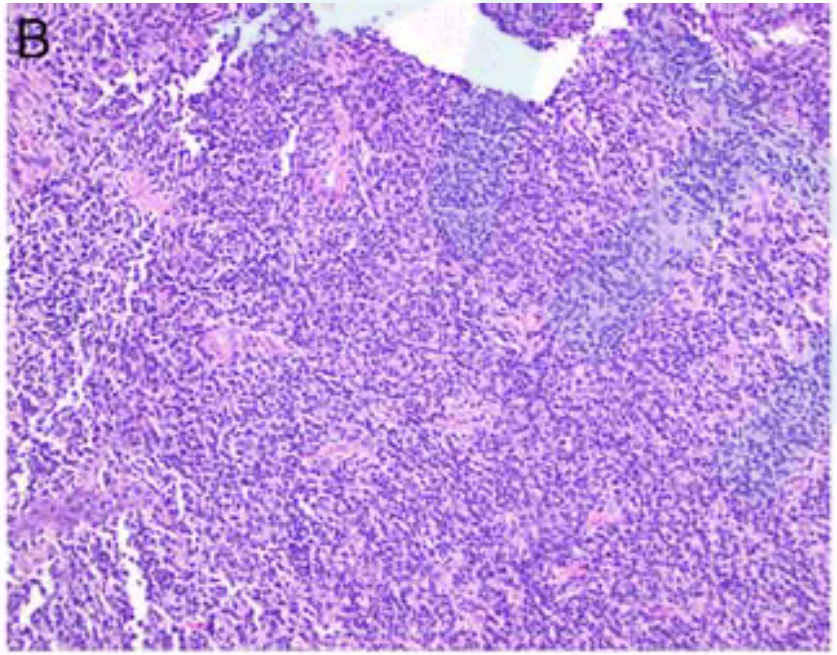
Important differential diagnosis —LBCL with IRF4 rearrangement

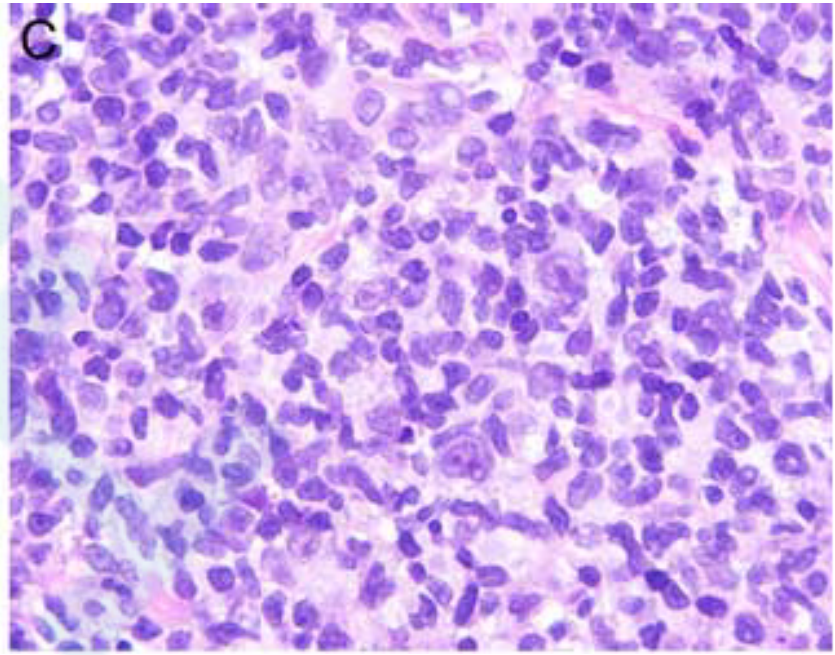
- At least a partially follicular growth pattern
- Express typical GC markers and coexpress MUM1
- Variably express BCL2 and also do not have BCL2 gene rearrangements

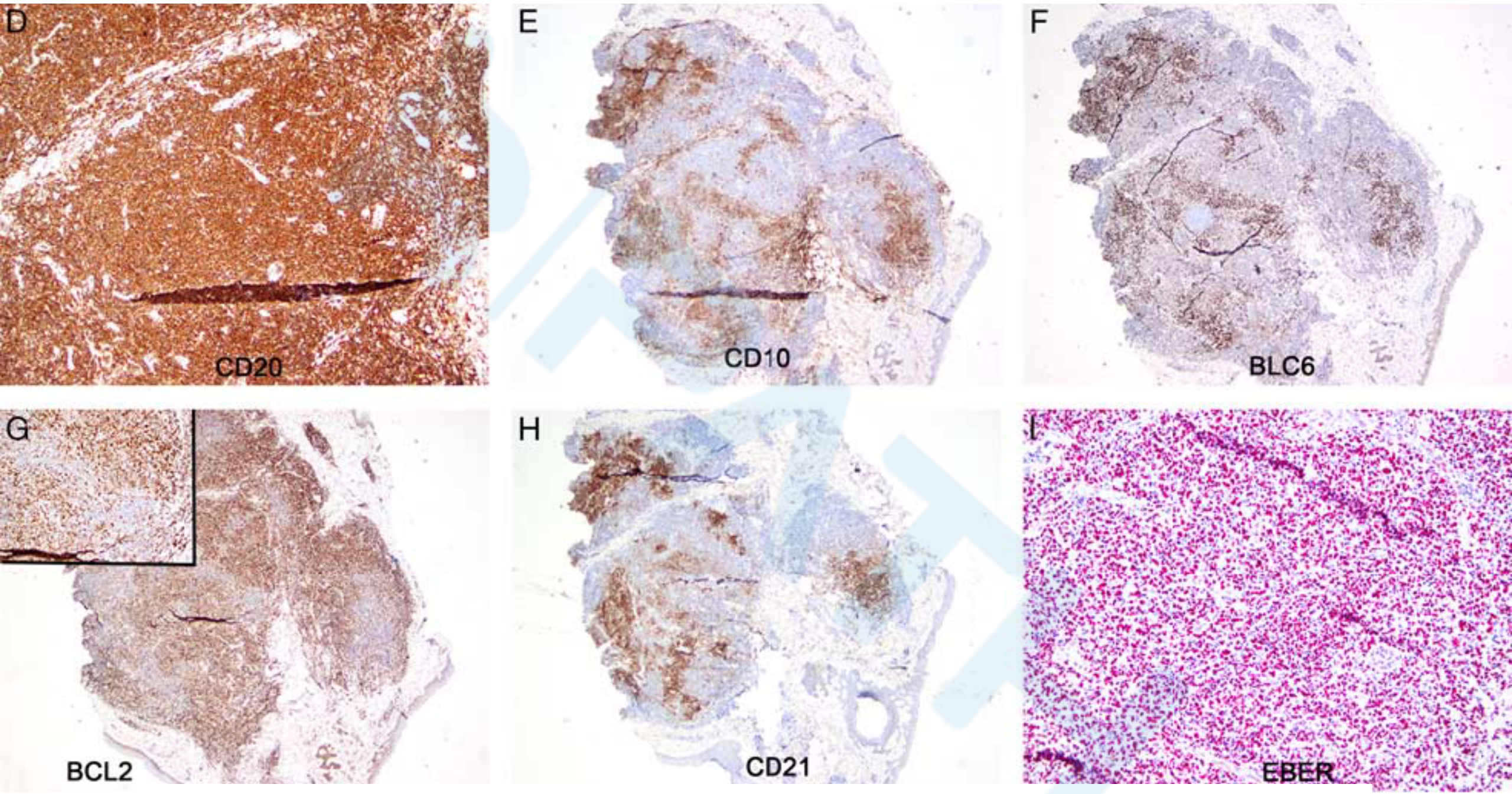
Case 7

- F 76 Left neck skin lesion
- Without systemic evidence of involvemen
- Skin shave biopsy









EBV positive primary cutaneous follicle center cell lymphoma, PCFCL

07 Epstein-Barr Virus–positive FL

EBV - positive FL

- 2.5% in unselected FL
- There were no morphologic or immunophenotypic characteristics associated with presence of EBV
- In the original PCFCL, EBV positivity was diffuse among B cells and positive in virtually all centrocytes

Histologic features typical of PCFCL, including

- Variable B-cell lymphoma size (from small to large)
- Follicular distribution

Histologically distinct from other EBV-related B-cell disorders that can involve skin such as diffuse LBCLs, plasmablastic lymphomas, or EBV-positive mucocutaneous ulcer

PCFCL has been proposed behave more aggressively

- The majority of patients with EBV - positive FL progressed to either a higher grade FL or to diffuse LBCL
- EBV status was associated with worse overall survival, although there were no transformations to diffuse LBCL
- One previously reported case evolved to EBV-positive diffuse LBCL involving a submandibular lymph node 10 months after initial diagnosis in the skin as PCFCL

CASE PRESENTATION & DISCUSSION

01 FL With Castleman-like Changes

02 FL With Plasmacytic Differentiation and IgG4-positive Plasma Cells

03 FL With MZ Differentiation Involving MALT Sites

04 Diffuse FL Variant

05 Mimicry of High-grade FL: Large B-cell Lymphoma With IRF4 Rearrangement

06 FL Negative for CD10, Positive for MUM1

07 Epstein-Barr Virus–positive FL

CONCLUSIONS

- The prototype of clinicopathologic heterogeneity within a lymphoma type is being developed in FL as unique entities having biologically significant differences are identified
- Hematopathologists will inevitably encounter other unusual FLs which may be more difficult to recognize
- Further studies will add to the spectrum of the current clinicopathologic heterogeneity in FL and likely will lead to recognition of new subtypes in the future lymphoma classification by WHO

谢谢观看！