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Indolent In Situ B-Cell Neoplasms With MYC Rearrangements Show Somatic Mutations in MYC and TNFRSF14 by Next-generation Sequencing

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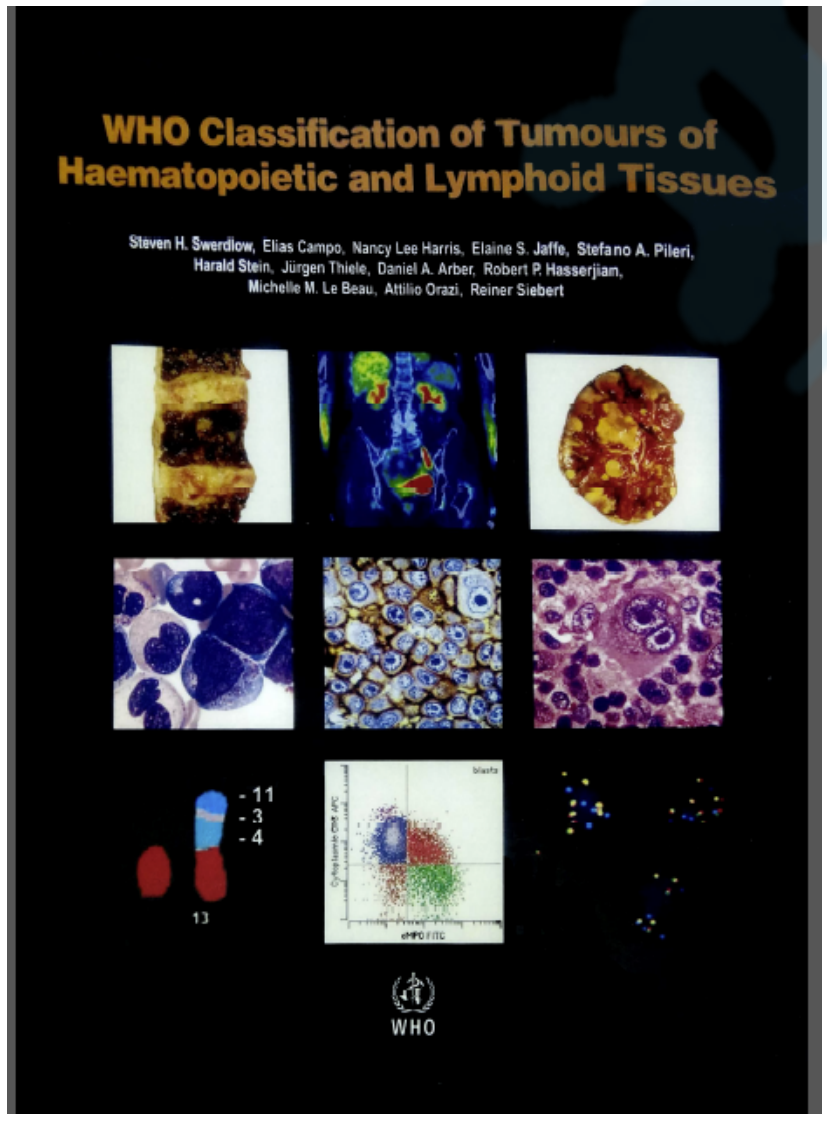
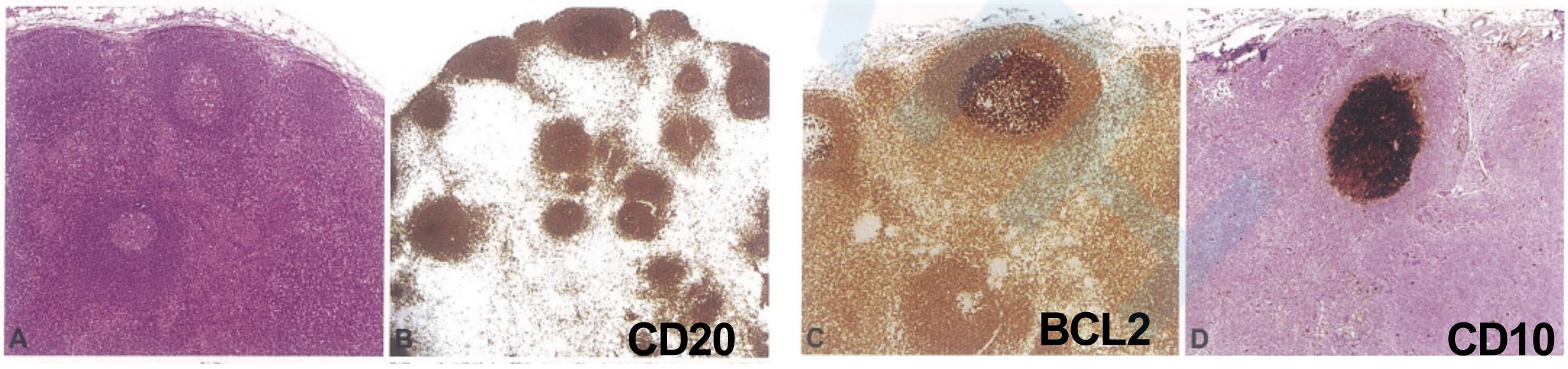
Mature B-cell neoplasms



In situ follicular neoplasia

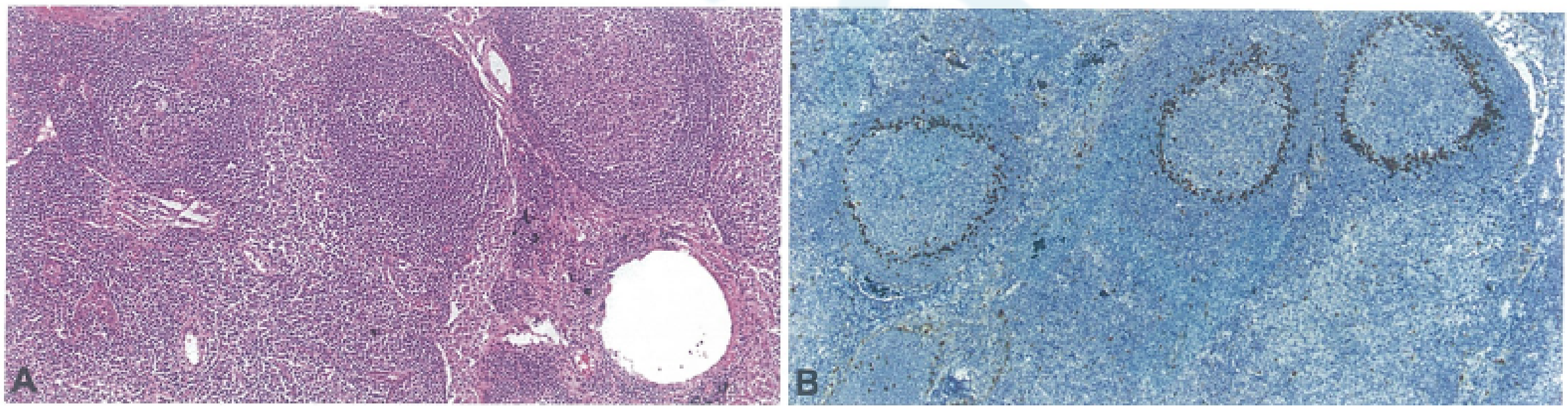
- **Definition**: In situ follicular neoplasia(ISFN) is defined as partial or total colonization of germinal centres by clonal B cells carrying the BCL2 translocatiion characterstic of FL in an otherwise reactive lymph node.

- **Prognosis**: For patients with incidentally diagnosed ISFN and no other evidence of FL on clinical evaluation, the risk of subsequent FL is very low(⩽5%).



In situ mantle cell neoplasia

- **Definition:** In situ mantle cell neoplasia is defined as the presence of cyclin D1-positive lymphoid cells with CCND1 rearrangements restricted to the mantle zone of otherwise hyperplastic-appearing lymphoid tissue.
- **Prognosis**:in situ mantle cell neoplasia is of uncertain significance with rare cases describing an indolent course with long-term survival even without therapy while other cases uncommonly have shown progression to overt MCL.



In situ mantle cell neoplasia, hilar lymph node. **A** There is architectural retention, with intact sinuses and scattered follicles with germinal centres and mantle zones(anthracotic pigment is present).B The follicles show **cyclin D1-positive** lymphocytes, mostly in the **inner** mantle zones.

High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements

- **Definition**: High-grade B-cell lymphoma(HGBL) with MYC and BCL2 and/or BCL6 rearrangements is an aggressive mature B-cell lymphoma that harbours a MYC rearrangement at chromosome 8q24 and a rearrangement in BCL2 and/or in BCL6.

- **prognosis**: With R-CHOP or comparable therapies the complete response rate is relatively low, and overall survival is short, with median survivals of 4.5-18.5 months.

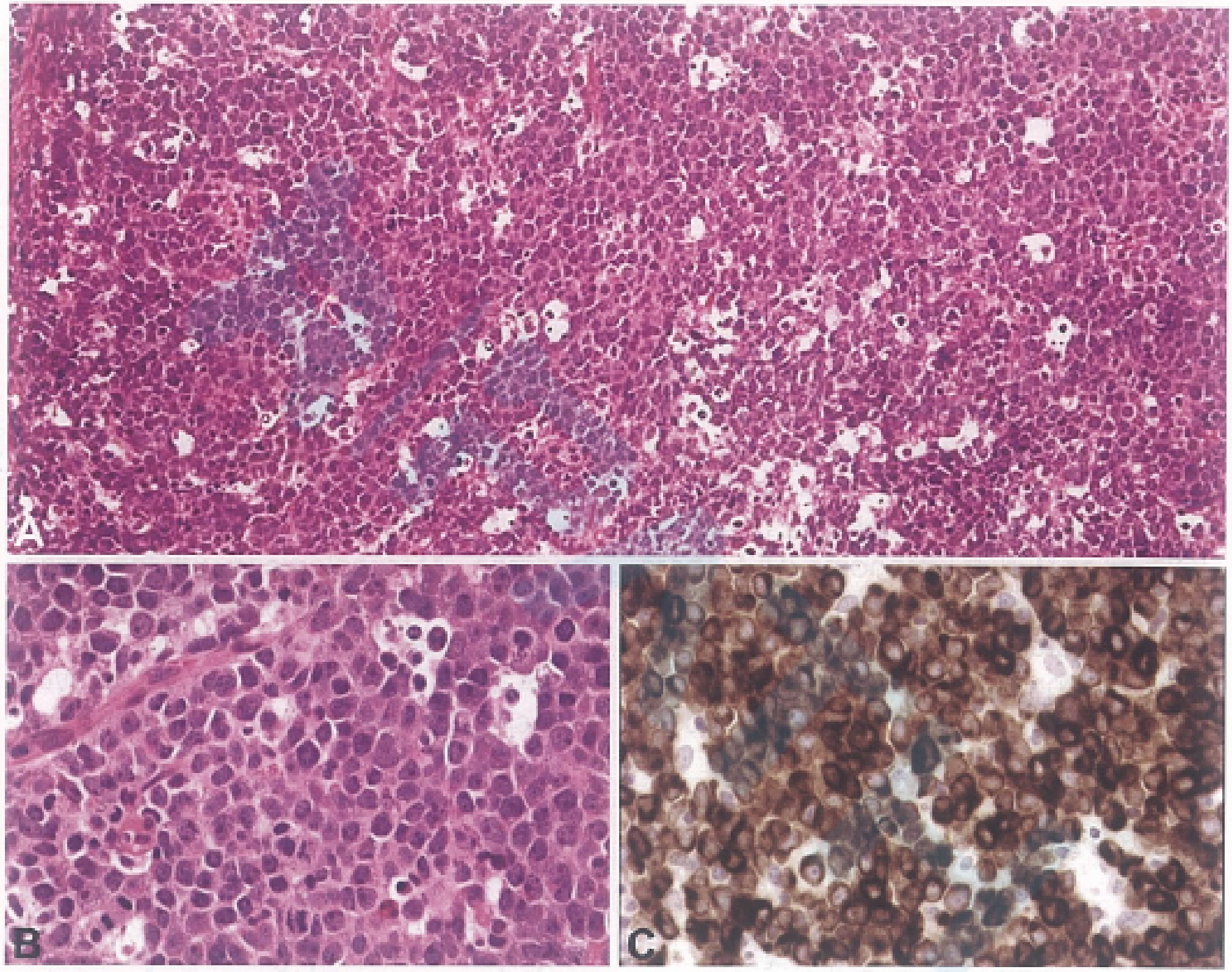


Fig. 13.164 Double-hit high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements. **A** At low magnification, many cases show a prominent starry-sky appearance. **B** In the same case, at higher magnification, note the intermediate size of the tumour cells, with slightly irregular contours and relatively large nucleoli, which are all features somewhat atypical for a Burkitt lymphoma. **C** BCL2 staining of the same case. In most cases with a *BCL2* breakpoint, BCL2 expression is very high, which is in contrast to cases with a *BCL6* breakpoint.

MATERIALS AND METHODS

- Histologic and Immunohistochemical Studies

  CD20、CD10、BCL2、c-Myc、Kappa、 lambda、Ki67

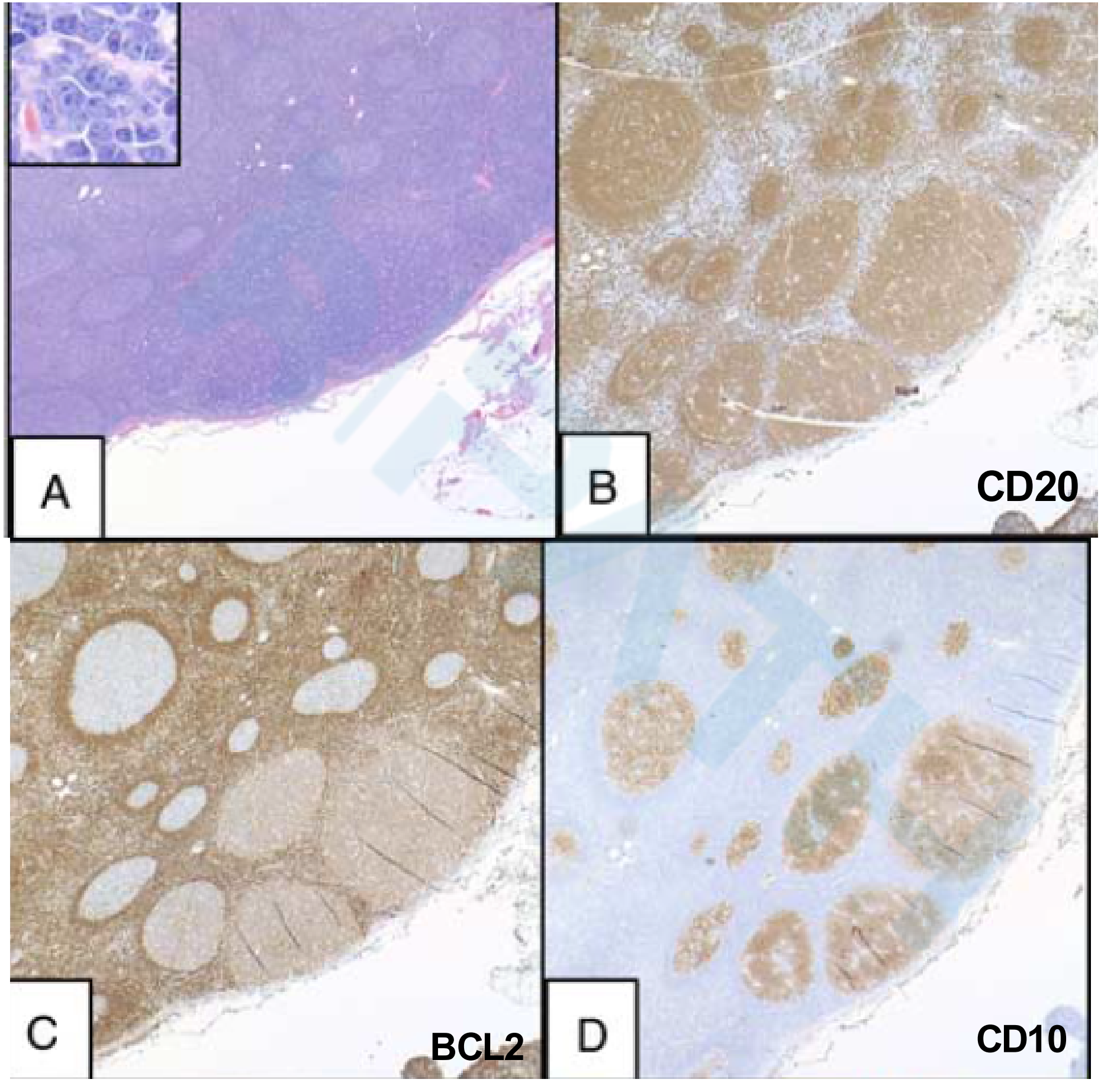
- Cytogenetic Studies

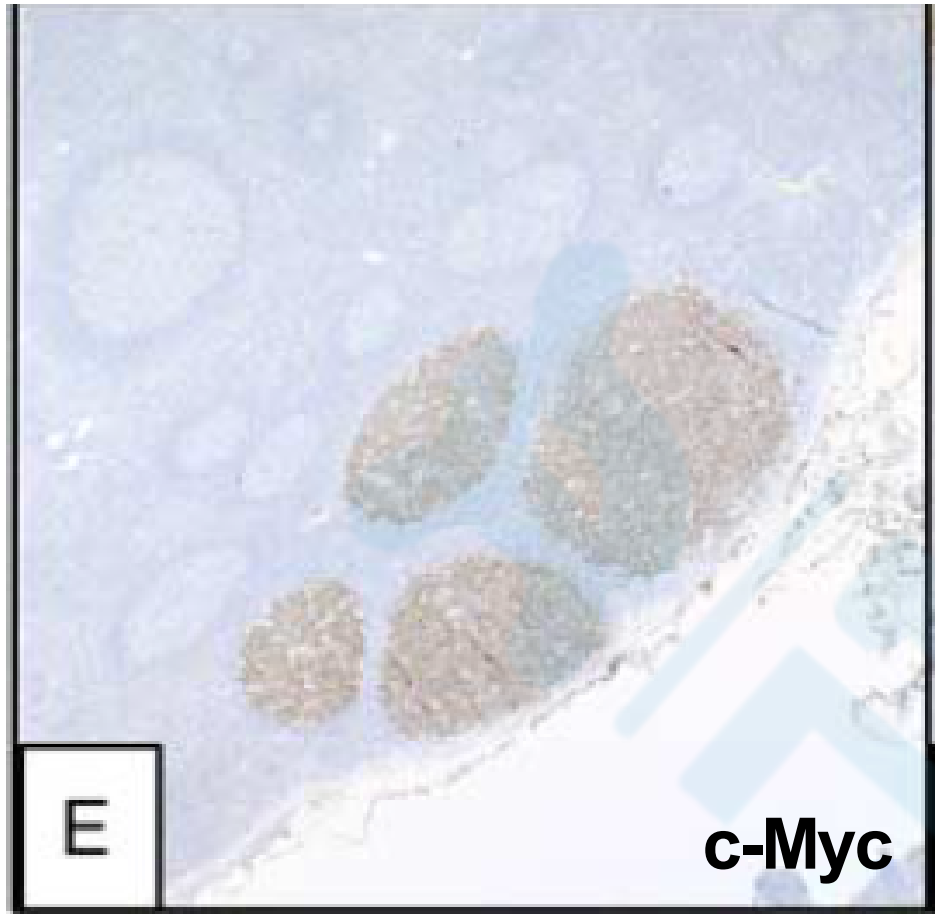
  Fluorescence in situ hybridization (FISH) studies for MYC, BCL2, and BCL6

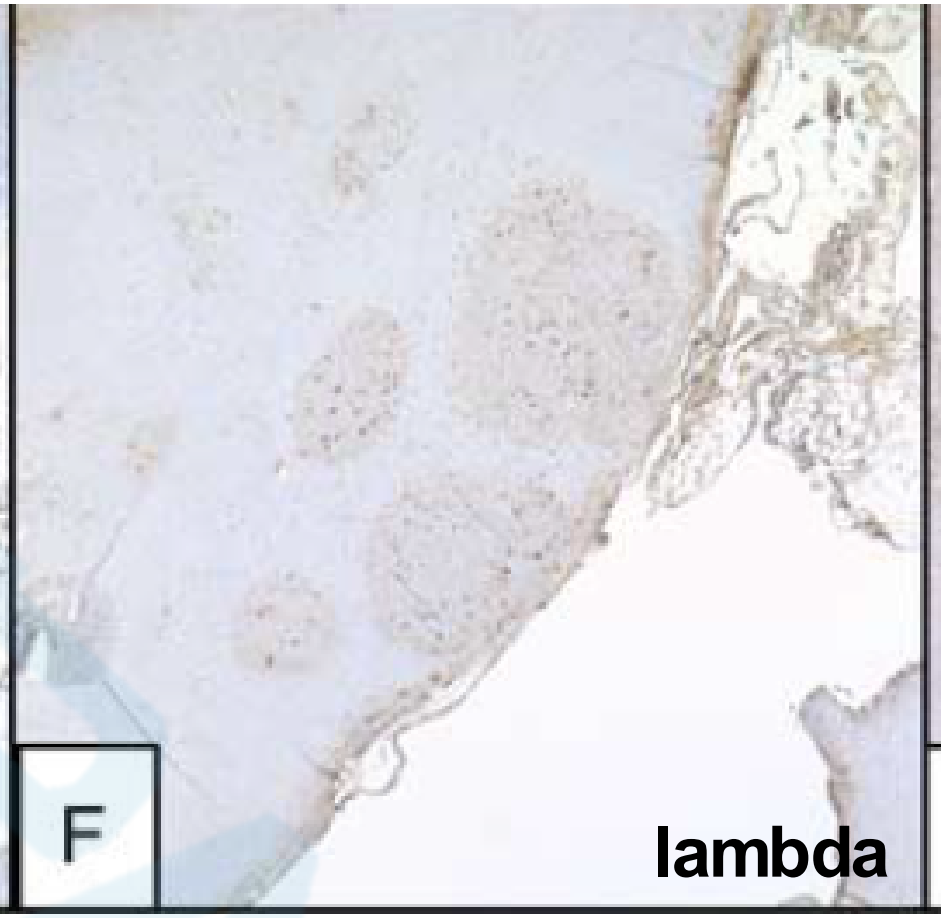
- Targeted Next-generation Sequencing

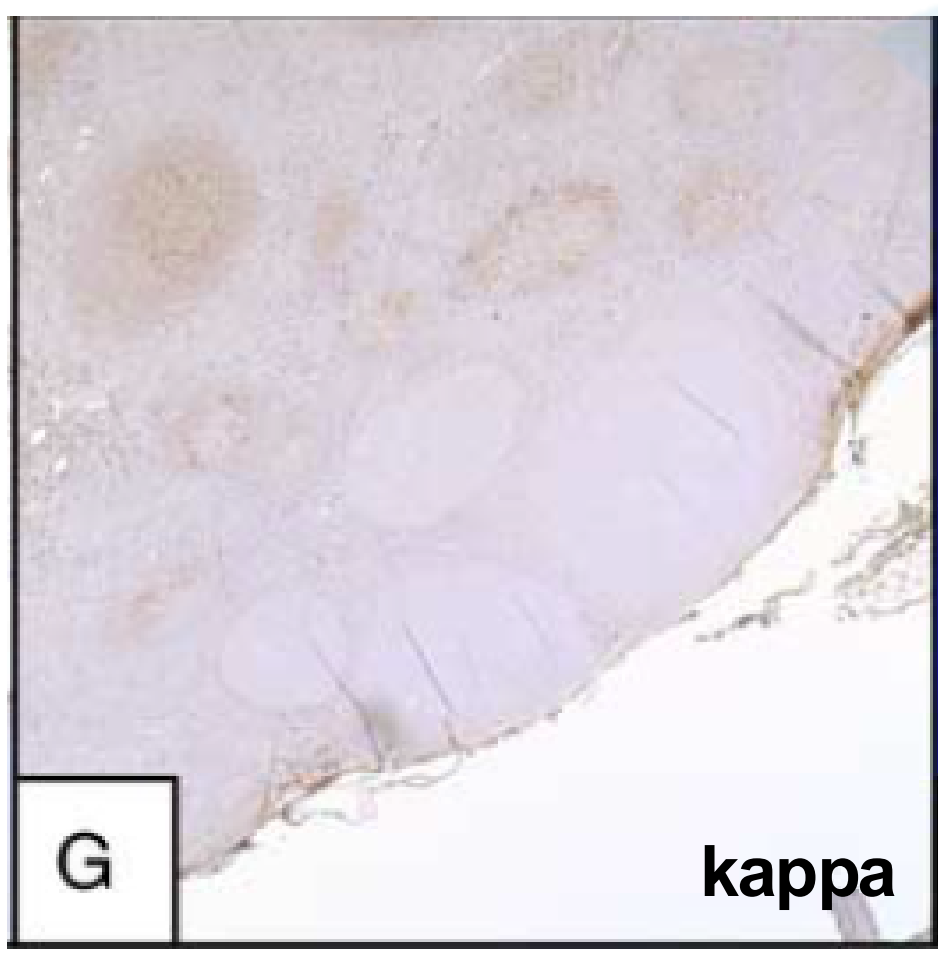
Case 1

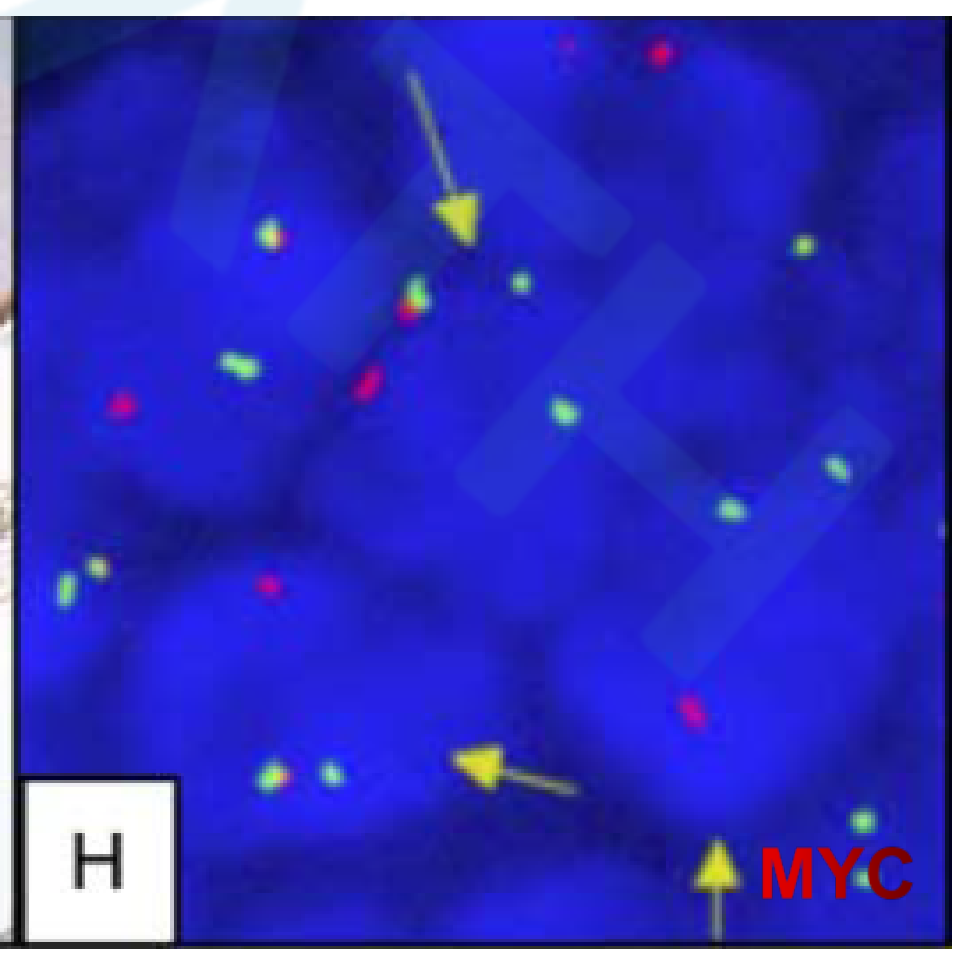
- 男性，58岁，体检发现右颈部包块5年。 否认肿块明显改变，体重减轻，发烧，或疼痛。家族史包括母亲有IV期淋巴瘤和胰腺癌病史。全血细胞计数未见异常。CT显示左颌下肿块大小约为2.4×1.5×2.2 cm；右颌下2枚肿块，大小分别为2.1×2.2×2.4和1.2×1.4×1.6 cm（表1）。
- 患者右颈部包块行细针穿刺未见恶性证据，随后行淋巴结切除及流式细胞学未显示疾病的免疫表型证据。


A
B
CD20
C
BCL2
D
CD10


E
c-Myc


F
lambda


G
kappa

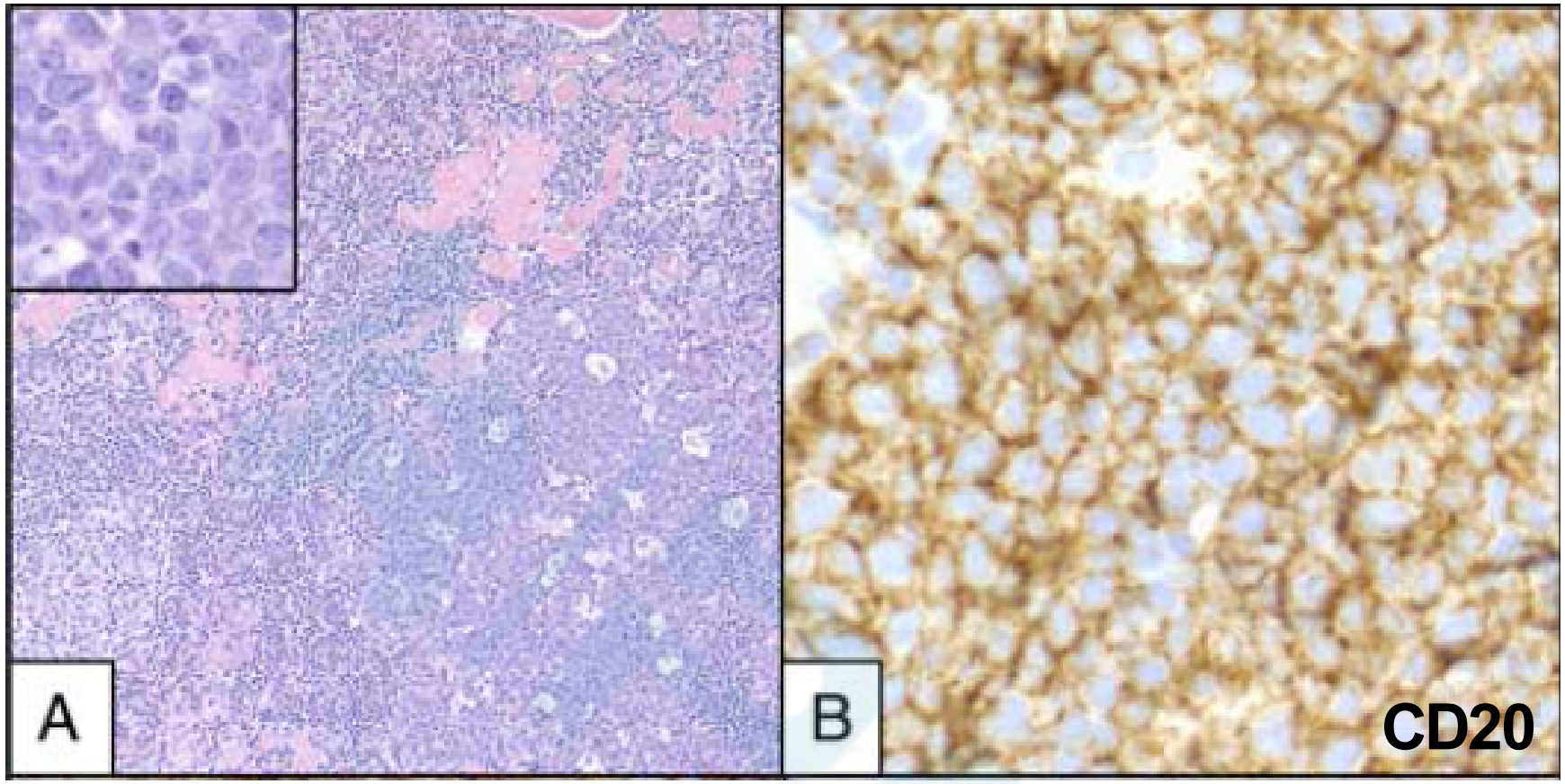

H
MYC

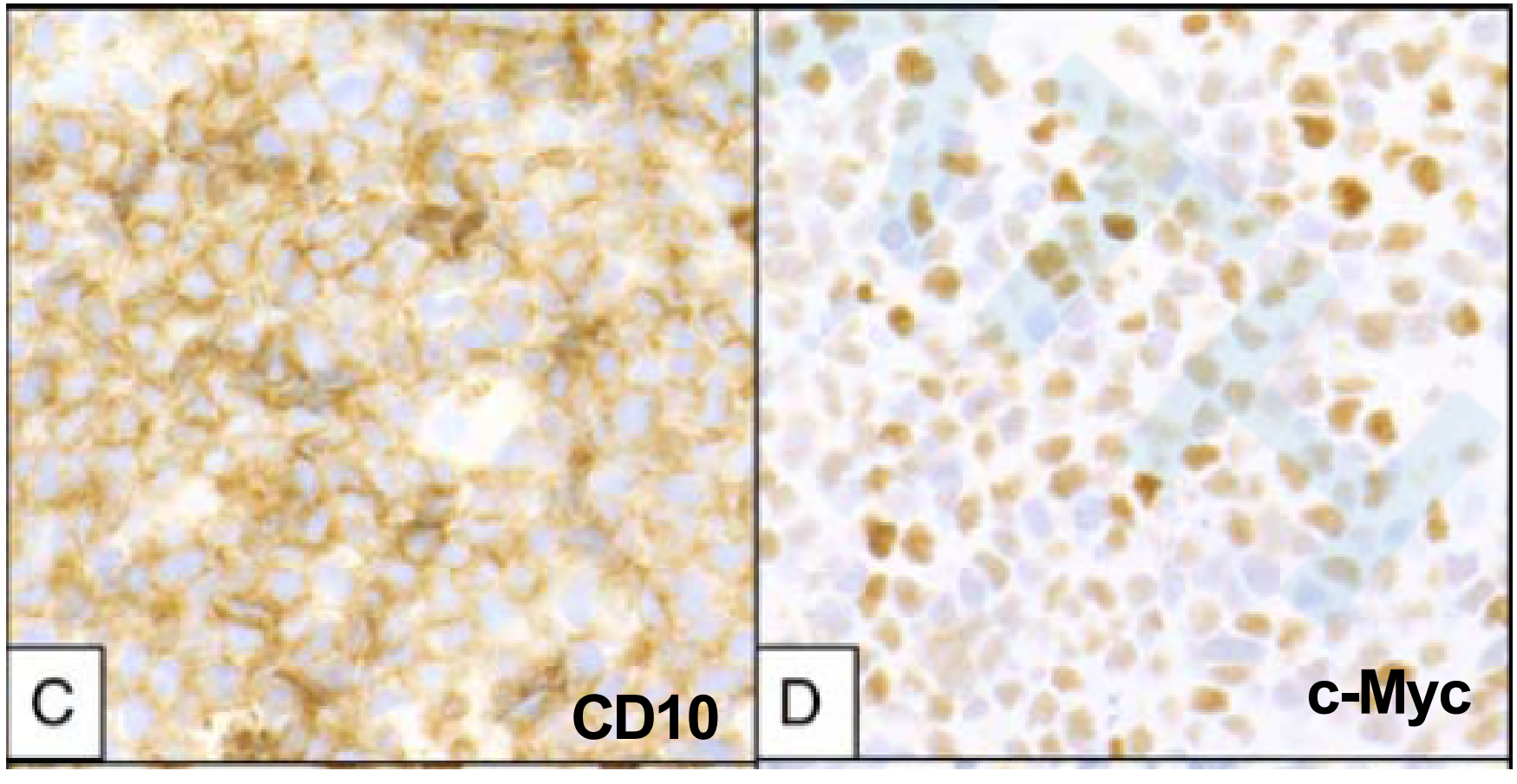
➢7个月后，患者行PET-CT显示左颌下淋巴结增大至2.0cm，行淋巴结切除显示反应性淋巴组织增生，进展性的生发中心转化，流式细胞学及二代测序均未显示异常；

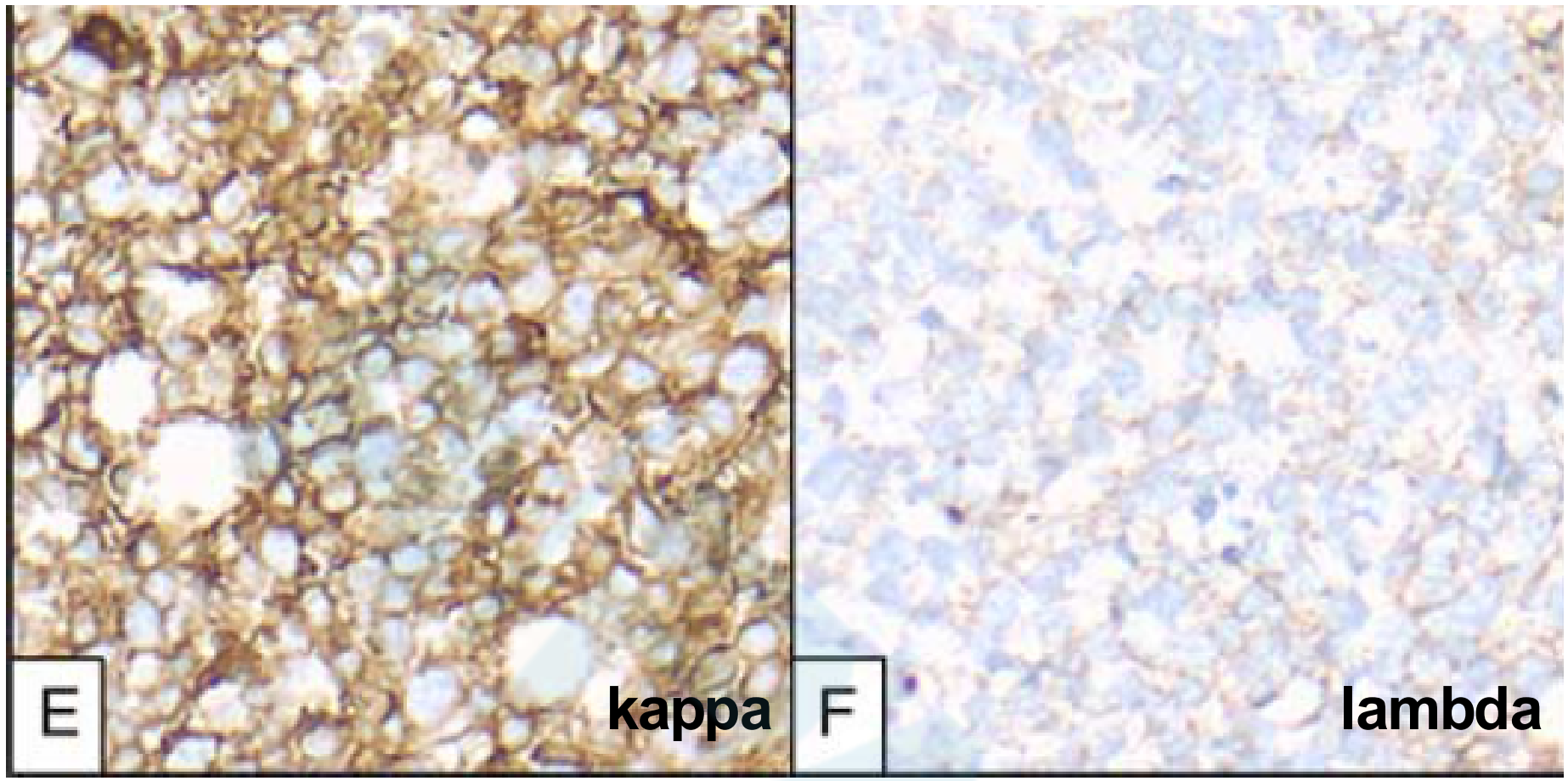
➢随访2年，患者无疾病进展或复发。

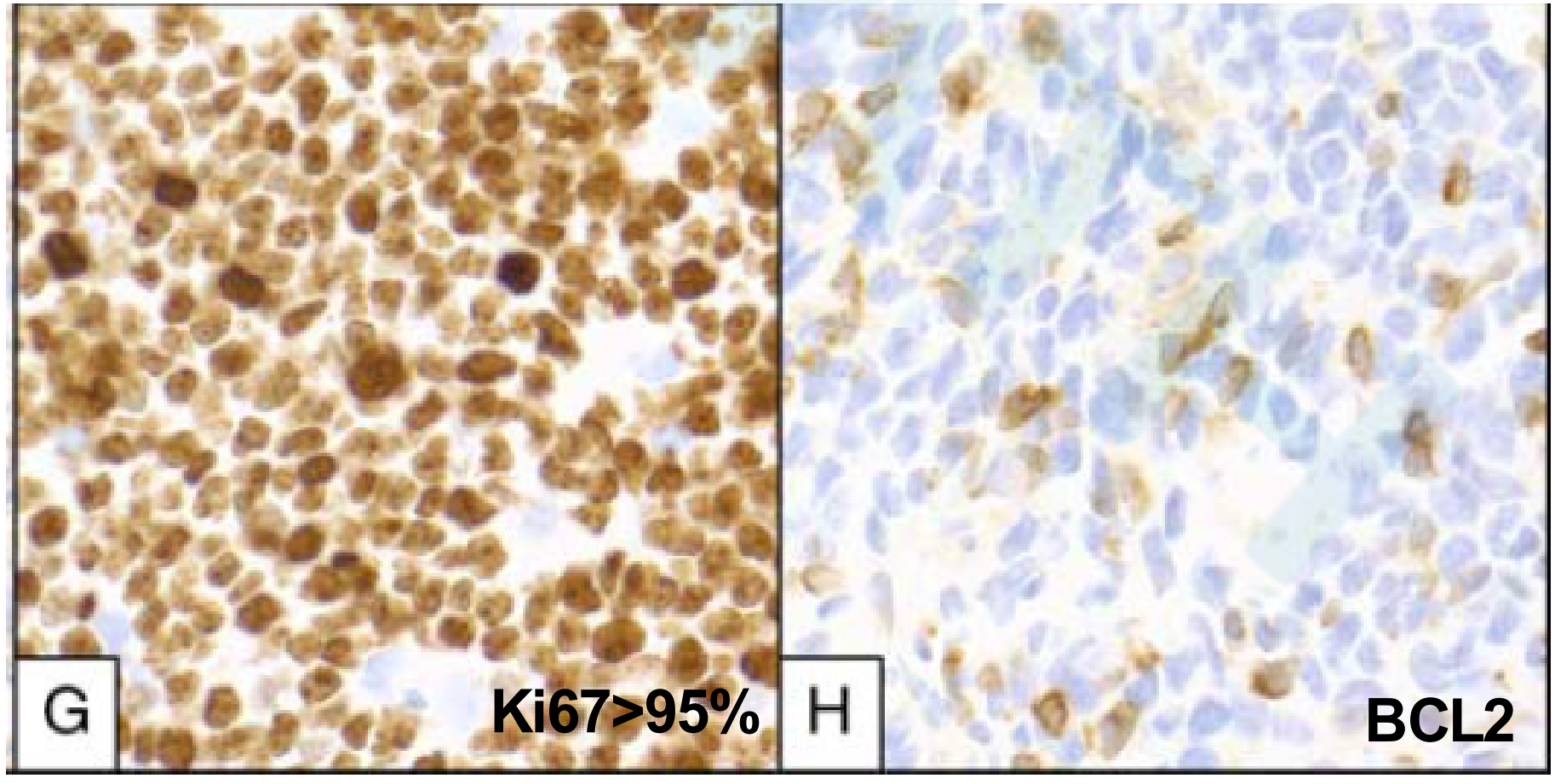
Case 2

- 男性，68岁，有骨关节炎病史，以双侧腹股沟疝和脐疝为症状，在腹腔镜下行疝气修补术时偶然发现了一个右髂淋巴结大小约2.2×1.8×0.9 cm并切除，否认其它淋巴造血疾病。
- 患者术后随访1年，没有任何症状。


A
B
CD20


C
CD10
D
c-Myc


E
kappa
F
lambda


G
Ki67>95%
H
BCL2

RESULTS

TABLE 1. Clinicopathologic Features of 2 Cases of In Situ B-Cell Neoplasms With *MYC* Gene Rearrangements (IS-BCN, *MYC*$^+$)

Case No.	Sex	Age (y)	Morphology	Immunophenotype	Cytogenetics	Site	Clinical Presentation	Treatment	Status (Time of Follow-up)
1	Male	58	Starry sky, medium-large cells with prominent nucleoli	CD20$^+$, lambda$^+$, BCL2$^+$ (dim), CD10$^+$, Ki67 >95%, c-myc$^+$	*MYC* gene rearrangement identified	Right neck	Isolated adenopathy	Surgical excision	Alive (29 mo)
2	Male	68	Starry sky, medium-large cells with prominent nucleoli	CD20$^+$, kappa$^+$, BCL2$^-$, CD10$^+$, Ki67 >95%, c-myc$^+$	*MYC* gene rearrangement identified	Right iliac	Incidental adenopathy noted before hernia repair	Surgical excision	Alive (16 mo)

TABLE 2. Somatic Mutations Identified by Next-generation Sequencing

Gene	Position	Variant Allele Frequency (%)	Nucleotide Change	Type of Mutation	AA Change	Combined Annotation Dependent Depletion	Pathway
Case 1							
MYC	Chr8:128748843	3.7	G > A	Missense	D2N	10.8	Cell cycle progression; apoptosis; cellular transformation
Case 2							
TNFRSF14	Chr1:2488160	2.6	CGTCTTGAGGCT > C	Deletion			Signal transduction pathways

- **MYC基因**是定位于染色体8q24 上的一种癌基因，编码myc蛋白，是在细胞周期进展、凋亡和细胞转化中起重要作用的转录因子。MYC 基因异常表达的淋巴瘤患者多呈现侵袭性临床进程。MYC突变在BL (50% ~ 70%)， DLBCL (5% ~ 33%) 。

- **TNFRSF14**：是肿瘤坏死因子受体超家族成员并编码疱疹病毒侵入介质，通过连接B细胞和T细胞上的衰减子限制T细胞激活，是一种淋巴瘤中的多功能肿瘤抑制子。TNFRSF14突变在HGBCLs（14% ）, DLBCLs（~20% ）和FL（~40%）。

DISCUSSION

- In case 1, we found a somatic MYC mutation, which was not seen in the directly adjacent uninvolved lymphoid tissue or the uninvolved reactive lymph node.

- In addition, in case 2, a deletion mutation of 11 bp in TNFRSF14 was identified.

- TNFRSF14 Mutations in FLs are believed to contribute to transformation to aggressive large B-cell lymphomas.

- In case 2 may indicate that the MYC translocation in concert with the mutation in TNFRSF14 facilitates progression to a high-grade morphologic phenotype.

- Although these are only 2 cases, it is interesting to note that the mutational burden for both was very low(1 additional genetic alteration).

- MYC translocation and MYC gene mutations in BLs was an early event whereas mutations in other genes, TP53, were a late event.

CONCLUSION

- Here we report examples of indolent in situ B-cell neoplasms with MYC gene rearrangements (IS-BCN, MYC+) and analyze the genetic features of these rare cases.

- Thus, the diagnosis of an in situ B-cell neoplasm with MYC gene rearrangement (IS-BCN, MYC+) may represent an important consideration in future classification systems.

谢谢!