Comparison of Myocyte Enhancer Factor 2B Versus Other Germinal Center-associated Antigens in the Differential Diagnosis of B-Cell Non-Hodgkin Lymphomas

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B细胞非霍奇金淋巴瘤（NHL）

- 2016版WHO30余种分类
- 具有不同的临床病理与分子遗传学特征
- 鉴别诊断具有重要的预后与治疗意义
- 仍有部分NHL难以明确诊断
- 边缘区淋巴瘤（MZL）*vs.*滤泡性淋巴瘤（FL）

B细胞NHL

慢性淋巴细胞性白血病/小淋巴细胞淋巴瘤（CLL/SLL）

脾MZL（SMZL）

脾脏弥漫红髓小B细胞淋巴瘤（SDBL）

黏膜相关淋巴组织结外边缘区淋巴瘤（MALT）

淋巴结MZL（NMZL）

滤泡性淋巴瘤（FL）

套细胞淋巴瘤(MCL)

弥漫大B细胞淋巴瘤(DLBCL)，非特指

GC型DLBCL

非GC型DLBCL

Burkitt淋巴瘤（BL）

B淋巴母细胞淋巴瘤（B-LL）

FL

- 占淋巴瘤的20%
- 主要累及淋巴结，也可见于脾、骨髓、外周血，可侵犯非造血系统的结外部位
- 诊断时往往全身广泛播散
- 根据中心母细胞数目分为3级
- 1-2级为惰性临床过程，3级更具侵袭性

- 典型形态学：
  - ✓由小到中等大小的中心细胞和大的中心母细胞组成
  - ✓淋巴结结构破坏被紧密排列的滤泡样结构取代
  - ✓肿瘤性滤泡边界不清，套区变薄或缺乏，细胞分布缺乏极向
  - ✓可见浆样分化
- 免疫组化：B细胞相关抗原、CD10、BCL6、 BCL2（+）
- 分子遗传学：IG基因重排、t(14;18)(q32;q21)易位与BCL2基因重排

MZL

- 分为MALT、 SMZL、NMZL，其中MALT常发生于胃肠道，尤其是胃
- MALT往往有慢性炎症史，SMZL脾大， NMZL淋巴结肿大
- 惰性临床过程， SMZL脾切除，MALT局部放疗
- 可向大B细胞淋巴瘤转化

- 典型形态学：
  - ✓小到中等大小淋巴细胞，核轻度不规则，染色质较疏松，胞浆丰富、淡染
  - ✓最初在反应性滤泡周围，分布在边缘带，扩散融合，最终侵占部分或全部滤泡
  - ✓可见浆样分化
- 免疫组化：B细胞抗原，IRTA1，MNDA，SMZL：sIgM、sIgD，MALT：IgM、CD43，NMZL：BCL2、CD43
- 分子遗传学：IG基因重排

肌细胞增强因子2B（MEF2B）

- 属于MEF2基因家族成员
- 在淋巴细胞的发育、分化、凋亡等生理过程中起作用
- 已发现是原癌基因BCL6的转录激活因子
- 正常生发中心（GC）细胞中，与BCL6有相似的表达模式
- 有可能成为重要的GC标记
- 但关于其在B细胞淋巴瘤中表达的报道很少

目的

1. 检测MEF2B在不同B细胞淋巴瘤中的表达模式
2. FL与MZL鉴别诊断中的作用
3. 与其他GC相关抗原比较效用

材料与方法

2000-2015来自匹兹堡大学医学中心

FL 31（10/31CD10-）
MALT 11
NMZL 8
SMZL 24
SDBL 2
CLL/SLLs 10
MCL 9
DLBCL 44
BL 10
B-LL 7
淋巴结反应性滤泡增生 12
PTCL 12 外周T细胞淋巴瘤

免疫组化

- **GC标记：**
  - ✓**LMO2：LIM-only转录调节因子**
  - ✓**HGAL：人类生发中心相关淋巴瘤基因**
  - ✓**MEF2B**
  - ✓**BCL6**
  - ✓**CD10**
- **CLL/SLL标记：淋巴样增强因子（LEF1）**
- **MCL标记：SOX11、cyclin D1**
- **MUM1、CD21**
- **MEF2B，HGAL和LMO2阳性标准：肿瘤细胞≥20%**

结果

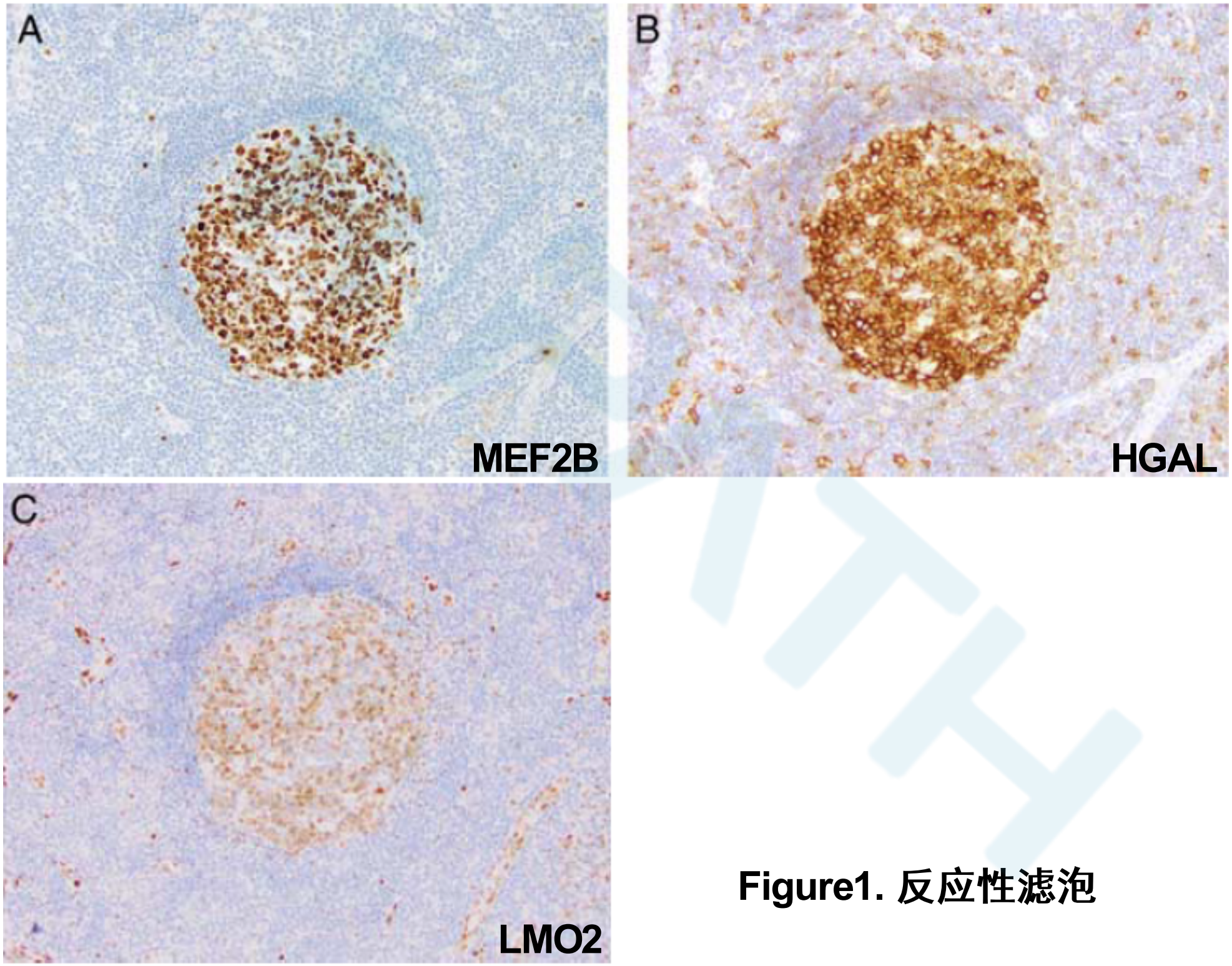


Figure1. 反应性滤泡

TABLE 1. MEF2B, LMO2, and HGAL in 156 B-Cell NHL

Lymphoma	MEF2B$^+$ (n/N [%])	LMO2$^+$ (n/N [%])	HGAL$^+$ (n/N [%])	BCL6$^+$ (n/N [%])	CD10$^+$ (n/N [%])
FL	31/31 (100)	26/30 (87)	29/30 (97)	31/31 (100)	21/31 (68)*
Grade 1-2/3	19/19 (100)	17/19 (89)	18/19 (95)	19/19 (100)	11/19 (58)
Grade 3A	6/6 (100)	5/6 (83)	6/6 (100)	6/6 (100)	6/6 (100)
Grade 3B	6/6 (100)	4/5 (80)	5/5 (100)	6/6 (100)	4/6 (67)
MALT	0/11 (0)	1/11 (9)	0/11 (0)	0/11 (0)	0/11 (0)
NMZL	0/8 (0)	4/8 (50)	4/8 (50)	1/8 (13)	0/8 (0)
SMZL	2/24 (8)	1/24 (4)	2/24 (8)	1/24 (4)	0/24 (0)
SDBL	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)
MCL	8/9 (89)	ND	ND	0/6 (0)	0/9 (0)
CLL/SLL	1/10 (10)	ND	ND	0/3 (0)	0/10 (0)
DLBCL	38/44 (86)	28/40 (70)	29/41 (71)	38/43 (88)	17/44 (39)
GC-DLBCL	22/25 (88)	19/22 (86)	18/23 (78)	23/24 (96)	17/25 (68)
Non–GC-type DLBCL	16/19 (84)	9/18 (50)	11/18 (61)	15/19 (79)	0/19 (0)
BL	10/10 (100	4/10 (40)	10/10 (100)	10/10 (100)	10/10 (100)
B-LL	0/7 (0)	ND	ND	1/2 (50)	4/7 (57)

*Cases included were enriched for CD10$^-$ FL.

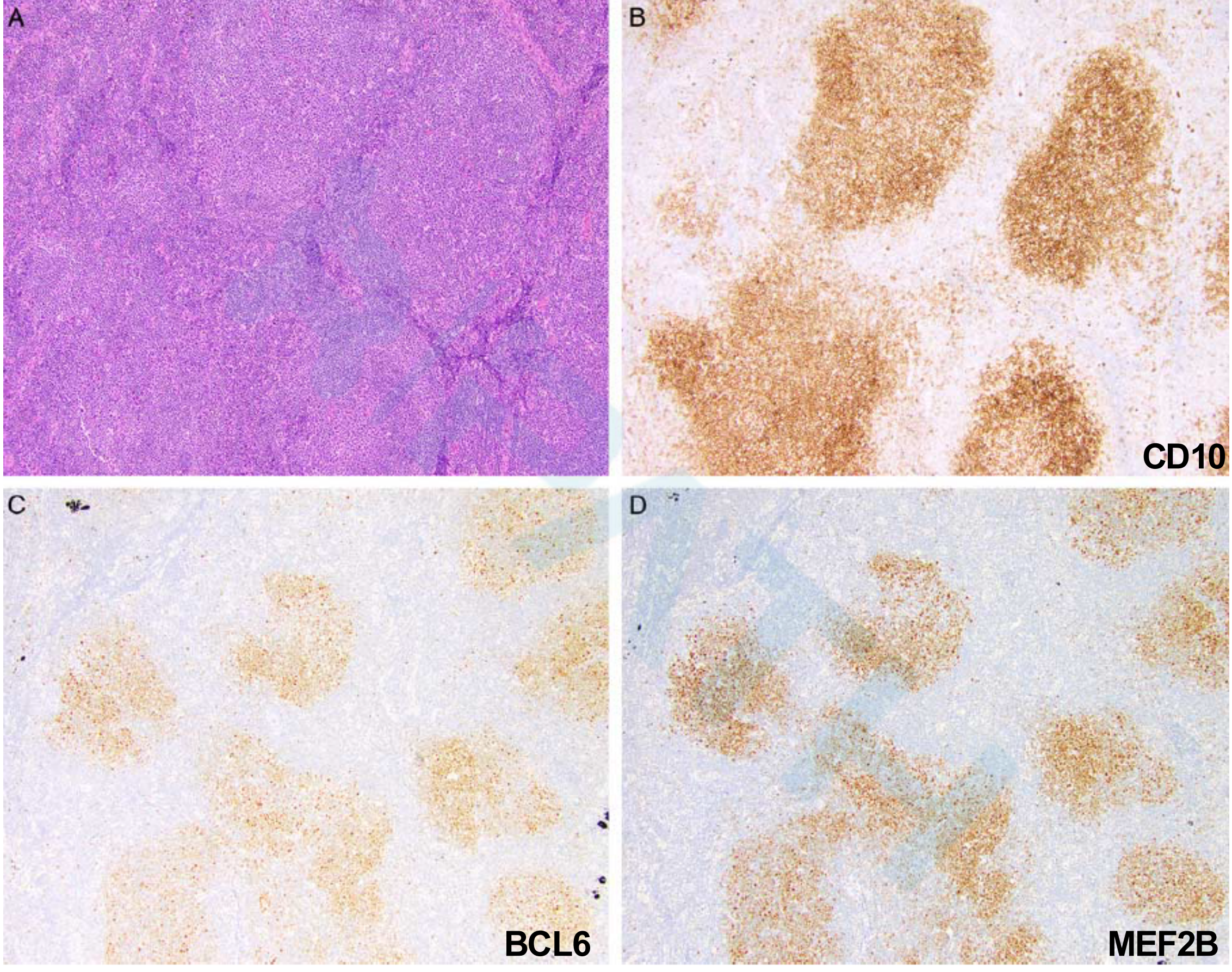
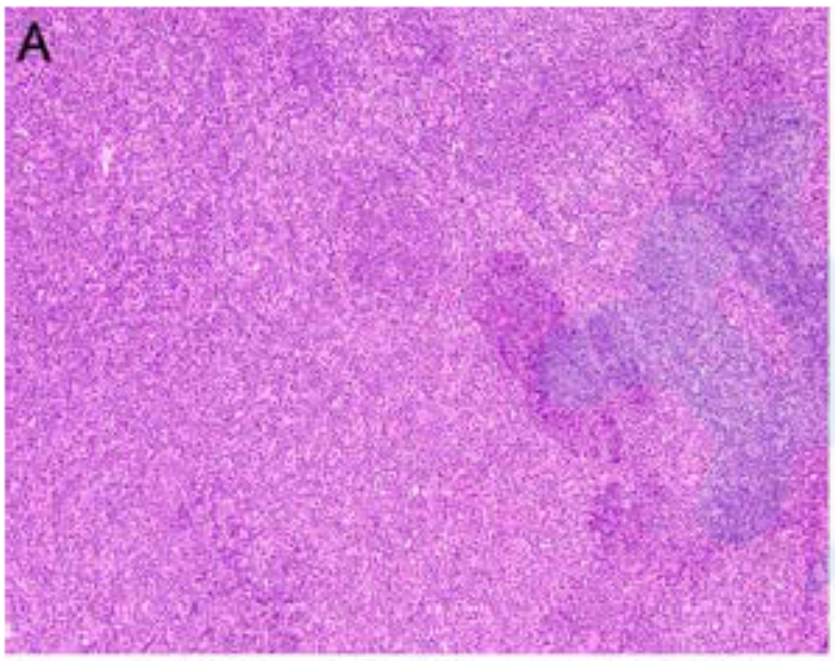
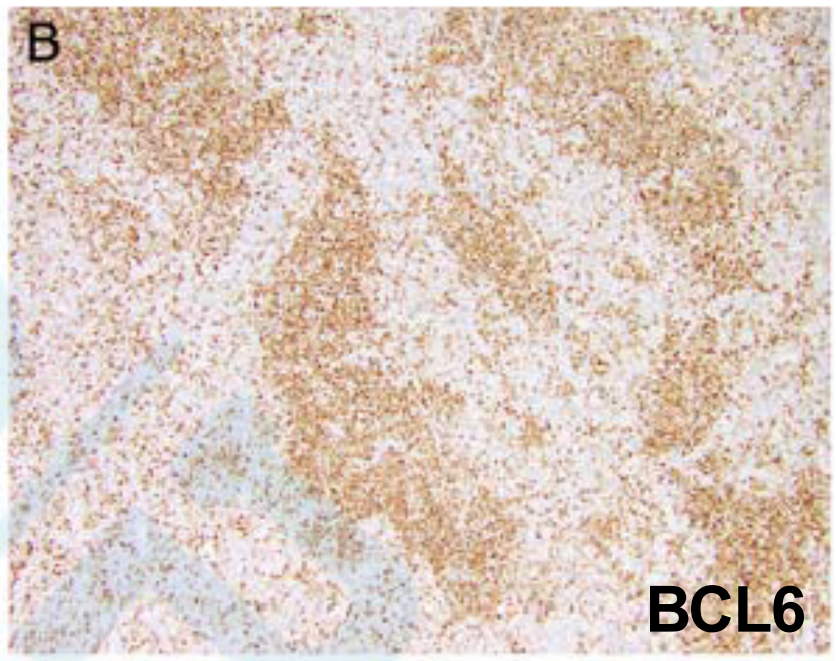
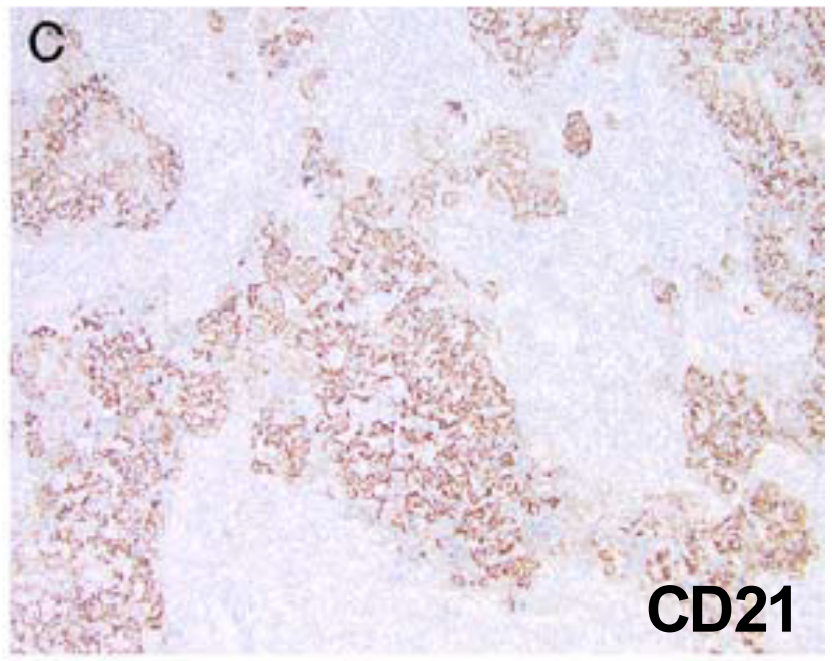
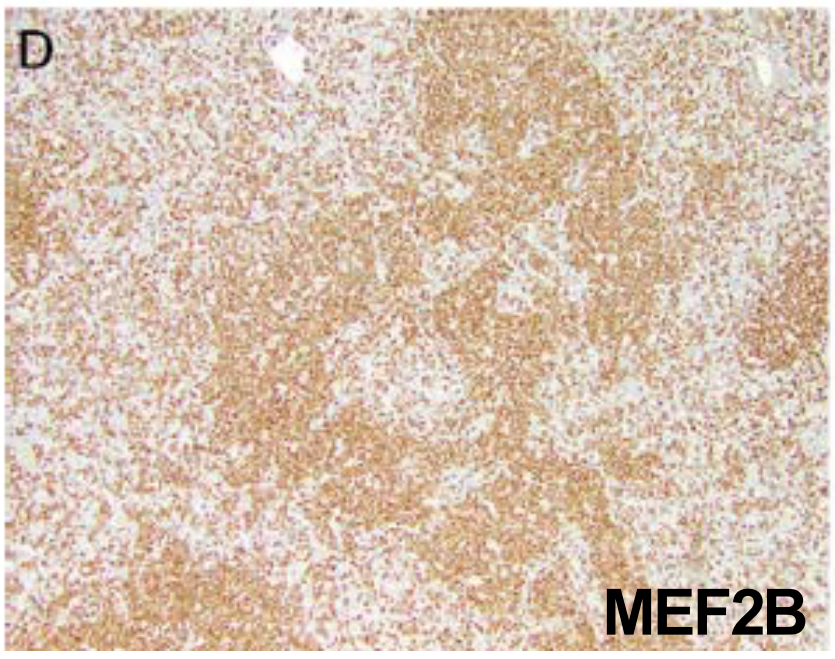


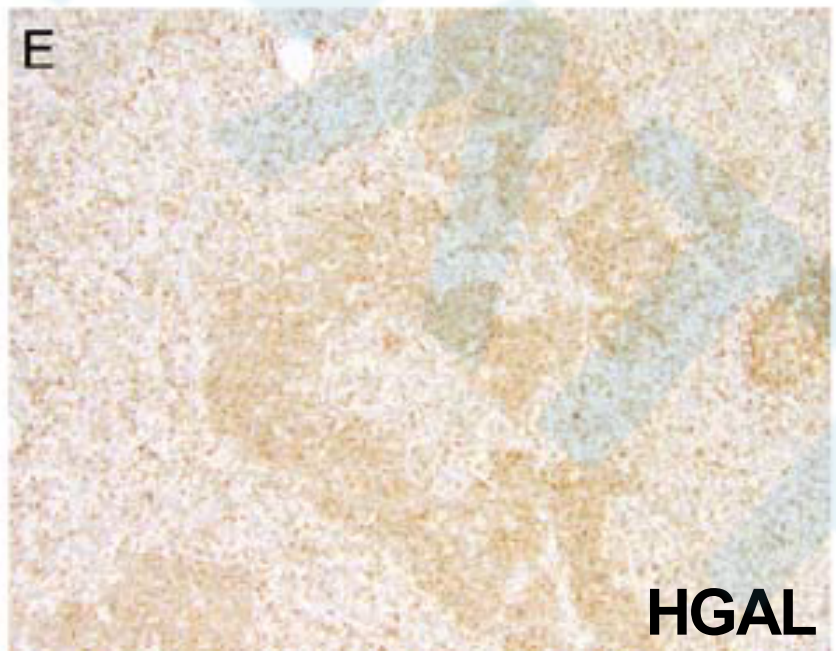
Figure2. CD10+FL











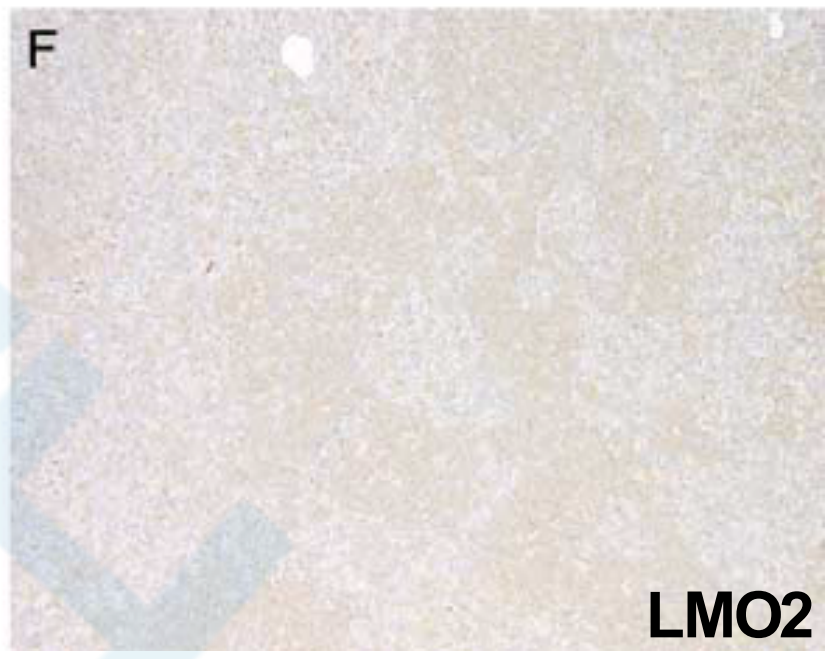
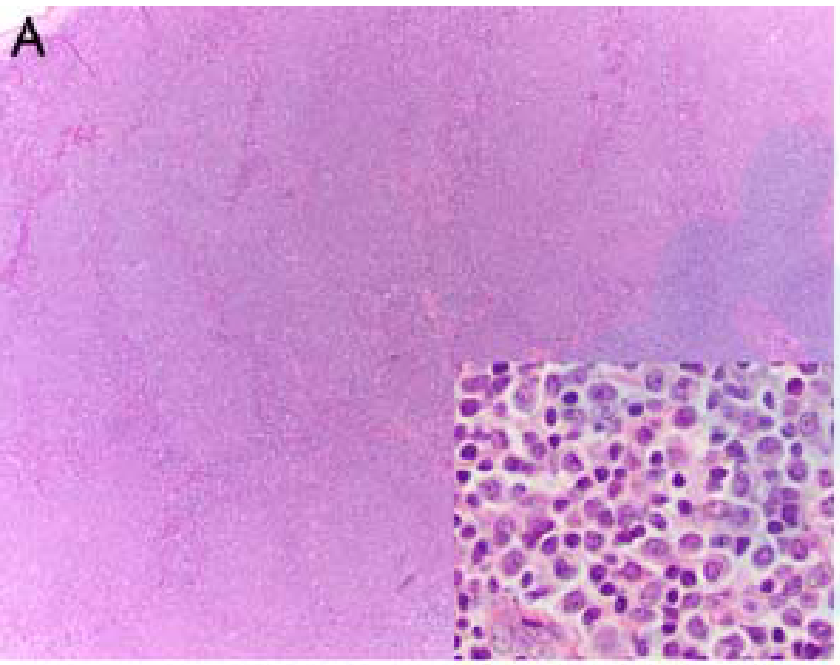
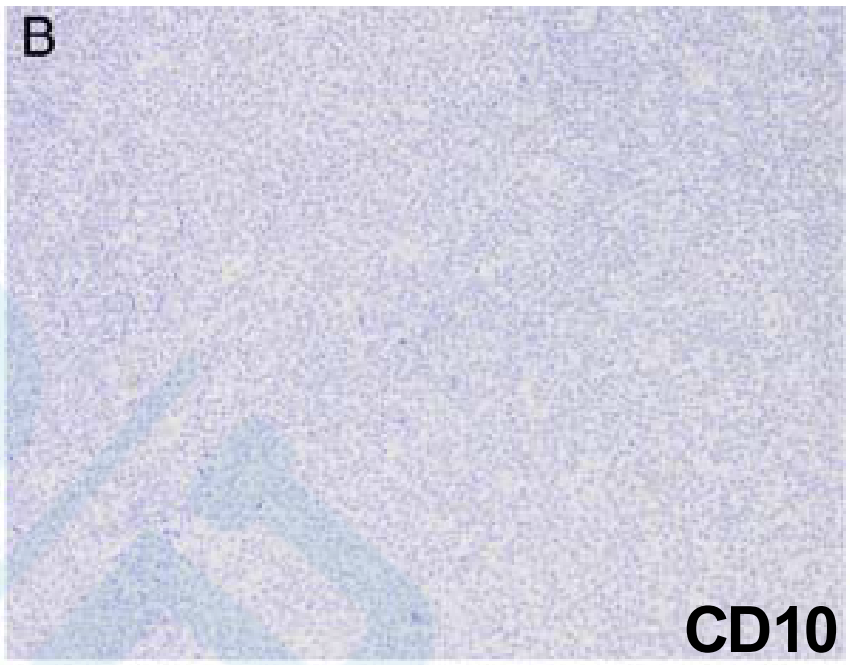
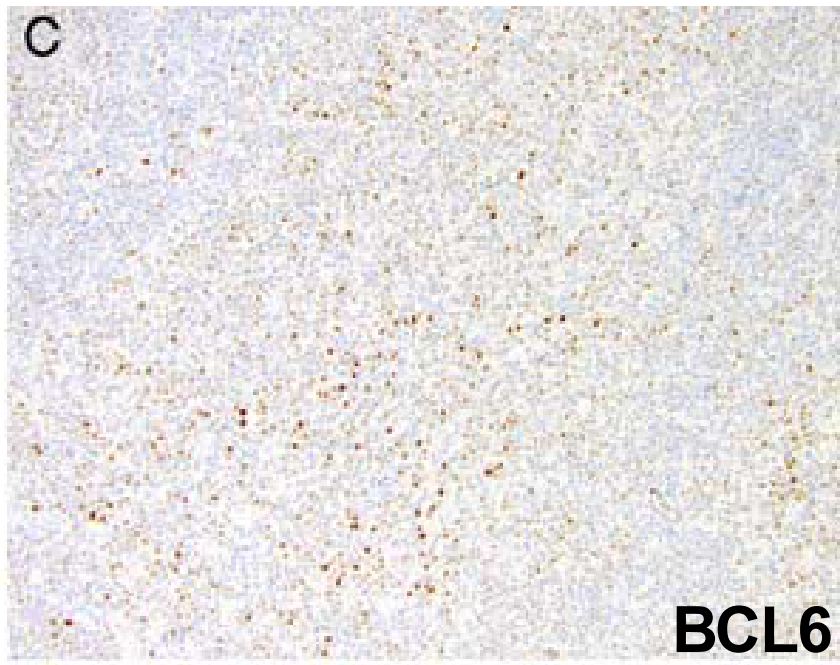
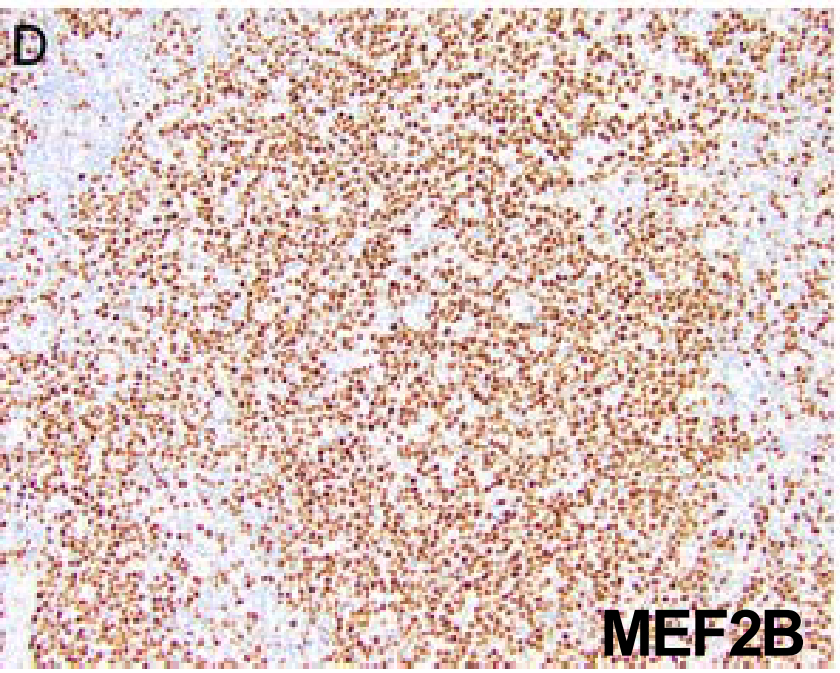


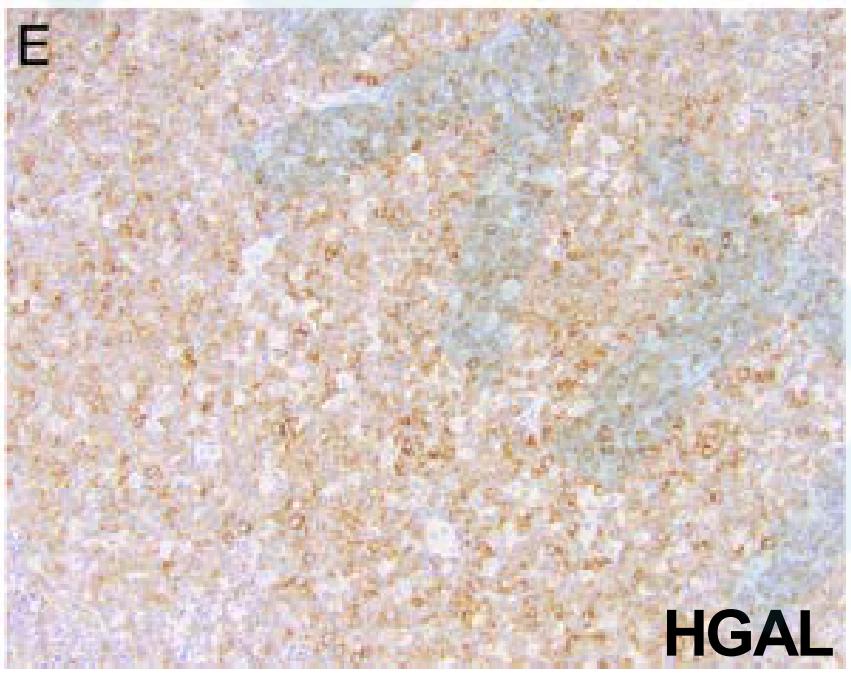
Figure3. CD10-FL











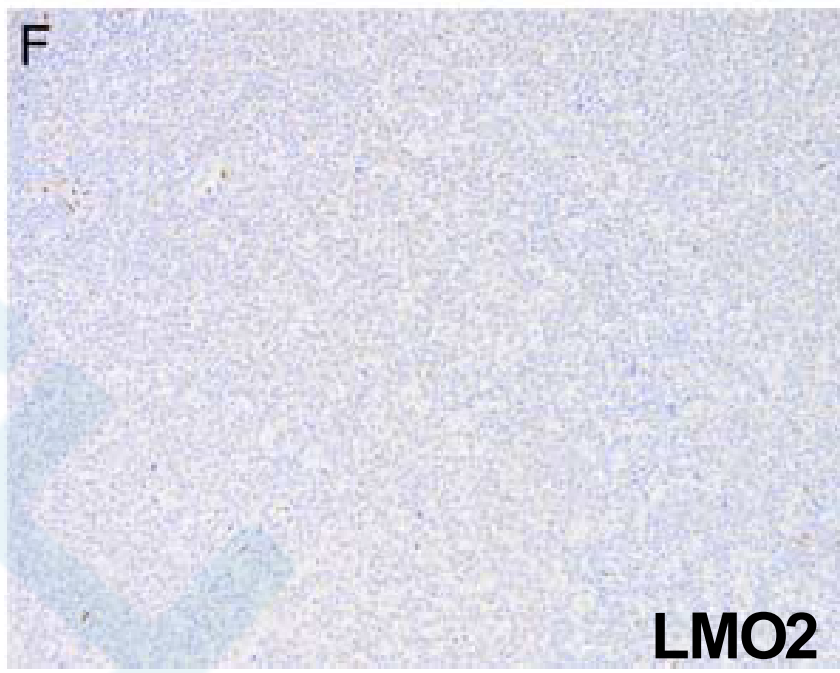


Figure4. 伴浆样分化的CD10-FL

TABLE 1. MEF2B, LMO2, and HGAL in 156 B-Cell NHL

Lymphoma	MEF2B$^+$ (n/N [%])	LMO2$^+$ (n/N [%])	HGAL$^+$ (n/N [%])	BCL6$^+$ (n/N [%])	CD10$^+$ (n/N [%])
FL	31/31 (100)	26/30 (87)	29/30 (97)	31/31 (100)	21/31 (68)*
Grade 1-2/3	19/19 (100)	17/19 (89)	18/19 (95)	19/19 (100)	11/19 (58)
Grade 3A	6/6 (100)	5/6 (83)	6/6 (100)	6/6 (100)	6/6 (100)
Grade 3B	6/6 (100)	4/5 (80)	5/5 (100)	6/6 (100)	4/6 (67)
MALT	0/11 (0)	1/11 (9)	0/11 (0)	0/11 (0)	0/11 (0)
NMZL	0/8 (0)	4/8 (50)	4/8 (50)	1/8 (13)	0/8 (0)
SMZL	2/24 (8)	1/24 (4)	2/24 (8)	1/24 (4)	0/24 (0)
SDBL	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)
MCL	8/9 (89)	ND	ND	0/6 (0)	0/9 (0)
CLL/SLL	1/10 (10)	ND	ND	0/3 (0)	0/10 (0)
DLBCL	38/44 (86)	28/40 (70)	29/41 (71)	38/43 (88)	17/44 (39)
GC-DLBCL	22/25 (88)	19/22 (86)	18/23 (78)	23/24 (96)	17/25 (68)
Non–GC-type DLBCL	16/19 (84)	9/18 (50)	11/18 (61)	15/19 (79)	0/19 (0)
BL	10/10 (100	4/10 (40)	10/10 (100)	10/10 (100)	10/10 (100)
B-LL	0/7 (0)	ND	ND	1/2 (50)	4/7 (57)

*Cases included were enriched for CD10$^-$ FL.

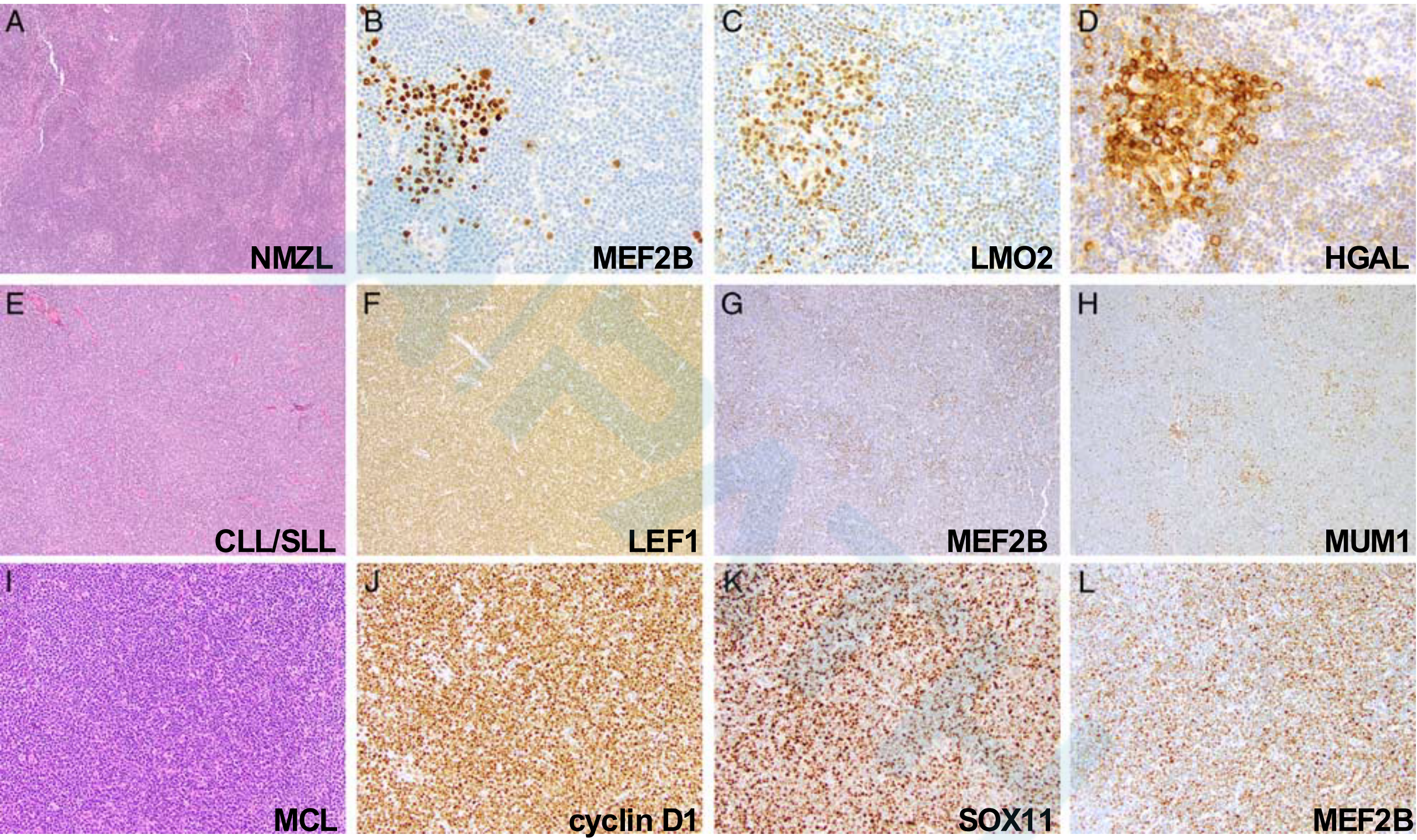


Figure5. 其他小B细胞淋巴瘤

TABLE 1. MEF2B, LMO2, and HGAL in 156 B-Cell NHL

Lymphoma	MEF2B$^+$ (n/N [%])	LMO2$^+$ (n/N [%])	HGAL$^+$ (n/N [%])	BCL6$^+$ (n/N [%])	CD10$^+$ (n/N [%])
FL	31/31 (100)	26/30 (87)	29/30 (97)	31/31 (100)	21/31 (68)*
Grade 1-2/3	19/19 (100)	17/19 (89)	18/19 (95)	19/19 (100)	11/19 (58)
Grade 3A	6/6 (100)	5/6 (83)	6/6 (100)	6/6 (100)	6/6 (100)
Grade 3B	6/6 (100)	4/5 (80)	5/5 (100)	6/6 (100)	4/6 (67)
MALT	0/11 (0)	1/11 (9)	0/11 (0)	0/11 (0)	0/11 (0)
NMZL	0/8 (0)	4/8 (50)	4/8 (50)	1/8 (13)	0/8 (0)
SMZL	2/24 (8)	1/24 (4)	2/24 (8)	1/24 (4)	0/24 (0)
SDBL	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)
MCL	8/9 (89)	ND	ND	0/6 (0)	0/9 (0)
CLL/SLL	1/10 (10)	ND	ND	0/3 (0)	0/10 (0)
DLBCL	38/44 (86)	28/40 (70)	29/41 (71)	38/43 (88)	17/44 (39)
GC-DLBCL	22/25 (88)	19/22 (86)	18/23 (78)	23/24 (96)	17/25 (68)
Non–GC-type DLBCL	16/19 (84)	9/18 (50)	11/18 (61)	15/19 (79)	0/19 (0)
BL	10/10 (100	4/10 (40)	10/10 (100)	10/10 (100)	10/10 (100)
B-LL	0/7 (0)	ND	ND	1/2 (50)	4/7 (57)

*Cases included were enriched for CD10$^-$ FL.

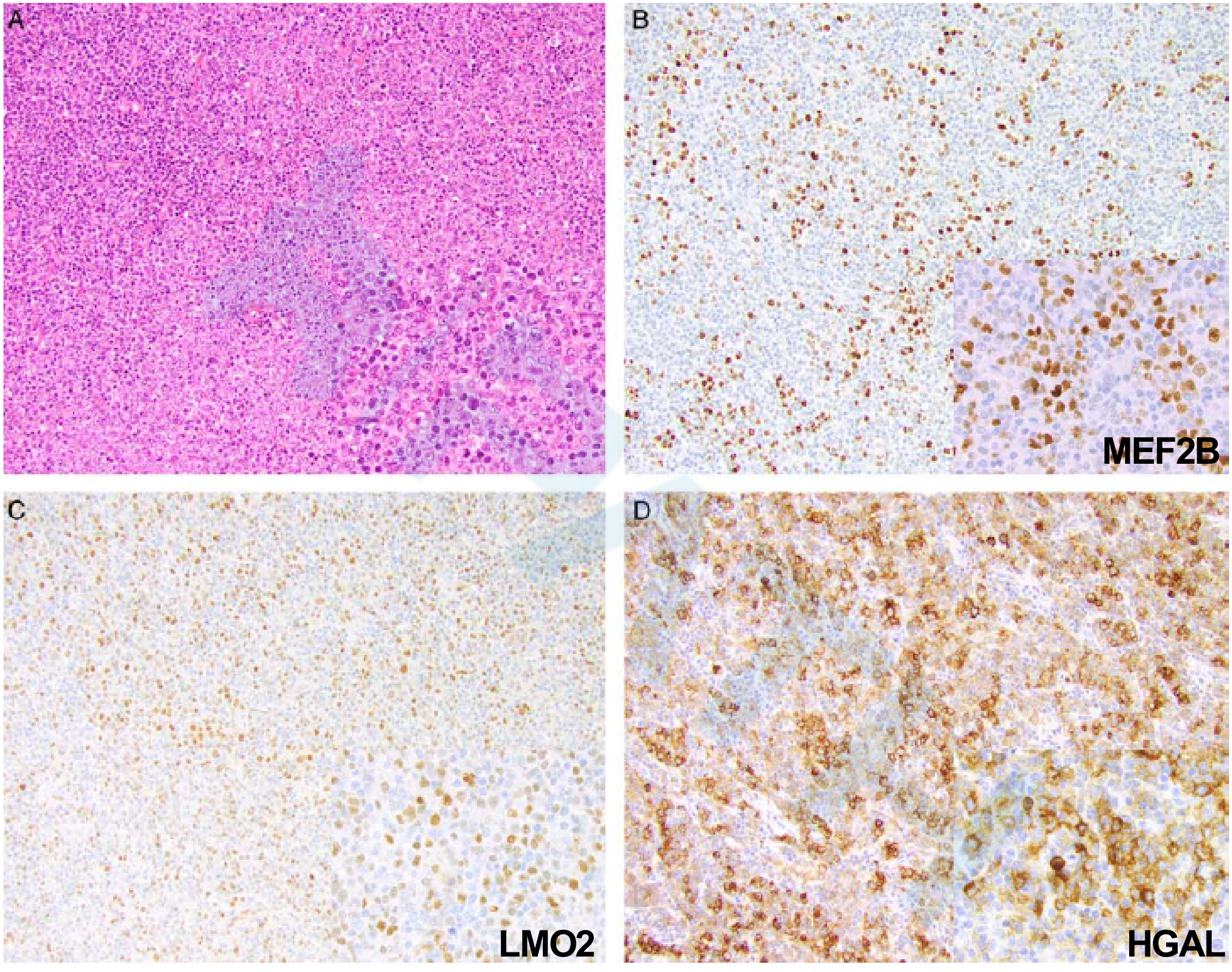


Figure6. GC型DLBCL，CD10+、BCL6-、MUM1-

TABLE 1. MEF2B, LMO2, and HGAL in 156 B-Cell NHL

Lymphoma	MEF2B$^+$ (n/N [%])	LMO2$^+$ (n/N [%])	HGAL$^+$ (n/N [%])	BCL6$^+$ (n/N [%])	CD10$^+$ (n/N [%])
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Grade 3B	6/6 (100)	4/5 (80)	5/5 (100)	6/6 (100)	4/6 (67)
MALT	0/11 (0)	1/11 (9)	0/11 (0)	0/11 (0)	0/11 (0)
NMZL	0/8 (0)	4/8 (50)	4/8 (50)	1/8 (13)	0/8 (0)
SMZL	2/24 (8)	1/24 (4)	2/24 (8)	1/24 (4)	0/24 (0)
SDBL	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)
MCL	8/9 (89)	ND	ND	0/6 (0)	0/9 (0)
CLL/SLL	1/10 (10)	ND	ND	0/3 (0)	0/10 (0)
DLBCL	38/44 (86)	28/40 (70)	29/41 (71)	38/43 (88)	17/44 (39)
GC-DLBCL	22/25 (88)	19/22 (86)	18/23 (78)	23/24 (96)	17/25 (68)
Non–GC-type DLBCL	16/19 (84)	9/18 (50)	11/18 (61)	15/19 (79)	0/19 (0)
BL	10/10 (100	4/10 (40)	10/10 (100)	10/10 (100)	10/10 (100)
B-LL	0/7 (0)	ND	ND	1/2 (50)	4/7 (57)

*Cases included were enriched for CD10$^-$ FL.

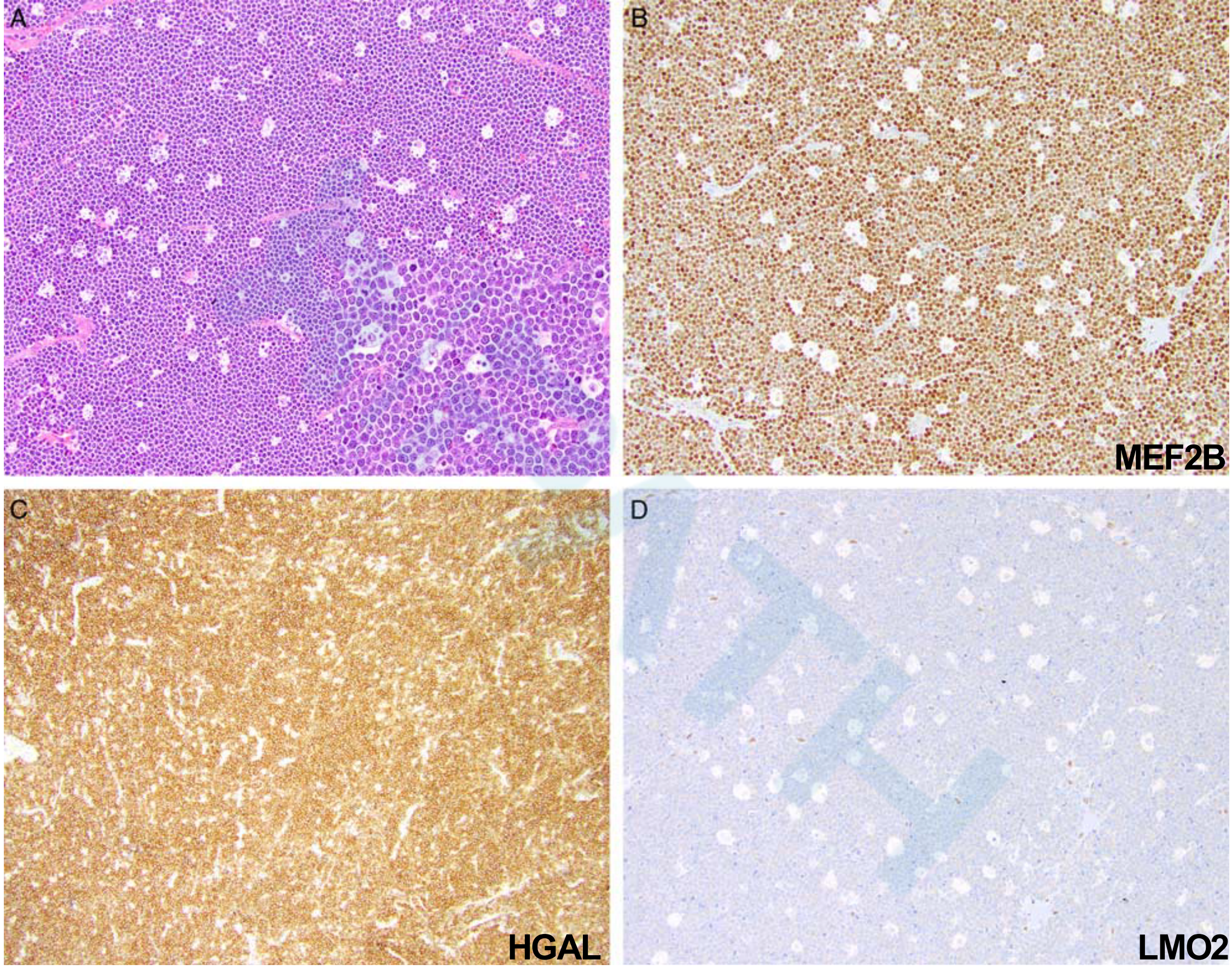

Figure7. BL

TABLE 1. MEF2B, LMO2, and HGAL in 156 B-Cell NHL

Lymphoma	MEF2B$^+$ (n/N [%])	LMO2$^+$ (n/N [%])	HGAL$^+$ (n/N [%])	BCL6$^+$ (n/N [%])	CD10$^+$ (n/N [%])
FL	31/31 (100)	26/30 (87)	29/30 (97)	31/31 (100)	21/31 (68)*
Grade 1-2/3	19/19 (100)	17/19 (89)	18/19 (95)	19/19 (100)	11/19 (58)
Grade 3A	6/6 (100)	5/6 (83)	6/6 (100)	6/6 (100)	6/6 (100)
Grade 3B	6/6 (100)	4/5 (80)	5/5 (100)	6/6 (100)	4/6 (67)
MALT	0/11 (0)	1/11 (9)	0/11 (0)	0/11 (0)	0/11 (0)
NMZL	0/8 (0)	4/8 (50)	4/8 (50)	1/8 (13)	0/8 (0)
SMZL	2/24 (8)	1/24 (4)	2/24 (8)	1/24 (4)	0/24 (0)
SDBL	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)
MCL	8/9 (89)	ND	ND	0/6 (0)	0/9 (0)
CLL/SLL	1/10 (10)	ND	ND	0/3 (0)	0/10 (0)
DLBCL	38/44 (86)	28/40 (70)	29/41 (71)	38/43 (88)	17/44 (39)
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BL	10/10 (100	4/10 (40)	10/10 (100)	10/10 (100)	10/10 (100)
B-LL	0/7 (0)	ND	ND	1/2 (50)	4/7 (57)

*Cases included were enriched for CD10$^-$ FL.

	MEF2B	LMO2	HGAL	BCL6
敏感度	100%	87%	97%	100%
特异度	95%	86%	86%	95%

MZL *vs.* FL

	MEF2B	LMO2	HGAL
敏感度	88%	86%	78%
特异度	16%	50%	39%

GC型DLBCL

	MEF2B	BCL6
敏感度	95%	98%
特异度	70%	76%

所有B细胞NHL

讨论

- 对于鉴别诊断FL与MZL，MEF2B的敏感度与特异度优于LMO2和HGAL
- 伴有浆样分化的CD10-FL，MEF2B染色比BCL6更强更广泛，可能与正常浆细胞表达MEF2B有关
- 在其他B细胞NHL和非淋巴瘤淋巴组织中，MEF2B不具有完全的GC特异性，与BCL6相似
- MCL中，MEF2B与SOX11表达相同，与两者的靶点基因都是BCL6有关

结论

优点：MEF2B对鉴别诊断FL与MZL具有重要作用，且优于其他标记物，包括BCL6、HGAL和LMO2

缺点：MEF2B对其他GC源性细胞并非完全特异

Thanks for your attention!