Morphologic Patterns and the Correlation With MYD88 L265P , CD79B Mutations in Primary Adrenal Diffuse Large B-Cell Lymphoma

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Background

◆**弥漫大B细胞淋巴瘤，非特殊类型（DLBCL NOS）**

弥漫大B细胞淋巴瘤（DLBCL）是一类由大B淋巴样细胞构成的肿瘤，呈弥漫性生长模式，肿瘤细胞的细胞核相当于甚至超过正常巨噬细胞的细胞核，或为正常淋巴细胞核的2倍以上。

◆**ICD-0 编码 9680/3**

◆**流行病学**

好发于老年人，中位年龄为70岁，也可见于儿童和青年，男性略高于女性。

◆**部位**

患者可以表现为结内或者结外累及。40%以上原发于结外，胃肠道(胃和回盲部)是最常见的结外好发部位，也可见于其他任何部位，如:骨、睾丸、脾脏、唾液腺、甲状腺、肝脏、肾脏和肾上腺等。

◆临床表现

患者通常表现为单个或者多个淋巴结迅速肿大，或者是结外部位出现迅速肿大的瘤块，约半数患者处于临床I期或II期，大部分没有明显临床症状，而且，症状的出现取决于肿瘤的累及部位。

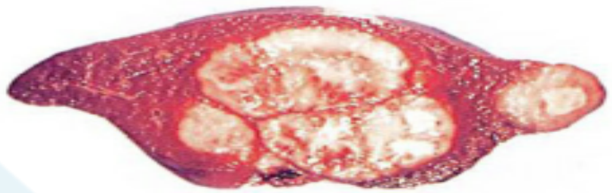


图 10.82　累及脾脏的大 B 细胞淋巴瘤，可见大瘤结节。

◆形态学

淋巴结病变表现为大淋巴细胞弥漫性增生，淋巴结结构完全(最常见模式)或部分破坏，部分累及滤泡间区，较少累计淋巴窦。结外组织经常受累，有时可以看到粗大的胶原纤维。

Diffuse large B-cell lymphoma,NOS

- Morphological variants
  - Centroblastic
  - Immunoblastic
  - Anaplastic
  - Other rare variants
- Molecular subtypes
  - Germinal centre B-cell subtype
  - Activated B-cell subtype

Other lymphomas of large B cells

- T-cell/histiocyte-rich large B-cell lymphoma
- Primary diffuse large B-cell lymphoma of the CNS
- Primary cutaneous diffuse large B-cell lymphoma,leg type
- EBV-positive diffuse large B-cell lymphoma,NOS
- Diffuse large B-cell lymphoma associated with chronic inflammation
- Lymphomatoid granulomatosis
- Large B-cell lymphoma with *IRF4* rearrangement
- Primary mediastinal (thymic)large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- HHV8-positive diffuse large B-cell lymphoma
- Primary effusion lymphoma

High-grade B-cell lymphoma

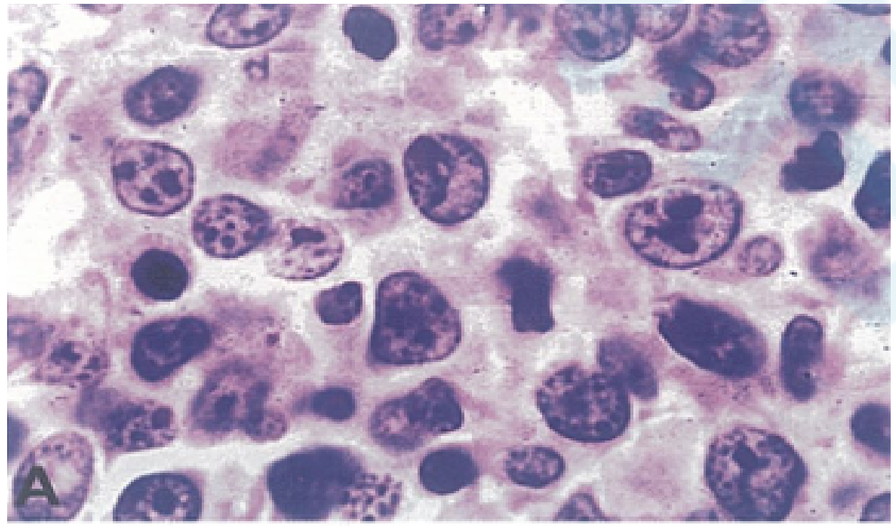
- High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
- High-grade B-cell lymphoma,NOS

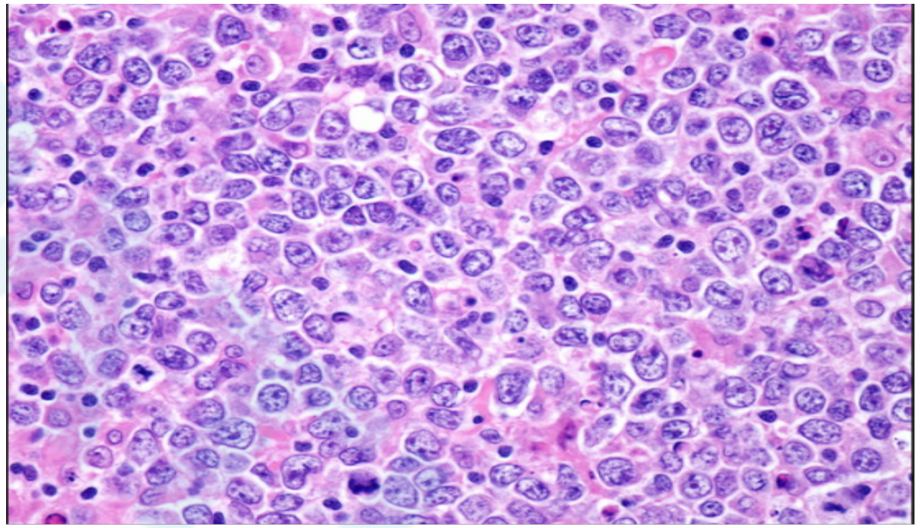
B-cell lymphoma,unclassifiable

- B-cell lymphoma,unclassifiable,with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma

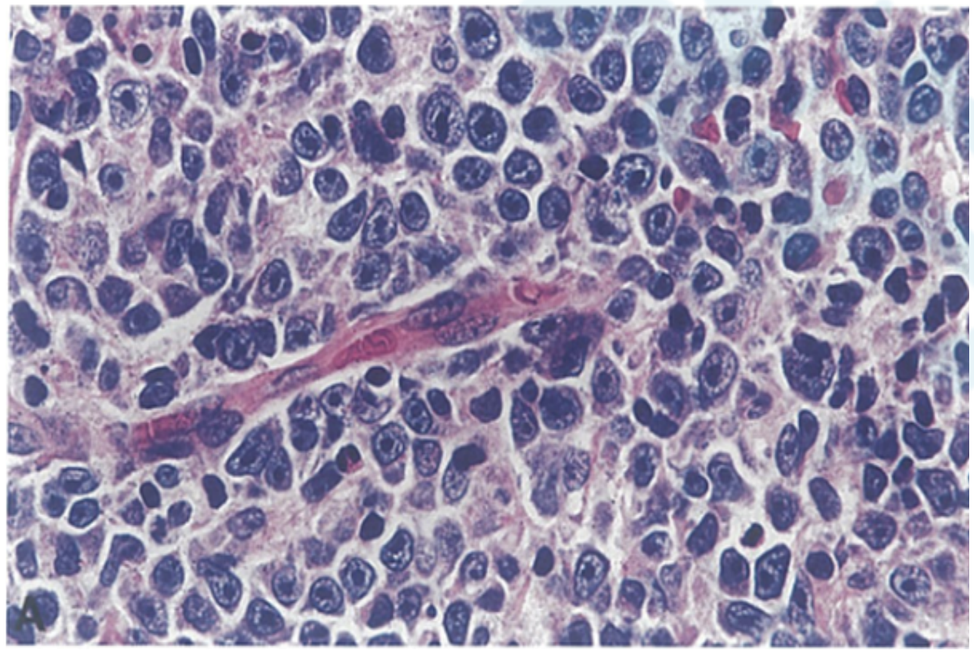
弥漫大B细胞淋巴瘤，非其他特殊类型（NOS）

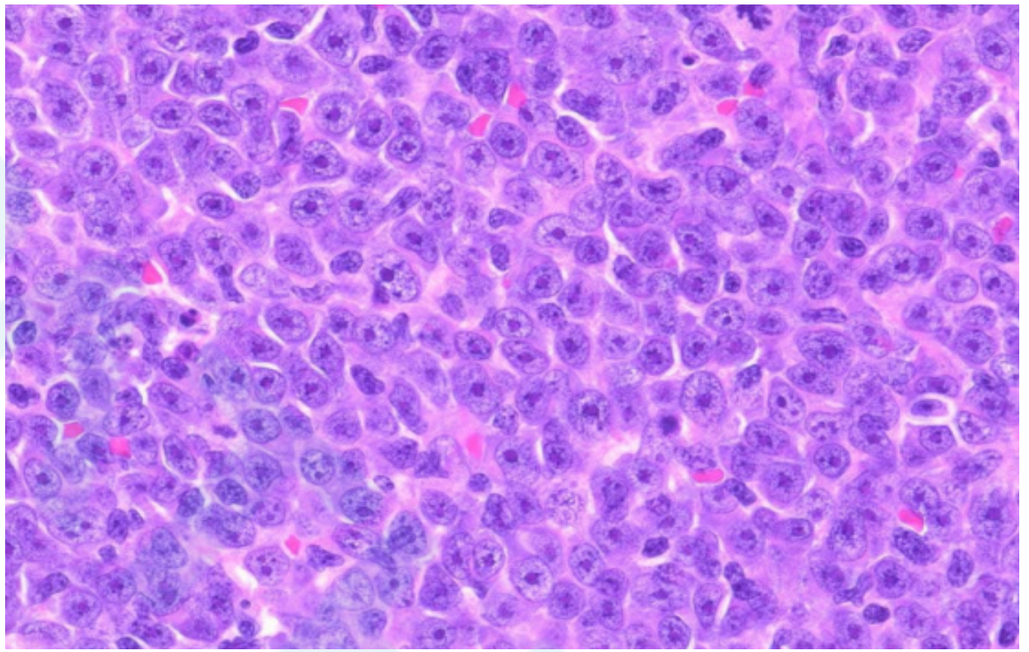
形态学变异型



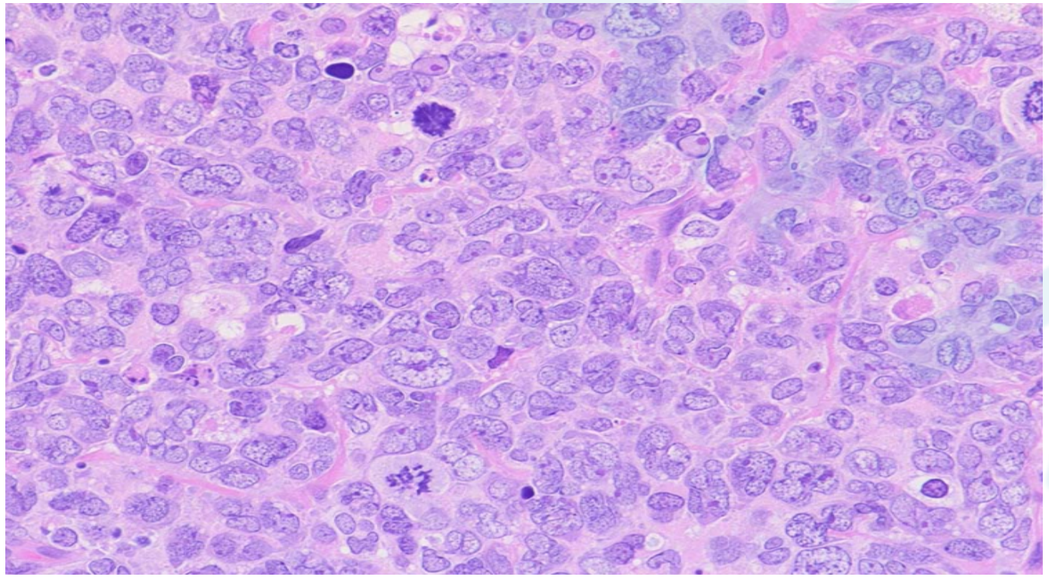


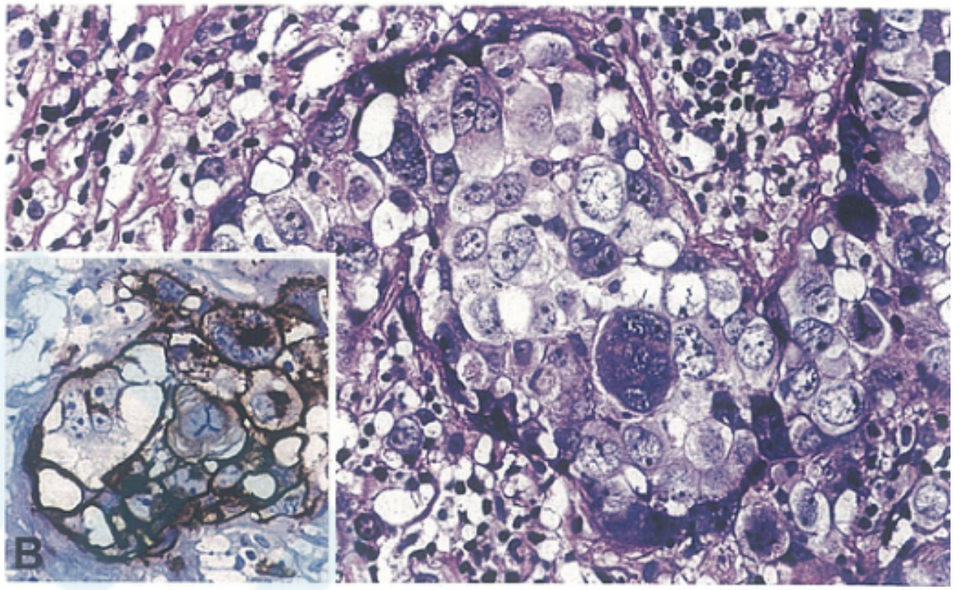
- **中心母细胞变异型：**最常见，表现为中等至大的淋巴细胞，核呈圆形、椭圆形或空泡样，染色质细腻，有2-4个靠近核膜的核仁，胞浆通常较少，双嗜性或嗜碱性，部分病例肿瘤的细胞形态学单一，大部分（>90%）由中心母细胞构成，大部分病例肿瘤细胞形态学多样，由中心母细胞和免疫母细胞混合而成。





◆**免疫母细胞变异型：**在这种类型中，90%以上的细胞为免疫母细胞，肿瘤细胞形态学表现一致，核仁居中，胞浆丰富嗜碱性，有时，还可以见到浆样分化的免疫母细胞。





- **间变型：**此种变异性的特点是细胞中等偏大，呈圆形、椭圆形或多角形，核形奇异，不规则，部分与霍奇金/R-S细胞相似，肿瘤细胞可呈窦内生长（右图示）或紧密生长模式，形态类似未分化癌，插入图片显示肿瘤细胞CD20呈膜和核旁阳性。

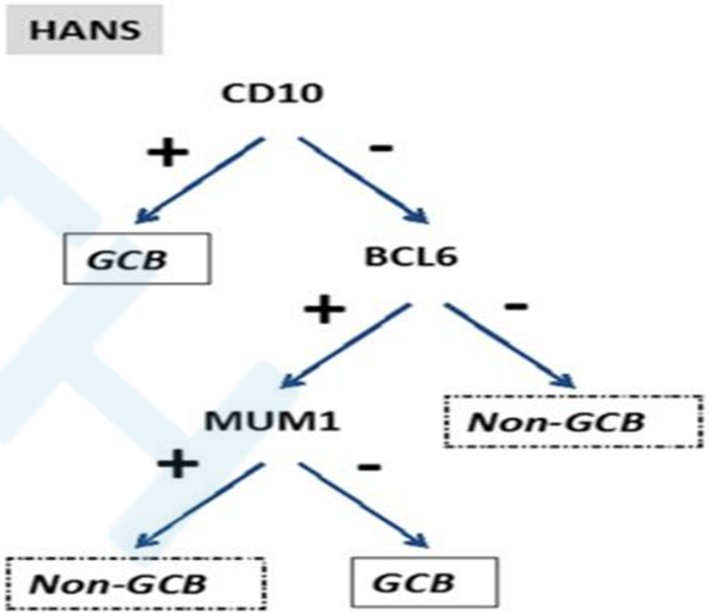
- **罕见的形态学变异型：**少数有黏液样基质及纤维间质，少数病例可形成假菊形团样结构，有时，肿瘤细胞还可表现为梭形或印戒样细胞特征。

分子亚型

- **生发中心B细胞（GCB）**
- **活化B细胞亚型（ACB）**

根据免疫表型分类的DLBCL NOS

- **生发中心样亚型（GCB）**
- **非生发中心样亚型（Non-GCB）**



- 结外DLBCL约占DLBCL的30%，PA-DLBCL罕见
- 几乎所 有的PA-DLBCL都被归类为非GCB亚型
- MYD88、CD79B以及CARD11等基因突变在非GCB亚型DLBCL中报道的频率高于GCB亚型

MATERIALS AND METHODS

- 病例选择
- 免疫组化、EBER染色以及荧光原位杂交分析。
- DNA提取、PCR及Sanger 测序。
- 数据分析

RESULTS

Clinical Features of PA-DLBC

TABLE 1. The Clinical Features of Primary Adrenal Diffuse Large B-Cell Lymphoma

Items	Number (n/N) (%)
Age (y), median (range)	62 (39-84)
Sex	
Male	26/42 (62)
Female	16/42 (38)
B symptoms	16/39 (41)
Site	
Right	8/42 (19)
Left	8/42 (19)
Bilateral	26/42 (62)
Anemia	24/39 (62)
Elevated LDH	33/39 (85)
Adrenal insufficiency	16/35 (46)
Stage	
Early stage (I/II)	9/40 (23)
Advanced stage (III/IV)	31/40 (78)
R-IPI	
Very good	1/39 (3)
Good	9/39 (23)
Poor	29/39 (74)
CNS progression/recurrence	7/40 (18)
Treatment	
Supportive care only	6/42 (14)
R-CHOP/R-CHOP like regimen	36/42 (86)

R-CHOP/R-CHOP like regimen: including standard R-CHOP, dose-adjusted R-CHOP and R-EPOCH.
LDH indicates lactate dehydrogenase.

Pathologic Features of PA-DLBC

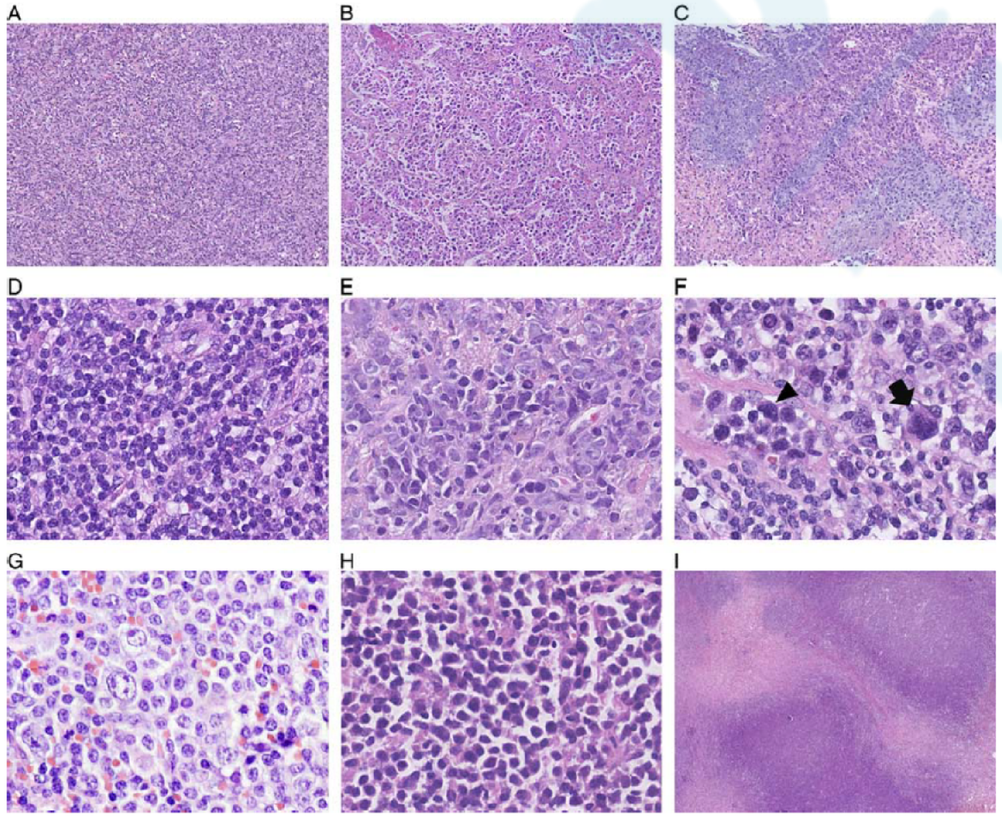


FIGURE 1. Morphologic features of primary adrenal diffuse large B-cell lymphoma. A, Diffuse growth pattern. B, Sinusoidal infiltration pattern. C, Cohesive arrangement pattern. D, Round or ovoid nucleus cells. E, Polygonal nucleus cells with condensed chromatin and inconspicuous nucleolus. F, RS-like cells, binuclear/bilobated cell (arrow) and multilobated cell (arrowhead). G, Round or ovoid cells with dispersed chromatin and obvious nucleolus. H, Round or ovoid cells with condensed chromatin and inconspicuous nucleolus. I, Geographic necrosis (hematoxylin & eosin staining).

TABLE 2. The Pathologic Features of Primary Adrenal Diffuse Large B-Cell Lymphoma

Items	Number (n/N) (%)
Morphology	
Growth pattern	
Diffuse	42/42 (100)
Sinusoidal	11/42 (26)
Cohesive arrangement	16/42 (38)
Cell size	
Large	24/42 (57)
Medium-large	18/42 (43)
Nucleus shape	
Round/ovoid	26/42 (62)
Polygonal	16/42 (38)
Chromatin	
Condensed	21/42 (50)
Dispersed	21/42 (50)
Nucleolus	
Obvious	22/42 (52)
Inconspicuous	20/42 (48)
Necrosis	7/42 (17)
Increased RS-like cells	11/42 (26)
Immunostaining	
Hans algorithms	
GCB	5/42 (12)
Non-GCB	37/42 (88)
BCL2 positive	34/40 (85)
C-MYC positive	24/40 (60)
DEL	22/40 (55)
EBER-ISH	0/42 (0)
Ki-67 (%), median (range)	80 (60-95)
Fluorescence in situ hybridization	
C-MYC abnormalities	0/7 (0)
BCL2 abnormalities	0/7 (0)
BCL6 abnormalities	4/7 (57)

Detection of MYD88 L265P and CD79B (Exon 5)Mutation in PA-DLBCL

◆42例中29例患者进行了MYD88 L265P和CD79B（exon 5）的Sanger测序。

◆29例中7例(24%)显示MYD88突变，15例(52%)发现CD79B突变。

◆4例(14%)同时检测到MYD88 L265P和CD79B(exon5)的突变。

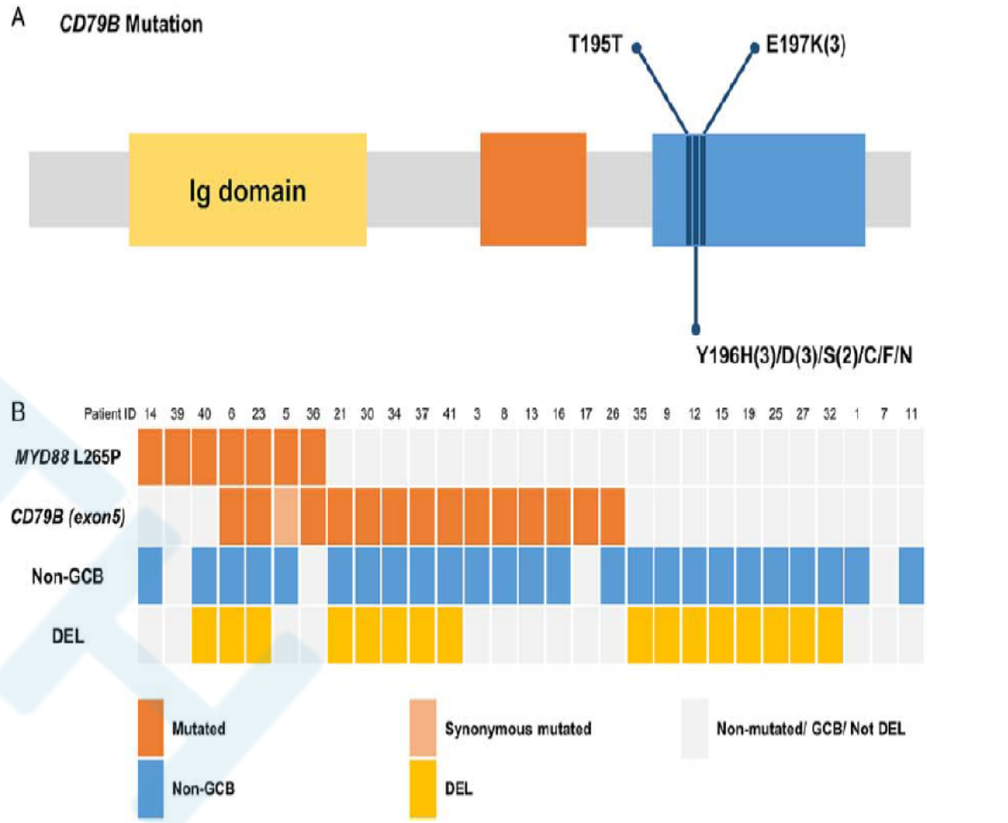
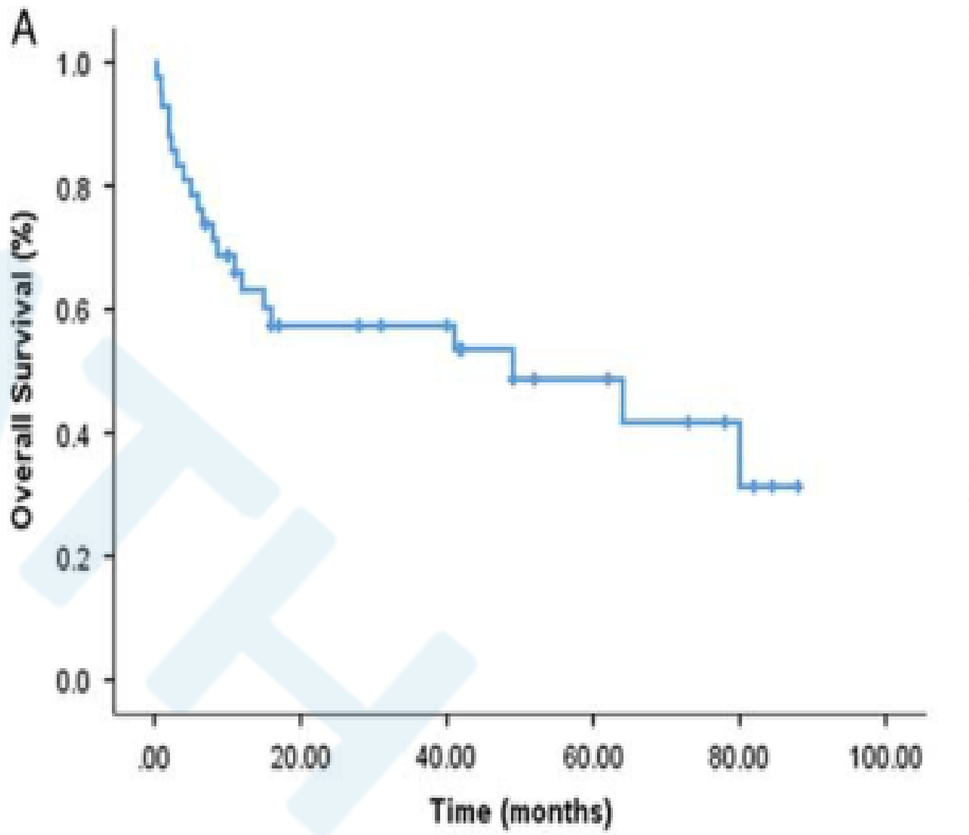


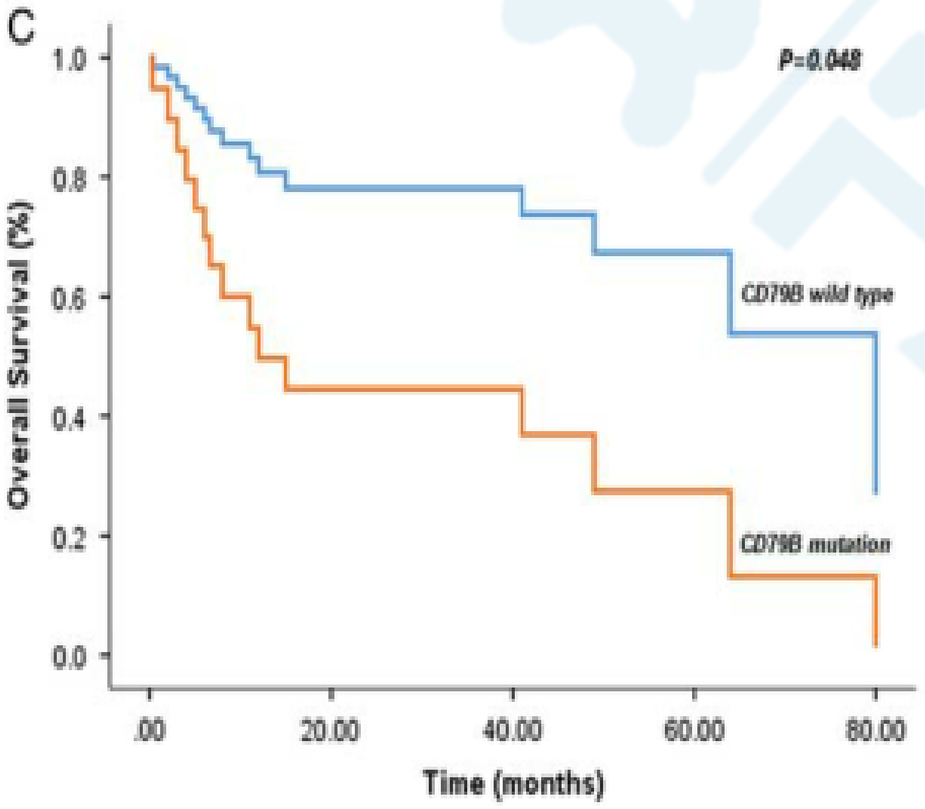
FIGURE 2. The frequency of *MYD88* L265P and *CD79B* (exon 5) mutation in PA-DLBCL. A, Distribution of *CD79B* mutations is shown. The lines show the position of the mutations, and the number of cases is indicated between the brackets when it is > 1. B, Summary of mutation statuses of *MYD88* and *CD79B* in 29 PA-DLBCL.

Survival and Prognostic Factors

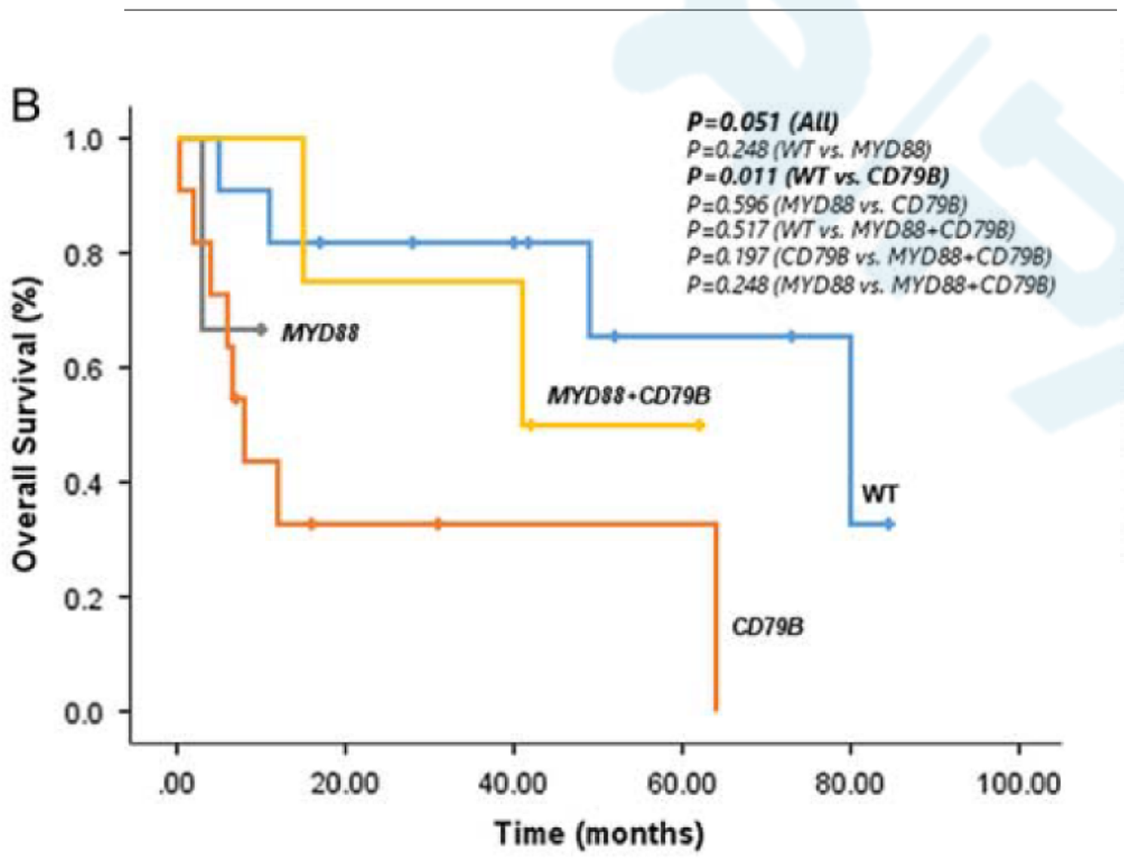
- 随访时间范围(0.3 ~ 88个月)，21例(50%)死于本病。
- 中位OS为49个月，
- OS>1年约占65%。

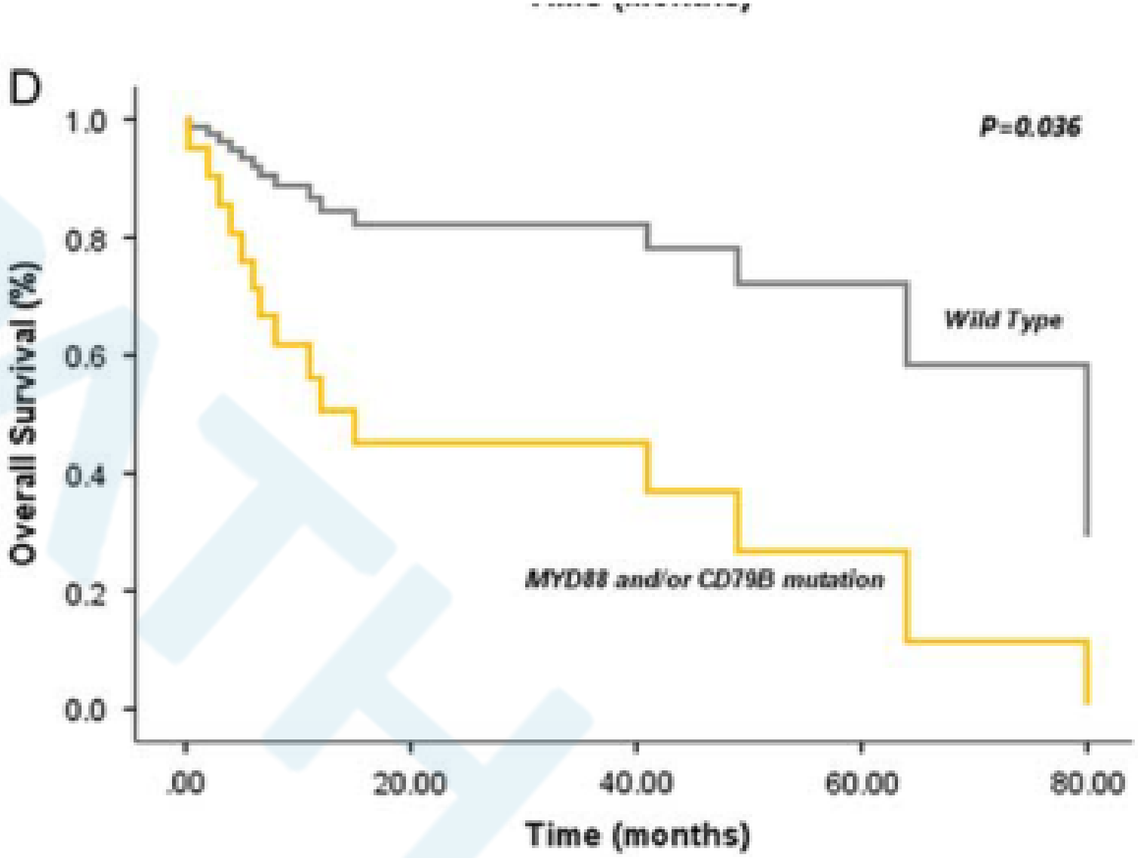


Prognostic Factors of Primary Adrenal Diffuse Large B-Cell Lymphoma



Variables	Unfavorable Factors	Univariate Analysis HR (95% CI)	*P*
Age (y)	≥ 60	2.217 (0.857-5.747)	0.100
B symptoms	Present	1.972 (0.767-5.051)	0.158
LDH	Elevated	4.739 (0.628-35.714)	0.131
Hb	< 12 g/L	1.437 (0.543-3.802)	0.465
Adrenal function	Insufficiency	2.273 (0.848-6.097)	0.103
Bilateral involvement	Present	1.883 (0.726-4.878)	0.193
CNS progression/ recurrence	Present	1.579 (0.453-5.509)	0.473
Stage	III/IV	1.658 (0.545-5.025)	0.373
R-IPI	Poor	1.912 (0.629-5.814)	0.253
Hans algorithms	Non-GCB	1.392 (0.404-4.803)	0.600
BCL2	Positive	2.114 (0.490-9.174)	0.315
C-MYC	Positive	1.697 (0.709-4.064)	0.235
DEL	Present	1.573 (0.658-3.760)	0.309
MYD88	Mutation	1.075 (0.295-3.922)	0.913
CD79B	Mutation	3.268 (1.010-10.638)	**0.048**
Coexist mutation of *MYD88* and *CD79B*	Present	1.265 (0.278-5.766)	0.761
Wild type*	Absent	0.248 (0.067-0.915)	**0.036**


B
Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
Time (months)
P=0.051 (All)
P=0.248 (WT vs. MYD88)
P=0.011 (WT vs. CD79B)
P=0.596 (MYD88 vs. CD79B)
P=0.517 (WT vs. MYD88+CD79B)
P=0.197 (CD79B vs. MYD88+CD79B)
P=0.248 (MYD88 vs. MYD88+CD79B)
MYD88
MYD88+CD79B
WT
CD79B


D
Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
Time (months)
P=0.036
Wild Type
MYD88 and/or CD79B mutation

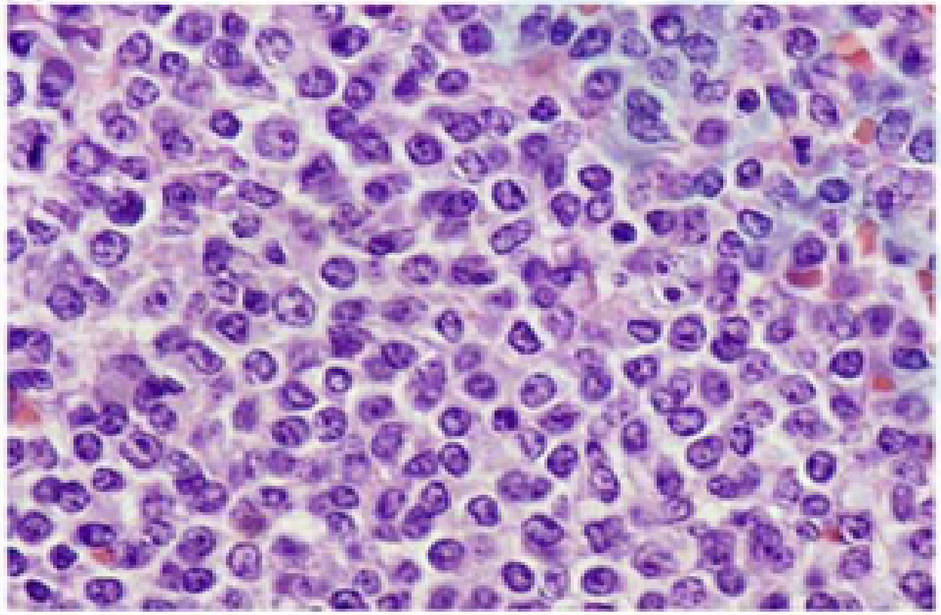
Correlation Between Morphologic Patterns andMYD88 L265P, CD79B Mutations

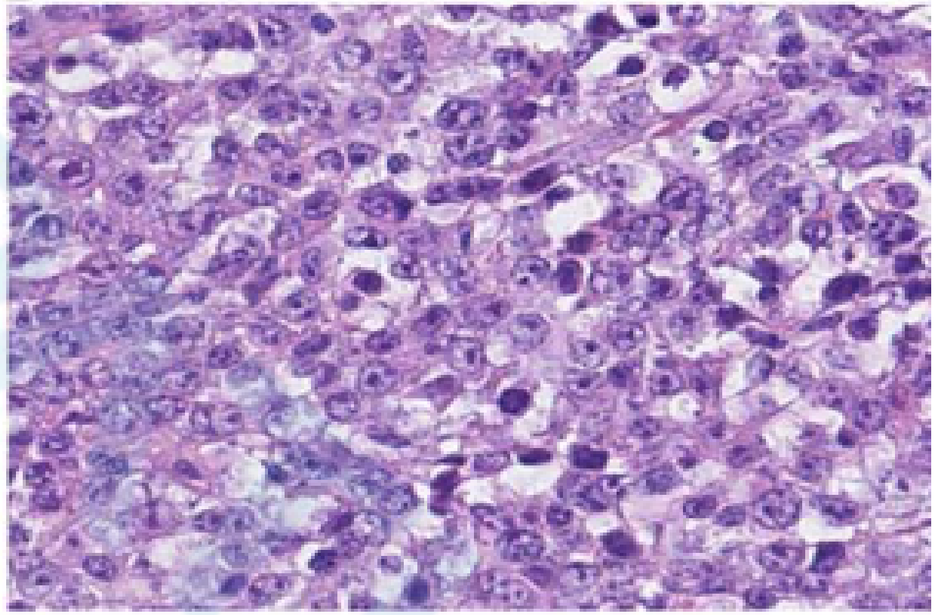
TABLE 4. Correlation Between Morphologic Features and Mutations (n = 29)

	N (%)			N (%)		
	CD79B MU	*CD79B* WT	*P*	*MYD88* L265P	*MYD88* WT	*P*
Growth pattern						
Diffuse	15 (100)	14 (100)	—	7 (100)	22 (100)	—
Sinusoidal	6 (40)	3 (21)	0.280	5 (71)	4 (18)	**0.008**
Cohesive arrangement	12 (86)	0 (0)	**< 0.001**	3 (43)	9 (41)	0.927
Cell size			0.876			0.430
Large	9 (60)	8 (57)		5 (71)	12 (55)	
Medium-large	6 (40)	6 (43)		2 (29)	10 (45)	
Nucleus shape			**< 0.001**			0.927
Round/ovoid	3 (20)	14 (100)		4 (57)	13 (59)	
Polygonal	12 (80)	0 (0)		3 (43)	9 (41)	
Chromatin			**< 0.001**			0.904
Condensed	14 (93)	2 (14)		4 (57)	12 (55)	
Dispersed	1 (7)	12 (86)		3 (43)	10 (45)	
Nucleolus			**< 0.001**			0.742
Obvious	2 (20)	12 (86)		3 (43)	11 (50)	
Inconspicuous	13 (80)	2 (14)		4 (57)	11 (50)	
Necrosis	1 (7)	3 (21)	0.249	2 (29)	2 (9)	0.193
Increased RS-like cells	4 (27)	3 (21)	0.742	7 (100)	0 (0)	**< 0.001**

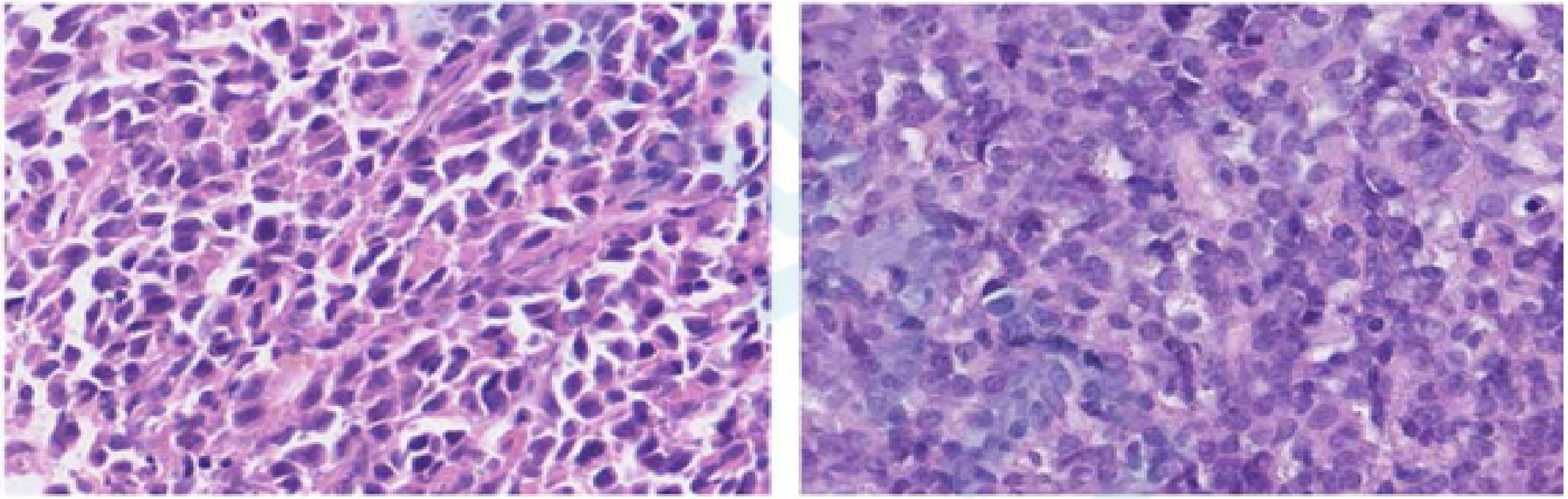
Bold value indicates statistically significant ($P < 0.05$).
MU indicates mutation; WT, wild type.

divided the 42 cases into 4 cate-gories according to the correlation between morphologic features and genetic changes

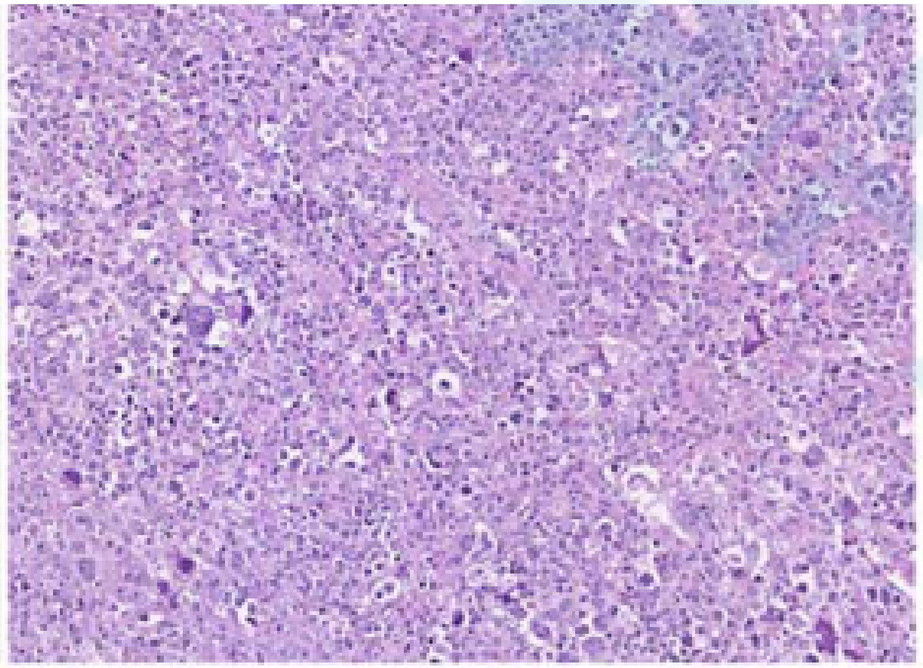


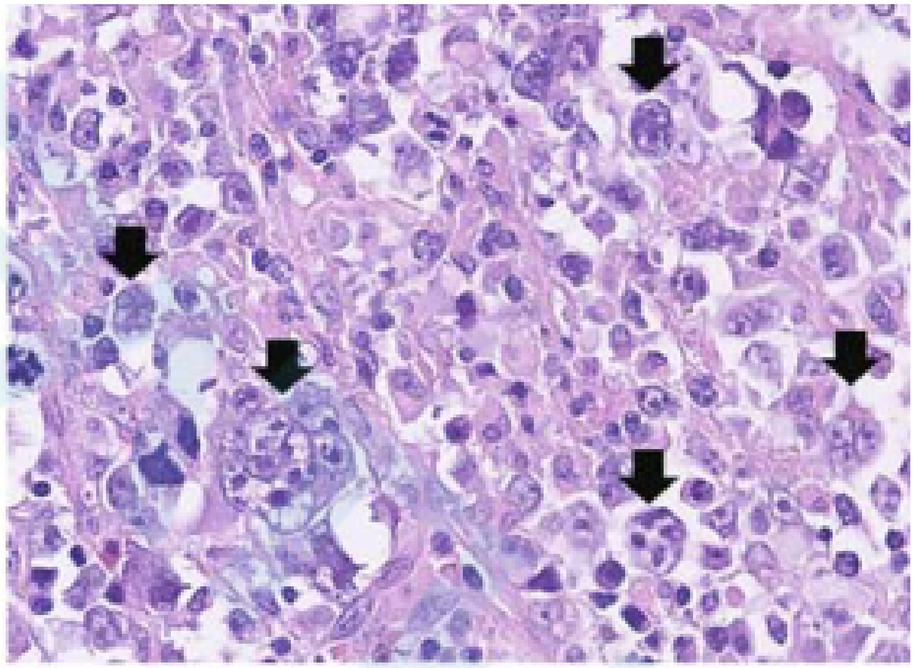


common type **(n=16, asso-ciated with no mutation of MYD88 L265P or CD79B [exon5]:**肿瘤细胞呈大或者中等大小，形状圆形或卵圆形，染色质分散，1个或数个明显的核仁，这种类型中包含了中心母细胞变异型和免疫母细胞变异型。

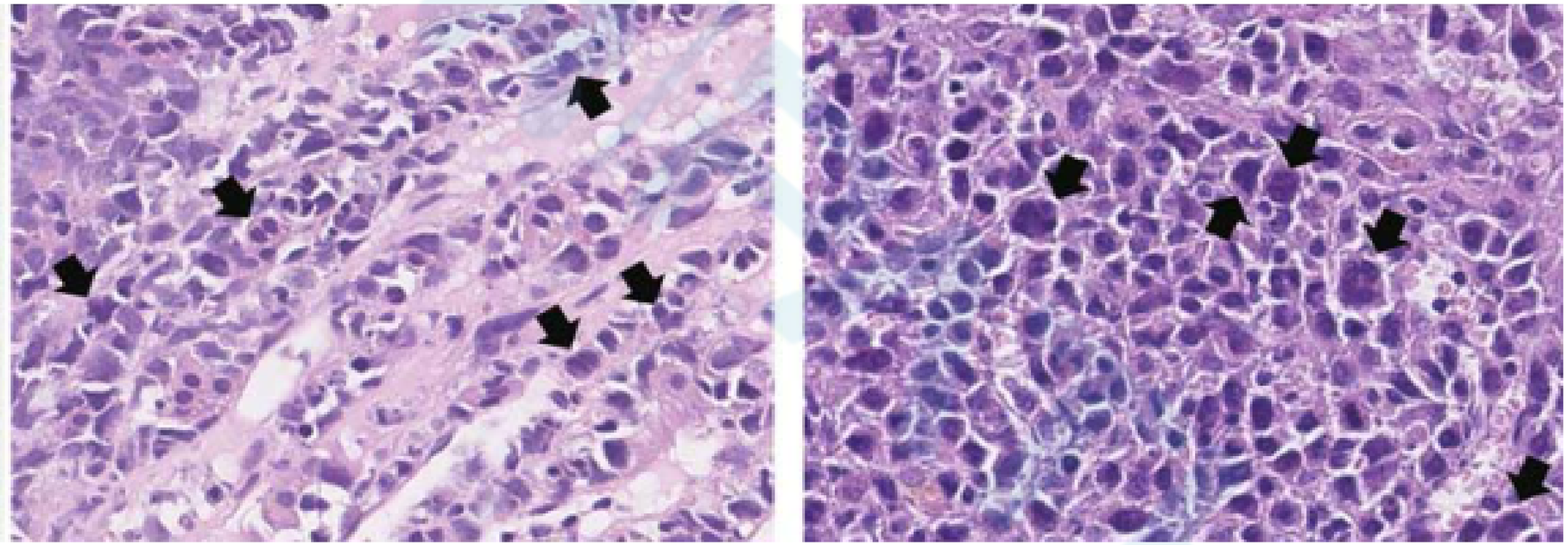


NEC-like type **(n=15, associated with mutation of CD79B [exon 5])**:这种类型的大多数典型细胞具有均匀的多边形细胞核、浓缩的染色质和不明显的核仁，少数细胞呈中-大圆形核，呈“盐-胡椒”样。





RS-like cell type **(n=6, associated with mutation of MYD88 L265P):**在这种类型中，类似于RS细胞的双核和/或多核细胞散在中心母细胞或免疫母细胞背景中，数量 ≥5%。



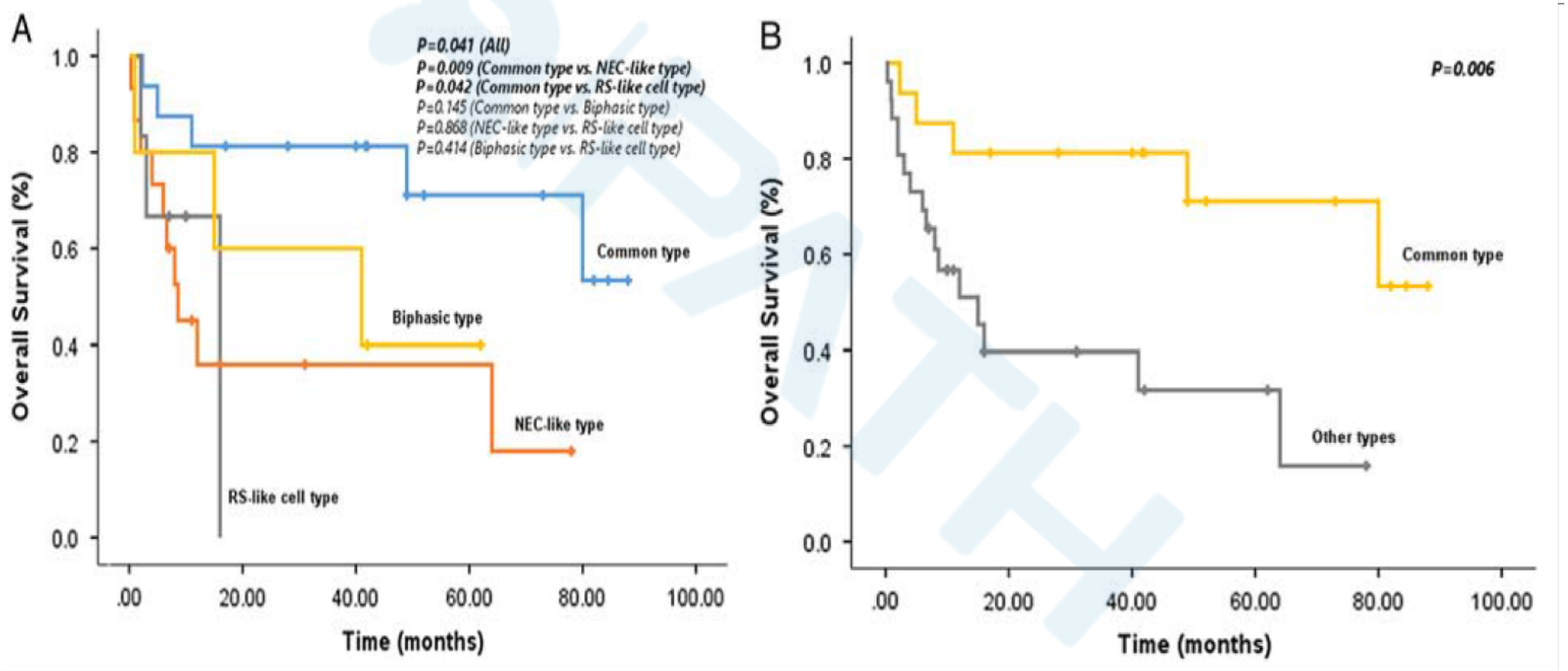
biphasic type **(n=5, associated with double mutation of MYD88 L265P and CD79B [exon 5]):**该类型表现为NEC-like type和 RS-like cell type的复合形态学特征，RS-like cells散在分布NEC-like背景中，另外RS样细胞也可见染色质浓缩，核仁不明显。

TABLE 5. Clinicopatholgic Features of Primary Adrenal Diffuse Large B-Cell Lymphoma in 4 Morphologic Categories

Items	n/N (%) Common Type	NEC-like Type	RS-like Cell Type	Biphasic Type	*P*
Age (y), median (range)	59.5 (43-79)	63 (41-84)	63 (39-68)	74 (59-82)	0.586
Sex					0.821
Male	9/16 (56)	9/15 (60)	4/6 (67)	4/5 (80)	
Female	7/16 (44)	6/15 (40)	2/6 (33)	1/5 (20)	
B symptoms	2/16 (13)	9/13 (69)	3/5 (60)	2/5 (40)	**0.012**
Site					0.212
Right	6/16 (38)	1/15 (7)	0/6 (0)	1/5 (20)	
Left	2/16 (12)	4/15 (27)	1/6 (17)	1/5 (20)	
Bilateral	8/16 (50)	10/15 (66)	5/6 (83)	3/5 (60)	
CNS progression/recurrence	3/16 (19)	1/14 (7)	3/5 (60)	0/5 (0)	**0.036**
Anemia	8/16 (50)	9/13 (69)	3/5 (60)	4/5 (80)	0.610
Elevated LDH	12/16 (75)	13/13 (100)	4/5 (80)	4/5 (80)	0.320
Adrenal insufficiency	6/16 (38)	7/12 (58)	2/3 (67)	1/4 (25)	0.519
Stage					0.120
Early stage (I/II)	6/16 (38)	1/13 (8)	0/5 (0)	2/5 (40)	
Advanced stage (III/IV)	10/16 (62)	12/13 (92)	5/5 (100)	3/5 (60)	
R-IPI					0.133
Very good	1/16 (6)	0/13 (0)	0/5 (0)	0/5 (0)	
Good	5/16 (32)	1/13 (8)	0/5 (0)	2/5 (40)	
Poor	10/16 (62)	12/13 (92)	5/5 (100)	3/5 (60)	
Non-GCB	14/16 (88)	14/15 (93)	5/6 (83)	4/5 (80)	0.855
BCL2	13/15 (87)	13/14 (93)	4/6 (67)	4/5 (80)	0.522
C-MYC	11/15 (73)	6/14 (43)	3/6 (50)	4/5 (80)	0.289
DEL	10/15 (67)	6/14 (43)	3/6 (50)	3/5 (60)	0.648
Ki-67 (%), median (range)	85 (60-95)	80 (70-90)	75 (70-90)	75 (60-85)	0.602
Mutation					**< 0.001**
MYD88	0/11 (0)	0/11 (0)	3/3 (100)	0/4 (0)	
CD79B	0/11 (0)	11/11 (100)	0/3 (0)	0/4 (0)	
MYD88+CD79B	0/11 (0)	0/11 (0)	0/3 (0)	4/4 (100)	
Wild type	11/11 (100)	0/11 (0)	0/3 (0)	0/4 (0)	

Bold value indicates statistically significant ($P < 0.05$).
LDH indicates lactate dehydrogenase.

Common type患者出现B症状的频率低于其他3类患者，RS-like型的患者更容易出现CNS进展/复发


A
P=0.041 (All)
P=0.009 (Common type vs. NEC-like type)
P=0.042 (Common type vs. RS-like cell type)
P=0.145 (Common type vs. Biphasic type)
P=0.868 (NEC-like type vs. RS-like cell type)
P=0.414 (Biphasic type vs. RS-like cell type)
Common type
Biphasic type
NEC-like type
RS-like cell type
Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
Time (months)
B
P=0.006
Common type
Other types
Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
Time (months)

DISCUSSION

◆在本研究中，作者回顾了PA-DLBCL的临床特点以及形态学特征，超过三分之一的病例表现为大细胞的窦内生长/或紧密的生长模式、多形性核和类似低分化癌的特征，因此，当我们观察到这种形态时，应将淋巴瘤作为鉴别诊断。

◆在26%的PA-DLBCL病例中检测到RS样细胞的增加，但其临床意义不明确，有待进一步研究。

◆本文研究提示MYD88 L265P和CD79B(外显子5)突变可能参与了PA-DLBCL肿瘤发生的初始阶段。

◆通过本文研究，作者考虑PA-DLBCL在形成、进展和预后方面可能与其他结外DLBCL不同。

TABLE 6. The Frequencies of *MYD88* and *CD79B* Mutations in Extranodal DLBCL[10–14,29–36]

Entity	Frequency of *MYD88* Mutation (%)	Frequency of *CD79B* Mutation (%)	Frequency of Coexist Mutation (%)
PA-DLBCL	24.1	57.1	13.8
PB-DLBCL	57.1-71.4	32.1-57.1	17.8-28.5
CNS-DLBCL	33-75	6.7-35	0-47.6
PT-DLBCL	42-78.6	18.9-71.4	18.9-64.3
PCDLBCL-LT	50-78	16.7-42.1	16.7-42.1
GI-DLBCL	2.8-20	5.4-10	0-10
IVLBCL	44-77.8	26-33.3	20-33.3

GI-DLBCL indicates gastrointestinal DLBCL; IVLBCL, intravascular large B-cell lymphoma; PB-DLBCL, primary breast DLBCL; PCDLBCL-LT, primary cutaneous DLBCL-leg type; PT-DLBCL, primary testicular DLBCL.

- CD79B突变或MYD88 L265P和CD79B突变的相互作用可能是导致不良预后的原因，需要进一步证实。
- 特定的分子靶向药物可以改善PA-DLBCL的OS。
- 通过形态学和基因突变之间的联系，提出一种新的组织分子分类系统，给诊断及临床治疗提供参考及帮助。
- 由于本文样本量少，尚需进一步研究。

Summary

- 在本文中，作者回顾了42例PA-DLBCL患者的临床病理特征，并使用sanger测序研究了MYD88 L265P和CD79B(外显子5)突变的频率，分析了形态学特征与基因突变之间的相关性，提出一种新分类系统，将其分为了四种类型，新提出的分类系统，可提示基因变化，促进风险分层，指导诊断、治疗和预测预后。

谢谢聆听