Bone Marrow Involvement in Patients With Nodular Lymphocyte Predominant Hodgkin Lymphoma

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de Boer WB, et.al. Am J Surg Pathol.Volume 42, Number 4, April 2018

- Nodular lymphocyte predominant Hodgkin lymphoma(NLPHL) is a erminal center B-cell–derived neoplasm that accounts for ~ 5% of all Hodgkin lymphoma cases.

•NLPHL is distinct from classic Hodgkin lymphoma by its clinical，morphologic, immunophenotypic, and molecular features.

•Most NLPHL patients have localized disease, stage I or II, and an excellent overall outcome.

（一）结节性淋巴细胞为主霍奇金淋巴瘤（NLPHL）

- 起源于生发中心B细胞，可进展为DLBCL（3-14%）
- 形态：主要大结节状、结节-弥漫状生长方式

  散在LP细胞/L&H细胞（“爆米花”细胞）

  大量反应细胞（淋巴细胞、组织细胞、上皮样组织细胞）

肿瘤细胞免疫表型

- 保存比较完整的B细胞免疫表型

大细胞	免疫特征
CD20, 45, 79α	+
CD19	-
OCT-2和Bob.1	+
CD30、CD15	-
BCL-6	+
CD10	-
EMA	+
LMO-2	+

背景成分免疫表型

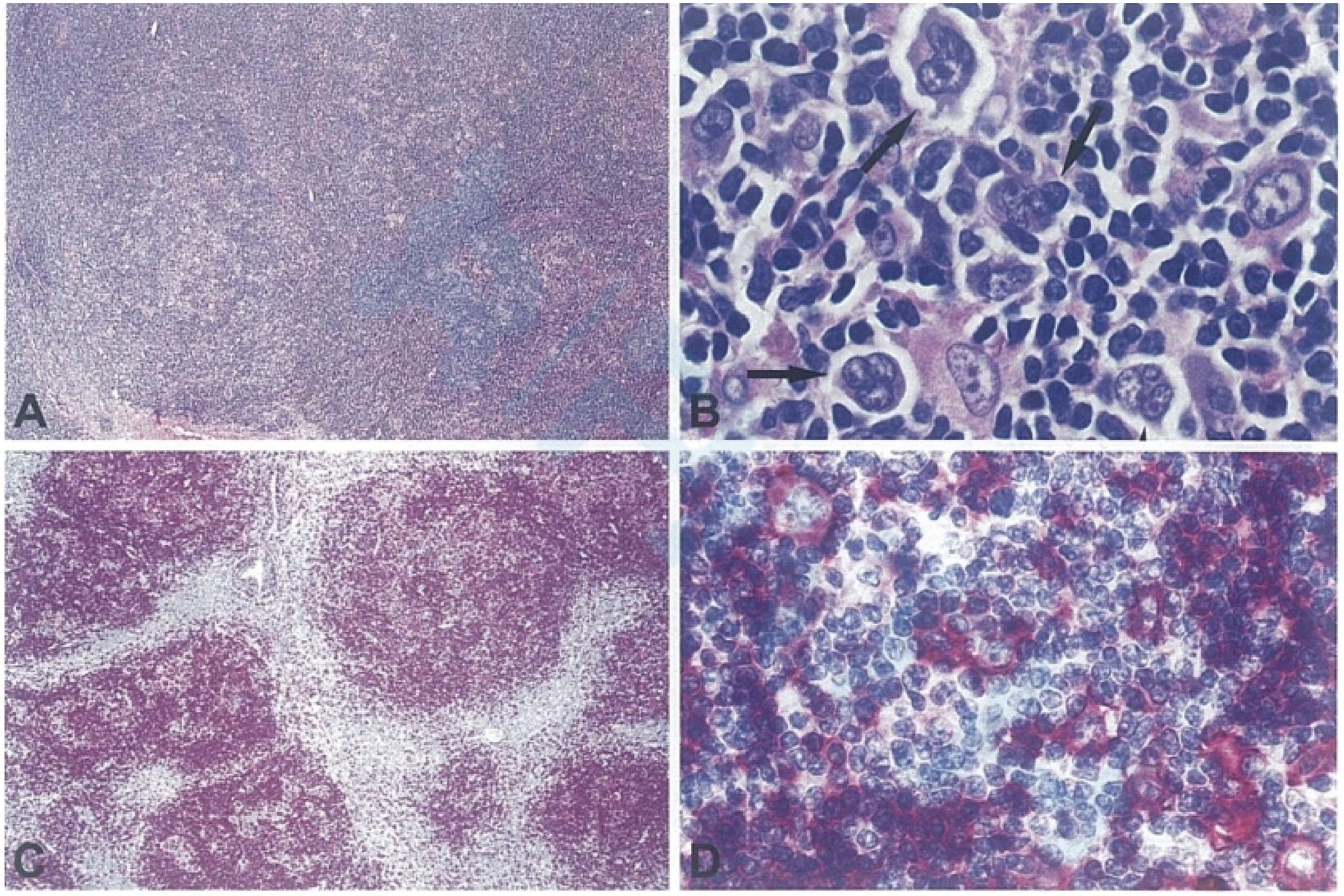
- 背景成分：含有FDC网的大结节

  CD21+、CD35+、CD23-大FDC网

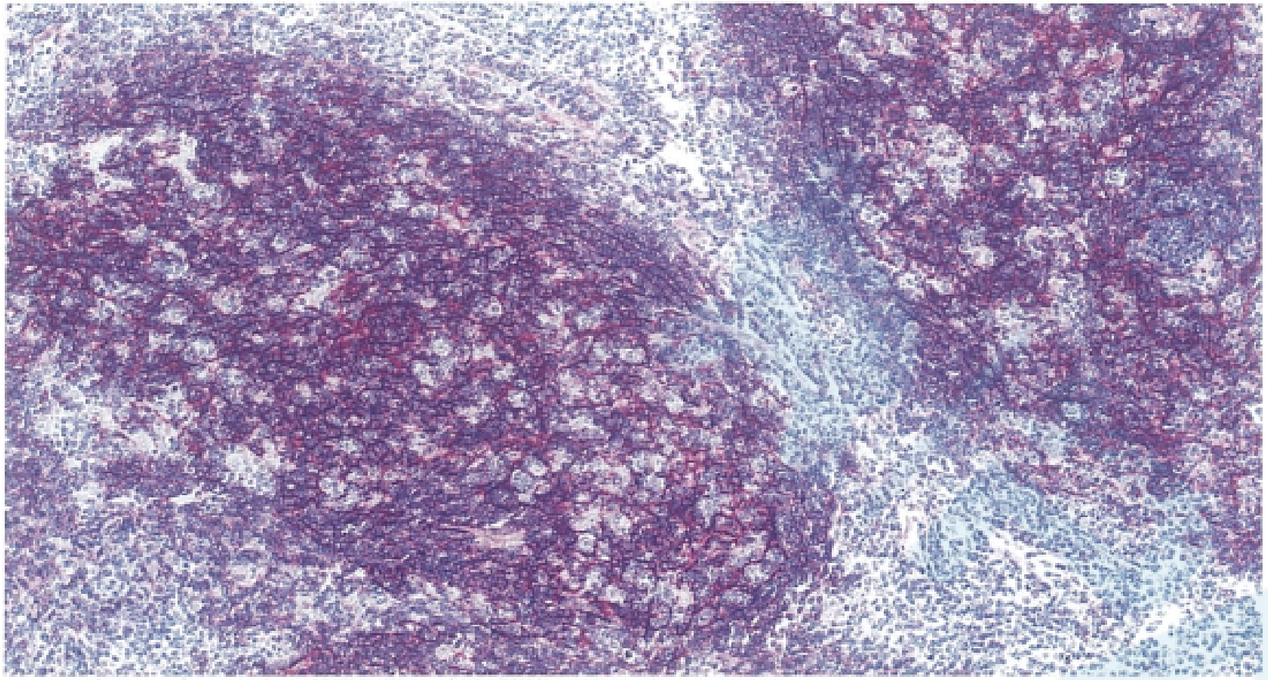
- 背景成分：主要由B细胞构成结节

  小B淋巴细胞CD20+、IgM +、IgD+

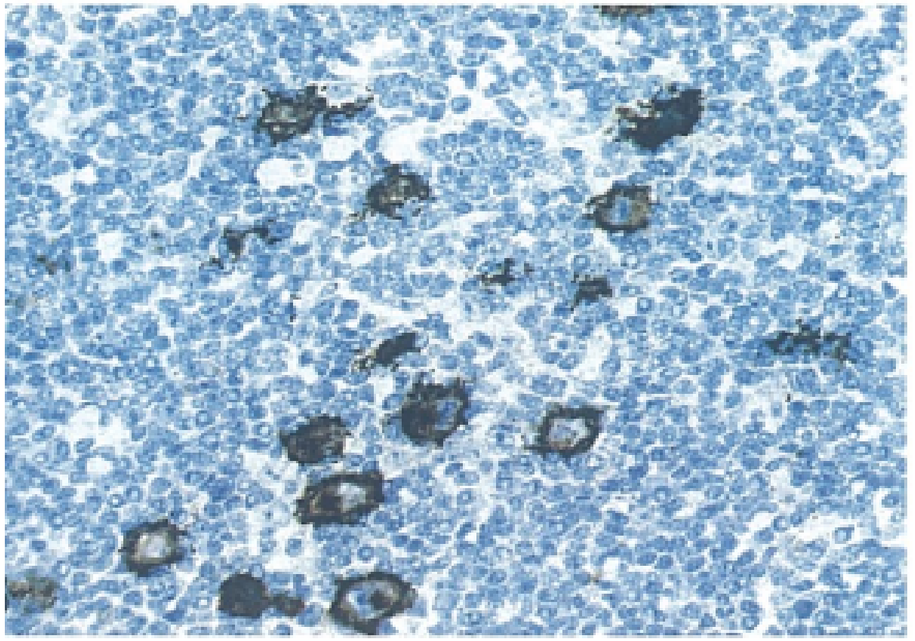
  肿瘤细胞吸引一圈反应T细胞CD3+、CD57+、PD1+



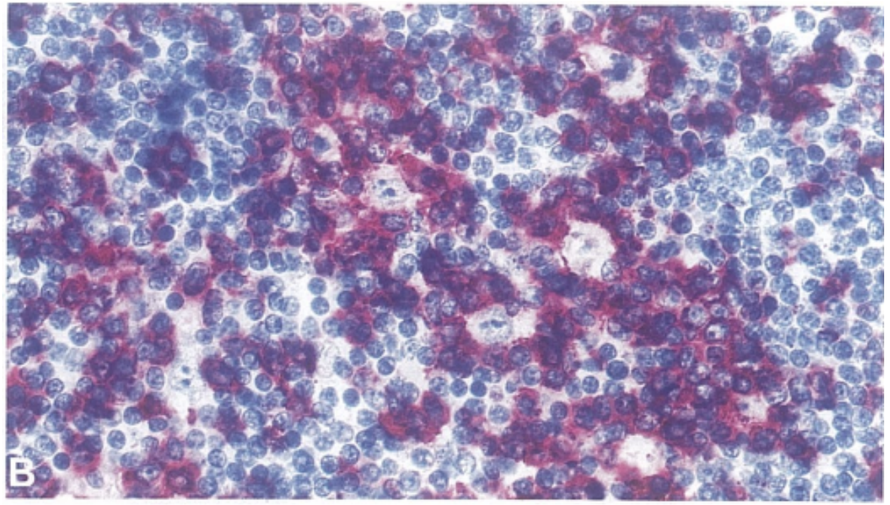
A.结节较滤泡性淋巴瘤的结节大。B.3个“爆米花”样细胞具有分裂的核，背景有小淋巴细胞及一些组织细胞。C.CD20免疫组化显示结节主要是由B细胞构成的。D.高倍镜下，CD20使LP细胞的细胞膜着色。



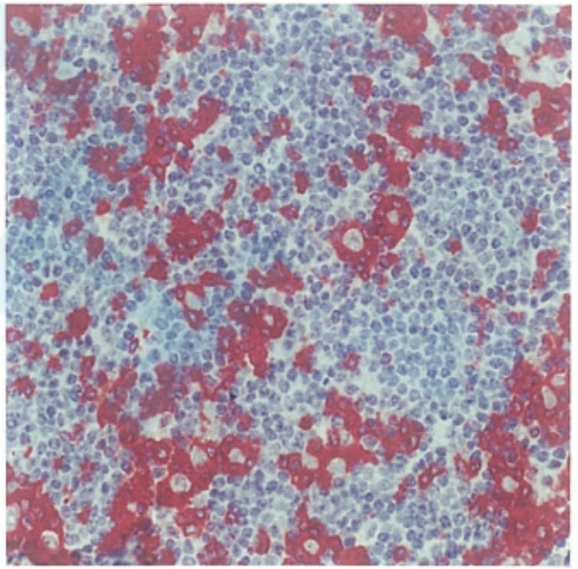
CD21勾勒出结节中的FDC网



LP细胞膜及高尔基体EMA（+）

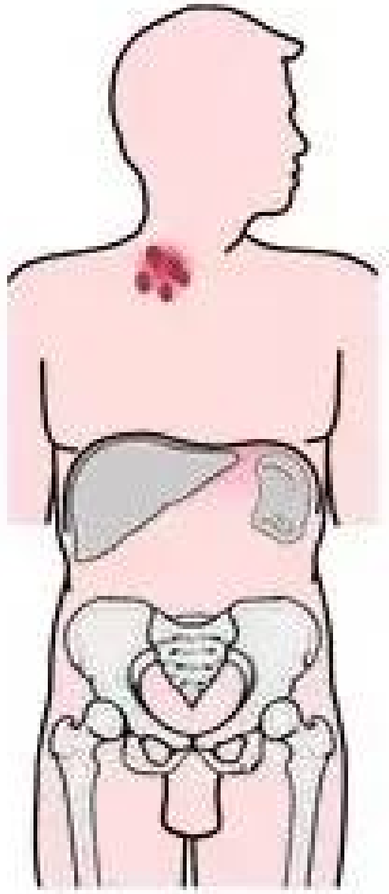


CD57+的T细胞包饶LP细胞。

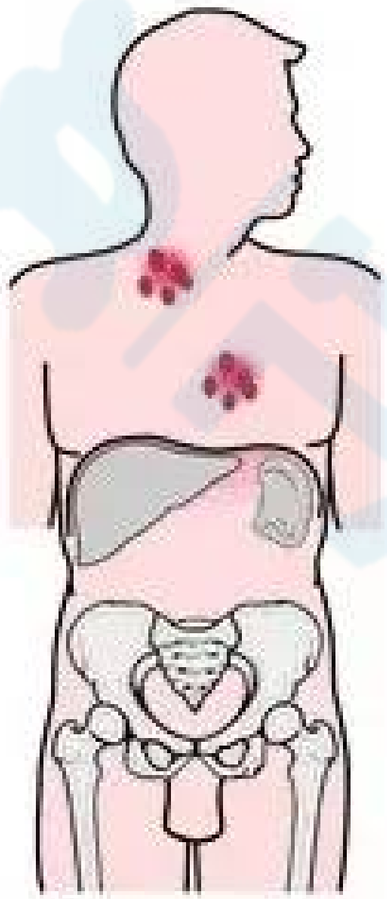


PD1+的T细胞
包绕着LP细胞

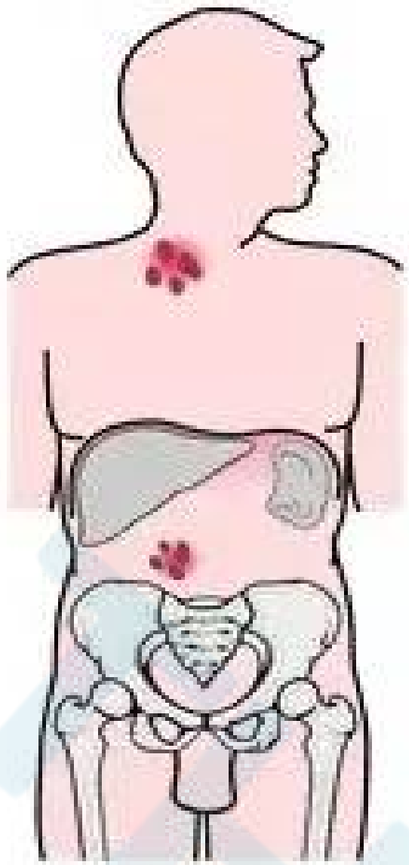
三：HL的分期/AnnArbor分期系统



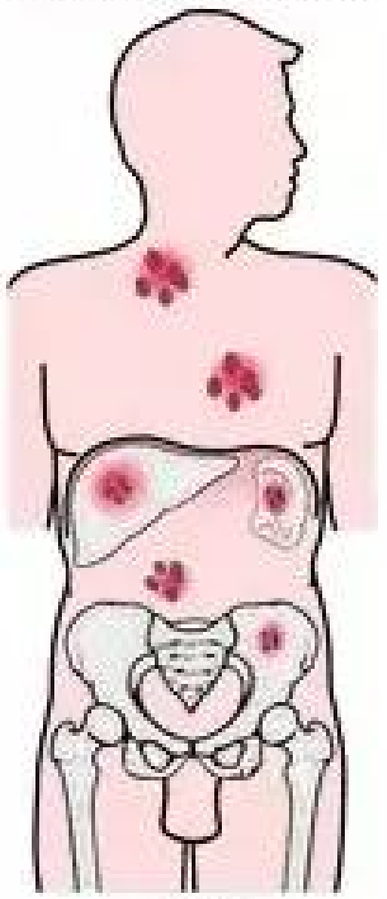
I期
单一淋巴结或
淋巴结组受累



II期
横膈同侧两个及以
上部位淋巴结受累



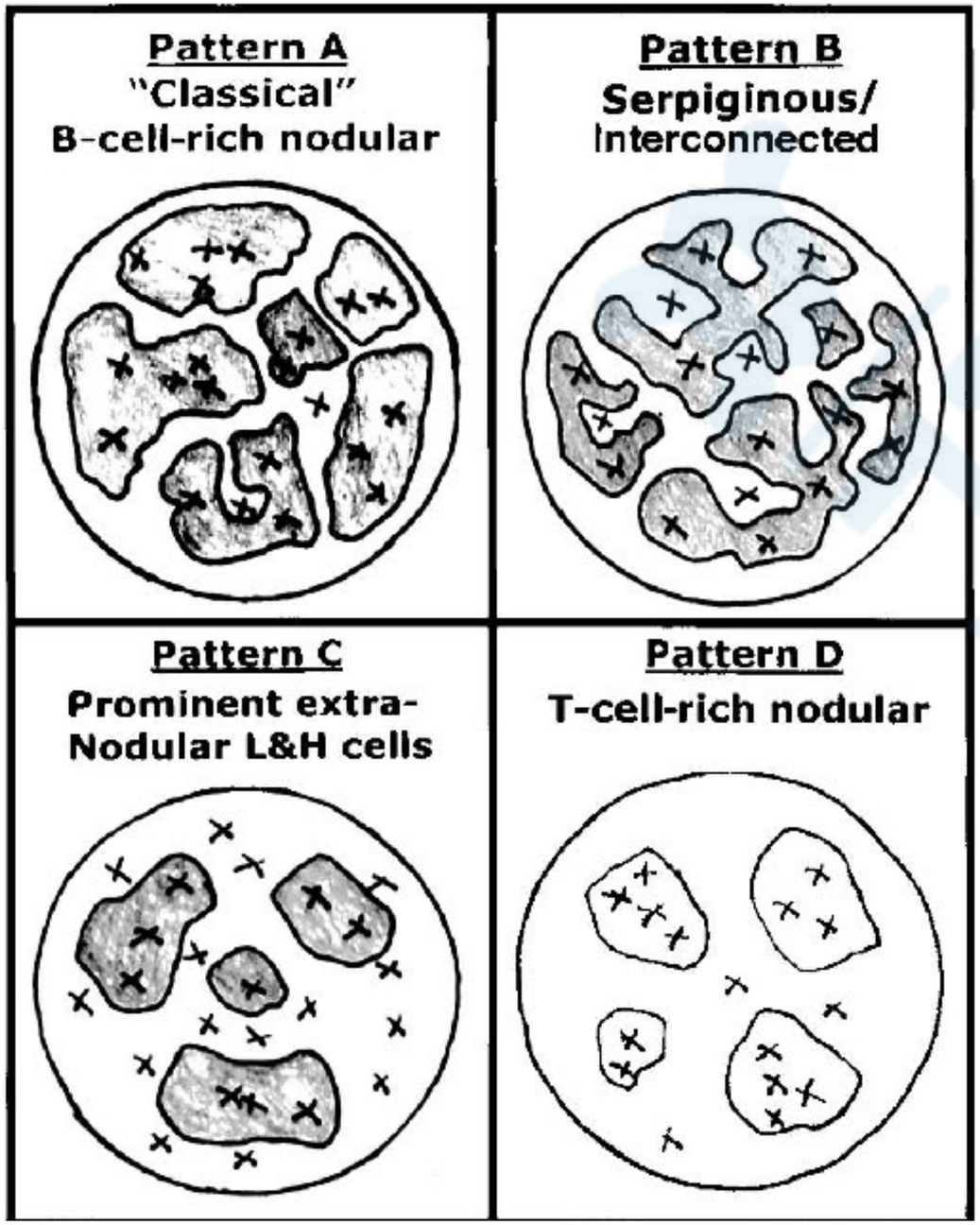
III期
横隔双侧均有受
累，常包括脾脏
或淋巴结外受累

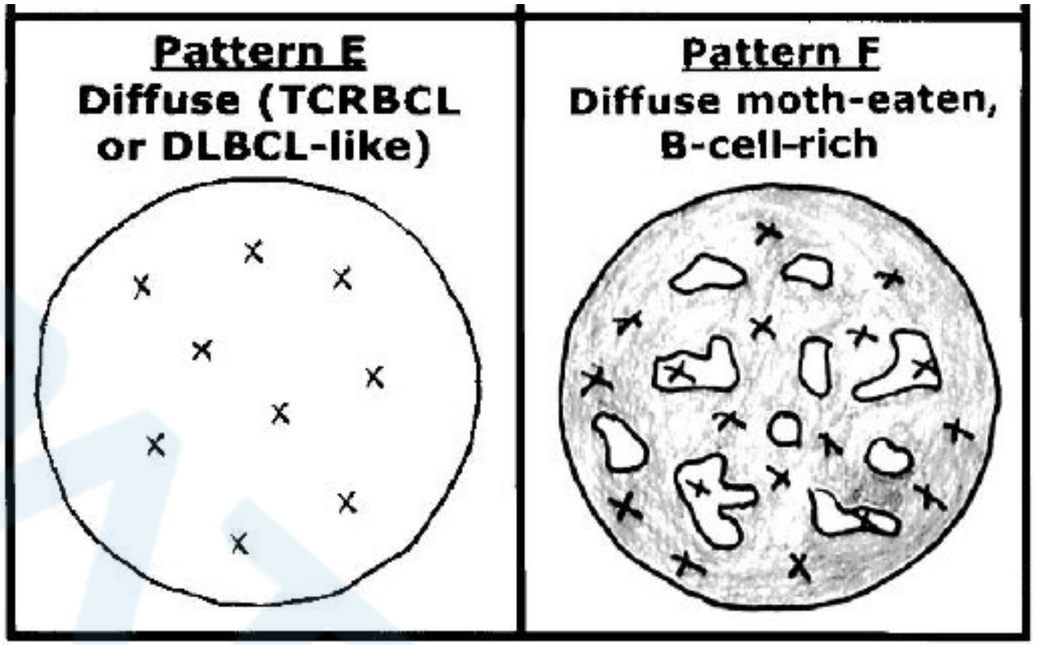


IV期
淋巴结外器官广泛受
累，包括肝、骨髓、
肺及皮肤

引自谢建兰教授幻灯

NLPHL的形态学亚型





In this schematic illustration, the X's represent lymphocyte predominant (LP) cells, the grey background a B-cell–rich background, and the white background a T-cell–rich background.

From: Fan Z, Natkunam Y, Bair E, Tibshirani R, Warnke RA. *Am J Surg Pathol* (2003) {1159}.

Am J Surg Pathol. 2004 Apr;28(4):489-95.

Bone marrow involvement in patients with nodular lymphocyte predominant Hodgkin lymphoma.

Khoury JD[1], Jones D, Yared MA, Manning JT Jr, Abruzzo LV, Hagemeister FB, Medeiros LJ.

The German Hodgkin Study Group reported 8 NLPHL patients with bone marrow involvement; in 7 patients the primary NLPHL tumor showed a **variant histologic pattern**. Bone marrow involvement in NLPHL is associated with a more **aggressive clinical course**.

BACKGROUD

Bone Marrow Lesion :

Typical NLPHL: the presence of large B cells in a background of nodular aggregates of small B cells.

Diffuse involvement typically : either by the presence of large B cells in a diffuse THRLBCL-like background or the presence of sheets of neoplastic large B cells in keeping with diffuse LBCL.

Lymphoid aggregates:Bone marrow biopsy specimens with aggregates composed only of small lymphocytes—without identifiable neoplastic large B cells.

The **differential prognostic** implications of bone marrow involvement by NLPHL versus bona fide large B-cell lymphoma (LBCL) have not been described

MATERIALS AND METHODS

Study Group

The University of Texas MD Anderson Cancer Center for patients（January 1, 1996 and December 31, 2015）

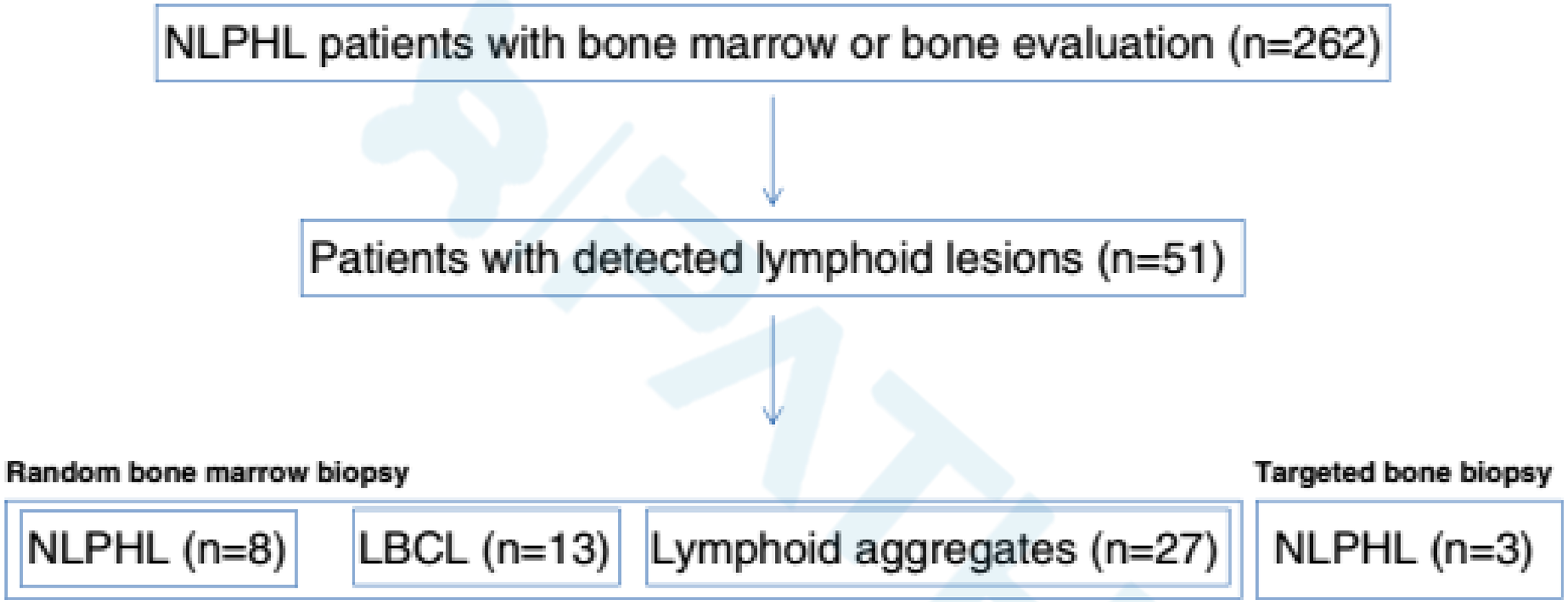
Histopathologic Evaluation

Immunohistochemistry

Statistical Analysis

EFS，OS (Kaplan-Meier method)

Schematic representation of the study design.



Case	Age (y)/Sex	Ann Arbor Stage at Diagnosis	Treatment(s) Received	Disease Relapse	Follow-up Duration (mo)	Vital Status at Last Follow-up
1	37/M	NA	NA	NA	NA	Alive
2	40/M	IV	Chemotherapy	No	4	Alive
3	45/M	NA	NA	NA	22	Alive
4	23/F	IVA	Chemotherapy+autologous SCT	Yes	2	Alive
5	41/M	IVB	Chemotherapy	No	178	Dead
6	39/F	II	Chemotherapy+radiotherapy	Yes	148	Alive
7	39/M	IVA	Chemotherapy	No	46	Alive
8	45/M	IVB	Chemotherapy+autologous SCT	Yes	83	Alive
9	14/M	IA	Chemotherapy+radiotherapy +autologous SCT	Yes	191	Alive
10	25/M	IV	Chemotherapy+autologous SCT	Yes	345	Alive
11	61/F	IA	Radiotherapy	No	148	Alive
12	64/M	IVA	Chemotherapy	No	51	Alive
13	30/F	IV	Chemotherapy+autologous SCT	Yes	93	Alive
14	12/M	IIA	Chemotherapy+radiotherapy +autologous SCT	Yes	26	Alive
15	50/M	IVB	Chemotherapy	No	52	Alive
16	65/M	IVA	Chemotherapy+autologous SCT	Yes	31	Alive
17	44/M	NA	NA	NA	43	Alive
18	51/M	IV	Chemotherapy+autologous SCT	Yes	5	Alive
19	49/M	IV	Chemotherapy	Yes	36	Dead
20	47/M	IV	Chemotherapy+allogeneic SCT	Yes	18	Dead
21	37/M	IV	Chemotherapy	No	26	Alive
22	37/M	IVB	Chemotherapy	No	107	Alive
23	44/F	IIIB	Chemotherapy	Yes	157	Alive
24	53/F	III	Chemotherapy+autologous SCT followed by allogeneic SCT	Yes	43	Dead

NA indicates not available; SCT, stem cell transplant.

Case	Age (y)/Sex	Ann Arbor Stage at Diagnosis	Treatment(s) Received	Disease Relapse	Follow-up Duration (mo)	Vital Status at Last Follow-up
25	35/M	IIIA	Chemotherapy	Yes	47	Alive
26	51/M	I	Surgical excision and watchful waiting	No	11	Alive
27	57/F	IIA	Radiotherapy	No	33	Alive
28	42/M	III	Chemotherapy	No	40	Alive
29	45/M	II	Radiotherapy	No	38	Alive
30	73/M	I	Surgical excision and watchful waiting	No	36	Alive
31	54/M	III	Chemotherapy	NA	102	Alive
32	46/M	IIIA	Chemotherapy+radiotherapy	Yes	18	Alive
33	31/F	IIA	Chemotherapy+radiotherapy	No	241	Alive
34	37/M	IIIA	Chemotherapy	No	65	Alive
35	24/F	IB	Radiotherapy	No	95	Alive
36	31/M	II	Chemotherapy	No	66	Alive
37	54/M	IIA	Radiotherapy	No	27	Alive
38	36/M	IIA	Chemotherapy	No	40	Dead
39	23/M	IIA	Radiotherapy	No	99	Alive
40	47/F	IIB	Chemotherapy	No	16	Alive
41	58/M	IIA	Chemotherapy+radiotherapy	No	160	Alive
42	62/M	I	Radiotherapy	No	22	Alive
43	38/M	NA	Chemotherapy+autologous SCT	Yes	86	Alive
44	43/M	IIA	Chemotherapy	Yes	151	Alive
45	43/M	IIIA	Chemotherapy	Yes	309	Alive
46	34/F	IVA	Chemotherapy	No	221	Alive
47	34/F	IE	Chemotherapy	Yes	198	Dead
48	30/F	I	Radiotherapy	Yes	147	Alive
49	10/M	IIA	Chemotherapy	No	162	Alive
50	34/M	III	Chemotherapy+autologous SCT	Yes	332	Alive
51	64/F	NA	Chemotherapy	No	125	Alive

NA indicates not available; SCT, stem cell transplant.

- The median follow-up time was 51.7 months (range, 2 to 345 mo).
- Disease recurrence or progression was documented in 21/47 (45%) patients, among whom 10(21%) had transformation to LBCL over the course of follow-up.
- At last follow-up, 44/51 (86.3%) patients were alive.
- By univariate analysis, elevated serum LDH, anemia,thrombocytopenia, and absolute neutrophil count were not associated with EFS.

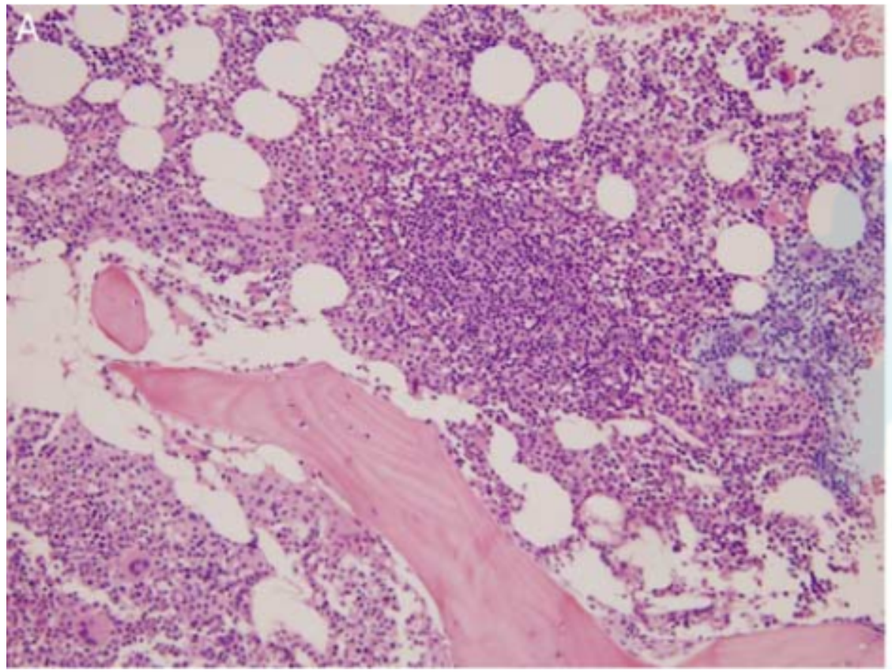
Case	NLPHL Growth Pattern at Primary Site	Bone Marrow or Targeted Bone Biopsy Site	Bone Marrow Lesion	Large B-cells	Extent of Bone Marrow Space Involvement (%)
1	A	Vertebral body, L2*	NLPHL	Present	40-50
2	A, B, C, D	Iliac bone	NLPHL	Present	30
3	Cannot be assessed†	Right iliac bone*	NLPHL	Present	10
4	D	Iliac bone	NLPHL	Present	5
5	A	Iliac bone	NLPHL	Present	10
6	A	Iliac bone	NLPHL	Present	10
7	A	Vertebral body, L5*	NLPHL	Present	20-30
8	NA	Iliac bone	NLPHL	Present	95
9	NA	Iliac bone	NLPHL	Present	50
10	NA	Iliac bone	NLPHL	Present	100
11	D	Iliac bone	NLPHL	Present	5
12	A, F	Iliac bone	LBCL	Present	30
13	C	Iliac bone	LBCL	Present	30
14	C	Iliac bone	LBCL	Present	50-60
15	E	Iliac bone	LBCL	Present	90
16	E	Iliac bone	LBCL	Present	30
17	D, E	Iliac bone	LBCL	Present	90
18	B, E	Iliac bone	LBCL	Present	30
19	D	Iliac bone	LBCL	Present	80
20	D	Iliac bone	LBCL	Present	10
21	B, E	Iliac bone	LBCL	Present	15
22	NA	Iliac bone	LBCL	Present	95
23	NA	Iliac bone	LBCL	Present	50
24	NA	Iliac bone	LBCL	Present	40
25	F	Iliac bone	Lymphoid aggregates	Absent	5

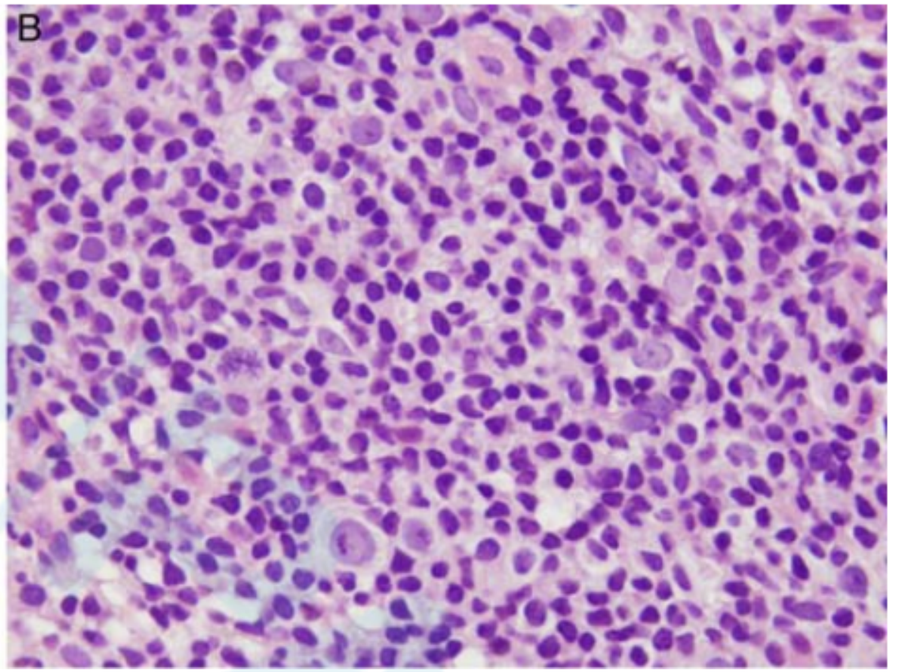
Case	NLPHL Growth Pattern at Primary Site	Bone Marrow or Targeted Bone Biopsy Site	Bone Marrow Lesion	Large B-cells	Extent of Bone Marrow Space Involvement (%)
26	C	Iliac bone	Lymphoid aggregates	Absent	5
27	A	Iliac bone	Lymphoid aggregates	Absent	10
28	B	Iliac bone	Lymphoid aggregates	Absent	5
29	D	Iliac bone	Lymphoid aggregates	Absent	5
30	A	Iliac bone	Lymphoid aggregates	Absent	5
31	A, B	Iliac bone	Lymphoid aggregates	Absent	NA
32	A	Iliac bone	Lymphoid aggregates	Absent	5
33	E	Iliac bone	Lymphoid aggregates	Absent	NA
34	A, B	Iliac bone	Lymphoid aggregates	Absent	NA
35	C	Iliac bone	Lymphoid aggregates	Absent	5
36	A	Iliac bone	Lymphoid aggregates	Absent	5
37	A	Iliac bone	Lymphoid aggregates	Absent	5
38	A	Iliac bone	Lymphoid aggregates	Absent	5
39	A	Iliac bone	Lymphoid aggregates	Absent	5
40	A	Iliac bone	Lymphoid aggregates	Absent	NA
41	B	Iliac bone	Lymphoid aggregates	Absent	5
42	NA	Iliac bone	Lymphoid aggregates	Absent	5
43	NA	Iliac bone	Lymphoid aggregates	Absent	NA
44	NA	Iliac bone	Lymphoid aggregates	Absent	5
45	NA	Iliac bone	Lymphoid aggregates	Absent	5
46	NA	Iliac bone	Lymphoid aggregates	Absent	5
47	NA	Iliac bone	Lymphoid aggregates	Absent	5
48	NA	Iliac bone	Lymphoid aggregates	Absent	5
49	NA	Iliac bone	Lymphoid aggregates	Absent	5
50	NA	Iliac bone	Lymphoid aggregates	Absent	NA
51	NA	Iliac bone	Lymphoid aggregates	Absent	5

*Targeted biopsy.
†Small size of this specimen (core needle biopsy) precludes assessment of pattern.
NA indicates not available.

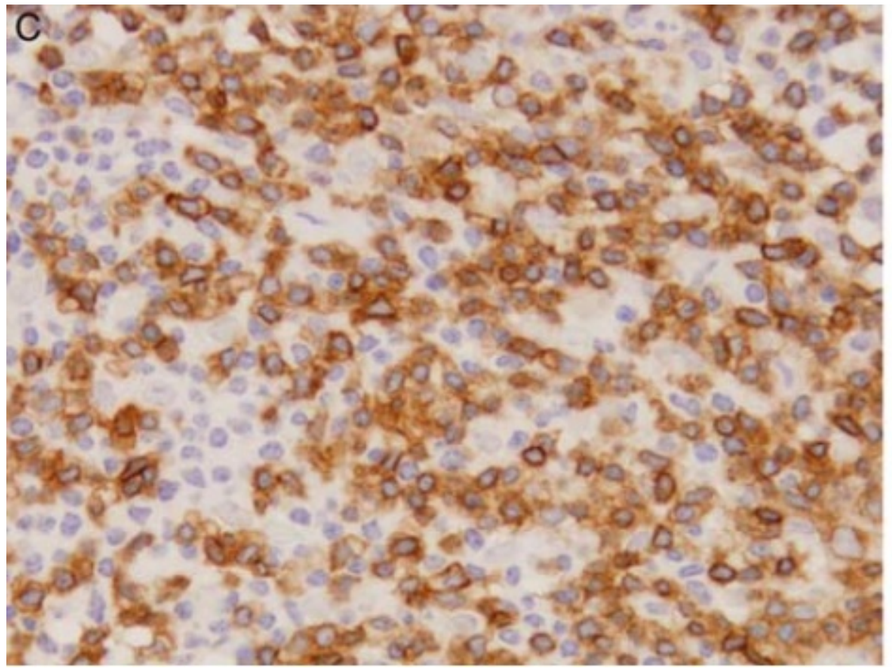
- Bone Marrow Lesions :
- NLPHL:n=11
- LBCL: n=13
- Lymphoid aggregates: n=27

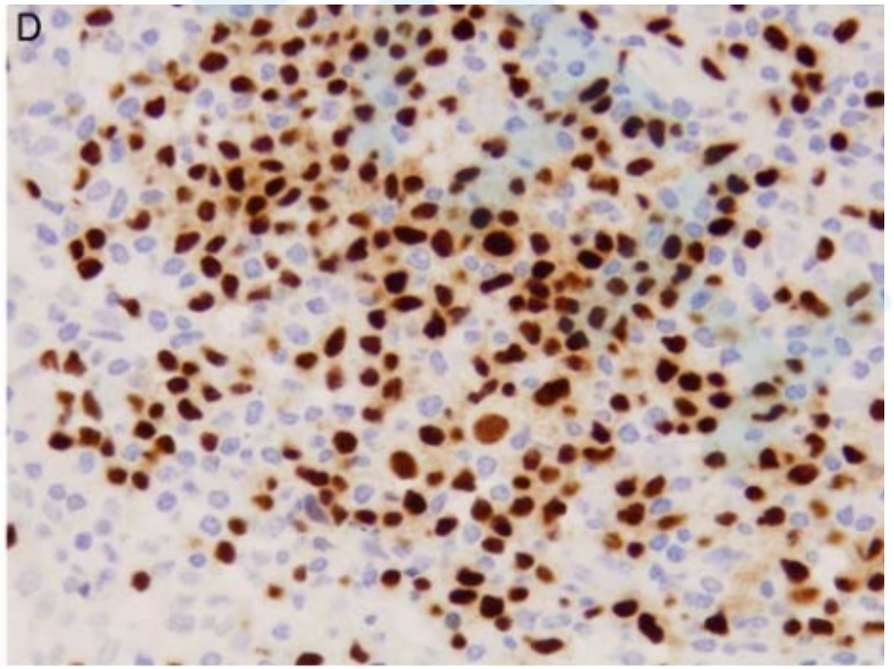
- classic patterns : n=16
- variant NLPHL histologic patterns: n=18



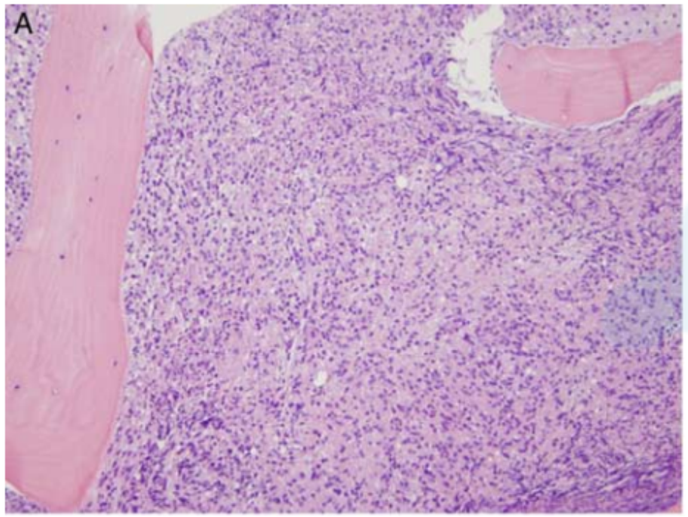


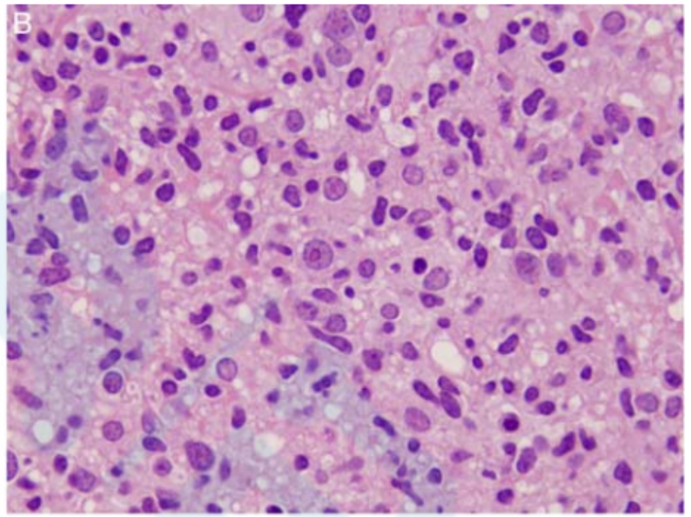
Bone marrow involvement by typical pattern NLPHL. A, A nodular, nonparatrabecular lymphoid aggregate is seen(hematoxylin and eosin). B, A few large atypical lymphocytes are seen admixed with many small lymphocytes (hematoxylin and eosin).



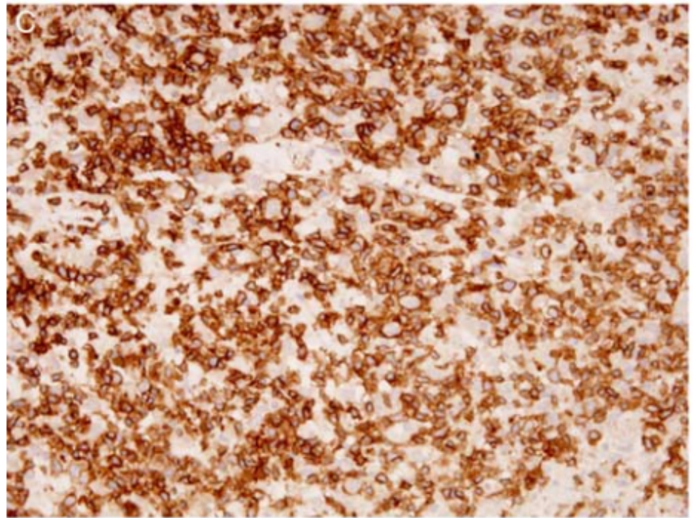


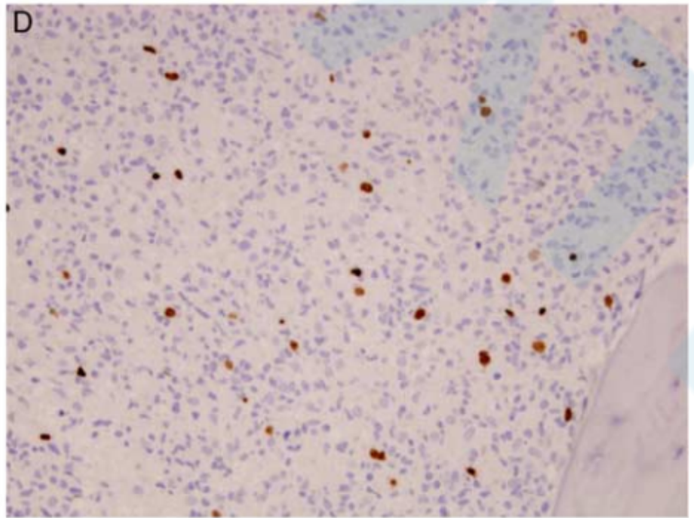
C, The lymphoid infiltrate is composed of a many CD3 positive T cells.
D, The infiltrate also includes many small B-cells and scattered atypical large B-cells, all of which express PAX5



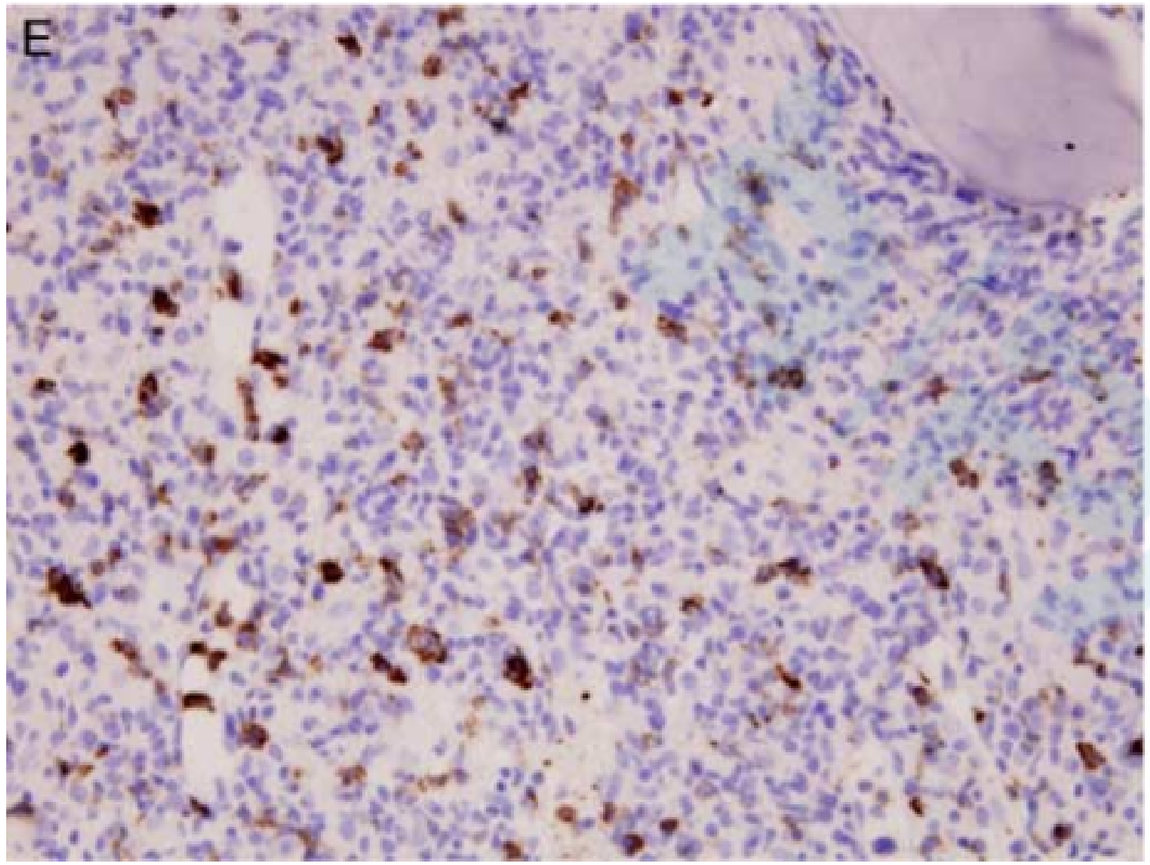


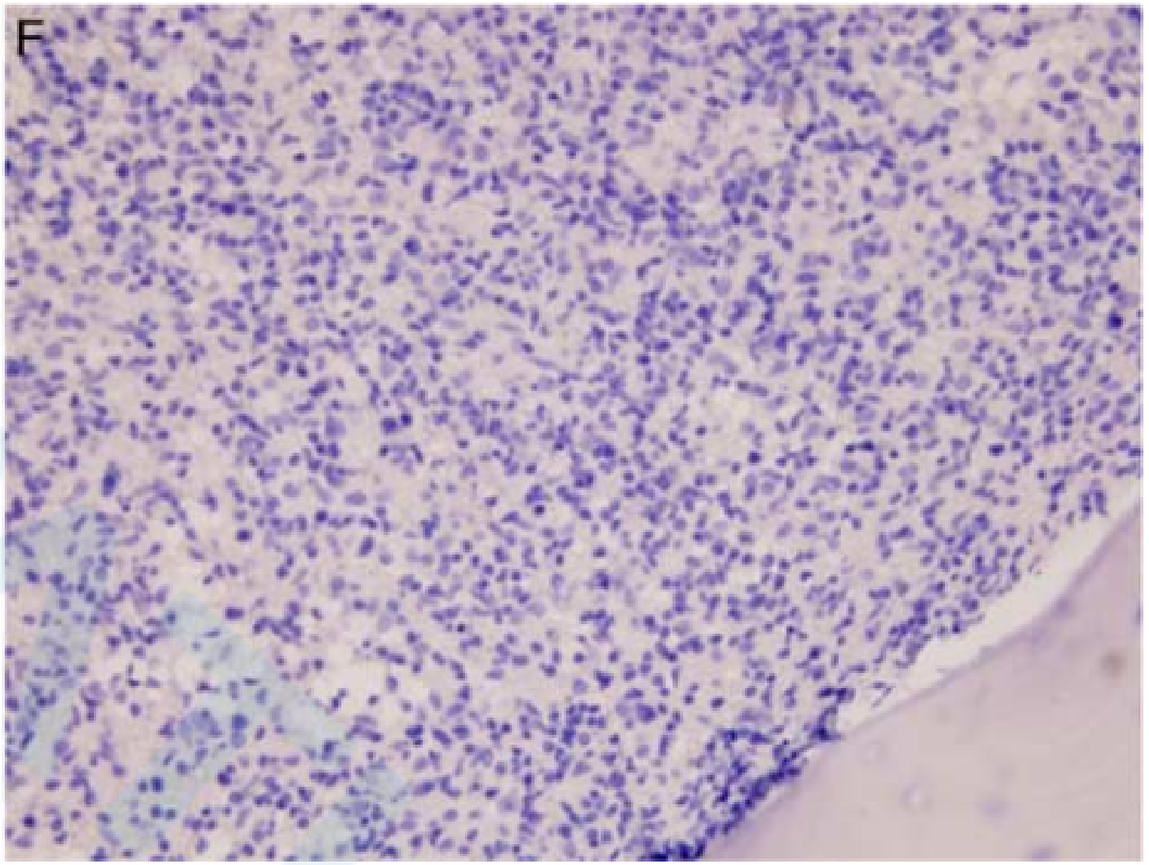
Bone marrow involvement by T-cell rich LBCL in a patient with NLPHL. A diffuse lymphoid infiltrate extensively replaces normal hematopoietic elements (hematoxylin and eosin).
B, Scattered large atypical lymphocytes are admixed with numerous histiocytes and occasional smaller lymphocytes (hematoxylin and eosin).



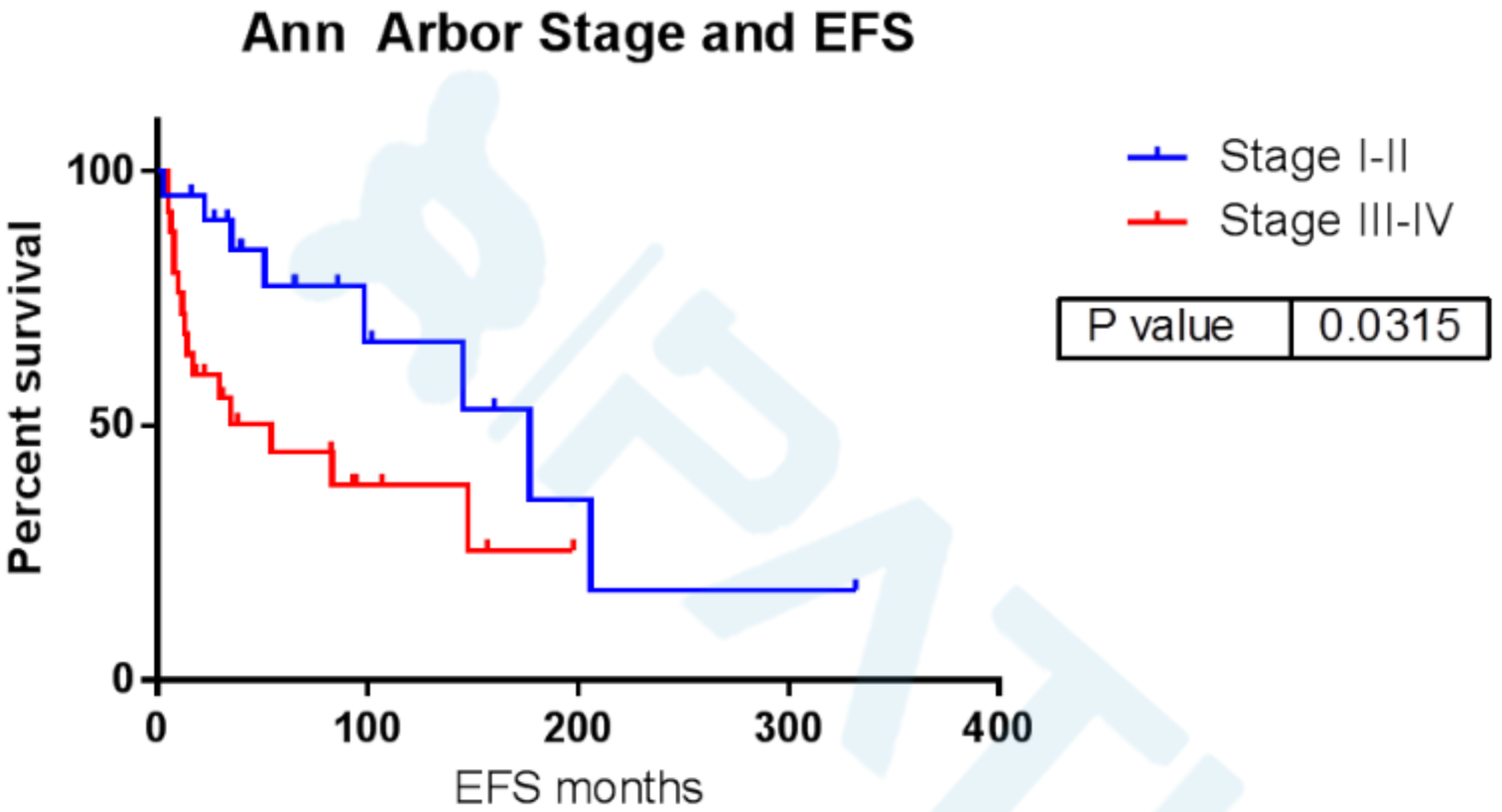


C, Immunohistochemical stains show numerous CD3-positive T cells (immunohistochemistry with hematoxylin counterstain).
D, Small B cells are virtually absent; the atypical large cells are PAX5-positive (immunohistochemistry with hematoxylin counterstain).





E, Scattered CD57-positive cells are present (immunohistochemistry with hematoxylin counterstain).
F, No follicular dendritic cell meshworks are identified by CD21 immunohistochemistry (immunohistochemistry with hematoxylin counterstain).



Comparison of event-free survival of nodular lymphocyte predominant Hodgkin lymphoma patients with low (I/II) and high (III/IV) Ann Arbor stage disease at presentation.

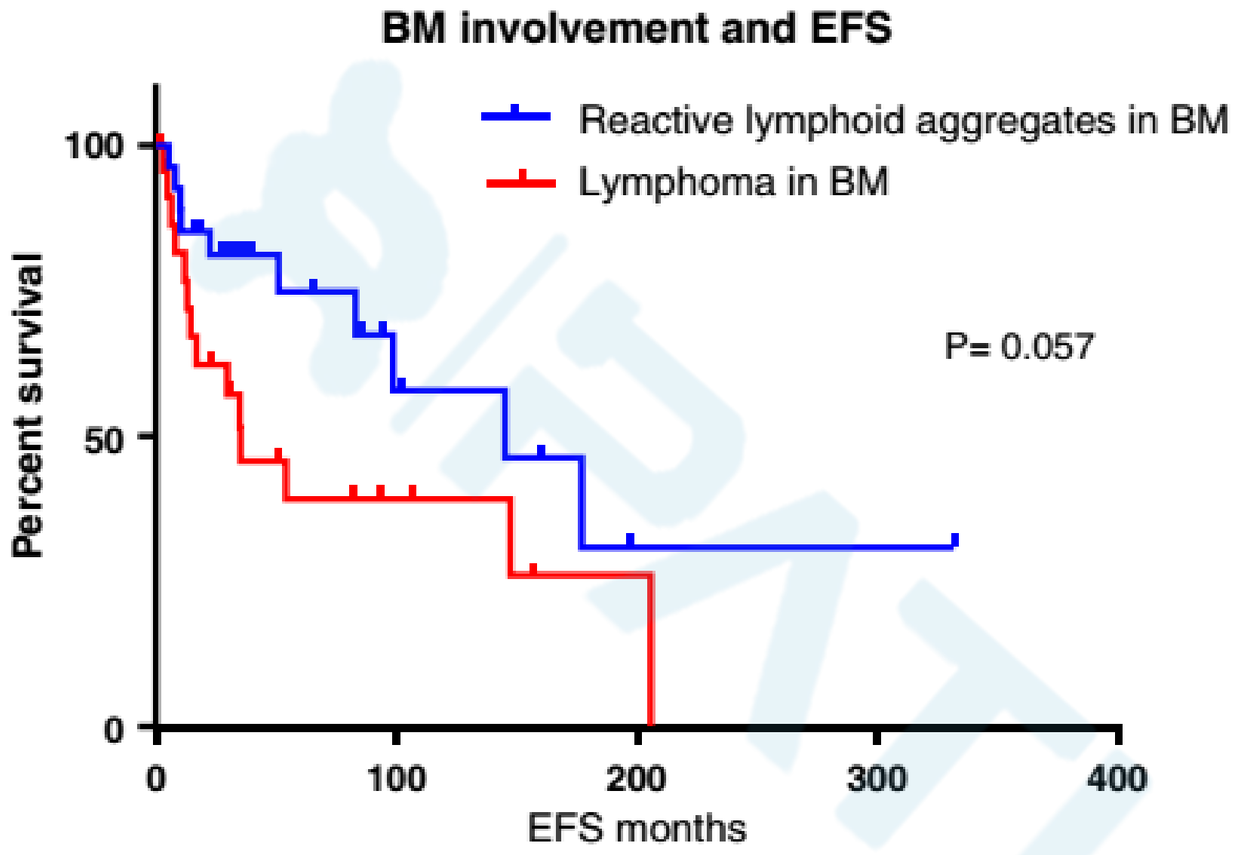
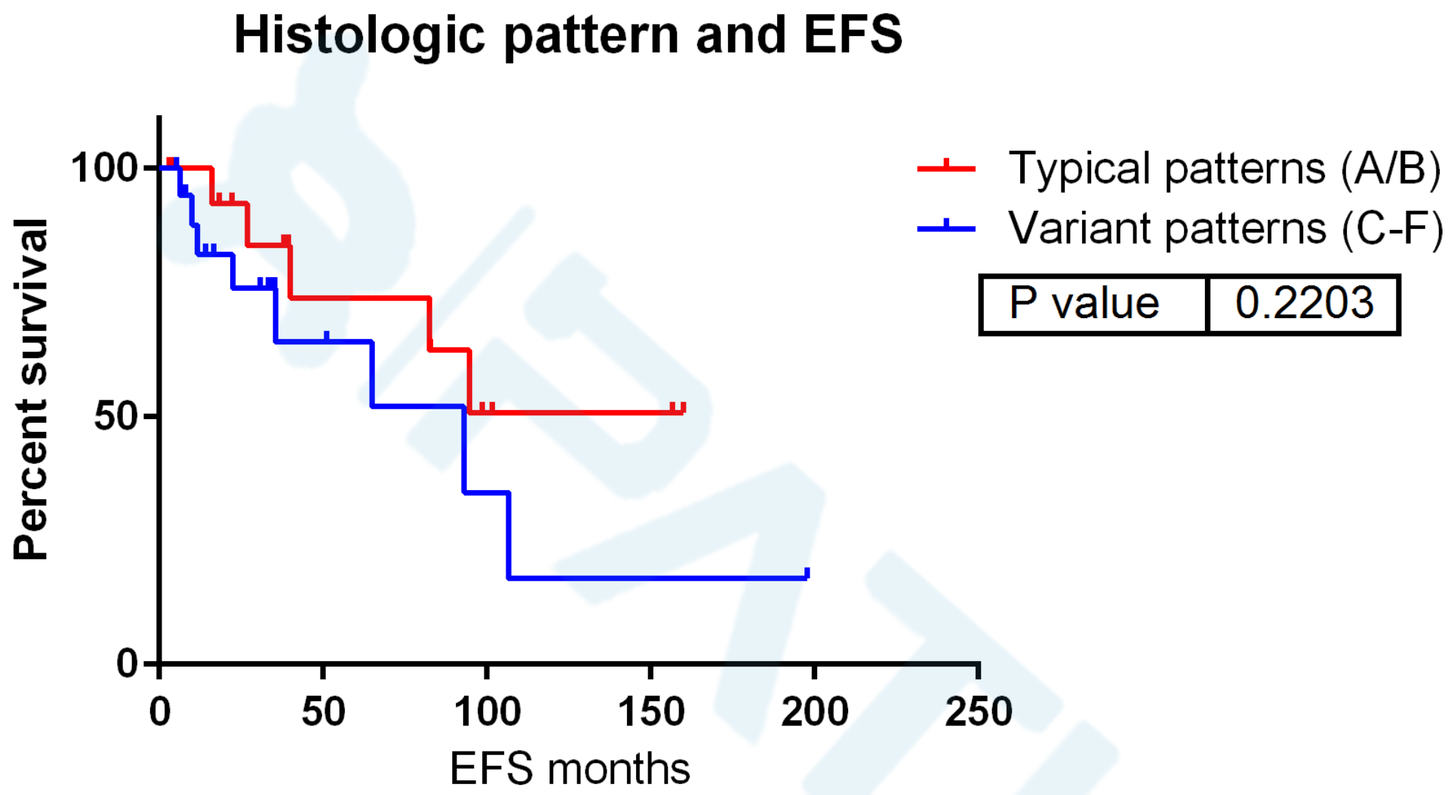


FIGURE 4. EFS in NLPHL patients who had bone marrow involvement by lymphoma (NLPHL or LBCL).



Comparison of event-free survival between nodular lymphocyte predominant Hodgkin lymphoma patients based on tumor pattern categories.

Other parameters		
bone marrow involvement & no bone marrow involvement	shorter EFS	P = 0.057
bone marrow involvement by lymphoma & lymphoid aggregates	recurrence/progression was higher	P = 0.04
bone marrow involvement by LBCL & bone marrow involvement by NLPHL	shorter median EFS	P = 0.3
bone marrow involvement by lymphoma & lymphoid aggregates	higher frequency of transformation to LBCL	P = 0.002
variant patterns & classic NLPHL patterns	more common Bone marrow involvement	P = 0.020
LBCL in the bone marrow & NLPHL or lymphoid aggregates involving bone marrow	a lower median platelet	P = 0.02
classic NLPHL in the primary lymph node & variant NLPHL	NLPHL in the bone marrow	P = 0.006

- **Bone marrow involvement** was more common in patients with **variant NLPHL histologic patterns** in the lymph node as compared with those who had classic patterns (12/18 vs. 4/16; P = 0.02).
- An additional 27 NLPHL patients **lymphoid aggregates** had a **longer event-free survival** than patients with lymphoma in the bone marrow (145 vs. 35 mo).
- **Disease recurrence or progression** was more frequent **NLPHL or LBCL**, compared with patients who had lymphoid aggregates (13/21 vs. 8/26; P = 0.04).

THANK YOU